SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-124967- -00000-0000

Fecha: 2011-09-23 16:50:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 243

Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: INHIBIDORES DE LA REPLICACIÓN DEL VIRUS DE LA HEPATITIS C.

SOLICITANTE: MERCK SHARP & DOHME CORP.

DIRECCIÓN: 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 E.U.A.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 22 de Septiembre de 2011

P2011/000164

OLARTEMOURE

OLARTE MOURE & ASOCIADOS

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-124967- -00000-0000
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Act: 411 PRESENTACION Folios: 243

PETITORIO - FORMULARIO ÚNICO
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000164**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

Nombre: MERCK SHARP & DOHME CORP.
Dirección: 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 E.U.A.
Nacionalidad o Domicilio: Estados Unidos
Lugar de Constitución: Estado Unidos

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

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

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Carrera 5 No. 34-03 Bogotá
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olartemoure.com

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

INVENTOR (ES) (72)

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

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2010/028653 Fecha Marzo 25, 2010

Publicación Internacional No. WO 2010/111483 Fecha Septiembre 30, 2010

(6) **Título (54)** **INHIBIDORES DE LA REPLICACIÓN DEL VIRUS DE LA HEPATITIS C.**

Clasificación Internacional (51) A01N 37/18; A01K 31/16.

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

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Marzo 27, 2009	61/163,958
US	Septiembre 30, 2009	61/247,318

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

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 10-030.403.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

LISTA DE INVENTORES

PCT/US2010/028653

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Shanghai 200131,
China
Nacionalidad: China

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

Industria y Comercio
SUPERINTENDENCIA

RECIBO DE CAJA

No. 11 - 0093306

Bogotá D.C., Septiembre 22 de 2011 - 14:40:32

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	408398605	21/09/2011	4.447.000.00

*** Conceptos Pagados ***

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

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

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-124967- -00000-0000
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WK 11657662

ESCRITURA PUBLICA NUMERO: (0 0 2 6) CERO CERO VEINTISEIS. ----------

En la ciudad de Bogotá, Distrito Capital, República de Colombia, a los Quince ----- (15) días del mes de Enero ---- del año dos mil diez --- (2010), ante mi MARIA EUGENIA ROJAS DE URUETA ----------NOTARIA(O) CUARENTA Y SEIS (46) DEL CIRCULO DE BOGOTA, se otorgó la escritura pública que se consigna en los siguientes términos: ----------

---

CLASE(S) DE ACTO: PROTOCOLIZACION POR CARLOS REINALDO OLARTE GARCIA, JAMES IAN RAISBECK LLINAS, JUAN GUILLERMO MOURE PEREZ, Y NATALIA CASTRO VELEZ ----------

C.C. Nos. 79.782.747, 79.376.996, 80.412.281 Y 52.008.577.----

---

Compareció CARLOS REINALDO OLARTE GARCIA, mayor de edad, vecino de Bogotá, identificado con la cédula de ciudadanía número 79.782.747, de estado civil casado con sociedad conyugal vigente, JAMES IAN RAISBECK LLINAS mayor de edad, vecino de ésta ciudad, identificado con la cédula de ciudadanía número 79.376.996, de estado civil casado con sociedad conyugal vigente, JUAN GUILLERMO MOURE PEREZ, mayor de edad, vecino de Bogotá, identificado con la cédula de ciudadanía número 80.412.281, de estado civil casado con sociedad conyugal vigente y NATALIA CASTRO VELEZ, mayor de edad, vecina de Bogotá, identificada con la cédula de ciudadanía número 52.008.577, de estado civil casada con sociedad conyugal vigente, obrando en sus propios nombres y dijeron: ----------

2 Copias

18 ENE 2010

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

PRIMERO.- Que presentan para su protocolización y custodia en los archivos de ésta notaría, bajo el número y lugar que a ésta escritura corresponda, en cuatro (4) folios autenticados, un poder, y sus traducciones el cual es del siguiente tenor: -- PODER GENERAL.----------

El suscrito, MERCK SHARP & DOHME, CORP domiciliado en 126 East Lincoln, Avenue Rahway, NJ 07065-0907 United States of America nombramos por el presente a Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro, nuestros representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia, la república de Bolivia, La República del Ecuador, la Republica del Perú y la Republica Bolivariana de Venezuela ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones, formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al

otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que expresa la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin todas las medidas que creyeren conducentes al resguardo de nuestros intereses- ----------

Firma X (ilegible) Mark R. Daniel, Managing Counsel, Patents.-

Fecha November 19 2009 ----------

Ciudad País: Rahway, NJ, USA.----------

Certificación Notarial- ----------

En esta fecha, November 19 ----------

El notario Público suscrito Certifica: ----------

1: Que Mark R. Daniel mayor de edad y domiciliado 126 East Lincoln Avenue, Rahway, NJ 07065, USA suscribió el documento que antecede ----------

2. Que el otorgante ha suscrito el referido documento en su carácter de Managing Counsel, Patents of MERCK SHARP & DOHME CORP, ----------

3. Que MERCK SHARP & DOHME con sede principal en 126 East Lincoln Avenue Rahway, NJ 07065-0907, United States of America esta legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden el objeto social. --

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

5. El fundamento de mis certificaciones contenidas en los puntos 2,3 y 4 fue la exhibición de los siguientes documentos auténticos. (Sigue texto sin traducir) ----------

Traducción oficial de un documento cuyo original está en

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

inglés.----------

APOSTILLA

(Convención de la Haye du 5 octobre 1961)

1. País: Distrito de Columbia Estados Unidos de América------

El presente documento público ----------

2. ha sido firmado Por: Violet Burgess ----------

3. Actuando en calidad de: Notario Público de New Jersey. ---

4. Lleva el sello/ estampilla de: Violet Burgess, Notario.- ----

Certificado

5 En: ---------- Trenton, New Jersey

6. El: ---------- 25 de noviembre de 2009

7. Por: ---------- R. David Rousseau, Tesorero de New Jersey

8. Bajo el No.: ---------- A380889

9. Sello/ estampilla: "El Gran Sello del Estado de New Jersey"

10. Firma: ---------- (Firmado)

Certificación: ----------

Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.----------

Documento: "Apostilla" ----------

Fecha:11 de Diciembre de 2009.----------

Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registrados ante el Ministerio de Relaciones Exteriores de Colombia).- ----------

Licencia # 376 de 1993, expedida por el Ministerio de Justicia.

Dirección Carrera 15 # 99-13 Of. 411, Bogotá D.C.----------

Teléfonos (571) 218 23 08 (571) 623 29 25.- ----------

E-mail: treser1@yahoo.com----------

Traducción # 14-278.- ----------

SEGUNDO.- Que solicita a la señora Notaria la incorporación de dichos documentos al protocolo de ésta notaría para que de

su tenor se expidan las copias que más adelante se soliciten ----------

---

La notaría advierte a los interesados que la protocolización de documentos no da mayor fuerza o autenticidad de la que tienen dichos documentos.-------

---

Esta escritura pública fue firmada fuera del Despacho Notarial, de conformidad con el artículo 12 del Decreto 2.148 de 1.983. -

---

Se advirtió a los otorgantes de esta escritura de la obligación que tienen de leer la totalidad de su texto, a fin de verificar la exactitud de todos los datos en ella consignados, con el fin de aclarar, modificar o corregir lo pertinente antes de firmarla, la firma de la misma demuestra su aprobación total del texto, en consecuencia, la notaria no asume ninguna responsabilidad por errores o inexactitudes establecidas con posterioridad a la firma de (el, los) otorgante(s) y de la notaría, en tal caso, este (os) debe(n) ser corregidos mediante el otorgamiento de una nueva escritura, suscrita por todos los que intervinieron en la inicial y sufragada por los mismos (articulo 35, decreto ley 960 de 1970).- ----------

ADVERTENCIA, OTORGAMIENTO Y AUTORIZACION.- Leído el presente instrumento por el (los) compareciente (s) y advertido (s) sobre las formalidades legales, lo aprueban y firman conmigo y ante mí la(el) Notaria(o) quién lo autoriza. A los otorgantes se les advirtió finalmente que una vez firmado el presente instrumento, La(el) Notaria(o) no aceptará correcciones o modificaciones sino en la forma y casos

ESTE PAPEL NO TIENE COSTO PARA EL USUARIO

previstos por la Ley. ---Se utilizaron las hojas de papel Notarial Nos .WK 11657662, WK 11657663, WK 11657664 Y WK 11657665.

DERECHOS LEGALES: $ 42.860.oo.

RESOLUCIONES 9306 Y 9500 DE 2008

IVA $ 11.682.oo.

CARLOS REINALDO OLARTE GARCIA
C.C.No. 79.782.747 Bta
TEL: 6017700

JAMES IAN RAISBECK LLINAS
C.C.No. 79.376.996 Bta
TEL: 6017700

JUAN GUILLERMO MOURE PEREZ
C.C.No. 80112281
TEL: 6017700

NATALIA CASTRO VELEZ,
C.C.No. 52008.517
TEL: 6017700

Apostilla:

APOSTILLA:
(Convention de La Haye du 5 octobre 1961)

1. País:	Estados Unidos de América
	El presente documento público
2. Ha sido firmado por:	Violet Burgess
3. Actuando en calidad de:	Notario Público de New Jersey
4. Lleva el sello/estampilla de:	Violet Burgess , Notario
	Certificado
5. En:	Trenton, New Jersey
6. El:	25 de noviembre de 2009
7. Por:	R. David Rousseau, Tesorero de New Jersey
8. Bajo el No.:	A380889
9. Sello / estampilla:	"El Gran Sello del Estado de New Jersey"
10. Firma:	(Firmado)

Certificado No. 115832008
Verifique este certificado por internet en:
https://www1.state.nj.us/TYTR-StandingCert/JSP/Verify_Cert.jsp

Certificación:
Certifico que la presente es una traducción auténtica y completa del inglés al español del documento adjunto, la cual he elaborado según mi leal saber y entender.
Documento: "Apostilla"
Fecha: 11 de diciembre de 2009.
Traductor: Jorge Enrique Sierra Reyes (Sello y firma digital debidamente registrados ante el Ministerio de Relaciones Exteriores de Colombia)
Licencia # 376 de 1993, expedida por el Ministerio de Justicia.
Dirección: Carrera 15 # 99-13 Of. 411, Bogotá, D.C.
Teléfonos: (571) 218 2308, (571) 623 2925.
E-mail: tesorero1@yahoo.com
Traducción # 14-278

Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Minjusticia

MINISTERIO DE
RELACIONES EXTERIORES

2006 DIC 19 A 8:07

JEFE DE LEGALIZACIONES
BOGOTA D.C.

NO SE ASUME
RESPONSABILIDAD
DEL TEXTO

003841

Jorge Sierra
SUPA FIRMA APARECE EN EL
DOCUMENTO DESEMPEÑA
LAS FUNCIONES INDICADAS

The undersigned **General Power**

El suscrito, **Poder General**

MERCK SHARP & DOHME CORP

domiciled in

domiciliado en

126 East Lincoln, Avenue Rahway, NJ 07065-0907
United States of America

by means of these presents hereby grants to **Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro** , legal representatives with faculties to receive notifications and to appoint judicial or extrajudicial agents in patent matters, who at the same time have the faculty to represent us before the administrative, judicial or police authorities of any hierarchy of the Republic of Colombia, the Republic of Bolivia, the Republic of Ecuador, the Republic of Peru, and the Bolivarian Republic of Venezuela, to initiate before said authorities all the necessary actions to accomplish said purposes and to intervene in all instances, grades and procedural levels; to file and prosecute applications, declarations, complaints, to claim, counterclaim, answer claims and counterclaims; to draw up specifications; to make amendments; oppositions and all types of objections and writings of any nature; cancellations and administrative injunction proceedings; to pay all installments and effect all other payments prescribed by law; to receive documents and monies; act as complainants as well as defendants, before the competent judges, with full powers to request preliminary injunctions of any nature, settle, make arrangements, to submit to arbitrators, to desist from claims or procedures, to accept claims, to collect, to ratify legal proceedings subscribed before the appointment and/or presentation of this Power, substitute or delegate the legal representation and other acts prescribed by law, in short, with all such further powers as may be required; to comply with all other requirements and, to take all those measures which they may deem fit for the protection of our interests.

nombramos por el presente a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Juan Guillermo Moure y/o Natalia Castro,** nuestros representantes legales con facultades para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales en materia de patentes, los cuales quedan a su vez facultados para representarnos ante las autoridades de cualquier jerarquía de la República de Colombia, la República de Bolivia, la República del Ecuador, la República del Perú y la República Bolivariana de Venezuela, ya sean administrativas, judiciales o de policía, para iniciar ante dichas autoridades todas las acciones necesarias para cumplir con el objeto indicado e intervenir en todas las instancias, grados o etapas procesales; elevar y tramitar solicitudes, declaraciones y reclamos, para demandar, reconvenir, contestar demandas y reconvenciones; formular descripciones, enmiendas, oposiciones y todo tipo de impugnaciones y escritos de cualquier naturaleza; instaurar cancelaciones y amparos administrativos; abonar todos los impuestos y cuotas y efectuar cualquier otro pago determinado por la ley; recibir todos los documentos y valores; intervenir como demandantes o demandados ante los jueces que sean competentes, pudiendo solicitar medidas cautelares de cualquier naturaleza, conciliar, transar, someter a árbitros, desistirse de la pretensión y/o el procedimiento, allanarse a la pretensión, percibir, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal y los demás actos que exprese la ley, con todas las demás facultades que resulten necesarias; llenar cualesquiera otros requisitos y tomar, en fin, todas las medidas que creyeren conducentes al resguardo de nuestros intereses.

NOTARIA CUARENTA Y SEIS
DEL CIRCULO DE BOGOTA D.C.

Signature/Firma: X
Mark R. Daniel, Managing Counsel, Patents

Date/Fecha: November 17, 2009

City,Country/Ciudad,País: Rahway, NJ, USA

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification	Certificación Notarial
On this date, November 17 2009	En esta fecha,
The undersigned Notary Public certifies:	el Notario Público suscrito certifica:
1. That Mark R. Daniel	1. Que
of legal age and domiciled in 126 East Lincoln Avenue, Rahway, NJ 07065, USA.	mayor de edad y domiciliado
signed the foregoing document.	suscribió el documento que antecede.
2. That the grantor has executed the foregoing document as Managing Counsel, Patents of MERCK SHARP & DOHME CORP.	2. Que el otorgante ha suscrito el referido documento en su carácter de
	de
3. That MERCK SHARP & DOHME CORP,	4. Que
having its principal place of business located in 126 East Lincoln, Avenue Rahway, NJ 07065-0907, United States of America	con sede principal ubicada en
is duly incorporated, is currently in existence, and that the purposes for which the General Power is granted are within the scope of its corporate purposes.	está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.
4. That the grantor has the authority to execute the General Power and that his/her representation is legal.	4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.
5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s): Corporate Resolution No. 5 – Patent Matters adopted November 3, 2009	5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

VIOLET BURGESS
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires May 30, 2012

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

2

1. COUNTRY: UNITED STATES OF AMERICA
2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
   VIOLET BURGESS
3. ACTING IN THE CAPACITY OF:
   NOTARY PUBLIC OF NEW JERSEY
4. BEARS THE SEAL/STAMP OF:
   VIOLET BURGESS, NOTARY

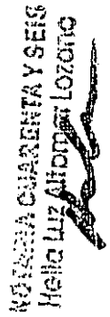
CERTIFIED

5. AT TRENTON, NEW JERSEY
6. THE 25TH DAY OF NOVEMBER 2009
7. BY: R. David Rousseau, NEW JERSEY TREASURER
8. NO: A380889
9. SEAL/STAMP:



10. SIGNATURE





Certificate Number: 115832008
Verify this certificate at
https://www1.state.nj.us/TYTR_StandingCert/JSP/Verify_Cert.jsp

WK 11657665

ESTA HOJA HACE PARTE DE LA ESCRITURA PUBLICA NUMERO: (0026) DE FECHA: 15 DE ENERO DE 2.010. - - - -

NOTARIA CUARENTA Y SEIS (46) DE BOGOTA

REFERENTE A LA PROTOCOLIZACION DE CARLOS REINALDO OLARTE GARCIA, JAMES IAN RAISBECK LLINAS, JUAN GUILLERMO MOURE PEREZ, Y NATALIA CASTRO VELEZ.- ----------

MARIA EUGENIA ROJAS DE URUETA

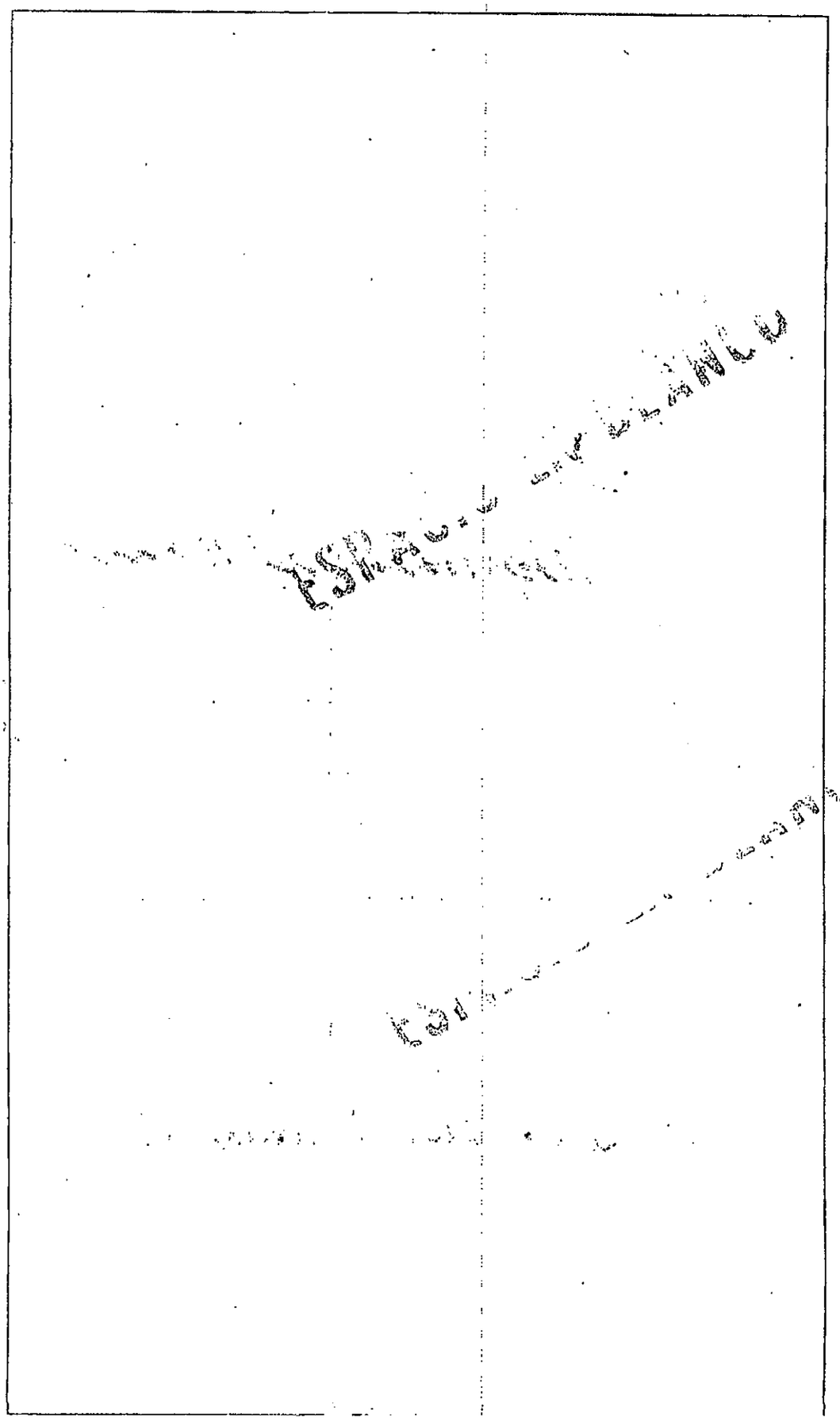
NOTARIA(O) CUARENTA Y SEIS (46) DE BOGOTA

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VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application MERCK SHARP & DOHME CORP. is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, COBURN, Craig, A.
VIII-2-1(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, MCCAULEY, John, A.
VIII-2-1(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, LUDMERER, Steven, W.
VIII-2-1(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, LIU, Kun
VIII-2-1(ii)		MERCK SHARP & DOHME CORP. was entitled as employer of the inventor, VACCA, Joseph, P.

VIII-3-1	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	In relation to this international application MERCK SHARP & DOHME CORP. is entitled to claim priority of earlier application No. 61/163,958 by virtue of the following:
VIII-3-1(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, COBURN, Craig, A.
VIII-3-1(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, MCCAULEY, John, A.
VIII-3-1(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, LUDMERER, Steven, W.
VIII-3-1(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, LIU, Kun
VIII-3-1(ii)		MERCK SHARP & DOHME CORP. was entitled as employer of the inventor, VACCA, Joseph, P.

VIII-3-2	**Declaration: Entitlement to claim priority** Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)) Name	In relation to this international application MERCK SHARP & DOHME CORP. is entitled to claim priority of earlier application No. 61/247,318 by virtue of the following:
VIII-3-2(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, COBURN, Craig, A.
VIII-3-2(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, MCCAULEY, John, A.
VIII-3-2(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, LUDMERER, Steven, W.
VIII-3-2(ii)		MERCK SHARP & DOHME CORP. is entitled as employer of the inventor, LIU, Kun
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(74) Common Representative: **MERCK SHARP & DOHME CORP.**; 126 East Lincoln Avenue, Rahway, New Jersey 07065-0907 (US).

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

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Declarations under Rule 4.17:

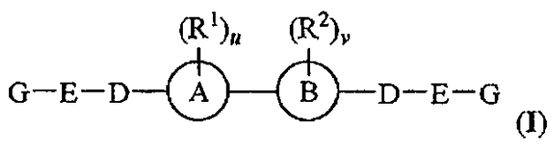
— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

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

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(54) Title: INHIBITORS OF HEPATITIS C VIRUS REPLICATION



(I)

(57) Abstract: The present invention relates to compounds of formula (I) that are useful as hepatitis C virus (HCV) NS5A inhibitors, the synthesis of such compounds, and the use of such compounds for inhibiting HCV NS5A activity, for treating or preventing HCV infections and for inhibiting HCV viral replication and/or viral production in a cell-based system.

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TITLE OF THE APPLICATION

INHIBITORS OF HEPATITIS C VIRUS REPLICATION

FIELD OF THE INVENTION

The present disclosure relates to antiviral compounds that are useful as inhibitors of hepatitis C virus (HCV) replication. The compounds are expected to act on HCV NS5A (non-structural 5A) protein. Compositions comprising such compounds, the use of such compounds for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection, methods for inhibiting the function of the NS5A non-structural protein, and methods for inhibiting HCV viral replication and/or viral production are also provided.

BACKGROUND OF THE INVENTION

Hepatitis C virus (HCV) infection is a major health problem that leads to chronic liver disease, such as cirrhosis and hepatocellular carcinoma, in a substantial number of infected individuals. Current treatments for HCV infection include immunotherapy with recombinant interferon-α alone or in combination with the nucleoside-analog ribavirin.

Several virally-encoded enzymes are putative targets for therapeutic intervention, including a metalloprotease (NS2-3), a serine protease (NS3, amino acid residues 1-180), a helicase (NS3, full length), an NS3 protease cofactor (NS4A), a membrane protein (NS4B), a zinc metalloprotein (NS5A) and an RNA-dependent RNA polymerase (NS5B).

One identified target for therapeutic intervention is HCV NS5A non-structural protein, which is described, for example, in Seng-Lai Tan & Michael G. Katze, *How Hepatitis C Virus Counteracts the Interferon Response: The Jury Is Still Out on NS5A*, 284 VIROLOGY 1-12 (2001); and in Kyu-Jin Park *et al.*, *Hepatitis C Virus NS5A Protein Modulates c-Jun N-terminal Kinase through Interaction with Tumor Necrosis Factor Receptor-associated Factor 2*, 278(33) J. BIO. CHEM. 30711 (2003). A non-structural protein, NS5A is an essential component for viral replication and assembly. Mutations in NS5A at or near known sites of phosphorylation can affect the ability for high-level replication in cell-culture systems, suggesting an important role for NS5A phosphorylation in viral replication efficiency. Inhibitors of the phosphorylation of NS5A can lead to reduced viral RNA replication.

NS5A is a zinc metalloprotein organized into three discreet domains. NS5A localizes to the membrane-associated site of RNA synthesis via an N-terminal amphipathic α-

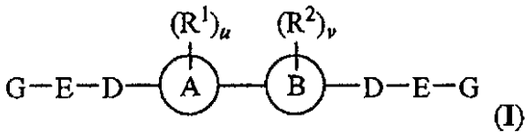
helix anchor. The crystal structure of domain I demonstrates that NS5A can exist as a dimer, with a large putative RNA binding groove located at the interface of the monomers. Timothy L. Tellinghuisen *et al.*, *Structure of the zinc-binding domain of an essential component of the hepatitis C viral replicase*, 435(7040) NATURE 374 (2005). Robert A. Love *et al.*, *Crystal Structure of a Novel Dimeric Form of NS5A Domain I Protein From Hepatitis C Virus*, 89(3) J. VIROLOGY 4395-403 (2009). The interaction of NS5A with RNA is thought to be critical for the function of this protein in RNA replication. No structural information has yet been obtained for domains II or III. Recent genetic mapping has shown that although some residues in domain II are essential for RNA replication, many portions of domain II and all of domain III are dispensable. Timothy L. Tellinghuisen *et al.*, *Identification of Residues Required for RNA Replication in Domains II and III of the Hepatitis C Virus NS5A Protein*, J. VIROLOGY 1073 (2008). Mutations constructed within domain III result in virus that can maintain RNA replication but that produces lower titers of infectious virus in cell culture, demonstrating a second distinct role for NS5A after RNA replication has occurred. Timothy L. Tellinghuisen *et al.*, *Regulation of Hepatitis C Virion Production via Phosphorylation of the NS5A Protein*, 4(3) PLOS PATHOGENS e1000032 (2008); Nicole Appel *et al.*, *Mutational Analysis of Hepatitis C Virus Nonstructural Protein 5A: Potential Role of Differential Phosphorylation in RNA Replication and Identification of a Genetically Flexible Domain*, 79(5) J. VIROLOGY 3187 (2005). NS5A, unlike the other non-structural proteins, can be trans-complemented, consistent with functions outside of the viral replicase. The interaction of NS5A with numerous host-signaling pathways has been described (Michael J. Gale Jr. *et al.*, *Evidence That Hepatitis C Virus Resistance to Interferon Is Mediated through Repression of the PKR Protein Kinase by the Nonstructural 5A Protein*, 230 VIROLOGY 217 (1997); Andrew Macdonald & Mark Harris, *Hepatitis C virus NS5A: tales of a promiscuous protein*, 85 J. GEN. VIROLOGY 2485 (2004).), suggesting this protein may modify the host cell environment to a state favorable for the virus, events that may require a form of NS5A dissociated from the replication complex.

There is a clear and long-felt need to develop effective therapeutics for treatment of HCV infection. Specifically, there is a need to develop compounds that are useful for treating HCV-infected patients and compounds that selectively inhibit HCV viral replication.

SUMMARY OF THE INVENTION

The present disclosure relates to novel compounds of formula (I) and/or pharmaceutically acceptable salts, hydrates, solvates, prodrugs or isomers thereof. These compounds are useful, either as compounds or their pharmaceutically acceptable salts (when appropriate), in the inhibition of HCV (hepatitis C virus) NS5A (non-structural 5A) protein, the prevention or treatment of one or more of the symptoms of HCV infection, the inhibition of HCV viral replication and/or HCV viral production, and/or as pharmaceutical composition ingredients. As pharmaceutical composition ingredients, these compounds, which includes reference to hydrates and solvates of such compounds, and their salts may be the primary active therapeutic agent, and, when appropriate, may be combined with other therapeutic agents including but not limited to other HCV antivirals, anti-infectives, immunomodulators, antibiotics or vaccines.

More particularly, the present disclosure relates to a compound of formula (I):



(I)

and/or a pharmaceutically acceptable salt thereof, wherein:

(A) is chosen from the group consisting of 9-membered bicyclic aryl ring systems that contain from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and that are substituted on C or N atoms by *u* substituents R^1,

each R^1 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-(CH_2)_{0-6}C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the

C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, and C_{3-8}cycloalkyl,

u is from 0 to 4,

each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl and C_{3-8}cycloalkyl, and

each R^{3a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

(B) is a group chosen from the group consisting of

(a) -C≡C- and

(b) aryl ring systems B' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems B' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by *v* substituents R^2,

each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})COR^4$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, $-N(R^{4a})SO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4,

v is from 0 to 4,

each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

R^1 and R^2 may be taken together with (A) and (B) to form a 5- to 9-membered carbocyclic ring containing 1 or 2 heteroatoms independently chosen from the group consisting of N, O and S;

each D is a group independently chosen from the group consisting of:

(a) a single bond,

(b) $-C(O)N(R^5)-$,

(c) $-N(R^5)C(O)-$, and

(d) a 5- or 6-membered aryl ring system D' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by from 0 to 2 substituents R^5,

each R^5 is independently chosen from the group consisting of hydrogen, halogen, -OR^6, -CN, -CO_2R^6, -$C(O)N(R^6)_2$, -$N(R^6)_2$, -$N(R^6)COR^6$, -SR^6, -$S(O)R^6$, -$S(O_2)R^6$, -$N(R^6)SO_2R^6$, -NCO_2R^6, -$NC(O)N(R^6)_2$, C_{1-6}alkyl substituted by from 0 to 3 R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 R^6, and

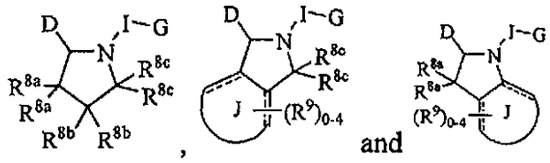
each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each E is a group independently chosen from the group consisting of:

(a) a single bond,

(b) -$(C(R^7)_2)_{0-2}NR^7C(O)O_{0-1}$-, and

(c) a pyrrolidinyl derivative chosen from the group consisting of:



I is a bivalent group chosen from -C(O)-, -CO_2- and -$C(O)N(R^7)$-,

J is a fused ring system chosen from the group consisting of 3- to 7-membered carbocycles and 5- or 6-membered aryl rings containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by substituents R^9,

each R^{8a} is independently chosen from the group consisting of hydrogen, halogen, -OH, -OC_{1-6}alkyl and C_{1-6}alkyl, or two R^{8a} may be taken together to form oxo,

each R^{8b} is independently chosen from the group consisting of hydrogen, halogen, -OH, -OC_{1-6}alkyl and C_{1-6}alkyl, or two R^{8b} may be taken together to form oxo,

each R^{8c} is independently chosen from the group consisting of hydrogen and C_{1-6}alkyl,

or any two groups selected from R^{8a}, R^{8b} and R^{8c} may be taken together to form a spiro-bicyclic or bridged bicyclic ring;

each R^9 is independently chosen from the group consisting of hydrogen, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NH-C_{1-6}alkyl and -NHC(O)-C_{1-6}alkyl,

each R^7 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and phenyl, and the C_{1-6}alkyl and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl and -S-C_{1-6}alkyl; and

each G is independently chosen from the group consisting of:

(a) hydrogen,

(b) $-OR^{10a}$,

(c) -CN,

(d) $-CO_2R^{10a}$,

(e) $-C(O)N(R^{10})_2$,

(f) $-SR^{10a}$,

(g) $-S(O)R^{10a}$,

(h) $-S(O_2)R^{10a}$,

(i) $-N(R^{10})_2$,

(j) $-N(R^{10})SO_2R^{10a}$,

(k) $-NCO_2R^{10a}$,

(l) $-NC(O)N(R^{10})_2$,

(m) C_{1-6}alkyl having 0 to 4 substituents R^{11},

each R^{11} is independently chosen from the group consisting of:

(i) -OH,

(ii) $-N(R^{10})_2$,

(iii) $=NR^{10}$,

(iv) -O-C_{1-6}alkyl,

(v) $-C(O)R^{10}$,

(vi) -S-C_{1-6}alkyl,

(vii) $-SO_2$-C_{1-6}alkyl,

(viii) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl having from 0 to 3 substituents chosen from R^{10}, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, $-OR^{10a}$, -CN, $-C(O)R^{10}$, $-CO_2R^{10a}$, $-C(O)N(R^{10})_2$, $-SR^{10a}$, $-S(O)R^{10a}$,

$-S(O_2)R^{10a}$, $-N(R^{10})SO_2R^{10a}$, $-NCO_2R^{10a}$, $-NC(O)N(R^{10})_2$ and $-N(R^{10})_2$, or two R^{12} are taken together to form oxo, and

(ix) 5- or 6-membered aryl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, $-O-C_{1-6}$alkyl and 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

(n) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{10} on N or C atoms; and

(o) aryl ring systems G' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems G' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by 0 to 3 substitutents R^{10};

each R^{10} is independently chosen from the group consisting of

(i) hydrogen,

(ii) -CN,

(iii) C_{1-6}alkyl,

(iv) $-O-C_{0-6}$alkyl,

(v) $-S-C_{0-6}$alkyl,

(vi) C_{1-6}alkyl-O-R^{14},

(vii) $-C(O)R^{14}$,

(viii) $-CO_2R^{14}$,

(ix) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

(xiii) $-NC(O)N(R^{14})_2$, and

(xiv) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

or two R^{10} may be taken together to form oxo;

each R^{10a} is independently chosen from the group consisting of

(i) hydrogen,

(ii) -CN,

(iii) C_{1-6}alkyl,

(iv) C_{1-6}alkyl-O-R^{14},

(v) $-C(O)R^{14}$,

(vi) $-CO_2R^{14}$,

(vii) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

(xiii) $-NC(O)N(R^{14})_2$, and

(xiv) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

and two R^{10} or R^{10a} groups can be taken together with the N to which they are attached to form a ring, which may be substituted by from 0 to 3 substituents R^{14}, and

each R^{14} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-(CH_2)_{0-3}C_{3-8}$cycloalkyl and phenyl.

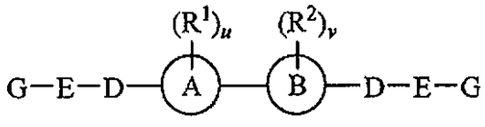
The present invention also includes pharmaceutical compositions containing a compound of the present invention and methods of preparing such pharmaceutical compositions. The present invention further includes methods of treating or reducing the likelihood or severity of HCV infection, methods for inhibiting the function of the NS5A protein, and methods for inhibiting HCV viral replication and/or viral production.

Other embodiments, aspects and features of the present invention are either further described in or will be apparent from the ensuing description, examples and appended claims.

DETAILED DESCRIPTION OF THE INVENTION

The present invention includes compounds of formula (I) above, and pharmaceutically acceptable salts thereof. The compounds of formula (I) are HCV NS5A inhibitors.

A first embodiment of the invention relates to compounds having structural formula (I):



(I)

and/or a pharmaceutically acceptable salt thereof, wherein:

(A) is chosen from the group consisting of 9-membered bicyclic aryl ring systems that contain from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and that are substituted on C or N atoms by ***u*** substituents R^1,

each R^1 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, $-O-C_{1-6}$alkyl and $-S-C_{1-6}$alkyl,

u is from 0 to 4,

each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, $-O-C_{1-6}$alkyl and C_{3-8}cycloalkyl, and

each R^{3a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

(B) is a group chosen from the group consisting of

(a) -C≡C- and

(b) aryl ring systems B' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems B' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by v substituents R^2,

each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})COR^4$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, $-N(R^{4a})SO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4,

v is from 0 to 4,

each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

R^1 and R^2 may be taken together with (A) and (B) to form a 5- to 9-membered carbocyclic ring containing 1 or 2 heteroatoms independently chosen from the group consisting of N, O and S;

each D is a group independently chosen from the group consisting of:

(a) a single bond,

(b) $-C(O)N(R^5)-$,

(c) $-N(R^5)C(O)-$, and

(d) a 5- or 6-membered aryl ring system D' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by from 0 to 2 substituents R^5,

each R^5 is independently chosen from the group consisting of hydrogen, halogen, $-OR^6$, -CN, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, C_{1-6}alkyl substituted by from 0 to 3 R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 R^6, and

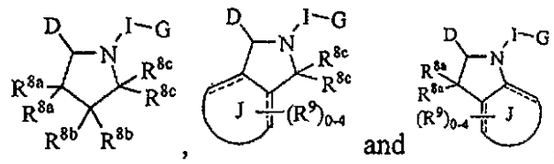
each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each E is a group independently chosen from the group consisting of:

(a) a single bond,

(b) $-(C(R^7)_2)_{0-2}NR^7C(O)O_{0-1}-$, and

(c) a pyrrolidinyl derivative chosen from the group consisting of:



and

I is a bivalent group chosen from -C(O)-, $-CO_2-$ and $-C(O)N(R^7)-$,

J is a fused ring system chosen from the group consisting of 3- to 7-membered carbocycles and 5- or 6-membered aryl rings containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by substituents R^9,

each R^{8a} is independently chosen from the group consisting of hydrogen, halogen, -OH, $-OC_{1-6}$alkyl and C_{1-6}alkyl, or two R^{8a} may be taken together to form oxo,

each R^{8b} is independently chosen from the group consisting of hydrogen, halogen, -OH, $-OC_{1-6}$alkyl and C_{1-6}alkyl, or two R^{8b} may be taken together to form oxo,

each R^{8c} is independently chosen from the group consisting of hydrogen and C_{1-6}alkyl,

or any two groups selected from R^{8a}, R^{8b} and R^{8c} may be taken together to form a spiro-bicyclic or bridged bicyclic ring;

each R^9 is independently chosen from the group consisting of hydrogen, halogen, C_{1-6}alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl and $-NHC(O)-C_{1-6}$alkyl,

each R^7 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and phenyl, and the C_{1-6}alkyl and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, C_{1-6}alkyl, $-O-C_{1-6}$alkyl and $-S-C_{1-6}$alkyl; and

each G is independently chosen from the group consisting of:

(a) hydrogen,

(b) $-OR^{10a}$,

(c) -CN,

(d) $-CO_2R^{10a}$,

(e) $-C(O)N(R^{10})_2$,

(f) $-SR^{10a}$,

(g) $-S(O)R^{10a}$,

(h) $-S(O_2)R^{10a}$,

(i) $-N(R^{10})_2$,

(j) $-N(R^{10})SO_2R^{10a}$,

(k) $-NCO_2R^{10a}$,

(l) $-NC(O)N(R^{10})_2$,

(m) C_{1-6}alkyl having 0 to 4 substituents R^{11},

each R^{11} is independently chosen from the group consisting of:

(i) -OH,

(ii) $-N(R^{10})_2$,

(iii) $=NR^{10}$,

(iv) $-O-C_{1-6}$alkyl,

(v) $-C(O)R^{10}$,

(vi) $-S-C_{1-6}$alkyl,

(vii) $-SO_2-C_{1-6}$alkyl,

(viii) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl having from 0 to 3 substituents chosen from R^{10}, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-OR^{10a}$, -CN, $-C(O)R^{10}$, $-CO_2R^{10a}$, $-C(O)N(R^{10})_2$, $-SR^{10a}$, $-S(O)R^{10a}$, $-S(O_2)R^{10a}$, $-N(R^{10})SO_2R^{10a}$, $-NCO_2R^{10a}$, $-NC(O)N(R^{10})_2$ and-$N(R^{10})_2$, or two R^{12} are taken together to form oxo, and

(ix) 5- or 6-membered aryl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, $-O-C_{1-6}$alkyl and 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

(n) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{10} on N or C atoms; and

(o) aryl ring systems G' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems G' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by 0 to 3 substitutents R^{10};

each R^{10} is independently chosen from the group consisting of

(i) hydrogen,

(ii) -CN,

(iii) C_{1-6}alkyl,

(iv) -O-C_{0-6}alkyl,

(v) -S-C_{0-6}alkyl,

(vi) C_{1-6}alkyl-O-R^{14},

(vii) -C(O)R^{14},

(viii) -CO_2R^{14},

(ix) -SO_2R^{14},

(x) -$N(R^{14})_2$,

(xi) -$N(R^{14})SO_2R^{14}$,

(xii) -NCO_2R^{14},

(xiii) -$NC(O)N(R^{14})_2$, and

(xiv) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

or two R^{10} may be taken together to form oxo;

each R^{10a} is independently chosen from the group consisting of

(i) hydrogen,

(ii) -CN,

(iii) C_{1-6}alkyl,

(iv) C_{1-6}alkyl-O-R^{14},

(v) -C(O)R^{14},

(vi) $-CO_2R^{14}$,

(vii) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

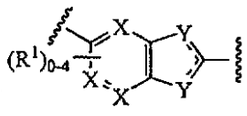
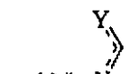
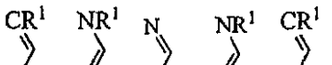
(xii) $-NCO_2R^{14}$,

(xiii) $-NC(O)N(R^{14})_2$, and

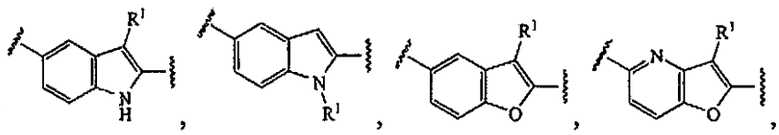
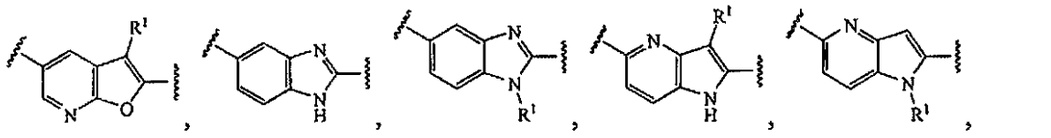
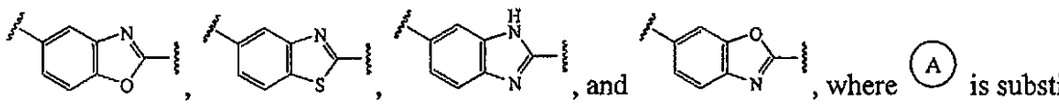
(xiv) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

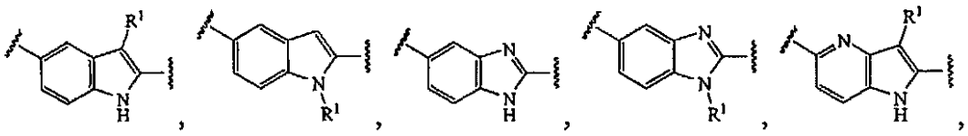
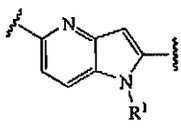
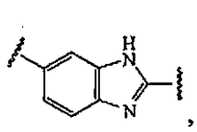
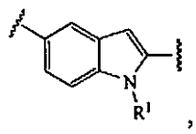
and two R^{10} or R^{10a} groups can be taken together with the N to which they are attached to form a ring, which may be substituted by from 0 to 3 substituents R^{14}, and

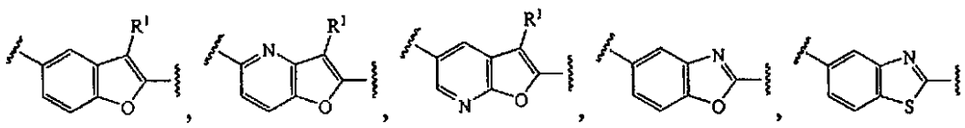
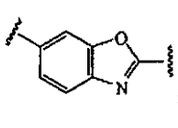
each R^{14} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-(CH_2)_{0-3}C_{3-8}$cycloalkyl and phenyl. In this embodiment, all other groups are as provided in the general formula above.

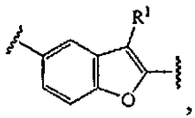
In a second embodiment of the invention, (A) is chosen from the group consisting of  , where each X is independently chosen from the group consisting of CR^1 and N,  is chosen from the group consisting of  ,  and , each R^1 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, -O-C_{1-6}alkyl and -S-C_{1-6}alkyl, each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl and C_{3-8}cycloalkyl, and each R^{3a} is independently chosen from the group consisting of hydrogen,

C_{1-6}alkyl and C_{3-8}cycloalkyl. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the first embodiment above.

In a first aspect of the second embodiment of the invention, (A) is chosen from the group consisting of  ,  ,  , and , where (A) is substituted by from 0 to 3 additional R^1, which are as provided above.

In a second aspect of the second embodiment, (A) is chosen from the group consisting of  ,  , and  , where (A) is substituted by from 0 to 3 additional R^1, which are as provided above. In preferred instances of this aspect, (A) is  , where (A) is substituted by from 0 to 3 additional R^1, which are as provided above.

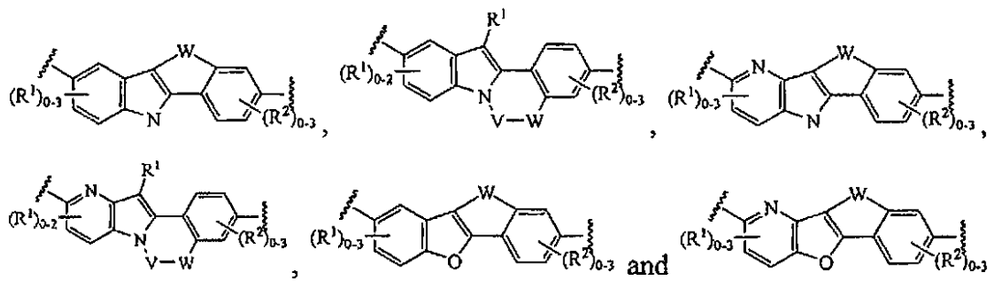
In a third aspect of the second embodiment, (A) is chosen from the group consisting of  , and  , where (A) is substituted by from 0 to 3 additional R^1, which are as

provided above. In preferred instances of this aspect, (A) is  , where (A) is substituted by from 0 to 3 additional R^1, which are as provided above.

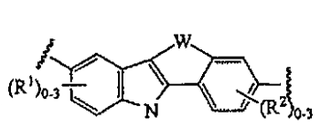
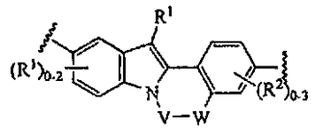
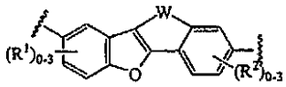
In further aspects of the second embodiment, each R^1 is chosen from the group consisting of hydrogen, halogen, -CN and C_{1-6}alkyl. In particular, each R^1 is chosen from the group consisting of hydrogen, fluorine and -CN.

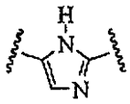
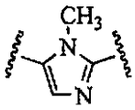
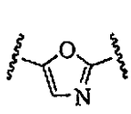
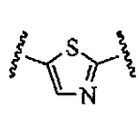
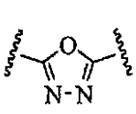
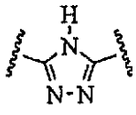
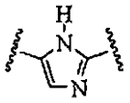
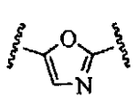
In a third embodiment of the invention, (B) is chosen from the group consisting of -C≡C-, phenyl, pyridinyl, pyrazinyl, pyrimidyl, 1,2,4-triazinyl, pyridazinyl, thiazyl and 9-membered bicyclic ring systems that contain from 1 to 3 heteroatoms independently chosen from the group consisting of N, O and S, v is from 0 to 4, each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})CO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, $-N(R^{4a})SO_2R^{4a}$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4, each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl, and each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl. In particular aspects of this embodiment, (B) is phenyl, v is from 0 to 2, and each R^2 is independently chosen from the group consisting of fluorine, chlorine, -OH, $-CH_3$, $-OCH_3$ and -CN. In all aspects of this embodiment, all other groups are as provided in the general formula above and/or in the first or second embodiments.

In a fourth embodiment of the invention, (A) and (B), taken together with one substituent R^1 and one substituent R^2, are represented by a group chosen from the group consisting of:

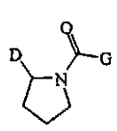
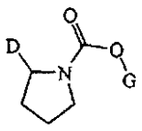
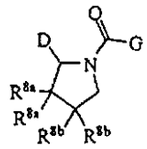
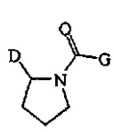
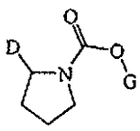
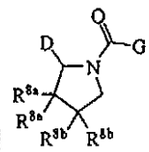


chosen from the group consisting of $-(CH_2)_{1-3}-$, $-(CH_2)_{0-2}NH(CH_2)_{0-2}-$, $-(CH_2)_{0-2}N(C_{1-6}alkyl)(CH_2)_{0-2}-$, $-(CH_2)_{0-2}O(CH_2)_{0-2}-$ and $-(CH_2)_{0-2}C(O)(CH_2)_{0-2}-$, where W is

substituted by from 0 to 4 R^W, where each R^W is independently selected from C_{1-6}alkyl and C_{3-8}cycloalkyl; and V is chosen from the group consisting of -C(O)- and -CH_2-, and where V is -CH_2-, V is substituted by from 0 to 2 R^V, where each R^V is independently selected from the group consisting of C_{1-6}alkyl and C_{3-8}cycloalkyl. In a first aspect of this embodiment,  and  , taken together with one substituent R^1 and one substituent R^2, are represented by a group chosen from the group consisting of  ,  , and  . In particular instances of this embodiment, and of the first aspect of this embodiment, W is chosen from the group consisting of -CH_2-, -NH-, -N(C_{1-6}alkyl)-, -C(O)-, -CH_2NH-, -CH_2N(C_{1-6}alkyl)-, -CH_2CH_2-, -C(O)CH_2-, -CH_2C(O)-, -CH_2O-, -$CH_2CH_2CH_2$-, -C(O)CH_2CH_2-, -CH_2C(O)CH_2-, -CH_2OCH_2-, -CH_2CH_2C(O)-, -CH_2CH_2O-, -CH_2CH_2NH-, -CH_2CH_2N(C_{1-6}alkyl)-, -CH_2NHCH_2-, -CH_2N(C_{1-6}alkyl)CH_2-, -NHCH_2CH_2-, and -N(C_{1-6}alkyl)CH_2CH_2-. In all aspects of this embodiment, all other groups are as provided in the general formula above.

In a fifth embodiment of the invention, each D is independently chosen from the group consisting of a single bond, -C(O)N(R^5)-, -NR^5C(O)-,  ,  ,  ,  ,  and  , where R^5 is independently chosen from the group consisting of hydrogen, halogen -OR^6, -CN, -CO_2R^6, -C(O)N(R^6)$_2$, -N(R^6)$_2$, -N(R^6)COR^6, -SR^6, -S(O)R^6, -S(O_2)R^6, -N(R^6)SO_2R^6, -NCO_2R^6, -NC(O)N(R^6)$_2$, C_{1-6}alkyl substituted by from 0 to 3 substituents R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 substituents R^6, and each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl. In particular aspects of this embodiment, each D is independently chosen from the group consisting of  and  . In this embodiment, all other

groups are as provided in the general formula above and/or in the first through fourth embodiments.

In a sixth embodiment of the invention, each E is independently chosen from the group consisting of a single bond, $-CH_2NHC(O)-$, $-CH_2N(CH_3)C(O)-$, $-C(CH_3)HNHC(O)-$, $-C(CH_3)HN(CH_3)C(O)-$, $-C(CH_3)_2NHC(O)-$, $-C(CH_3)_2N(CH_3)C(O)-$, $-CH_2NHC(O)O-$, $-CH_2N(CH_3)C(O)O-$, $-C(CH_3)HNHC(O)O-$, $-C(CH_3)HN(CH_3)C(O)O-$, $-C(CH_3)_2NHC(O)O-$, $-C(CH_3)_2N(CH_3)C(O)O-$,  ,  and  where one of R^{8a} and R^{8b} is -OH or fluorine. In a first aspect of this embodiment, each E is independently chosen from the group consisting of a single bond,  ,  and  where one of R^{8a} and R^{8b} is -OH or fluorine. In all aspects of this embodiment, all other groups are as provided in the general formula above and/or in the first through fifth embodiments.

In some embodiments, adjacent D and E groups each may be selected to be a single bond. In such embodiments, D and E are combined to be one single bond, and all other groups are as provided in the general formula above and/or in the first, second, third and fourth embodiments. That is, where D is a single bond and the adjacent E is a single bond, (A) or (B) is connected directly to G by one single bond.

In a seventh embodiment of the invention, each G is independently chosen from the group consisting of:

(a) $C_{1\text{-}6}$alkyl having 0 to 4 substituents R^{11},

(b) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{10} on N or C atoms; and

(c) aryl ring systems G' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems G' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by 0 to 3 substitutents R^{10}. In all aspects of the seventh embodiment, G is chosen such that stable compounds result. In all aspects of this seventh embodiment, all other groups are as provided in the general formula above and/or in the first through sixth embodiments.

In an eighth embodiment, each G is independently chosen from the group consisting of:

(a) hydrogen,

(b) -CN,

(c) C_{1-5}alkyl having 1 to 3 substituents R^{11},

each R^{11} is independently chosen from the group consisting of -OH, $-NH_2$, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, =NH, $=NCH_3$, -C(O)H, -C(O)OH, $-C(O)CH_3$, $-C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl, and oxacyclohexyl, phenyl, pyridinyl, pyrimidinyl and pyrrolyl, where

the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl are substituted by from 0 to 2 substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl and -S-C_{1-6}alkyl; and

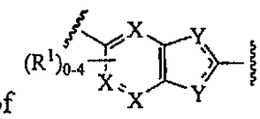
the phenyl, pyridinyl, pyrimidinyl and pyrrolyl are substituted by from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl and 3- to 8-membered cycloalkyl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

(d) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl having from 0 to 3 substitutents R^{10} on N or C atoms, the R^{10} independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, phenyl and benzyl, and

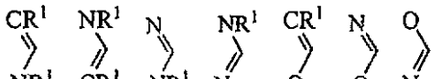
(e) aryl ring systems G' chosen from the group consisting of: phenyl, pyridinyl and 9-membered bicyclic ring systems containing from 0 to 2 heteroatoms independently chosen from the group consisting of N and O.

In a first aspect of the eighth embodiment, G is independently chosen from the group consisting of C_{1-4}alkyl having 1 to 2 substituents R^{11}, wherein each R^{11} is independently

chosen from the group consisting of -OH, -NH_2, -NCH_3H, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, -$C(O)OCH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl, oxacyclohexyl, phenyl, pyridinyl, pyrimidinyl and pyrrolyl. In all aspects of the eighth embodiment, G is chosen such that stable compounds result. In all aspects of this eighth embodiment, all other groups are as provided in the general formula above and/or in the first through sixth embodiments.

In a ninth embodiment of the invention, (A) is chosen from the group consisting of  , where

each X is independently chosen from the group consisting of CR^1 and N,

 is chosen from the group consisting of 

and ,

each R^1 is independently chosen from the group consisting of hydrogen, halogen, -OR^{3a}, -CN, -$C(O)R^3$, -CO_2R^{3a}, -$C(O)N(R^{3a})_2$, -SR^{3a}, -$S(O)R^{3a}$, -$S(O_2)R^{3a}$, -$(CH_2)_{0-6}N(R^{3a})_2$, -$N(R^{3a})SO_2R^{3a}$, -$N(R^{3a})CO_2R^{3a}$, -$N(R^{3a})C(O)R^3$, -$N(R^{3a})COR^{3a}$, -$N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, -OR^{3a}, -CN, -CO_2R^{3a}, -$C(O)N(R^{3a})_2$, -$N(R^{3a})_2$, -$N(R^{3a})CO_2R^{3a}$, -SR^{3a}, -$S(O)R^{3a}$, -$S(O_2)R^{3a}$, -$N(R^{3a})SO_2R^{3a}$, -$N(R^{3a})CO_2R^3$, -$N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, -O-C_{1-6}alkyl and –S-C_{1-6}alkyl,

each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl and C_{3-8}cycloalkyl, and

each R^{3a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

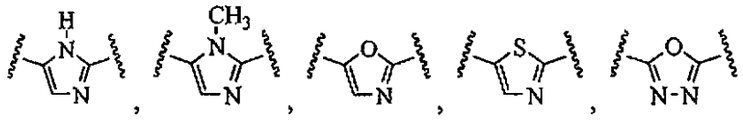
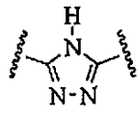
(B) is chosen from the group consisting of -C≡C-, phenyl, pyridinyl, pyrazinyl, pyrimidyl, 1,2,4-triazinyl, pyridazinyl, thiazyl and 9-membered bicyclic ring systems that contain from 1 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

v is from 0 to 4,

each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})CO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, $-N(R^{4a})SO_2R^{4a}$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4,

each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl, and

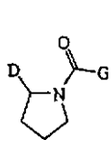
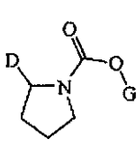
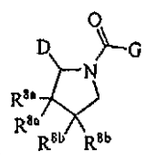
each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

wherein each D is independently chosen from the group consisting of a single bond, $-C(O)N(R^5)-$, $-NR^5C(O)-$,  ,  and , where

R^5 is independently chosen from the group consisting of hydrogen, halogen $-OR^6$, -CN, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, C_{1-6}alkyl substituted by from 0 to 3 substituents R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 substituents R^6, and

each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

wherein each E is independently chosen from the group consisting of a single bond, $-CH_2NHC(O)-$, $-CH_2N(CH_3)C(O)-$, $-C(CH_3)HNHC(O)-$, $-C(CH_3)HN(CH_3)C(O)-$, $-C(CH_3)_2NHC(O)-$, $-C(CH_3)_2N(CH_3)C(O)-$, $-CH_2NHC(O)O-$, $-CH_2N(CH_3)C(O)O-$, $-C(CH_3)HNHC(O)O-$, $-C(CH_3)HN(CH_3)C(O)O-$, $-C(CH_3)_2NHC(O)O-$, $-C(CH_3)_2N(CH_3)C(O)O-$,

 ,  and  where one of R^{8a} and R^{8b} is -OH or fluorine;

wherein each G is independently chosen from the group consisting of

(a) hydrogen,

(b) -CN,

(c) C_{1-5}alkyl having 1 to 3 substituents R^{11},

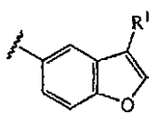
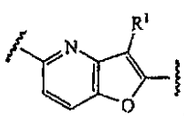
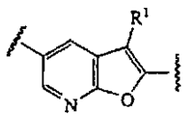
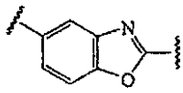
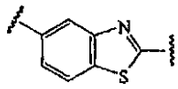
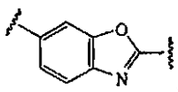
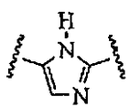
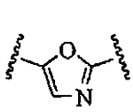
each R^{11} is independently chosen from the group consisting of -OH, $-NH_2$, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, =NH, $=NCH_3$, -C(O)H, -C(O)OH, $-C(O)CH_3$, $-C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl, and oxacyclohexyl, phenyl, pyridinyl, pyrimidinyl and pyrrolyl, where

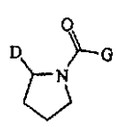
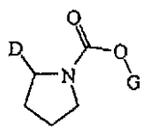
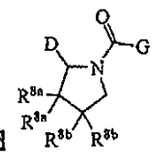
the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl are substituted by from 0 to 2 substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl and -S-C_{1-6}alkyl; and

the phenyl, pyridinyl, pyrimidinyl and pyrrolyl are substituted by from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl and 3- to 8-membered cycloalkyl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

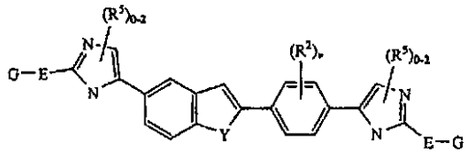
(d) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl having from 0 to 3 substitutents R^{10} on N or C atoms, the R^{10} independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, phenyl and benzyl, and

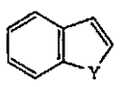
(e) aryl ring systems G' chosen from the group consisting of: phenyl, pyridinyl and 9-membered bicyclic ring systems containing from 0 to 2 heteroatoms independently chosen from the group consisting of N and O. In all aspects of this embodiment, all other groups are as provided in the general formula above.

In a tenth embodiment of the invention, (A) is chosen from the group consisting of  ,  ,  ,  ,  and  , where (A) is substituted by from 0 to 3 additional R^1; (B) is phenyl; v is from 0 to 2; each R^2 is independently chosen from the group consisting of fluorine, chlorine, -OH, $-CH_3$, $-OCH_3$ and -CN; each D is independently chosen from the group consisting of  and  ; each E is independently chosen from the group consisting of a

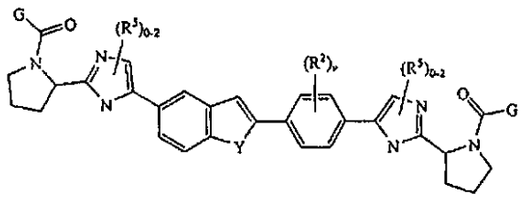
single bond,  ,  and  where one of R^{8a} and R^{8b} is -OH or fluorine; and each G is independently chosen from the group consisting of C_{1-4}alkyl having 1 to 2 substituents R^{11}, wherein each R^{11} is independently chosen from the group consisting of -OH, $-NH_2$, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-C(O)OCH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl, oxacyclohexyl, phenyl, pyridinyl, pyrimidinyl and pyrrolyl. In all aspects of this embodiment, all other groups are as provided in the general formula above or in the eighth embodiment.

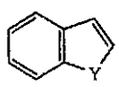
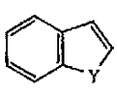
In an eleventh embodiment of the invention, the compound having structural formula (**I**) is a compound having structural formula (**Ia**):

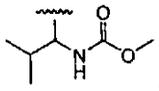
 (**Ia**)

or a pharmaceutically acceptable salt thereof, wherein  is substituted by ***u*** substituents R^1, and Y is selected from the group consisting of O and NR^1. In all aspects of this embodiment, all other groups are as provided in the general formula above or in any one of the first through tenth embodiments.

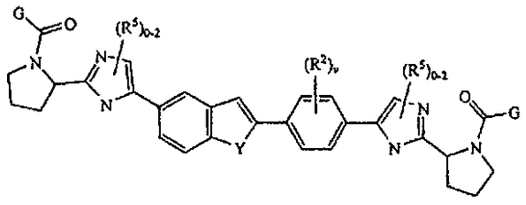
In a twelfth embodiment of the invention, the compound having structural formula (**Ia**) is a compound having structural formula (**Ib**):

 (**Ib**)

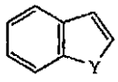
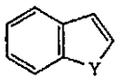
or a pharmaceutically acceptable salt thereof, wherein  is substituted by ***u*** substituents R^1, and Y is selected from the group consisting of O and NR^1. In particular aspects of this embodiment,  is substituted by ***u*** substituents R^1, Y is O, and both instances of G are

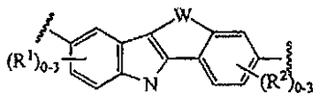
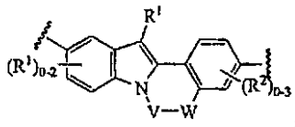
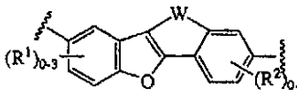
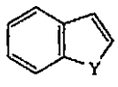
 . In all aspects of this embodiment, all other groups are as provided in the general formula above or in the eleventh embodiment.

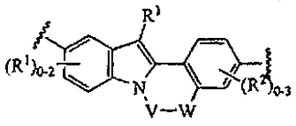
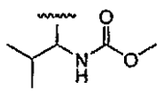
In a thirteenth embodiment of the invention, the compound having structural formula (**Ia**) is a compound having structural formula (**Ib**):



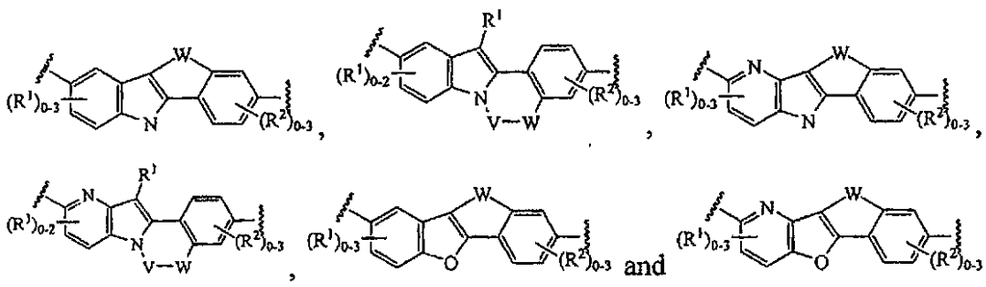
(**Ib**)

or a pharmaceutically acceptable salt thereof, wherein said  is substituted by ***u*** substituents R^1, and said  and said  , taken together with one substituent R^1 and one substituent R^2, are represented by a group chosen from the group consisting of

 ,  , and  . In particular aspects of this embodiment,  and said  , taken together with one substituent R^1 and one substituent R^2, are represented by

 wherein V is $-CH_2-$, W is $-(CH_2)_{0-2}O(CH_2)_{0-2}-$, R^1 is fluorine, and both instances of G are  . In all aspects of this embodiment, all other groups are as provided in the general formula above or in the eleventh embodiment.

In a fourteenth embodiment of the invention, (A) and (B), taken together with one substituent R^1 and one substituent R^2, are represented by a group chosen from the group consisting of:



where

W is chosen from the group consisting of $-(CH_2)_{1-3}-$, $-(CH_2)_{0-2}NH(CH_2)_{0-2}-$, $-(CH_2)_{0-2}N(C_{1-6}alkyl)(CH_2)_{0-2}-$, $-(CH_2)_{0-2}O(CH_2)_{0-2}-$ and $-(CH_2)_{0-2}C(O)(CH_2)_{0-2}-$, where W is substituted by from 0 to 4 R^w, where each R^w is independently selected from C_{1-6}alkyl and C_{3-8}cycloalkyl; and

V is chosen from the group consisting of -C(O)- and $-CH_2-$, and where V is $-CH_2-$, V is substituted by from 0 to 2 R^v, where each R^v is independently selected from the group consisting of C_{1-6}alkyl and C_{3-8}cycloalkyl;

each R^1 is independently chosen from the group consisting of hydrogen, halogen, $-OR^3$, -CN, $-C(O)R^3$, $-CO_2R^3$, $-C(O)N(R^{3a})_2$, $-SR^3$, $-S(O)R^3$, $-S(O_2)R^3$, $-N(R^{3a})_2$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^3$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})COR^3$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, -O-C_{1-6}alkyl and –S-C_{1-6}alkyl,

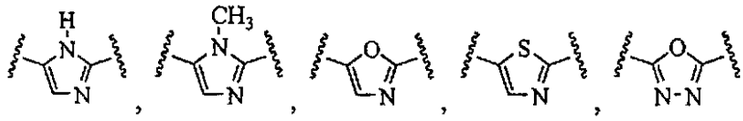
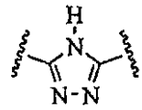
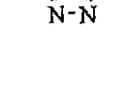
each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, -O-C_{1-6}alkyl and C_{3-8}cycloalkyl, and

each R^{3a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})CO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, $-N(R^{4a})SO_2R^{4a}$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4,

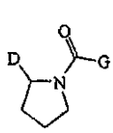
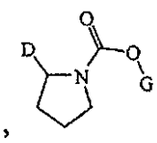
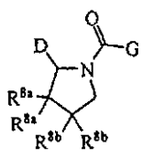
each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl, and

each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

wherein each D is independently chosen from the group consisting of a single bond, $-C(O)N(R^5)-$, $-NR^5C(O)-$,  ,  and  , where

R^5 is independently chosen from the group consisting of hydrogen, halogen $-OR^6$, $-CN$, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, C_{1-6}alkyl substituted by from 0 to 3 substituents R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 substituents R^6, and

each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

wherein each E is independently chosen from the group consisting of a single bond, $-CH_2NHC(O)-$, $-CH_2N(CH_3)C(O)-$, $-C(CH_3)HNHC(O)-$, $-C(CH_3)HN(CH_3)C(O)-$, $-C(CH_3)_2NHC(O)-$, $-C(CH_3)_2N(CH_3)C(O)-$, $-CH_2NHC(O)O-$, $-CH_2N(CH_3)C(O)O-$, $-C(CH_3)HNHC(O)O-$, $-C(CH_3)HN(CH_3)C(O)O-$, $-C(CH_3)_2NHC(O)O-$, $-C(CH_3)_2N(CH_3)C(O)O-$,  ,  and  where one of R^{8a} and R^{8b} is -OH or fluorine;

wherein each G is independently chosen from the group consisting of

(a) hydrogen,

(b) -CN,

(c) C_{1-5}alkyl having 1 to 3 substituents R^{11},

each R^{11} is independently chosen from the group consisting of -OH, $-NH_2$, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, =NH, $=NCH_3$, -C(O)H, -C(O)OH, $-C(O)CH_3$, $-C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl, and oxacyclohexyl, phenyl, pyridinyl, pyrimidinyl and pyrrolyl, where

the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl are substituted by from 0 to 2

substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl and –S-C_{1-6}alkyl; and

the phenyl, pyridinyl, pyrimidinyl and pyrrolyl are substituted by from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl and 3- to 8-membered cycloalkyl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

(d) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl having from 0 to 3 substitutents R^{10} on N or C atoms, the R^{10} independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, phenyl and benzyl, and

(e) aryl ring systems G' chosen from the group consisting of: phenyl, pyridinyl and 9-membered bicyclic ring systems containing from 0 to 2 heteroatoms independently chosen from the group consisting of N and O. In all aspects of this embodiment, all other groups are as provided in the general formula above.

In another embodiment of the invention, the compound of the invention is selected from the exemplary species depicted in Examples 1 through 215 shown below, or pharmaceutically acceptable salts thereof.

In another embodiment of the invention, for the compounds of formula (I), variables $\textcircled{A}$, $\textcircled{B}$, D, E, G, R^1, R^2, u, v, R^3, R^{3a}, R^4, R^{4a}, R^5, R^6, R^7, I, J, R^{8a}, R^{8b}, R^{8c}, R^9, R^{10}, R^{10a}, R^{11}, R^{12}, R^{13}, R^{14}, W, R^w, V, and R^v, are selected independently from each other.

Other embodiments of the present invention include the following:

(a) A pharmaceutical composition comprising an effective amount of a compound of formula (I) and a pharmaceutically acceptable carrier.

(b) The pharmaceutical composition of (a), further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(c) The pharmaceutical composition of (b), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(d) A pharmaceutical combination that is (i) a compound of formula (I) and (ii) a second therapeutic agent selected from the group consisting of HCV antiviral agents,

immunomodulators, and anti-infective agents; wherein the compound of formula (**I**) and the second therapeutic agent are each employed in an amount that renders the combination effective for inhibiting HCV NS5A activity, or for treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection, or for inhibiting HCV viral replication and/or HCV viral production in a cell-based system.

(e) The combination of (d), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(f) A method of inhibiting HCV NS5A activity in a subject in need thereof, which comprises administering to the subject an effective amount of a compound of formula (**I**).

(g) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof, which comprises administering to the subject an effective amount of a compound of formula (**I**).

(h) The method of (g), wherein the compound of formula (**I**) is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(i) The method of (h), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(j) A method of inhibiting HCV viral replication and/or HCV viral production in a cell-based system, which comprises administering to the subject an effective amount of a compound of formula (**I**).

(k) The method of (j), wherein the compound of formula (**I**) is administered in combination with an effective amount of at least one second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

(l) The method of (k), wherein the HCV antiviral agent is an antiviral selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

(m) A method of inhibiting HCV NS5A activity in a subject in need thereof, which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

(n) A method of treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection in a subject in need thereof, which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

(o) A method of inhibiting HCV viral replication and/or HCV viral production in a cell-based system, which comprises administering to the subject the pharmaceutical composition of (a), (b), or (c) or the combination of (d) or (e).

In the embodiments of the compounds and salts provided above, it is to be understood that each embodiment may be combined with one or more other embodiments, to the extent that such a combination provides a stable compound or salt and is consistent with the description of the embodiments. It is further to be understood that the embodiments of compositions and methods provided as (a) through (o) above are understood to include all embodiments of the compounds and/or salts, including such embodiments as result from combinations of embodiments.

The present invention also includes a compound of the present invention for use (i) in, (ii) as a medicament for, or (iii) in the preparation of a medicament for: (a) inhibiting HCV NS5A activity, or (b) treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection, or (c) inhibiting HCV viral replication and/or HCV viral production in a cell-based system, or (d) use in medicine. In these uses, the compounds of the present invention can optionally be employed in combination with one or more second therapeutic agents selected from HCV antiviral agents, anti-infective agents, and immunomodulators.

Additional embodiments of the invention include the pharmaceutical compositions, combinations and methods set forth in (a)-(o) above and the uses set forth in the preceding paragraph, wherein the compound of the present invention employed therein is a compound of one of the embodiments, aspects, classes, sub-classes, or features of the compounds described above. In all of these embodiments, the compound may optionally be used in the form of a pharmaceutically acceptable salt, or may be present in the form of a solvate or hydrate as appropriate.

As used herein, all ranges are inclusive, and all sub-ranges are included within such ranges, although not necessarily explicitly set forth. In addition, the term "or," as used herein, denotes alternatives that may, where appropriate, be combined; that is, the term "or" includes each listed alternative separately as well as their combination.

As used herein, the term "alkyl" refers to any linear or branched chain alkyl group having a number of carbon atoms in the specified range. Thus, for example, "C_{1-6} alkyl" (or "C_1-C_6 alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, *iso*-, *sec*- and *tert*-butyl, n- and isopropyl, ethyl and methyl. As another example, "C_{1-4} alkyl" refers to n-, *iso*-, *sec*- and *tert*-butyl, n- and isopropyl, ethyl and methyl. Where indicated, "C_0" refers to hydrogen; thus, for example, "C_{0-6} alkyl" (or "C_0-C_6 alkyl") refers to all of the hexyl alkyl and pentyl alkyl isomers as well as n-, *iso*-, *sec*- and *tert*-butyl, n- and *iso*propyl, ethyl, methyl and hydrogen. Alkyl groups may be substituted as indicated.

The term "halogenated" refers to a group or molecule in which a hydrogen atom has been replaced by a halogen. Similarly, the term "haloalkyl" refers to a halogenated alkyl group. The term "halogen" (or "halo") refers to atoms of fluorine, chlorine, bromine and iodine (alternatively referred to as fluoro, chloro, bromo, and iodo), preferably fluorine.

The term "alkoxy" refers to an "alkyl-O-" group, where alkyl is as defined above. Alkoxy groups may be substituted as indicated.

The term "cycloalkyl" refers to any cyclic ring of an alkane or alkene having a number of carbon atoms in the specified range. Thus, for example, "C_{3-8} cycloalkyl" (or "C_3-C_8 cycloalkyl") refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "cycloalkoxy" refers to a "cycloalkyl-O-" group, whre cycloalkyl is as defined above. Cycloalkyl groups may be substituted as indicated.

The term "aryl" (or "aryl ring system") refers to aromatic mono- and poly-carbocyclic or heterocyclic ring systems wherein the individual carbocyclic rings in the polyring systems are fused or attached to each other via a single bond. As used herein, the term aryl includes aromatic mono- and poly-carbocyclic ring systems that include from 0 to 4 heteroatoms (non-carbon atoms) that are independently chosen from N, O and S. Suitable aryl groups include phenyl, naphthyl, biphenylenyl, pyridinyl, pyrimidinyl and pyrrolyl, as well as those discussed below. Aryl groups may be substituted as indicated. Aryl ring systems may include, where appropriate, an indication of the variable to which a particular ring atom is attached. Unless otherwise indicated, substituents to the aryl ring systems can be attached to any ring atom, provided that such attachment results in formation of a stable ring system.

The term "carbocycle" (and variations thereof such as "carbocyclic") as used herein, unless otherwise indicated, refers to (i) a C_5 to C_7 monocyclic, saturated or unsaturated ring, or (ii) a C_8 to C_{10} bicyclic saturated or unsaturated ring system. Each ring in (ii) is either

independent of, or fused to, the other ring, and each ring is saturated or unsaturated. Carbocycle groups may be substituted as indicated. When the carbocycles contain one or more heteroatoms independently chosen from N, O and S, the carbocycles may also be referred to as "heterocycles," as defined below. The carbocycle may be attached to the rest of the molecule at any carbon or nitrogen atom that results in a stable compound. The fused bicyclic carbocycles are a subset of the carbocycles; *i.e.*, the term "fused bicyclic carbocycle" generally refers to a C_8 to C_{10} bicyclic ring system in which each ring is saturated or unsaturated and two adjacent carbon atoms are shared by each of the rings in the ring system. A fused bicyclic carbocycle in which both rings are saturated is a saturated bicyclic ring system. Saturated carbocyclic rings are also referred to as cycloalkyl rings, *e.g.*, cyclopropyl, cyclobutyl, etc. A fused bicyclic carbocycle in which one or both rings are unsaturated is an unsaturated bicyclic ring system. Carbocycle ring systems may include, where appropriate, an indication of the variable to which a particular ring atom is attached. Unless otherwise indicated, substituents to the ring systems can be attached to any ring atom, provided that such attachment results in formation of a stable ring system.

Unless indicated otherwise, the term "heterocycle" (and variations thereof such as "heterocyclic" or "heterocyclyl") broadly refers to (i) a stable 5- to 7-membered, saturated or unsaturated monocyclic ring, or (ii) a stable 8- to 10-membered bicyclic ring system, wherein each ring in (ii) is independent of, or fused to, the other ring or rings and each ring is saturated or unsaturated, and the monocyclic ring or bicyclic ring system contains one or more heteroatoms (*e.g.*, from 1 to 6 heteroatoms, or from 1 to 4 heteroatoms) independently selected from N, O and S and a balance of carbon atoms (the monocyclic ring typically contains at least one carbon atom and the bicyclic ring systems typically contain at least two carbon atoms); and wherein any one or more of the nitrogen and sulfur heteroatoms is optionally oxidized, and any one or more of the nitrogen heteroatoms is optionally quaternized. Unless otherwise specified, the heterocyclic ring may be attached at any heteroatom or carbon atom, provided that attachment results in the creation of a stable structure. Heterocycle groups may be substituted as indicated, and unless otherwise specified, the substituents may be attached to any atom in the ring, whether a heteroatom or a carbon atom, provided that a stable chemical structure results. Representative examples include pyranyl, piperidinyl, piperazinyl, azepanyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, isothiazolidinyl, and tetrahydrofuryl (or tetrahydrofuranyl). Unless expressly stated to the

contrary, the term "heteroaryl ring system" refers to aryl ring systems, as defined above, that include from 1 to 4 heteroatoms (non-carbon atoms) that are independently chosen from N, O and S. In the case of substituted heteraromatic rings containing at least one nitrogen atom (*e.g.*, pyridine), such substitutions can be those resulting in N-oxide formation. Representative examples of heteroaromatic rings include pyridyl, pyrrolyl, pyrazinyl, pyrimidinyl, pyridazinyl, thienyl (or thiophenyl), thiazolyl, furanyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isooxazolyl, oxadiazolyl, thiazolyl, isothiazolyl, and thiadiazolyl. Representative examples of bicyclic heterocycles include benzotriazolyl, indolyl, isoindolyl, indazolyl, indolinyl, isoindolinyl, quinoxalinyl, quinazolinyl, cinnolinyl, chromanyl, isochromanyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, 2,3-dihydrobenzofuranyl, 2,3-dihydrobenzo-1,4-dioxinyl and benzo-1,3-dioxolyl.

Unless otherwise specifically noted as only "substituted", alkyl, cycloalkyl, and aryl groups are not substituted. If substituted, preferred substituents are selected from the group that includes, but is not limited to, halo, C_1-C_{20} alkyl, $-CF_3$, $-NH_2$, $-N(C_1$-C_6 alkyl$)_2$, $-NO_2$, oxo, $-CN$, $-N_3$, $-OH$, $-O(C_1$-C_6 alkyl), C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, (C_0-C_6 alkyl)$S(O)_{0\text{-}2}$-, aryl-$S(O)_{0\text{-}2}$-, (C_0-C_6 alkyl)$S(O)_{0\text{-}2}$(C_0-C_6 alkyl)-, (C_0-C_6 alkyl)C(O)NH-, H_2N-C(NH)-, $-O(C_1$-C_6 alkyl)CF_3, (C_0-C_6 alkyl)C(O)-, (C_0-C_6 alkyl)OC(O)-, (C_0-C_6alkyl)O(C_1-C_6 alkyl)-, (C_0-C_6 alkyl)$C(O)_{1\text{-}2}$(C_0-C_6 alkyl)-, (C_1-C_6 alkyl)OC(O)NH-, aryl, aralkyl, heteroaryl, heterocycloalkyl, halo-aryl, halo-aralkyl, halo-heterocycle and halo-heterocycloalkyl.

Unless expressly stated to the contrary, all ranges cited herein are inclusive. For example, a heteroaryl ring described as containing from "0 to 3 heteroatoms" means the ring can contain 0, 1, 2, or 3 heteroatoms. It is also to be understood that any range cited herein includes within its scope all of the sub-ranges within that range. The oxidized forms of the heteroatoms N and S are also included within the scope of the present invention.

When any variable (for example, R^1 or R^3) occurs more than one time in any constituent or in formula (**I**) or in any other formula depicting and describing compounds of the invention, its definition on each occurrence is independent of its definition at every other occurrence. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

Unless expressly stated to the contrary, substitution by a named substituent is permitted on any atom provided such substitution is chemically allowed and results in a stable compound. A "stable" compound is a compound that can be prepared and isolated and that has a

structure and properties that remain or can be caused to remain essentially unchanged for a period of time sufficient to allow use of the compound for the purposes described herein (*e.g.*, therapeutic or prophylactic administration to a subject).

As used herein, the term "compound" is intended to encompass chemical agents described by generic formula (**I**) in all forms, including hydrates and solvates of such chemical agents.

In the compounds of generic formula (**I**), the atoms may exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. The present invention is meant to include all suitable isotopic variations of the compounds of generic formula (**I**). For example, different isotopic forms of hydrogen (H) include protium (^{1}H) and deuterium (^{2}H or D). Protium is the predominant hydrogen isotope found in nature. Enriching for deuterium may afford certain therapeutic advantages, such as increasing *in vivo* half-life or reducing dosage requirements, or may provide a compound useful as a standard for characterization of biological samples. Isotopically-enriched compounds within generic formula (**I**) can be prepared without undue experimentation by conventional techniques well known to those skilled in the art or by processes analogous to those described in the Schemes and Examples herein using appropriate isotopically-enriched reagents and/or intermediates.

As a result of the selection of substituents and substituent patterns, certain of the compounds of the present invention can have asymmetric centers and can occur as mixtures of stereoisomers, or as individual diastereomers, or enantiomers. All isomeric forms of these compounds, whether isolated or in mixtures, are within the scope of the present invention.

As would be recognized by one of ordinary skill in the art, certain of the compounds of the present invention can exist as tautomers. For the purposes of the present invention a reference to a compound of formula (**I**) is a reference to the compound *per se*, or to any one of its tautomers *per se*, or to mixtures of two or more tautomers.

The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" refers to a salt that possesses the effectiveness of the parent compound and that is not biologically or otherwise undesirable (*e.g.*, is neither toxic nor otherwise deleterious to the recipient thereof). Suitable salts include acid addition salts that may, for example, be formed by mixing a solution of the

compound of the present invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, acetic acid, trifluoroacetic acid, or benzoic acid. Many of the compounds of the invention carry an acidic moiety, in which case suitable pharmaceutically acceptable salts thereof can include alkali metal salts (*e.g.*, sodium or potassium salts), alkaline earth metal salts (*e.g.*, calcium or magnesium salts), and salts formed with suitable organic ligands such as quaternary ammonium salts. Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed to modify the solubility or hydrolysis characteristics of the compound.

The term "administration" and variants thereof (*e.g.*, "administering" a compound) in reference to a compound of the invention mean providing the compound or a prodrug of the compound to the individual in need of treatment. When a compound of the invention or a prodrug thereof is provided in combination with one or more other active agents (*e.g.*, antiviral agents useful for treating HCV infection), "administration" and its variants are each understood to include concurrent and sequential provision of the compound or salt (or hydrate) and other agents.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients, as well as any product that results, directly or indirectly, from combining the specified ingredients.

By "pharmaceutically acceptable" is meant that the ingredients of the pharmaceutical composition must be compatible with each other and not deleterious to the recipient thereof.

The terms "subject" (alternatively referred to herein as "patient") as used herein, refer to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment.

The term "effective amount" as used herein means that amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician. In one embodiment, the effective amount is a "therapeutically effective amount" for the alleviation of one or more symptoms of the disease or condition being treated. In another embodiment, the effective amount is a "prophylactically effective amount" for reduction of the severity or likelihood of one or more symptoms of the disease or condition. In another embodiment, the effective amount is a "therapeutically effective amount" for inhibition of HCV

viral replication and/or HCV viral production. The term also includes herein the amount of active compound sufficient to inhibit HCV NS5A and thereby elicit the response being sought (*i.e.*, an "inhibition effective amount"). When the active compound (*i.e.*, active ingredient) is administered as the salt, references to the amount of active ingredient are to the free acid or free base form of the compound.

It is understood that claimed compounds cause inhibition in replicon assay testing. Thus, compounds described herein are useful for inhibiting HCV replication, specifically the NS5A protein. Compounds described herein have different uses, including the prevention or treatment of one or more of the symptoms of HCV infection, the inhibition of HCV viral replication and/or HCV viral production, and/or as pharmaceutical composition ingredients.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for identifying resistant HCV replicon cell lines harboring mutations within NS5A, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to the HCV replicase.

For the purposes of inhibiting HCV NS5A protein, treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection and inhibiting HCV viral replication and/or HCV viral production, the compounds of the present invention, optionally in the form of a salt or a hydrate, can be administered by any means that produces contact of the active agent with the agent's site of action. They can be administered by one or more conventional means available for use in conjunction with pharmaceuticals, either as individual therapeutic agents or in a combination of therapeutic agents. They can be administered alone, but typically are administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. The compounds of the invention can, for example, be administered by one or more of the following: orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation (such as in a spray form), or rectally, in the form of a unit dosage of a pharmaceutical composition containing an effective amount of the compound and conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles. Liquid preparations suitable for oral administration (*e.g.*, suspensions, syrups, elixirs and the like) can be prepared according to techniques known in the art and can employ any of the usual media such as water,

glycols, oils, alcohols and the like. Solid preparations suitable for oral administration (*e.g.*, powders, pills, capsules and tablets) can be prepared according to techniques known in the art and can employ such solid excipients as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like. Parenteral compositions can be prepared according to techniques known in the art and typically employ sterile water as a carrier and optionally other ingredients, such as solubility aids. Injectable solutions can be prepared according to methods known in the art wherein the carrier comprises a saline solution, a glucose solution or a solution containing a mixture of saline and glucose. Further description of methods suitable for use in preparing pharmaceutical compositions of the present invention and of ingredients suitable for use in said compositions is provided in Remington's Pharmaceutical Sciences, 18th edition (ed. A. R. Gennaro, Mack Publishing Co., 1990).

The compounds of this invention can be administered orally in a dosage range of 0.001 to 1000 mg/kg of mammal (*e.g.*, human) body weight per day in a single dose or in divided doses. One dosage range is 0.01 to 500 mg/kg body weight per day orally in a single dose or in divided doses. Another dosage range is 0.1 to 100 mg/kg body weight per day orally in single or divided doses. For oral administration, the compositions can be provided in the form of tablets or capsules containing 1.0 to 500 mg of the active ingredient, particularly 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400, and 500 mg of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

As noted above, the present invention also relates to a method of inhibiting HCV replicon activity, inhibiting HCV viral replication and/or HCV viral production, treating HCV infection and/or reducing the likelihood or severity of symptoms of HCV infection with a compound of the present invention in combination with one or more therapeutic agents and a pharmaceutical composition comprising a compound of the present invention and one or more therapeutic agents selected from the group consisting of a HCV antiviral agent, an immunomodulator, and an anti-infective agent. Such therapeutic agents active against HCV include, but are not limited to, ribavirin, levovirin, viramidine, thymosin alpha-1, R7025 (an

enhanced interferon (Roche)), interferon-β, interferon-α, pegylated interferon-α (peginterferon-α), a combination of interferon-α and ribavirin, a combination of peginterferon-α and ribavirin, a combination of interferon-α and levovirin, and a combination of peginterferon-α and levovirin. The combination of peginterferon-α and ribaviron represents the current Standard of Care for HCV treatment. The combination of one or more compounds of the present invention with the Standard of Care for HCV treatment, pegylated-interferon and ribaviron is specifically contemplated as being encompassed by the present invention. Interferon-α includes, but is not limited to, recombinant interferon-α2a (such as ROFERON interferon), pegylated interferon-α2a (PEGASYS), interferon-α2b (such as INTRON-A interferon), pegylated interferon-α2b (PEGINTRON), a recombinant consensus interferon (such as interferon alphacon-1), albuferon (interferon-α bound to human serum albumin (Human Genome Sciences)), and a purified interferon-α product. Amgen's recombinant consensus interferon has the brand name INFERGEN. Levovirin is the L-enantiomer of ribavirin which has shown immunomodulatory activity similar to ribavirin. Viramidine represents an analog of ribavirin disclosed in International Patent Application Publication WO 01/60379. In accordance with the method of the present invention, the individual components of the combination can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms.

Ribavirin, levovirin, and viramidine may exert their anti-HCV effects by modulating intracellular pools of guanine nucleotides via inhibition of the intracellular enzyme inosine monophosphate dehydrogenase (IMPDH). IMPDH is the rate-limiting enzyme on the biosynthetic route in *de novo* guanine nucleotide biosynthesis. Ribavirin is readily phosphorylated intracellularly and the monophosphate derivative is an inhibitor of IMPDH. Thus, inhibition of IMPDH represents another useful target for the discovery of inhibitors of HCV replication. Therefore, the compounds of the present invention may also be administered in combination with an inhibitor of IMPDH, such as those disclosed in International Patent Application Publications WO 97/41211, WO 01/00622 and WO 00/25780; or mycophenolate mofetil. *See* Anthony C. Allison and Elsie M. Eugui, *Immunosuppressive and Other Anti-Rheumetic Activities of Mychophenolate Mofetil*, 44 (SUPPL.) AGENTS ACTION 165 (1993).

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with the antiviral agent polymerase inhibitor R7128 (Roche).

The compounds of the present invention may also be combined for the treatment of HCV infection with antiviral 2'-*C*-branched ribonucleosides disclosed in Rogers E. Harry-O'Kuru *et al.*, *A Short, Flexible Route to 2'*-C-*Branched Ribonucleosides*, 62 J. ORG. CHEM. 1754-59 (1997); Michael S. Wolfe and Rogers E. Harry-O'Kuru, *A Consise Synthesis of 2'*-C-*Methylribonucleosides*, 36 TET. LETT. 7611-14 (1995); U.S. Patent No. 3,480,613; and International Patent Application Publications WO 01/90121, WO 01/92282, WO 02/32920, WO 04/002999, WO 04/003000 and WO 04/002422; the contents of each of which are incorporated by reference in their entirety. Such 2'-*C*-branched ribonucleosides include, but are not limited to, 2'-*C*-methyl-cytidine, 2'-*C*-methyl-uridine, 2'-*C*-methyl-adenosine, 2'-*C*-methyl-guanosine, and 9-(2-*C*-methyl-β-D-ribofuranosyl)-2,6-diaminopurine, and the corresponding amino acid ester of the ribose C-2', C-3', and C-5' hydroxyls and the corresponding optionally substituted cyclic 1,3-propanediol esters of the 5'-phosphate derivatives.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS3 serine protease. HCV NS3 serine protease is an essential viral enzyme and has been described to be an excellent target for inhibition of HCV replication. Exemplary substrate and non-substrate based inhibitors of HCV NS3 protease inhibitors are disclosed in International Patent Application Publications WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, WO 02/48116, WO 02/48172, WO 2008/057208 and WO 2008/057209, in British Patent No. GB 2 337 262, and in U.S. Patent Nos. 6,323,180, 7,470,664, and 7,012,066 and in Ashok Arasappan *et al.*, *Discovery of Narlaprevir (SCH 900518): A Potent, Second Generation HCV NS3 Serine Protease Inhibitor*, ACS MED. CHEM. LETT. DOI: 10.1021/ml9000276 (February 15, 2010).

The compounds of the present invention may also be combined for the treatment of HCV infection with nucleosides having anti-HCV properties, such as those disclosed in International Patent Application Publications WO 02/51425, WO 01/79246, WO 02/32920, WO 02/48165 and WO 2005/003147 (including R1656, (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine, shown as compounds 3-6 on page 77); WO 01/68663; WO 99/43691; WO 02/18404 and WO 2006/021341, and U.S. Patent Application Publication US 2005/0038240, including 4'-azido nucleosides such as R1626, 4'-azidocytidine; U.S. Patent Application Publications US 2002/0019363, US 2003/0236216, US 2004/0006007, US 2004/0063658 and US 2004/0110717; U.S. Patent Nos. 7,105,499, 7,125,855, 7,202,224; and

International Patent Application Publications WO 02/100415, WO 03/026589, WO 03/026675, WO 03/093290, WO 04/011478, WO 04/013300 and WO 04/028481; the content of each is incorporated herein by reference in its entirety.

For the treatment of HCV infection, the compounds of the present invention may also be administered in combination with an agent that is an inhibitor of HCV NS5B polymerase. Such HCV NS5B polymerase inhibitors that may be used as combination therapy include, but are not limited to, those disclosed in International Patent Application Publications WO 02/057287, WO 02/057425, WO 03/068244, WO 2004/000858, WO 04/003138 and WO 2004/007512; U.S. Patent Nos. 6,777,392, 7,105,499, 7,125,855, 7,202,224 and U.S. Patent Application Publications US 2004/0067901 and US 2004/0110717; the content of each is incorporated herein by reference in its entirety. Other such HCV polymerase inhibitors include, but are not limited to, valopicitabine (NM-283; Idenix) and 2'-F-2'-beta-methylcytidine (*see also* WO 2005/003147).

In one embodiment, nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV inhibitors are selected from the following compounds: 4-amino-7-(2-C-methyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-methylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-dimethylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C-vinyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C-hydroxymethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C-fluoromethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-5-methyl-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine-5-carboxylic acid; 4-amino-5-bromo-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-5-chloro-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-5-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2,4-diamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2-amino-4-cyclopropylamino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 2-amino-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one; 4-amino-7-(2-C-ethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2-C,2-O-dimethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 7-(2-C-methyl-β-D-

ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one; 2-amino-5-methyl-7-(2-C, 2-O-dimethyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-4(3*H*)-one; 4-amino-7-(3-deoxy-2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-deoxy-2-C-methyl-β-D-arabinofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-2-fluoro-7-(2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-C-methyl-β-D-xylofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(2,4-di-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; 4-amino-7-(3-deoxy-3-fluoro-2-C-methyl-β-D-ribofuranosyl)-7*H*-pyrrolo[2,3-*d*]pyrimidine; and the corresponding 5'-triphosphates; or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may also be combined for the treatment of HCV infection with non-nucleoside inhibitors of HCV polymerase such as those disclosed in U.S. Patent Applciation Publications US 2006/0100262 and US 2009-0048239; International Patent Application Publications WO 01/77091, WO 01/47883, WO 02/04425, WO 02/06246, WO 02/20497, WO 2005/016927 (in particular JTK003), WO 2004/041201, WO 2006/066079, WO 2006/066080, WO 2008/075103, WO 2009/010783 and WO 2009/010785; the content of each is incorporated herein by reference in its entirety.

In one embodiment, non-nucleoside HCV NS5B polymerase inhibitors that are used in combination with the present HCV NS5A inhibitors are selected from the following compounds: 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-*a*] [2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; methyl ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetate; ({[(14-cyclohexyl-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocin-11-yl)carbonyl]amino}sulfonyl)acetic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-3-methoxy-6-methyl-5,6,7,8-tetrahydroindolo[2,1-*a*] [2,5]benzodiazocine-11-carboxamide; 3-chloro-14-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine 11-carboxylic acid; *N*'-(11-carboxy-14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5]benzoxazocin-7-yl)-*N*,*N*-dimethylethane-1,2-diaminium bis(trifluoroacetate); 14-cyclohexyl-7,8-dihydro-6*H*-indolo[1,2-*e*][1,5] benzoxazocine-11-carboxylic acid; 14-

cyclohexyl-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo [2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-3-methoxy-6-methyl-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-3-methoxy-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[3-(dimethylamino)propyl]-7-oxo-5,6,7,8-tetrahydroindolo [2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(2-morpholin-4-ylethyl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(diethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-(1-methylpiperidin-4-yl)-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-*N*-[(dimethylamino)sulfonyl]-7-oxo-6-(2-piperidin-1-ylethyl)-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-*N*-[(dimethylamino)sulfonyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxamide; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-7-oxo-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 6-allyl-14-cyclohexyl-3-methoxy-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclopentyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 14-cyclohexyl-6-[2-(dimethylamino)ethyl]-5,6,7,8-tetrahydroindolo[2,1-*a*][2,5]benzodiazocine-11-carboxylic acid; 13-cyclohexyl-5-methyl-4,5,6,7-tetrahydrofuro[3',2':6,7][1,4]diazocino[1,8-*a*]indole-10-carboxylic acid; 15-cyclohexyl-6-[2-(dimethylamino)ethyl]-7-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,6]benzodiazonine-12-carboxylic acid; 15-cyclohexyl-8-oxo-6,7,8,9-tetrahydro-5*H*-indolo[2,1-*a*][2,5]benzodiazonine-12-carboxylic acid; 13-cyclohexyl-6-oxo-6,7-dihydro-5*H*-indolo[1,2-*d*][1,4]benzodiazepine-10-carboxylic acid; and pharmaceutically acceptable salts thereof.

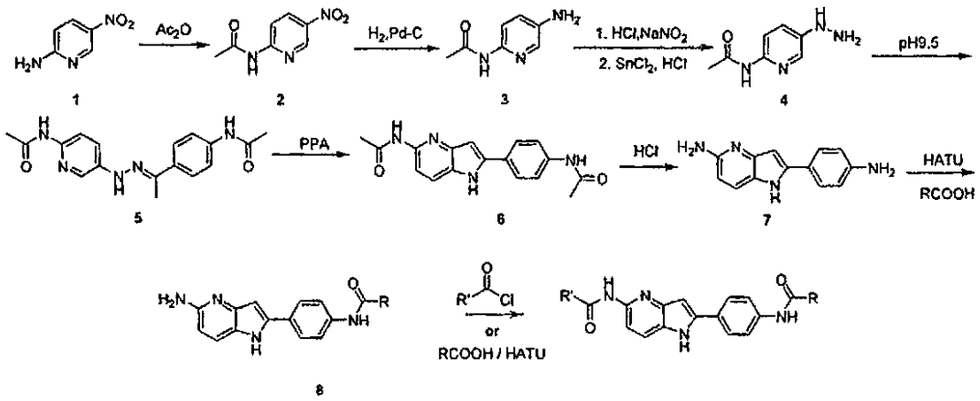
The HCV replicons and NS5A inhibitory activity of the present compounds may be tested using assays known in the art. HCV inhibitors, such as those described in the Examples herein have activities in genotype 1b, 2a and 1a replicon assays of from about 1 pM to about 1 μM. The assay is performed by incubating a replicon harboring cell-line in the presence of inhibitor for a set period of time and measuring the effect of the inhibitor on HCV replicon replication either directly by quantifying replicon RNA level, or indirectly by measuring

enzymatic activity of a co-encoded reporter enzyme such as luciferase or β-lactamase. By performing a series of such measurements at different inhibitor concentrations, the effective inhibitory concentration of the inhibitor (EC_{50} or EC_{90}) is determined. *See* Jan M. Vrolijk *et al.*, *A replicons-based bioassay for the measurement of interferons in patients with chronic hepatitis C*, 110 J. VIROLOGICAL METHODS 201 (2003). Such assays may also be run in an automated format for high through-put screening. *See* Paul Zuck *et al.*, *A cell-based β-lactamase reporter gene assay for the identification of inhibitors of hepatitis C virus replication*, 334 ANALYTICAL BIOCHEMISTRY 344 (2004).

The present invention also includes processes for making compounds of formula (I). The compounds of the present invention can be readily prepared according to the following reaction schemes and examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art, but are not mentioned in greater detail. Furthermore, other methods for preparing compounds of the invention will be readily apparent to the person of ordinary skill in the art in light of the following reaction schemes and examples. Unless otherwise indicated, all variables are as defined above. The following reaction schemes and examples serve only to illustrate the invention and its practice.

General Schemes

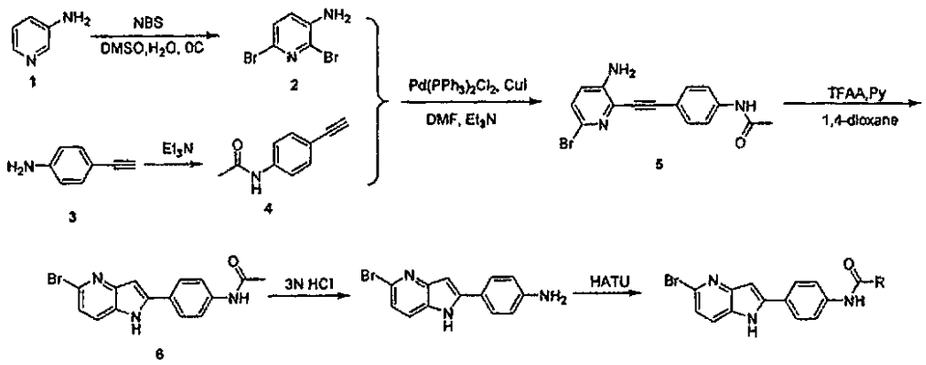
Scheme A-1



The synthesis of analogs containing the 4-azaindole core can be accomplished starting from a suitably protected 2-amino-5-nitropyridine **2**, which can then be reduced by catalytic hydrogenation in order to convert the resulting free amino group to its hydrazine by the action of $NaNO_2$ and $SnCl_2$. The resulting pyridylhydrazine can be condensed with a ketone

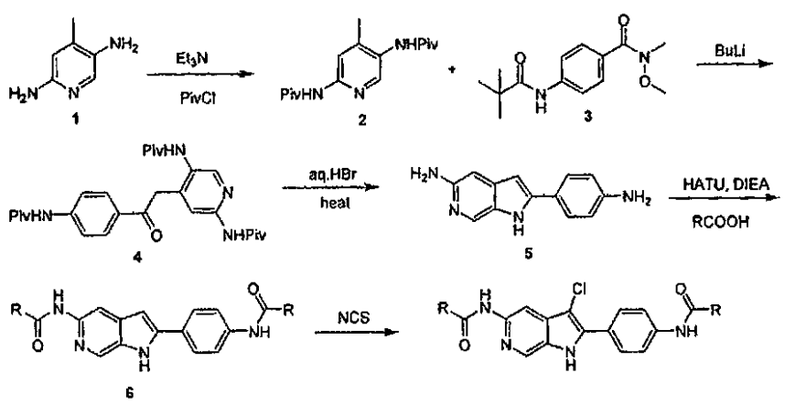
then subjected to Fisher indole cyclization conditions to afford the indole **6**. Acidic deprotection of the acetyl groups can be accomplished by using a strong acid to liberate the diamine, which can be selectively coupled on the more reactive aniline nitrogen using standard coupling agents, such as HATU. The aminopyridine group can then be acylated with a reagent, such as acetyl chloride or a carboxylic acid, in the presence of an amide bond-forming reagent.

Scheme A-2



2-Bromo-3-aminopyridines can be coupled to a terminally substituted alkyne using standard Sonagashira coupling procedures to give intermediates **5**, which can undergo TFAA-mediated cyclization to provide the 4-azaindole compounds **6**. Protecting groups can be removed with a strong acid, such as aqueous HCl, and the resulting amine can be acylated using an appropriately substituted carboxylic acid and an amide bond forming reagent, such as HATU.

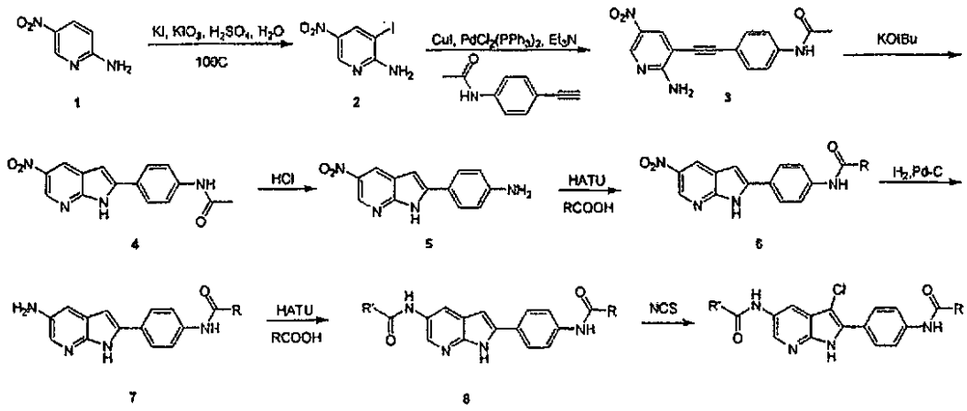
Scheme B



The synthesis of scaffolds B containing a 6-azaindole core can be accomplished by the metallation of the 4-methylpyridine analog **2** with a strong base, such as BuLi, and quenching the resulting anion with the acylating agent, such as **3**. Intermediate **4** can be globally deprotected by the action of a strong acid, such as HBr, to give the diamino azaindole structure **5**. Both amino groups can be acylated using an appropriately substituted carboxylic acid and an

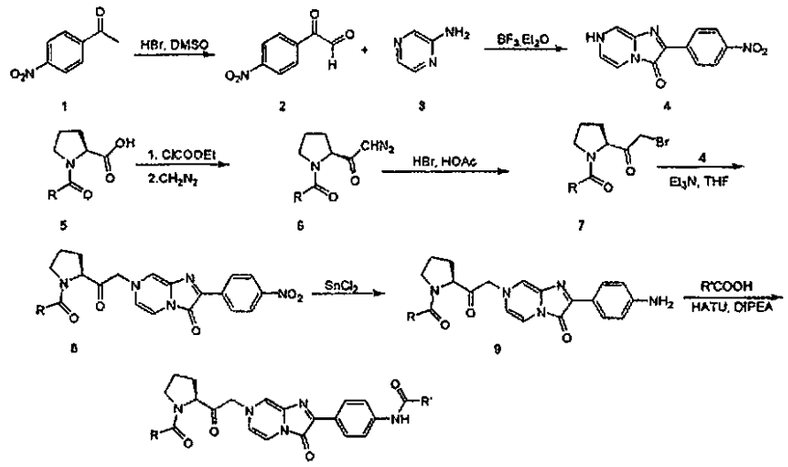
amide bond forming reagent, such as HATU. Compounds **6** can be further functionalized at the C-3 indole position with electrophiles, such as NCS.

Scheme C



Iodo aminopyridines **2** can be coupled to a terminally substituted alkyne using standard Sonagashira coupling procedures to give intermediates **5**, which can undergo a base-mediated cyclization using a reagent, such as KOtBu, to provide the 7-azaindole compounds **4**. Protecting groups can be removed with a strong acid, such as aqueous HCl, and the resulting amine can be acylated using an appropriately substituted carboxylic acid and an amide bond forming reagent, such as HATU. Compounds **6** can then be reduced using hydrogen and a catalyst then coupled a second time with a carboxylic acid and HATU to provide **8**. Treatment of **8** with an electrophilic agent, such as NCS, provides the desired compounds.

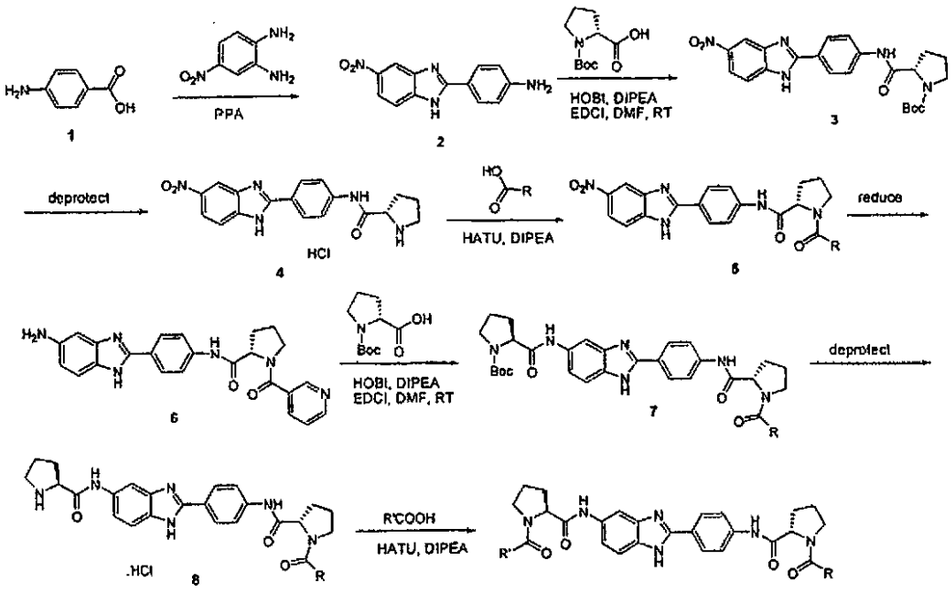
Scheme D



Compounds in the D series can be synthesized by reacting dicarbonyl intermediate **2** with a 2-aminopyrimidine derivative in the presence of a Lewis acid, such as

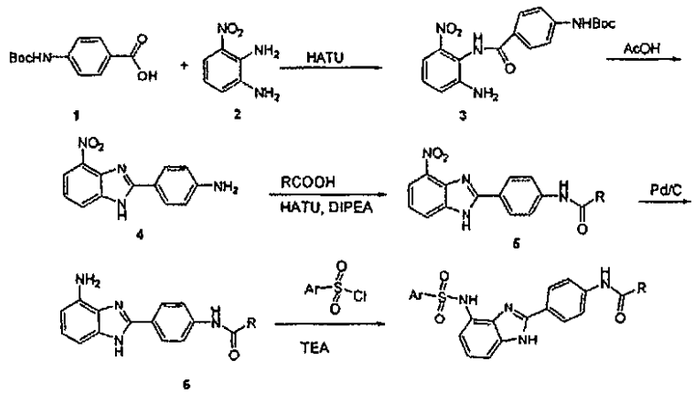
boron trifluoride etherate. The resulting heterocycle can be alkylated with a bromoketone analog of an amino acid, such as proline, in the presence of a tertiary amine base. The nitro group can be reduced, and the resulting aniline can be acylated using an appropriately substituted carboxylic acid and an amide bond forming reagent, such as HATU, to give the final products.

Scheme E-1



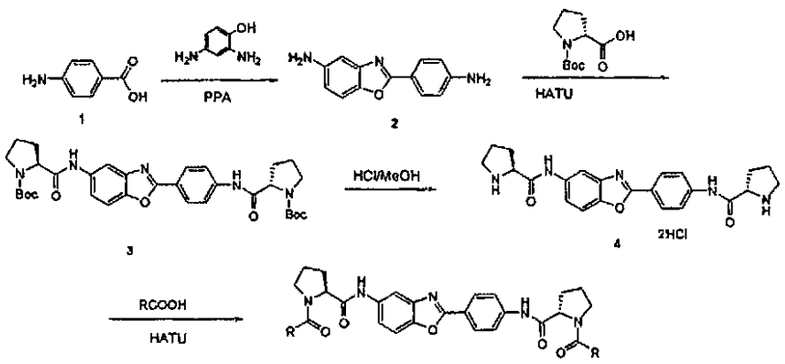
Scaffold E-1 can be prepared by the condensing a benzoic acid derivative, such as **1**, with a phenylenediamine counterpart **2** in the presence of a dehydrating agent, such as polyphosphoric acid. The resulting aniline can be acylated using an appropriately substituted carboxylic acid, such as N-Boc-L-proline, and an amide bond-forming reagent, such as HATU, and can then be subjected to acidic conditions to remove the Boc group. Compounds **4** can be coupled again with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU. The nitro group in **5** can be reduced under catalytic hydrogenating conditions, and the resulting aniline can be further coupled with various amines to give the target compounds.

Scheme E-2



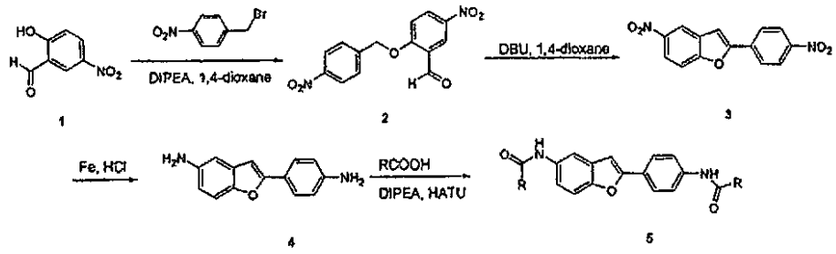
Scaffold E-2 can be prepared by the reacted with a benzoic acid derivative with a phenylenediamine analog and an amide bond-forming reagent, such as HATU, to give amides **3**, which can be cyclodehydrated by heating with a reagent, such as HOAc. The resulting aniline can be acylated using an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU, to give intermediates **5**. The nitro group can be reduced under catalytic hydrogenating conditions, and the resulting aniline can be sulfonylated with an appropriately substituted sulfonyl chloride and a tertiary amine base to give the targets.

Scheme F



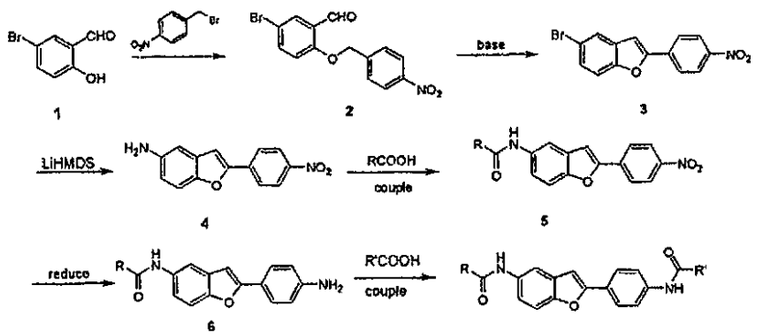
Scaffold F can be prepared by the condensing a benzoic acid derivative, such as **1**, with an amino phenol counterpart **2** in the presence of a dehydrating agent, such as polyphosphoric acid. The resulting aniline can be acylated using an appropriately substituted carboxylic acid, such as N-Boc-L-proline, and an amide bond-forming reagent, such as HATU, and can then be subjected to acidic conditions to remove the Boc group. Compounds **4** can be coupled again with an appropriately substituted carboxylic acid and an amide bond -forming reagent, such as HATU.

Scheme G-1



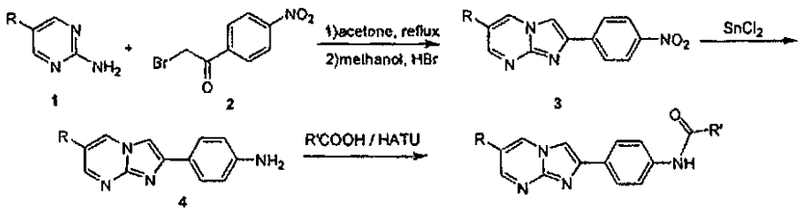
Compounds having the benzofuran structure G can be prepared by reacting an appropriately substituted salicylaldehyde with a benzyl halide, such as 4-nitrobenzyl bromide, in the presence of a tertiary amine base to give ethers **2**. The benzylic ethers can be treated with a base, such as DBU, and heated to elevated temperatures to effect cyclization to the benzofurans **3**. The nitro groups in **3** can be reduced under catalytic hydrogenating conditions, and the resulting anilines can be coupled with various carboxylic acids to give the target compounds G-1.

Scheme G-2



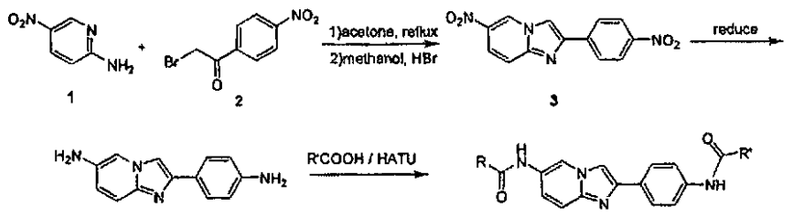
For differentially substituted compounds (R, R') having the benzofuran structure G, the synthesis can be modified by reacting an appropriately substituted bromo salicylaldehyde with a benzyl halide, such as 4-nitrobenzyl bromide, in the presence of a tertiary amine base to give ethers **2**. The benzylic ethers can be treated with a base, such as DBU, and heated to elevated temperatures to effect cyclization to the benzofurans **3**. The aryl bromide can be converted to the aryl amine by reaction with LHMDS and a palladium catalyst to provide **4**, which can be coupled to an appropriately substituted carboxylic acid to give **5**. The nitro group in **5** can be reduced under catalytic hydrogenating conditions, and the resulting aniline can be coupled with a second carboxylic acid analog to give the target compounds G-2.

Scheme H



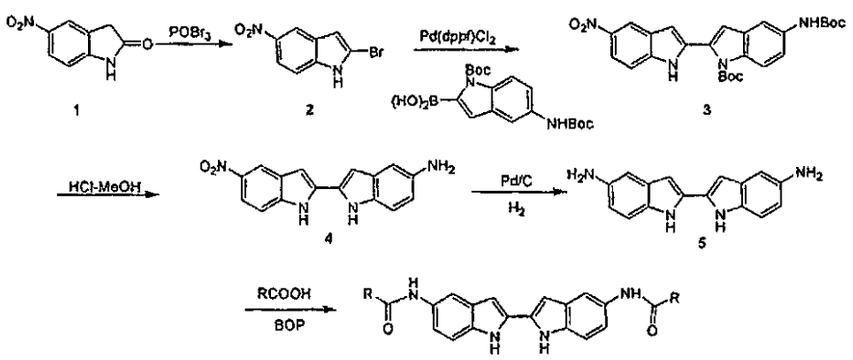
Appropriately substituted aminopyrimidines can be cyclodehydrated after acylation with an appropriately substituted ketone, such as 4'-nitro-2-bromobenzophenone, by heating in a solvent, such as MeOH, and an acid source, such as HBr. The resulting heterocyclic nitro compound can be converted to the aromatic amine by reduction with a reagent, such as $SnCl_2$. The final compounds H can be obtained by reacting **4** with an appropriately substituted carboxylic acid and an amide bond-forming reagent such as HATU.

Scheme I



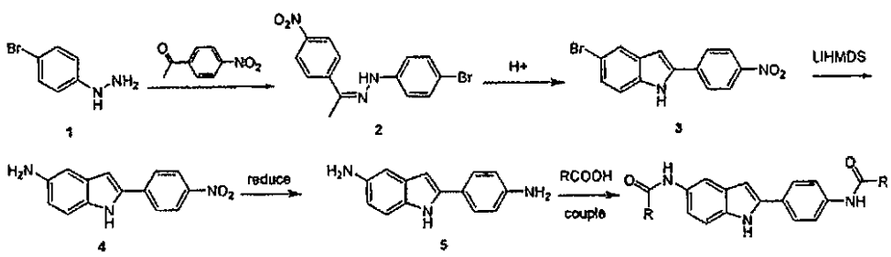
Compounds in scheme I can be prepared by reacting the appropriately substituted aminopyridine with 4'-nitro-2-bromobenzophenone by heating in a solvent, such as acetone, then effecting a cyclodehydration reaction using methanol and an acid source, such as HBr. The resulting heterocyclic nitro compound **3** can be converted to the aromatic amine by reduction with a reagent such as $SnCl_2$. The final compounds can be obtained by reacting **4** with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU.

Scheme J



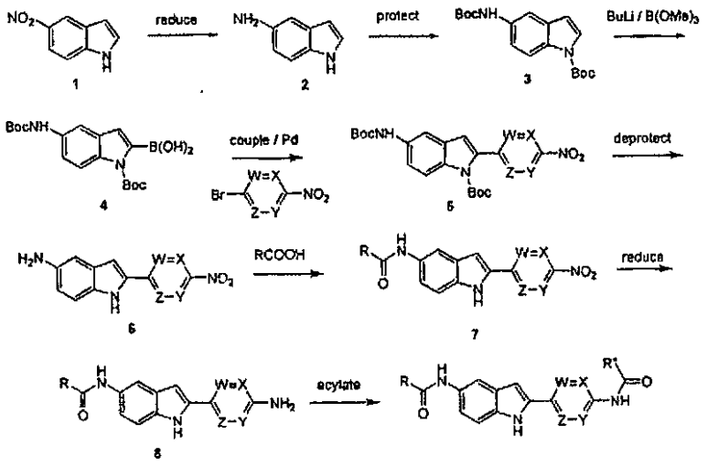
Compounds in scheme J can be prepared by coupling indole boronic acids with an appropriately substituted 2-bromoindole, such as **2**, under standard Suzuki conditions. The protecting groups can be removed with HCl, and the nitro group in **4** can be reduced under catalytic hydrogenation conditions. The penultimate diamine can be coupled with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as BOP, reagent to give compounds with the targeted central scaffold.

Scheme K-1



The synthesis of compounds with the indole core scaffold K can be prepared using standard Fisher indole synthesis protocol starting for an aryl hydrazine and a ketone such as **2**. Conversion of the aryl bromide to the aryl amine **4** could be effected by the Pd-catalyzed reaction with LHMDS. The nitro group could be reduced and the diamine can be coupled with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU, to give compounds with the targeted scaffold.

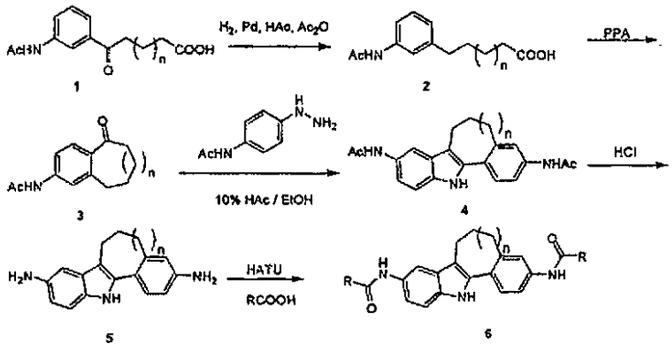
Scheme K-2



In an alternative procedure indoles K can be prepared starting from a suitably protected and substituted aminoindole **3**. Lithiation and quenching with a boronate ester affords key intermediate **4**, which can be coupled to an appropriately substituted aryl or heteroaryl halide to provide targets **5**. The Boc groups can be removed with acid, and the resulting aniline can be

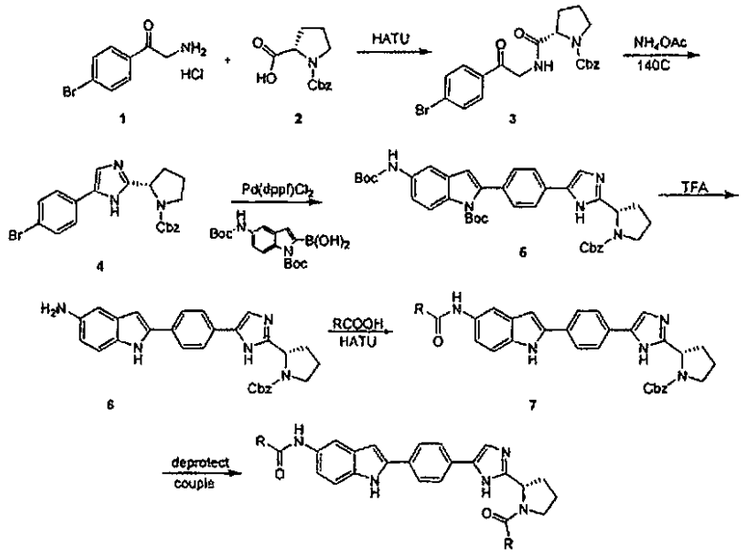
coupled with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU. The nitro group in **7** can be reduced and coupled in a second amide coupling reaction to give the desired compounds.

Scheme L



Tetracyclic indole scaffold L can be prepared as outline in the scheme above. Cyclization of a carboxylic acid derivative **2** with PPA can provide the ketones **3**, which can participate in a Fischer indole reaction with an appropriately substituted phenylhydrazine to give **4**. The acetamide groups can be deprotected under acidic conditions and the resulting aryl amines can be coupled with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU, to give compounds with the targeted scaffold.

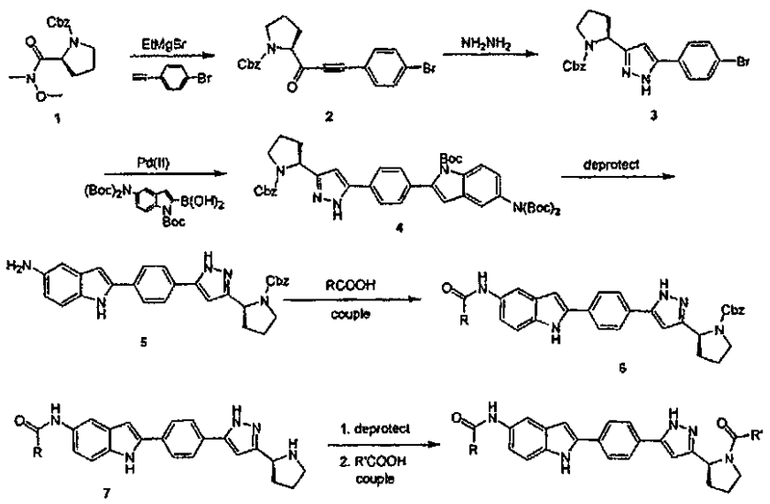
Scheme M-1



Scaffold M-1 compounds can be prepared by coupling proline **2** to amino ketone **1** using standard amide bond-forming procedures to provide **3**, which can be cyclized upon heating with ammonium acetate at elevated temperatures. Intermediate **4** can be coupled to

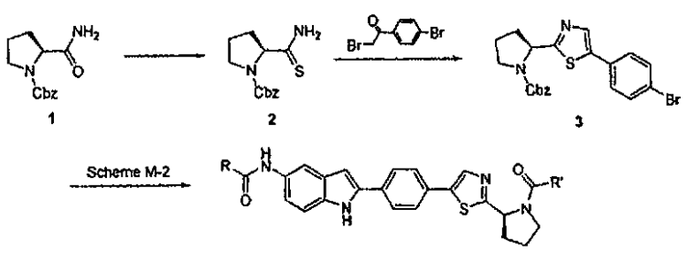
indole boronic acids, such as using standard Suzuki-type conditions. The Boc groups can be removed with acid, and the resulting aniline can be coupled with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU. The pyrrolidine protecting group can be removed under hydrogenating conditions, and the resulting amine can coupled in a second amide coupling reaction to give the desired compounds.

Scheme M-2



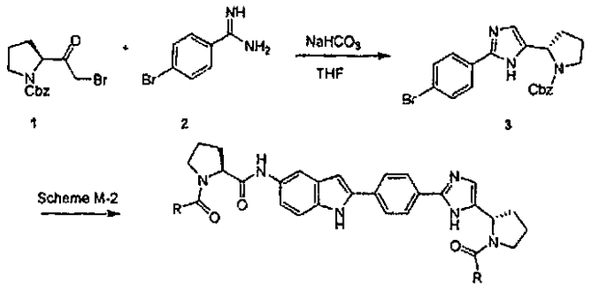
Scaffold M-2 compounds can be prepared by reacting proline **1** with an anion of 4-ethynylbenzene to give intermediate ketone **2**, which can be cyclized with hydrazine. Intermediate **3** can be coupled to indole boronic acids, such as using standard Suzuki-type conditions. The Boc groups can be removed with acid and the resulting aniline can be coupled with an appropriately substituted carboxylic acid, and an amide bond-forming reagent such as HATU. The pyrrolidine protecting group can be removed under hydrogenating conditions, and the resulting amine can coupled in a second amide coupling reaction to give the desired compounds.

Scheme M-3



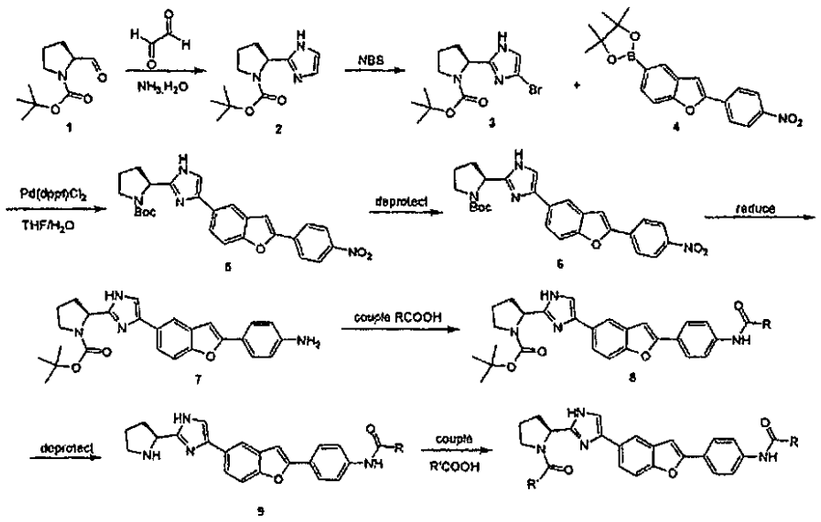
Thiazole analogs of scaffold M can be prepared from the cyclocondensation reaction of Z-proline thioamide **2** with an alpha-bromoacetophenone. Products **3** can be processed to the final compounds using methodology similar to that described in scheme M-2.

Scheme M-4



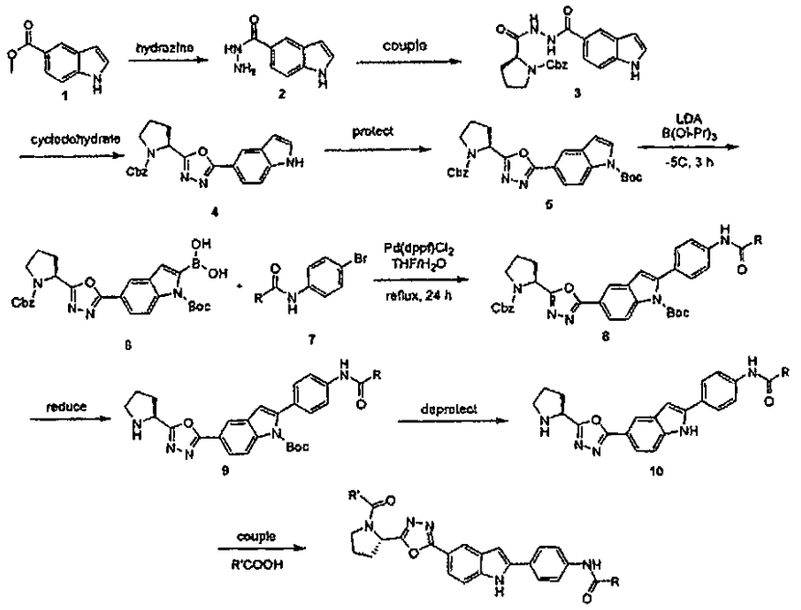
Imidazole analogs of scaffold M can be prepared from the cyclocondensation reaction of Z-proline bromomethyl ketone **1** with an aromatic amidine derivative. Products **3** can be processed to the final compounds using methodology similar to that described in scheme M-2.

Scheme M-5



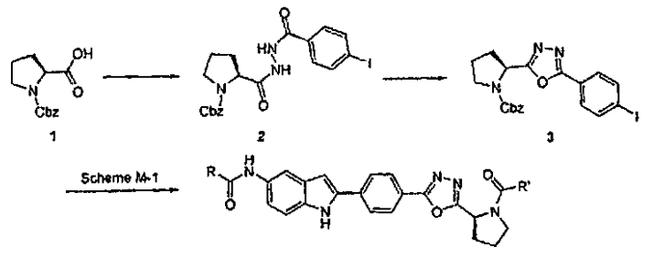
Isomeric imidazoles can be prepared starting from a protected amino acid aldehyde, such as **1**, and glyoxal in the presence of ammonia. Halogenation of the resulting imidazole **2** with NBS can be followed by a Pd-catalyzed cross coupling reaction with a functionalized indole boronate ester, such as **4**. Deprotection, reduction and coupling with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU, can provide intermediate compounds **8**. A second deprotection/amide-coupling procedure can provide the targeted M-5 scaffold.

Scheme M-6



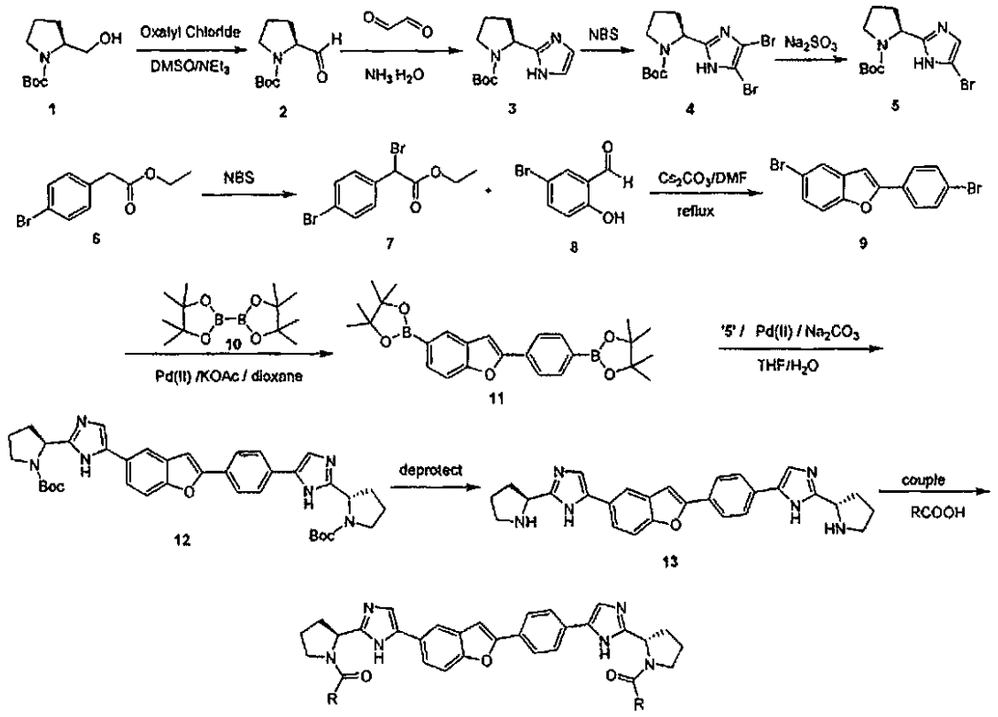
Oxadiazole compounds can be prepared starting from indole hydrazide **2** and coupling to an amino acid, such as Z-proline. Cyclodehydration of intermediate **3** can be effected with a reagent, such as TPP/iodine, to give the desired oxadiazole, which can be protected on the indole nitrogen with Boc anhydride. Introduction of the boronic acid functional group activates compound **6** for coupling with a substituted aryl halide **7** to give intermediate **8**. Removal of the cbz and Boc groups afford the penultimate structure **10**, which can be coupled with an appropriately substituted carboxylic acid and an amide bond-forming reagent to give the targets M-6.

Scheme M-7



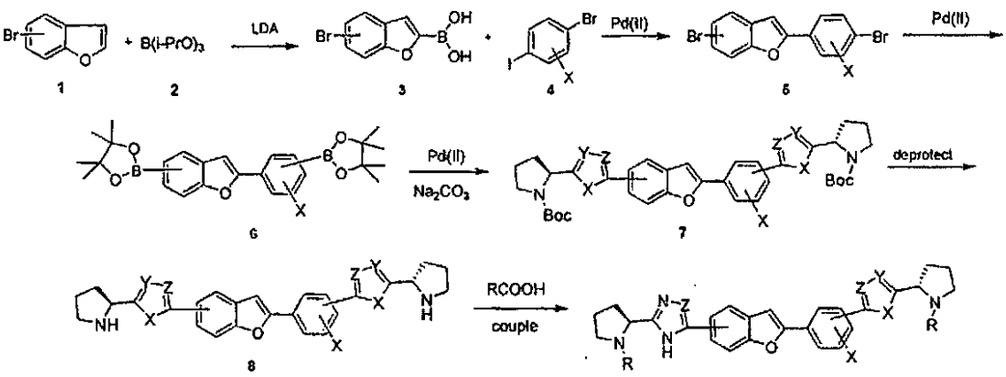
Oxadiazole analogs of scaffold M can be prepared by cyclocondensation reactions of diacylhydrazines **2**. Coupling to heterocyclic boronic acids using methodology similar to that described in scheme M-1 can provide the targeted compounds.

Scheme M-8



Double imidazole containing benzofuran compounds can be prepared starting from a protected amino acid aldehyde, such as **2**, and glyoxal in the presence of ammonia. Halogenation of the resulting imidazole **3** with NBS can ultimately provide intermediate **5**, which can be coupled to a functionalized boronate ester, such as **11**, to provide **12**. Deprotection and coupling with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU, can provide the targeted M-8 scaffold.

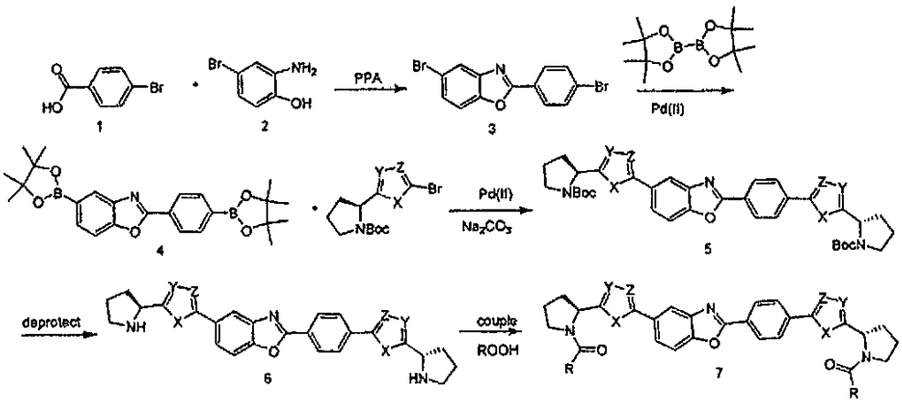
Scheme M-9



An alternative synthesis of benzofurans can be realized starting from benzofuran **1**, which can be converted to boronate ester **2**, which can then coupled to an appropriately

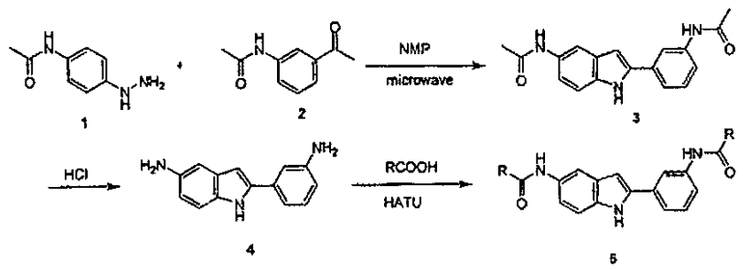
substituted aryl halide to afford **5**. Intermediate **5** can subsequently be converted to a functionalized boronate ester and converted to the final products in a manner similar to that described in Scheme M-8.

Scheme M-10



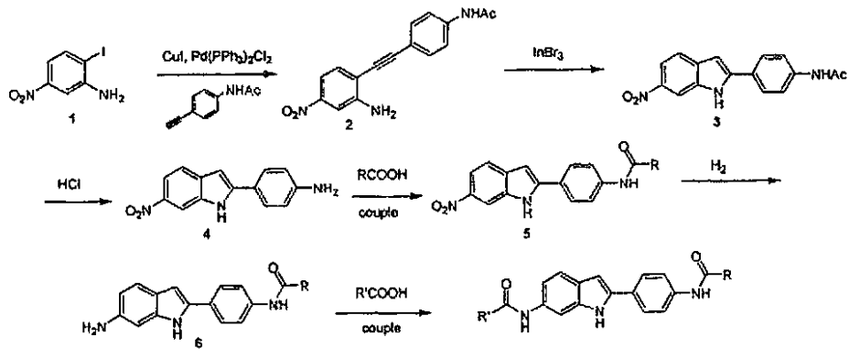
Benzoxazoles **3** can be prepared starting from a suitable substituted benzoic acid and an aminophenol, such as **2**, in the presence of polyphosphoric acid. Such products can be converted to the corresponding boronate esters using standard procedures. Intermediates 4 can subsequently be coupled to a heterocyclic halide in the presence of a Pd(II) catalyst to provide compounds **5**. Deprotection and coupling with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU, can provide the targeted M-10 scaffold.

Scheme N-1



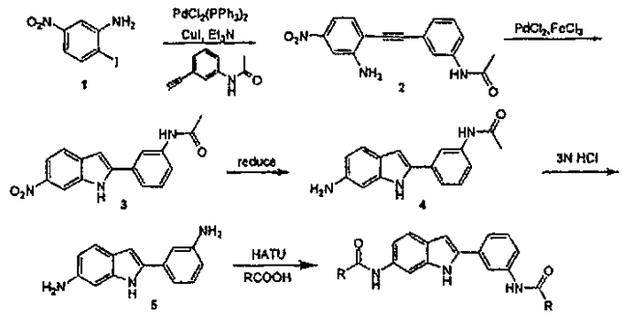
The compounds in scheme N-1 can be prepared by heating hydrazines **1** with ketones **2** in a microwave reactor in a polar aprotic solvent, such as NMP. The indole acetamides **3** can be deprotected with strong acid, such as HCl. The resulting aryl amines can be coupled with an appropriately substituted carboxylic acid, and an amide bond-forming reagent, such as HATU, to give compounds of the targeted scaffold.

Scheme N-2



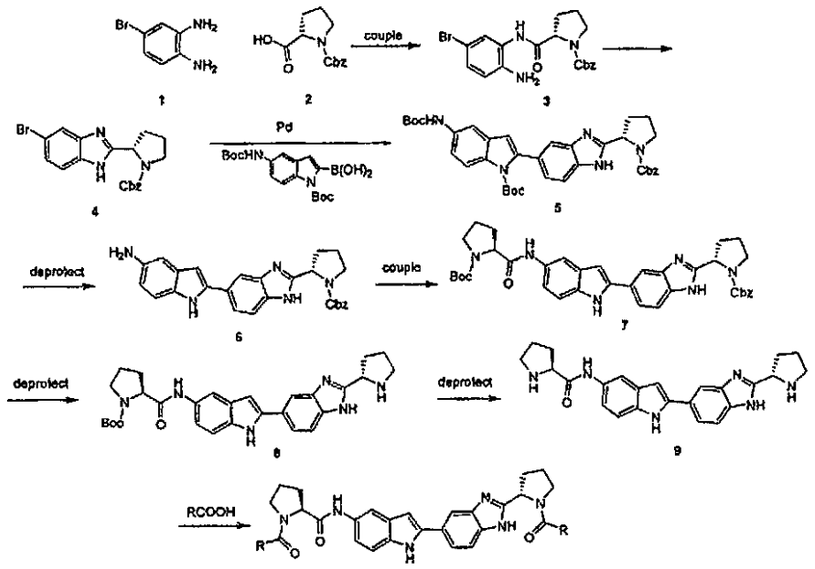
Iodo anilines **1** can be coupled to a terminally substituted alkyne using standard Sonagashira coupling procedures to give intermediates **2**, which can undergo cyclization using a reagent, such as indium bromide, to provide the indole compounds **3**. Protecting groups can be removed with a strong acid, such as aqueous HCl, and the resulting amine can be acylated using an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU. Compounds **5** can then be reduced using hydrogen and a catalyst, then coupled a second time with a carboxylic acid and HATU to provide the desired compounds.

Scheme N-3



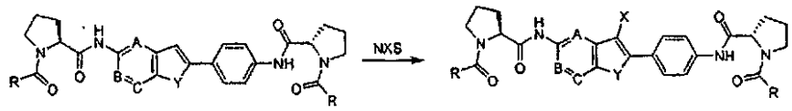
In a slight variation of scheme N-2, iodo anilines **1** can be coupled to a terminally substituted alkyne using standard Sonagashira coupling procedures to give intermediates **2**, which can undergo cyclization using a reagent such as palladium chloride/ferric chloride to provide the indole compounds **3**. Compounds **3** can then be reduced using H_2, and the protecting group can be removed with a strong acid, such as aqueous HCl, and the resulting amines can be acylated using an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU.

Scheme O



Scaffold O can be prepared by reacting a protected proline compound (such as Cbz) with a phenylenediamine analog and an amide bond-forming reagent, such as HATU, to give amides **3**, which can be cyclodehydrated by heating with a reagent, such as HOAc. The resulting benzimidazole can be coupled to an indole boronic acid derivative using standard Suzuki conditions to provide **5**. Removal of the Boc groups with acid provides **7**, which can be acylated using an appropriately substituted carboxylic acid, such as Boc-L-proline, and an amide bond-forming reagent, such as HATU, to give intermediates **7**. The Cbz group can be reduced under catalytic hydrogenating conditions, and the Boc group can be deprotected with acid to provide penultimate compounds **9**. Amide bond formation between **9** and carboxylic acids afford the targeted compounds.

Scheme P-1



Heterocycles can be halogenated at C-3 by the action of electrophilic agents, such as N-halosuccinimides, to provide targets P-1.

Scheme P-2



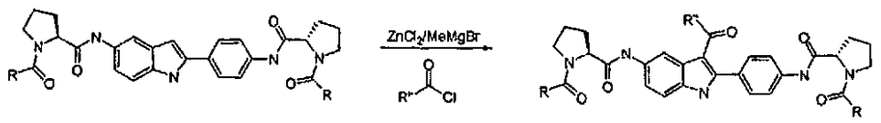
Heterocycles can be fluorinated at C-3 by the action of electrophilic fluorinating agents, such as SELECTFLUOR, to provide targets P-1.

Scheme P-3



C-3 halogenated compounds can be converted to the corresponding cyano analogs by cyanating agents, such as CuCN.

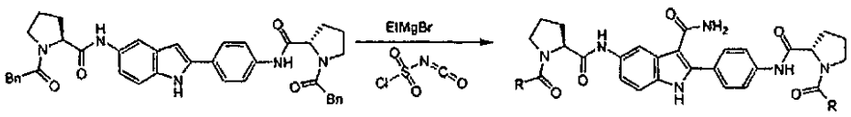
Scheme P-4



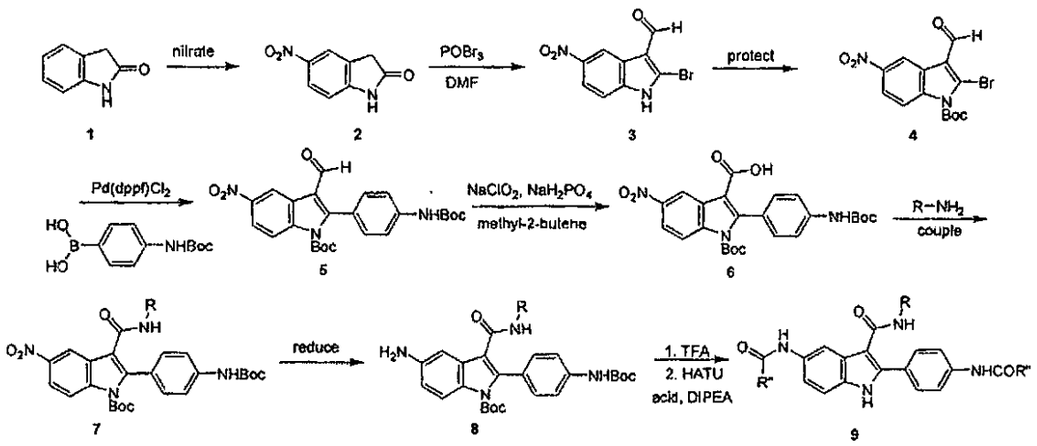
The compounds in scheme P-4 can be functionalized by the acylating indoles with Grignard reagents and zinc chloride.

Scheme P-5

R = H



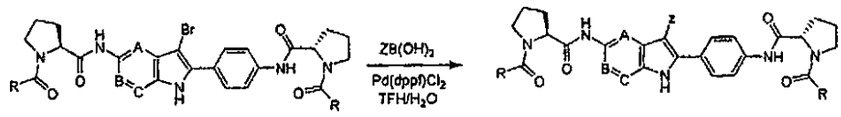
R > H



The compounds in scheme P-5 can be functionalized by deprotonating the indoles with a base such as ethylmagnesium bromide and treating the resulting intermediate with chlorosulfonyl isocyanate. Alternatively, the indoles **3** can be prepared using Vilsmeier-Haack conditions, which can subsequently be protected and coupled under Suzuki conditions to give intermediates **5**. The aldehydes can be oxidized using standard methodology for carboxylic acid

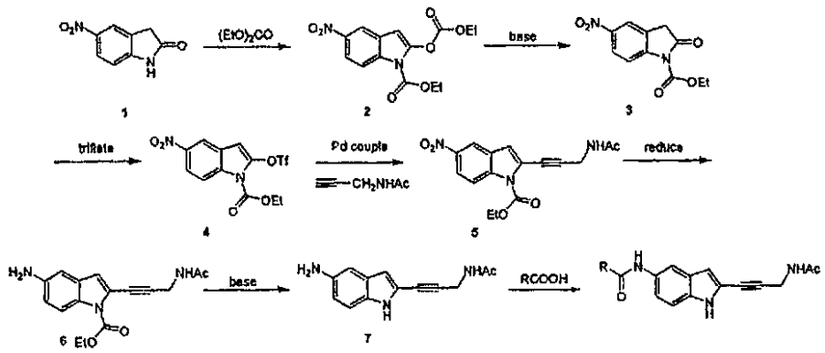
formation. Indole carboxylic acids **6** can be coupled to amines using a reagent, such as HATU, to give 7, which can be further functionalized by reduction of the nitro group, deprotection of the Boc group and coupling of the anilines to an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU.

Scheme P-6



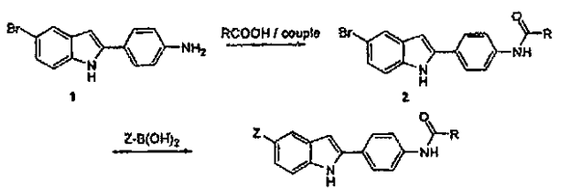
C-3 halogenated compounds can be coupled to a variety of alkyl and aryl boronic acids using standard Suzuki conditions.

Scheme Q



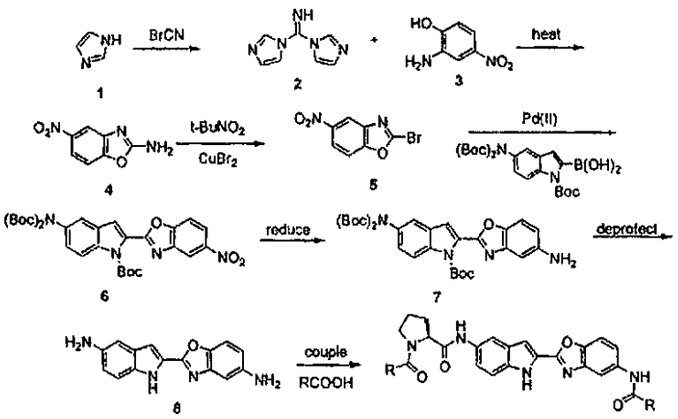
Compounds of scheme Q can be prepared starting from the lactam **1**. Reaction with ethyl chloroformate and treatment of the product with a mild base, such as ammonium carbonate, provides intermediate **3**, which can be activated for coupling by conversion to the corresponding vinyl triflate **4**. Sonagashira coupling provides compounds **5**, which can be reduced with iron and ammonium chloride to provide aniline **6**. Deprotection of the indole and coupling of the aniline to an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU, provides the desired targets.

Scheme R



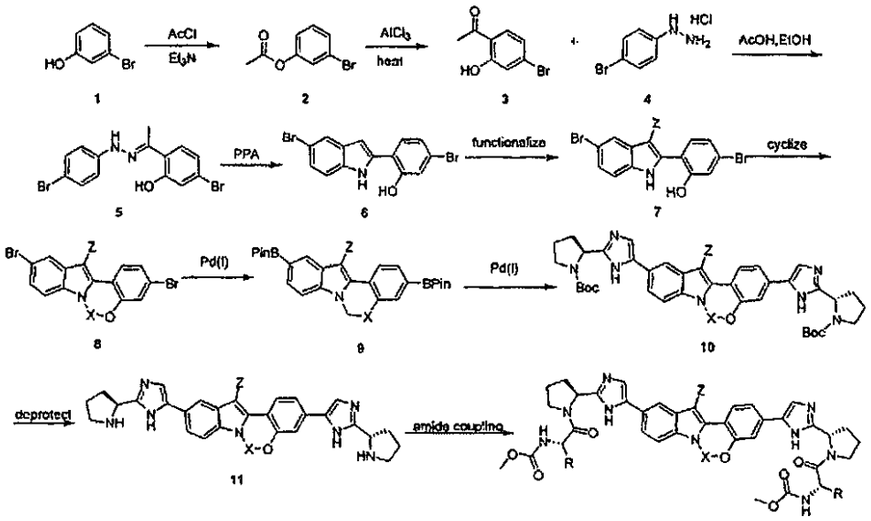
Amide coupling of the aniline from scheme K-1 with an appropriately substituted carboxylic acid and a coupling agent can provide intermediates **2**, which can then be subjected to Pd-catalyzed cross-coupling reactions to provide the final targets R.

Scheme S



Compounds in scheme S can be prepared by coupling indole boronic acids with an appropriately substituted 2-bromobenzoxazoles, such as **5**, under standard Suzuki conditions. The nitro group in **6** can be reduced under catalytic hydrogenation conditions and the protecting groups can be removed with HCl. The penultimate diamine can be coupled with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as BOP, reagent to give compounds with the targeted central scaffold.

Scheme T



Compounds in scheme T can be prepared by starting from a suitably substituted phenol **3** and a hydrazine reagent, such as **4**, using established Fisher indole conditions. The indole 3 position can then be functionalized or the indole NH can be cyclized onto the C-2 aromatic ring using standard conditions to give tetracycles **8**, which can subsequently be converted to the corresponding boronate esters using standard procedures. Intermediates **9** can

then be coupled to a heterocyclic halide in the presence of a Pd(II) catalyst to provide compounds **10**. Deprotection and coupling with an appropriately substituted carboxylic acid and an amide bond-forming reagent, such as HATU, can provide the targeted T scaffold.

The following examples serve only to illustrate the invention and its practice. The examples are not to be construed as limitations on the scope or spirit of the invention.

List of Abbreviations

Ac_2O	Acetic anhydride
$B(OiPr)_3$, $(iPrO)_3B$	Tri*iso*propyl borate
$B(OMe)_3$	Trimethyl borate
BF_3	Boron trifluoride
BOC, Boc, boc	*tert*-Butyloxycarbonyl
BOP	Benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate
BrCN	Cyanogen bromide
BuLi, n-BuLi	Butyl lithium
CBZ, Cbz, cbz	Benzyloxycarbonyl
$CDCl_3$	Deuterio-trichloromethane
CH_3CN, MeCN	Acetonitrile
Cs_2CO_3	Cesium carbonate
$CuBr_2$	Copper(II) bromide
CuCN	Copper(I) cyanide
CuI	Copper iodide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM, CH_2Cl_2	Dichloromethane
DIPEA, DIEA	Diisopropylethylamine
DMAP	4-Dimethylamino pyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DPPF, Dppf, dppf	1,1'-bis(Diphenylphosphino)ferrocene
EDC, EDCI	*N*-(3-Dimethylaminopropyl)-*N'*-ethylcarbodiimide
Et_2O	Diethyl ether

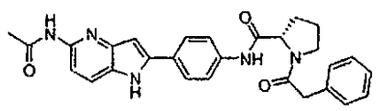
Et_3N, TEA	Triethylamine
EtMgBr	Bromo(ethyl)magnesium or ethyl magnesium bromide
EtOAc	Ethyl acetate
EtOH	Ethanol
$FeCl_3$	Ferric chloride or Iron(III) chloride
H_2	Hydrogen or hydrogen atmosphere
H_2O	Water
H_2SO_4	Sulfuric acid
HATU	*O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
HBr	Hydrobromic acid
HCl	Hydrochloric acid
HNO_3	Nitric Acid
HOAc, HAc	Acetic acid
HOBT, HOBt	1-Hydroxy benzotriazole
HPLC	High performance liquid chromatography
$InBr_3$	Indium tribromide
iPr_2NH	Di*iso*propylamine
K_2CO_3	Potassium carbonate
KI	Potassium iodide
KIO_3	Potassium iodate
KOAc, AcOK	Potassium acetate
KOH	Potassium hydroxide
LDA	Lithium diisopropylamide
LHMDS, LiHMDS	Lithium hexamethyldisilamide
MeMgBr	Bromo(methyl)magnesium or methyl magnesium bromide
MeOD	Methan(^{2}H)ol
MeOH, CH_3OH	Methanol
$MgSO_4$	Magnesium sulfate
MOC, Moc	Methoxy carbonyl
MS	Mass spectroscopy
N_2	Nitrogen or nitrogen atomosphere
Na_2CO_3	Sodium carbonate

Na_2SO_4	Sodium sulfate (anhydrous)
$NaClO_2$	Sodium perchlorate
NaH_2PO_4	Dihydrogen sodium phosphate
$NaHCO_3$	Sodium hydrogen carbonate (sodium bicarbonate)
$NaNO_2$	Sodium nitrite
NaOH	Sodium hydroxide
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NH_4OAc	Ammonium acetate
NMM	*N*-methylmorpholine
NMR, ^{1}H-NMR	Proton nuclear magnetic resonance spectroscopy
NXS	N-halosuccinimide
P_2O_5, P_4O_{10}	Phosphorus pentoxide
Pd	Palladium
$Pd(dppf)Cl_2$	Dichloro(1,1'-bis(Diphenylphosphino)ferrocene) palladium(II)
Pd(II)	Palladium(II)
$Pd(PPh_3)_2Cl_2$, $PdCl_2(PPh_3)_2$	Dichlorobis(triphenylphosphine)palladium(II)
$Pd(PPh_3)_4$	Tetrakis(triphenylphosphine)palladium(0)
Pd/C, Pd-C	Palladium on carbon
$Pd_2(dba)_3$	Tris(dibenzylidene acetone)dipalladium(0)
$PdCl_2$	Palladium(II) chloride
PE	Petroleum ether
Phg	Phenylglycine
$PhCH_3$, PhMe	Toluene
Piv	Pivaloyl
PivCl	Pivaloyl chloride
$POBr_3$	Phosphorus oxybromide
PPA	Polyphosphoric acid
PPH_3, TPP	Triphenylphosphine
Pro	Proline
Proc	*iso*-Propylcarbamate
P^tBu_3	Tri-*tert*-butyl phosphine

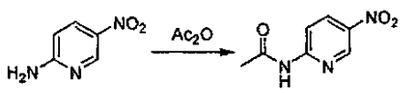
Py	Pyradine
PyBOP	(Benzotriazole-1-yl-oxy)-tripyrrolidinophosphonium hexafluorophosphate
RPLC	Reverse phase liquid chromatography
RT, rt, r.t.	Room temperature, approximately 25°C
SiO_2	Silica or silica gel
$SnCl_2$	Stannous chloride or Tin(II) chloride
$SOCl_2$	Thionyl chloride
STP	Standard temperature and pressure
t-BuLi	*tert*-Butyl lithium
t-$BuNO_2$	*tert* -Butyl nitrate
t-BuOH	*tert* -Butanol
t-BuOK, KO*t*-Bu	Potassium *tert* -butoxide
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
$ZnCl_2$	Zinc chloride

EXAMPLES

Example 1 – N-{4-[5-(acetylamino)-1H-pyrrolo[3,2-b]pyridin-2-yl]phenyl}-1-(phenylacetyl)-L-prolinamide

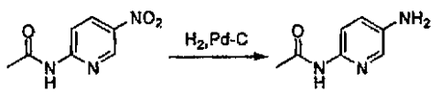


Step 1



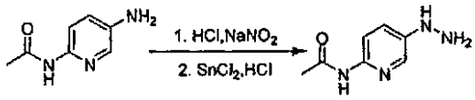
To a suspension of 2-amino-5-nitropyridine (25.0 g, 0.18 mol) and 0.5 g of DMAP in 200 mL of pyridine, Ac_2O (37 g, 0.36 mol) was added drop wise at 0°C. The mixture was stirred at RT for 5 hours. The volatile was removed *in vacuo*. The residue was washed with EtOAc to yield an off-white solid (28 g, 86%). MS (ESI) m/e ($M+H^+$): 182.

Step 2



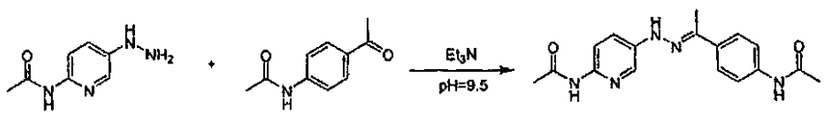
A heterogeneous mixture of 2-acetamido-5-nitropyridine (28 g, 0.15 mol) and 10% Pd/C (2.8 g) in 300 mL of MeOH was stirred in 50 psi of H_2 for 6 hours. The mixture was filtered through CELITE, and concentrated *in vacuo* to yield a solid (20.5 g). MS (ESI) m/e ($M+H^+$): 152.

Step 3



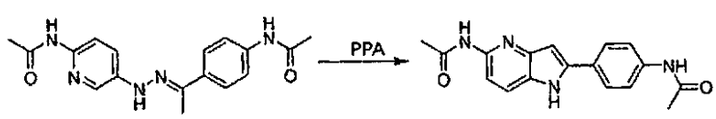
$NaNO_2$ (5.4 g, 78.2 mmol) was added slowly to a solution of 2-acetamido-5-aminopyridine (9.0 g, 60 mmol) in 6 M aqueous HCl (300 mL) at 0°C and was stirred for 45 minutes. A solution of $SnCl_2$ (40.5 g, 180 mmol) in 15 mL of 6 M aqueous HCl was added, and the reaction mixture was allowed to warm to RT slowly while stirring for 16 hours. The reaction mixture was basified with 40 percent aqueous KOH, extracted with EtOAc (3x), and the organic layers are combined, dried over Na_2SO_4 and concentrated *in vacuo* to give the desired compound (3.2 g). MS (ESI) m/e ($M+H^+$): 167.

Step 4



A suspension of the product from step 3 (3.32 g, 20 mmol) and *N*-(4-acetylphenyl)acetamide (3.54 g, 20 mmol) in 8 mL of EtOH was diluted with TEA to adjust the pH to about 9.5. The resulting reaction mixture was refluxed for 3 hours. The solvent was removed *in vacuo*, and the resulting residue was treated with 5 % aqueous citric acid to form a precipitate. The precipitate was filtrated, washed with water and dried *in vacuo* (3.2 g). MS (ESI) m/e ($M+H^+$): 326.

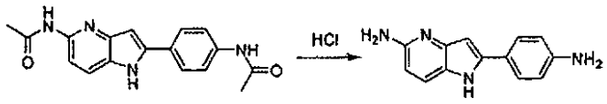
Step 5



A mixture of the product from step 4 above (0.6 g, 1.8 mmol) and PPA (5 mL) was heated to 90°C for 75 minutes under N_2. After cooling to RT, the reaction mixture was

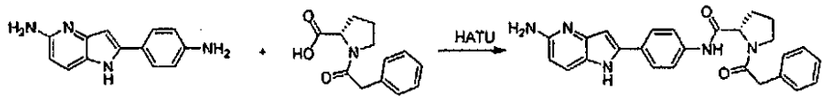
poured to an ice water, neutralized with solid NaOH, while maintaining the temperature of the mixture at or below RT. A solution of *iso*-propanol and DCM (1:3) was added to exact the organic. The combine organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative HPLC to yield a solid (280 mg). MS (ESI) m/e ($M+H^+$): 309.

Step 6



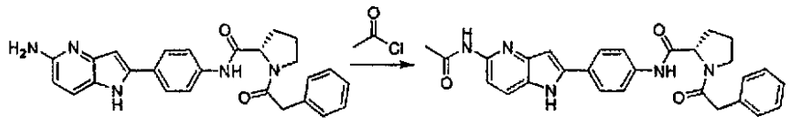
A mixture of the 4-azaindole (280 mg, 0. 9 mmol) in 10 mL of 3 N HCl was refluxed for 2 hours. The solvent was removed *in vacuo*. The residue was purified by HPLC to yield a solid (120 mg). MS (ESI) m/e ($M+H^+$): 225.

Step 7



To a suspension of the product from step 6 (23 mg, 0.1 mmol), acid (23 mg, 0.1 mmol) and DIPEA (20 mg, 0.15 mmol) in 1 mL of CH_3CN was added HATU (42 mg, 0.12 mmol). The resulting mixture was stirred at RT overnight. After reaction completed, the mixture was purified by pre-HPLC (10 mg). MS (ESI) m/e ($M+H^+$): 440.

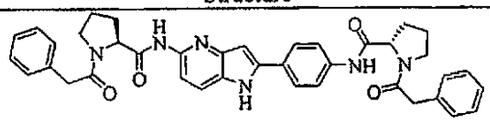
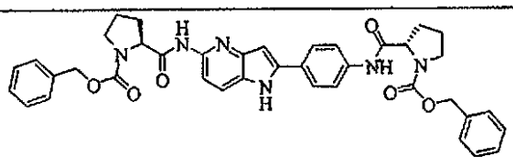
Step 8



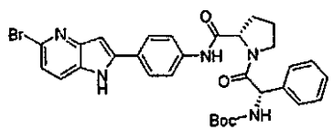
A mixture of product from step 7 (10 mg, 0.023 mmol) and TEA (3 g, 0.03 mmol) in CH_3CN (100 mL) was stirred at 0°C. Acetyl chloride (2 mg, 0.023 mmol) was added dropwise, and the resulting mixture was stirred at RT for 0.5 hour. The solvent was evaporated *in vacuo*, and the residue was purified by preparative HPLC to afford the desired product (5 mg). MS (ESI) m/e ($M+H^+$): 482. ^1H NMR (MeOD): δ 8.25 (d, J=8.4 Hz, 1H), 7.74 ~ 7.89 (m, 4H), 7.26 ~ 7.32 (m, 5H), 7.00 ~ 7.02 (m, 2H), 4.63 ~ 4.64 (m, 1H), 3.72 ~ 3.84 (m, 4H), 2.18 ~ 2.33 (m, 2H), 2.07 ~ 2.10 (m, 5H).

Examples 2-3

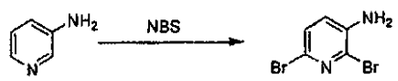
The compounds of Examples 2 and 3 were prepared in a similar manner starting from intermediate 7 in step 6.

Example	Structure	MW	Name
2		654.776	(2*S*)-1-(phenylacetyl)-*N*-{2-[4-({[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1*H*-pyrrolo[3,2-*b*]pyridin-5-yl}pyrrolidine-2-carboxamide
3		686.774	benzyl (2*S*)-2-[(2-{4-[({(2*S*)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1*H*-pyrrolo[3,2-b]pyridin-5-yl)carbamoyl]pyrrolidine-1-carboxylate

Example 4 – tert-butyl {(1S)-2-[(2S)-2-{[4-(5-bromo-1H-pyrrolo[3,2-b]pyridin-2-yl)phenyl]carbamoyl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

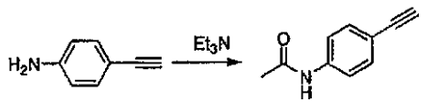


Step 1



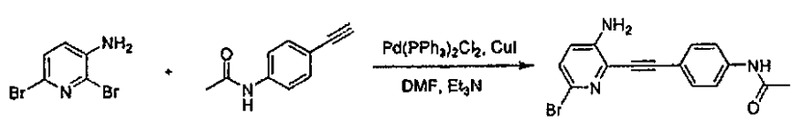
NBS (14.9 g, 84 mmol) was added portion wise to a solution of compound 3-aminopyridine (14.9 g, 84 mmol) in DMSO (80 mL) and water (20 mL) at 0°C, and the reaction was stirred at RT for 3 hours. The mixture was poured into ice-water (250 mL) and stirred for 30 minutes. The precipitate was collected and dried to yield a solid (7.0 g). MS (ESI) m/e ($M+H^+$): 250. ^1H NMR (DMSO): δ 7.28 (d, J=7.6 Hz, 1H), 7.03 (d, J=7.6 Hz, 1H), 5.69 (s, 2H).

Step 2



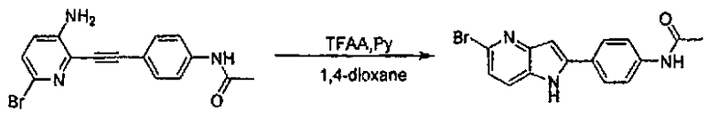
4-Ethynylacetanilide was prepared using the similar method shown in Example 1, step 1. MS (ESI) m/e ($M+H^+$): 160.

Step 3



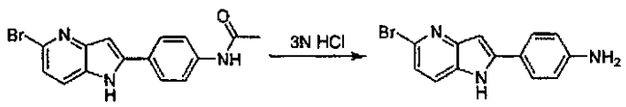
To a solution of 3-amino-2,6-dibromopyridine (9.41 g, 37.5 mmol), 4-ethynylacetanilide (4.77 g, 30 mmol) and $Pd(PPh_3)_2Cl_2$ (1.31 g, 1.9 mmol) in a mixture of 150 mL of Et_3N and 50 mL of DMF was added CuI (0.71 g, 0.4 mmol) under N_2. The resulting mixture was stirred at RT overnight. The solvent was removed, and the residue was purified by chromatography (8.5 g). MS (ESI) m/e ($M+H^+$): 331. ^{1}HNMR (DMSO): δ 7.59 (d, J=8.8 Hz, 2H), 7.54 (d, J=8.4 Hz, 2H), 7.21 (d, J=8.8 Hz, 2H), 7.07 (d, J=8.4 Hz, 2H), 2.12 (s, 3H).

Step 4



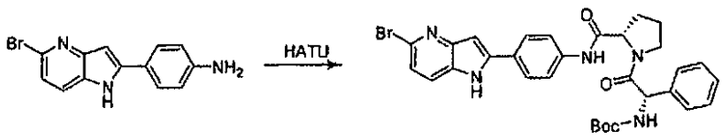
To a 0°C solution of the product from step 3 (8.5 g, 25.7 mmol) and pyridine (4.0 g, 51.4 mmol) in 50 mL of 1,4-dioxane was added TFAA (10.8 g, 51.4 mmol). The resulting mixture was then heated to 100°C overnight. The mixture was cooled and poured into 200 mL of water, and the precipitate was filtered and washed by water then dried to give a solid (1.3 g). MS (ESI) m/e ($M+H^+$): 331.

Step 5



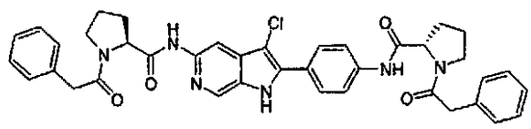
The reaction was conducted similar to that describe in Example 1, step 6. MS (ESI) m/e ($M+H^+$): 288.

Step 6

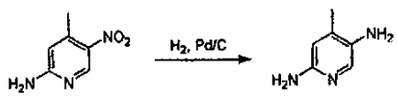


To a suspension of the product from step 5 (0.1 mmol), N-Boc-L-Phg-L-Pro-OH (0.1 mmol) and DIPEA (20 mg, 0.15 mmol) in 1 mL of CH_3CN was added HATU (42 mg, 0.12 mmol). The resulting mixture was stirred at RT overnight, concentrated and purified by RPLC to give the desired compound. MS (ESI) m/e ($M+H^+$): 619. ^{1}H NMR (MeOD 400) δ: 7.85 ~ 7.77 (m, 5 H), 7.43 ~ 7.36 (m, 6 H), 6.89 (s, 1 H), 5.50(s, 1H), 4.54 (d, J=8.0 Hz 1H), 3.93(t, 1 H), 2.10 ~ 1.87 (m, 4 H) 1.41 (s, 9 H).

Example 5 – (2S)-N-{3-chloro-2-[4-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino) phenyl]-1H-pyrrolo[2,3-c]pyridin-5-yl}-1-(phenylacetyl)pyrrolidine-2-carboxamide

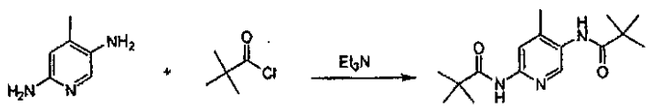


Step 1



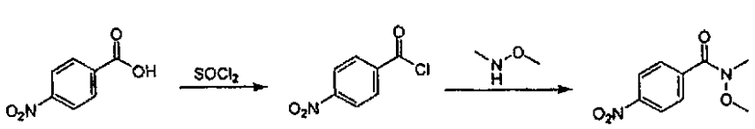
A heterogeneous mixture of 2-amino-4-methyl-5-nitropyridine (4.15 g, 27 mmol) and 10% Pd/C (0.4 g) in 50 mL of THF was stirred in 50 psi of H_2 for 3 hours. The mixture was filtered through CELITE and concentrated to yield a yellow solid (3.20 g). MS (ESI) m/e ($M+H^+$): 124. ^{1}H NMR (DMSO): δ 7.38 (s, 1 H), 6.16 (s, 1 H), 4.84 (s, 2 H), 4.06 (s, 2 H), 1.96 (s, 3 H).

Step 2



A mixture of diamine from step 1 (3.20 g, 26 mmol), TEA (5.25 g, 52 mmol) and a catalytic amount of DMAP in THF (100 mL) was stirred at 5-10°C, then treated with pivaloyl chloride (3.74 g, 31 mmol). The resulting mixture was stirred at RT for 5 hours, diluted with a 5% solution of citric acid, and extracted with EtOAc. The combined organic extracts were sequentially washed with water and brine, dried, filtered, and the filtrate was concentrated *in vacuo* to yield a residue. The residue was purified by column chromatography on silica gel to afford 7.4 g of the desired compound. MS (ESI) m/e ($M+H^+$): 292. ^{1}H NMR ($CDCl_3$): δ 8.77 (s, 1 H), 8.47 (s, 1 H), 8.20 (s, 1 H), 7.15 (s, 1 H), 2.24 (s, 3 H), 1.30~1.32 (m, 18 H).

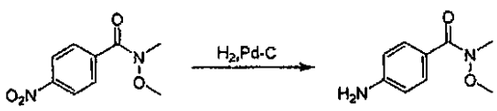
Step 3



To a cooled solution of 4-nitrobenzoic acid (12 g, 72 mmol) in 50 mL of PhMe was added 20 mL of $SOCl_2$ drop wise. After the addition, the suspension was heated to reflux for 4 hours. The solvent was removed, and the residue was azeotroped with 50 mL of PhMe to afford 14.5 g of crude acid chloride. To a solution of TEA (101 g, 100 mmol), a catalytic amount of DMAP and *N,O*-dimethylhydroxylamine (5.3 g, 87 mmol) in 100 mL of DCM was

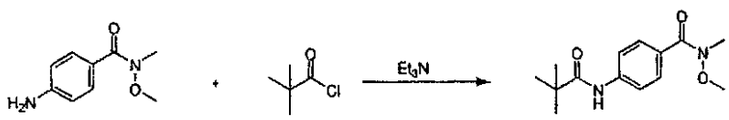
added drop wise 14.5 g of the freshly prepared acid chloride in 100 mL of DCM. The resulting mixture was stirred at RT for 5 hours, then diluted with a 5 % solution of citric acid, and extracted with DCM. The combined organic extracts were sequentially washed with water and brine, dried and filtered, and the filtrate was concentrated to yield a residue. The residue was purified by column chromatography on silica gel to afford 7.0 g of the Weinreb amide. MS (ESI) m/e ($M+H^+$): 211. ^1H NMR ($CDCl_3$): δ 8.25 (d, J=8.8 Hz, 2 H), 7.82 (d, J=9.6 Hz, 2 H), 3.52 (s, 3 H), 3.82 (s, 3 H).

Step 4



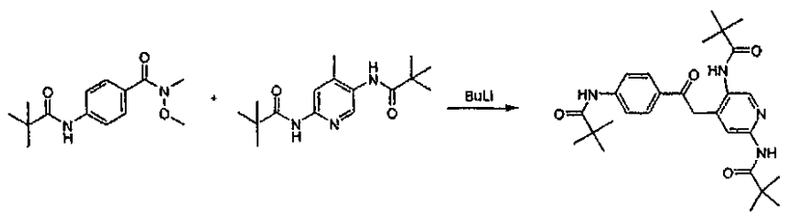
A heterogeneous mixture of the nitro compound above and 10% Pd/C in THF was stirred at STP with a balloon of H_2 for 3 hours. The mixture was filtered through CELITE, and concentrated to yield a yellow solid MS (ESI) m/e ($M+H^+$): 181.

Step 5



The product from step 4 was pivaloylated using conditions described in step 2. MS (ESI) m/e ($M+H^+$): 265. ^1H NMR ($CDCl_3$): δ 7.66 (d, J=8.4 Hz, 2 H), 7.56 (d, J=8.8 Hz, 2 H), 3.51 (s, 3 H), 3.32 (s, 3 H).

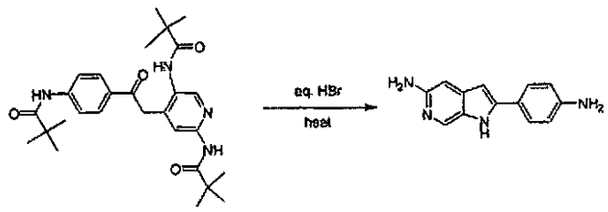
Step 6



A solution of compound isolated from step 2 above (2.2 g, 7.5 mmol) in 15 mL of THF was cooled to below -40°C. *t*-BuLi in hexane (15 mL, 2.5 M, 37.5 mmol) was added dropwise, and the resulting solution was stirred at -40°C for 1 hour. A solution of compound from step 5 (2.2 g, 8.25 mmol) in 10 mL of THF was added drop wise, and the resulting solution was continued to stir at this temperature for 30 minutes before being warmed to RT and stirred for 30 minutes again. An aqueous 5 % citric acid solution was added to quench the reaction, which was extracted with DCM (×3), and the combined organic layers were washed with water

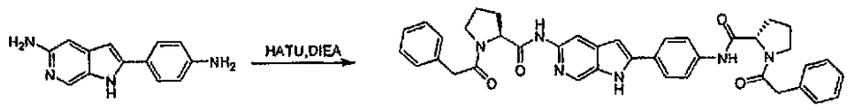
and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by preparative HPLC to yield a solid (0.4 g). MS (ESI) m/e ($M+H^+$): 495. ^1H NMR ($CDCl_3$): δ 8.85 (s, 1 H), 8.68 (s, 1 H), 8.26 (s, 1 H), 8.03~8.05 (m, 3 H), 7.21 (d, *J*=8.8 Hz, 2 H), 7.53 (s, 1 H), 4.20 (s, 2 H), 1.33~1.29 (m, 27 H).

Step 7



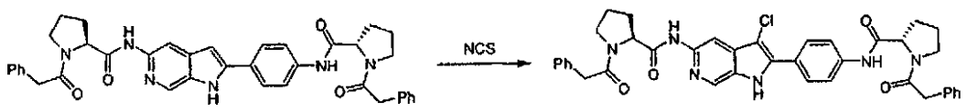
A solution of the product from step 6 (400 mg, 0.8 mmol) in 33% aqueous HBr (15 mL) was refluxed overnight. After cooling, the mixture was concentrated *in vacuo*. The residue was purified by preparative HPLC to give a solid (120 mg). MS (ESI) m/e ($M+H^+$): 225. ^1H NMR (MeOD): δ 8.04 (s, 1 H), 7.78 (d, 2 H), 7.04 (d, 2 H), 6.86 (s, 1 H), 6.71 (s, 1 H).

Step 8



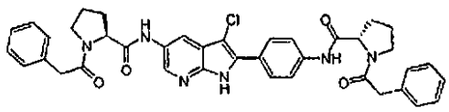
The product from step 7 was coupled to 2 equivalents of *N*-phenylacetyl-L-proline using 2 equivalents of HATU and DIEA in a manner similar to that shown in Example 1. MS (ESI) m/e ($M+H^+$): 687. ^1H NMR (MeOD): δ 8.49~8.57 (m, 1 H), 7.38~7.45 (m, 2 H), 7.72~7.80 (m, 2 H), 5.15~5.20 (m, 4 H), 4.42~4.50 (m, 2 H), 3.57~2.59 (m, 4 H), 2.31~2.42 (m, 4 H), 1.89~2.15 (m, 6 H).

Step 9

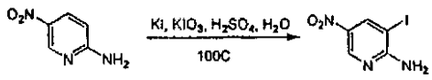


To a solution of product from step 8 (15 mg, 0.02 mmol) in 2 mL of dry THF was added NCS (2 mg, 0.015 mmol). The resulting mixture was stirred at RT for 30 minutes. The solvent was evaporated, and the residue was purified by prep HPLC to give 5 mg of the desired product. MS (ESI) m/e ($M+H^+$): 689. ^1H NMR (MeOD): δ 8.53 (s, 1 H), 7.91 (d, *J*=9.2 Hz, 2 H), 7.77 (d, *J*=8.8 Hz, 2 H), 7.49 (s, 1 H), 7.20~7.23 (m, 10 H), 4.53~4.59 (m, 2 H), 3.64~3.79 (m, 8 H), 1.98~2.25 (m, 8 H).

Example 6 – (2S)-N-{3-chloro-2-[4-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-1-(phenylacetyl)pyrrolidine-2-carboxamide

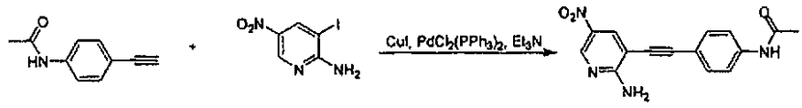


Step 1



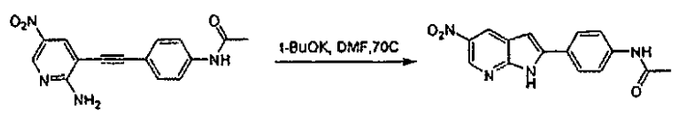
2-Amino-5-nitropyridine (7.00 g, 50.0 mmol) was dissolved in H_2SO_4 (2 M, 100 mL). Potassium iodate (4.28 g, 20 mmol) was added portion at RT with stirring. The solution was heated to 100°C under reflux. Potassium iodide (8.00 g, 48.2 mmol) was added drop wise over 1 hour as a solution in water (20 mL). A brown solution resulted, with solid iodine collecting in the reflux condenser. Heating at reflux was continued for 30 minutes, and the mixture was cooled to RT. The mixture was adjusted to pH 7 with the careful addition of solid $NaHCO_3$. The mixture was diluted with water (200 mL) and CH_2Cl_2 (250 mL) was added. Solid sodium thiosulfate was added with vigorous stirring until the iodine coloration had been disappeared. A significant amount of yellowish solid remained out of solution, which was collected by filtration, washed with water and dried to give a yellow solid (10.5 g). The CH_2Cl_2 fraction was filtered through a silicone-treated filter paper and evaporated to give a yellow solid (2.4 g). The solids were combined to give the desired iodopyridine (12.7 g). MS (ESI) m/e ($M+H^+$): 266. ^1H NMR (DMSO): δ 8.89 (s, 1 H), 8.62 (s, 1 H), 7.75 (bs, 1 H).

Step 2



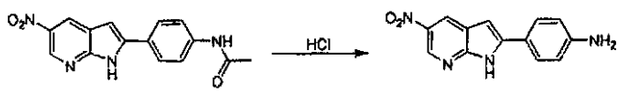
A solution of the iodide (1.05 g, 4.8 mmol), 4-ethynylacetanilide (636 mg, 4.0 mmol) and $Pd(PPh_3)_2Cl_2$ (76 mg, 0.4 mmol) in 10 mL of Et_3N and 5 mL of DMF was stirred at RT over 17 hours under N_2. The solvent was removed, and the residue was purified by column chromatography to give the product (0.9 g). MS (ESI) m/e ($M+H^+$): 297. ^1H NMR (DMSO): δ 10.11 (s, 1H), 8.80 (s, 1H), 8.22 (s, 1H), 7.59 (s, 1H), 2.01 (s, 3H).

Step 3



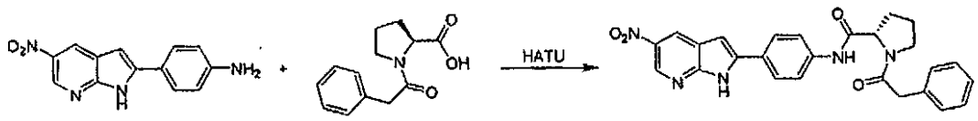
To a solution of the product from step 2 (730 mg, 2.5 mmol) in 3 mL of THF and 6 mL of DMF was added *t*-BuOK (580 mg, 5.25 mmol). The resulting mixture was heated to 70°C for 6 hours. The solvent was removed and 10 mL of DCM, 5 mL of water was added, and the resulting precipitate was filtered to give the desired product as a yellow solid (680 mg). MS (ESI) m/e ($M+H^+$): 297. ^{1}H NMR (DMSO): δ 10.11 (s, 1 H), 8.96 (s, 1 H), 8.65 (s, 1 H), 7.88 (d, *J*=8.8 Hz, 2 H), 7.63 (d, *J*=8.8 Hz, 2 H), 6.98 (s, 1 H), 2.02 (s, 3 H).

Step 4



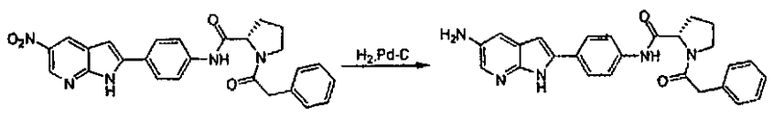
The synthetic method for the removal of the acetyl group was the same as used in Example 1, step 6. MS (ESI) m/e ($M+H^+$): 285.

Step 5



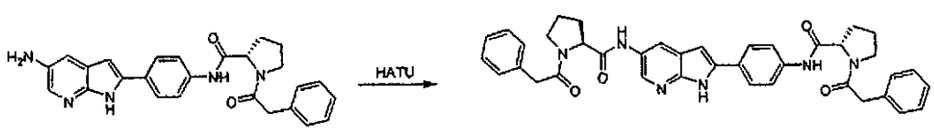
The synthetic method used for the coupling of the proline analog to the aniline prepared in step 4 was the same as used in Example 1, step 7. MS (ESI) m/e ($M+H^+$): 470.

Step 6



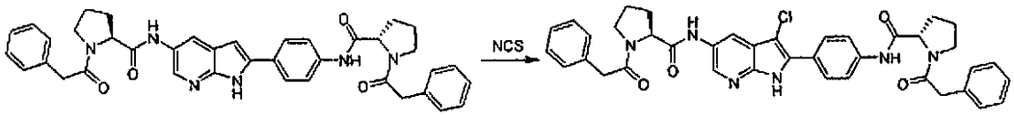
A heterogeneous mixture of product from step 6 (20 mg, 0.04 mmol) and 10% Pd/C in 5 mL of MeOH was stirred in 10 psi of H_2 for 3 hours. The mixture was filtered through CELITE, and concentrated *in vacuo* to yield a yellow solid (17 g). MS (ESI) m/e ($M+H^+$): 440.

Step 7



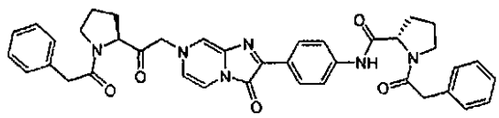
The product from step 6 was coupled to 1 equivalent of *N*-phenylacetyl-L-proline using 1 equivalent of HATU and DIEA in a manner similar to that shown in Example 1. MS (ESI) m/e ($M+H^+$): 655. ^{1}H NMR (MeOD): δ 8.26 (s, 1 H), 8.19 (s, 1 H), 7.30~7.51 (m, 3 H), 7.18~7.27 (m, 1 H), 6.65 (s, 1 H), 4.51~4.56 (m, 2 H), 3.61~3.76 (m, 8 H), 1.95~2.15 (m, 8 H).

Step 8

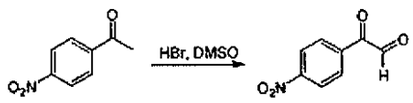


To a solution of product from step 7 (30 mg, 0.04 mmol) in 4 mL of dry THF was added NCS (4 mg, 0.03 mmol). The resulting mixture was stirred at RT for 30 minutes. The solvent was evaporated, and the residue was purified by prep HPLC to give the desired product. MS (ESI) m/e ($M+H^+$): 690. ^1H NMR (MeOD): δ 8.29 (s, 1 H), 8.20 (s, 1 H), 7.81~7.84 (m, 2 H), 7.66~7.69 (m, 2 H), 7.18~7.29 (m, 10 H), 4.52~4.55 (m, 2H), 3.62~3.78 (m, 8 H), 1.90~2.29 (m, 8 H).

Example 7 – N-[4-(3-oxo-7-{2-oxo-2-[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]ethyl}-3,7-dihydroimidazo[1,2-a]pyrazin-2-yl)phenyl]-1-(phenylacetyl)-L-prolinamide

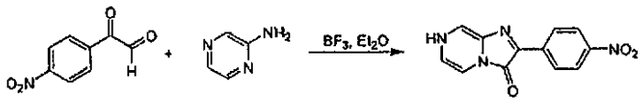


Step 1



To a stirred solution of 4-nitroacetophenone (20 g, 121 mmol) in 100 ml of DMSO was added slowly 42 ml of 48% aqueous HBr (363 mmol). The solution was stirred in an open flask at 55°C and the reaction was followed by TLC. When the starting material was consumed, the solution was poured into ice. The solid products were filtered, washed with water, and dried under vacuum at RT over P_2O_5.

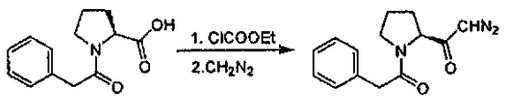
Step 2



Arylglyoxal hydrate (5g, 27.8mmol) was added in one portion over a slurry of the heterocyclic amine (2.773 g, 29.2 mmol) in methylene chloride (10 ml). The resulting suspension was treated with 1 drop of freshly distilled $BF_3{\cdot}Et_2O$ and stirred until most of the amine was consumed. The reaction products were isolated as hydrates by filtration of the thick, intensely colored reaction mixture. The residue obtained by concentration is allowed to cool,

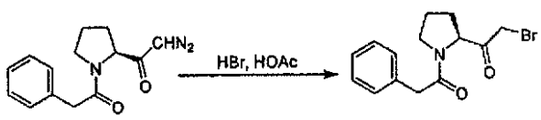
filtered with suction, washed twice with diethyl ether and dried under reduced pressure to give the desired product (4 g). MS (ESI) m/e ($M+H^+$): 256.

Step 3



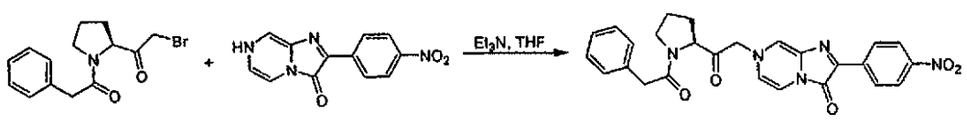
The *N*-protected proline (10 g, 42.8 mmol) in dry ether (60ml) and THF (60ml) was stirred under argon at -25°C. TEA (42.8 mol, 4.08 ml) and ethyl chloroformate (42.8 mmol, 2.6 4.14 ml) were added to this solution. The solution was stirred for further 30 minutes, the temperature then allowed to reach -10°C, and the diazomethane solution in ether (2-3 equivalents) was added drop wise. The suspension was stirred for an additional 3 hours and allowed to reach ambient temperature. The triethylamine hydrochloride was then filtered off, and the filtrate was evaporated to half of its original volume. The resulting solution was washed with saturated aqueous $NaHCO_3$ (50 ml) and brine (50 ml). The organic layer was dried and evaporated to give a crude product, which was used without further purification. MS (ESI) m/e ($M+H^+$): 258.

Step 4



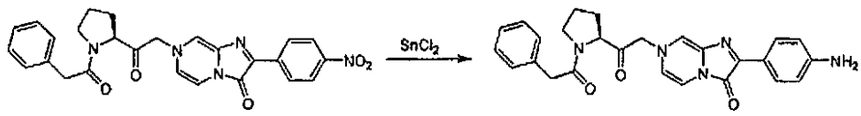
To a solution of a-diazoketone (2 g, 7.78 mmol) in glacial HOAc (25ml) was treated with 48% HBr (2.8 ml) drop wise with stirring. After stirring for 1 hour, the reaction mixture was extracted with DCM and washed with water. Evaporation of the solvent and crystallization from ether-pet ether gave the pure product. MS (ESI) m/e ($M+H^+$): 310.

Step 5



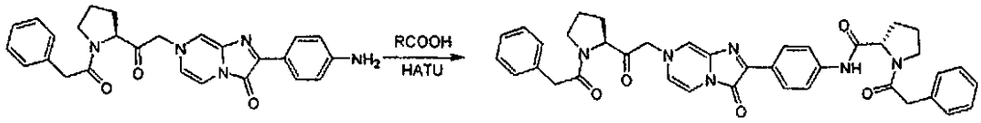
The product from step 4 (420 mg, 1.35 mmol) and the heterocycle from step 2 (347 mg, 1.35 mmol) in THF (2ml) were stirred at RT overnight with Et_3N (0.3 mL). When the reaction was completed, the mixture was concentrated, and the residue was purified by RPLC to give the product (300 mg). MS (ESI) m/e ($M+H^+$): 486.

Step 6



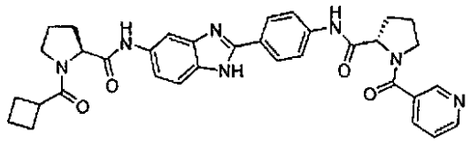
A solution of the product from step 5 (180 mg, 0.371 mmol) in absolute EtOH (3 ml) was added to stannous chloride dihydrate (418.6 mg, 1.85 mmol), and the mixture was stirred at 70°C for 2 hours. The reaction mixture was cooled to RT and poured into ice/water (50 ml), and the pH was made strongly alkaline by the addition of saturated NaOH (100 ml) before being extracted with EtOAc (2x). The organic phase was combined and washed with brine, dried by $MgSO_4$, filtered, and concentrated to yield the crude product (150mg). MS (ESI) m/z : $(M+H^+)$ 456.

Step 7

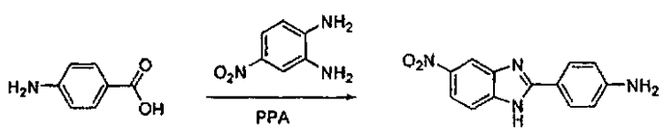


The mixture of the product from step 6 (30 mg, 0.066 mmol), *N*-phenylacetyl-L-proline (46.08 mg, 0.197 mmol), DIPEA (50.1 mg, 0.197 mmol) in CH_3CN (2 mL) was stirred at RT for 5 minutes, then HATU (74.86 mg, 0.197 mmol) was added into the mixture. The mixture was stirred at RT overnight, concentrated, and the residue was purified by RPLC to give the desired compound (20mg). ^1H NMR (DMSO) δ: 9.26 (s, 1H), 8.84-8.86 (m, 2H), 7.79-8.03 (m, 4H), 7.11-7.31(m, 12H), 4.41~4.63 (m, 2H), 3.52~3.80 (m, 12H), 2.26~2.12 (m, 2H), 1.87~1.75 (m, 6H).

Example 8 – (2S)-1-(cyclobutylcarbonyl)-N-{2-[4-({[(2S)-1-(pyridin-3-ylcarbonyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-benzimidazol-5-yl}pyrrolidine-2-carboxamide



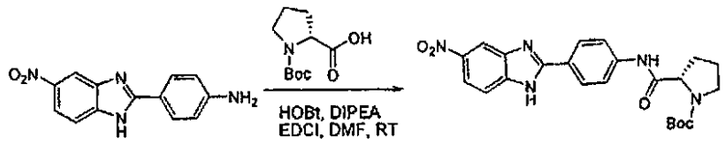
Step 1



p-Aminobenzoic acid (0.200 g, 1.45 mmol) and nitrophenylene diamine (0.221 g, 1.45 mmol) were added into PPA (30 mL). The mixture was stirred at 210°C for 20 minutes.

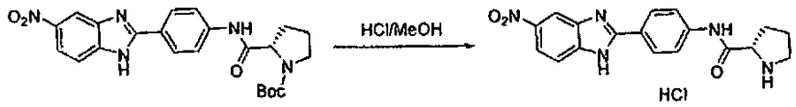
Then, it was poured into ice water and extracted with DCM. The organic layer was washed with brine, dried ($NaSO_4$), filtered and concentrated to afford 200 mg of the desired compound. MS m/z: 255 (M+1).

Step 2



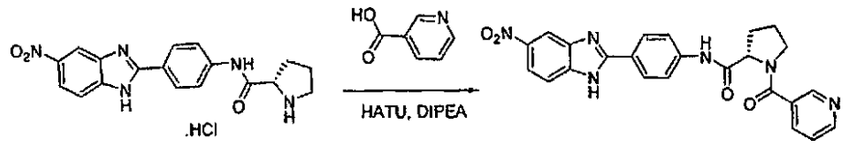
Compound from step 1 above (1.2 g, 4.7 mmol), *N*-Boc-proline (1.52 g, 7.07 mmol), EDCI (1.8 g, 9.44 mmol), HOBT (1.27 g, 9.44 mmol) and DIPEA (2.4 g, 18.8 mmol) were taken in DMF (30 mL) and stirred for overnight at RT. DMF was removed under reduced pressure, and the residue was extracted with DCM/water. The organic layer was washed with brine, dried ($NaSO_4$), concentrated and purified by column (DCM: MeOH/100:1) to afford 1.2 g of the desired compound. ^{1}H NMR (MeOD) δ 8.49 (s, 1H), 8.28-8.19 (m, 3H), 7.79-7.76 (d, J = 4.4Hz, 2H), 7.72-7.65 (m, 1H), 4.41-4.29 (t, J = 8.8Hz, 1H), 3.59-3.51 (m, 2H), 2.18-1.95 (m, 4H), 1.49 (s, 9H).

Step 3



Compound from step 2 (0.600 g, 1.06 mmol) was stirred in MeOH/HCl (10 mL) for 1 hour at RT, and solvent was removed under reduced pressure. The resulting compound was dried at high vacuum to afford 370 mg of desired compound.

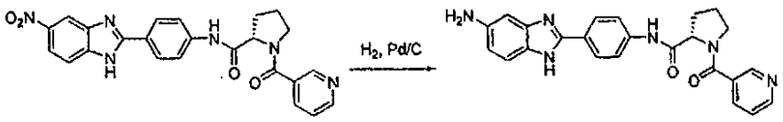
Step 4



The product from step 3 (0.370 g, 1.052 mmol), pyridine-3-carboxylic acid (0.157 g, 1.27 mmol), HATU (1.2 g, 3.18 mmol) and DIPEA (0.814 g, 6.36 mmol) were taken in DMF (10 mL) and stirred for overnight at RT. DMF was removed under reduced pressure, and the residue was extracted with DCM/water. The organic layer was washed with brine, dried ($NaSO_4$), concentrated and purified by column (DCM: MeOH/100:1) to afford 300 mg of desired compound. ^{1}H NMR (MeOD) δ ppm: 0.883 (s, 1H), 0.87-0.85 (d, J = 4.4Hz, 1H), 8.49 (s, 1H),

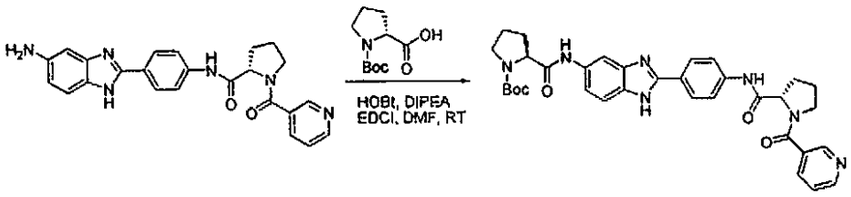
8.21-8.18 (m, 1H), 8.17-8.10 (m, 3H), 7.98-7.95 (d, J = 8.8Hz, 2H), 7.73-7.68 (m, 1H), 7.60-7.51 (m, 1H), 4.79-4.76 (t, J = 6Hz, 1H), 3.77-3.73 (m, 2H), 3.27-3.19 (m, 2H), 2.19-2.12 (m, 2H).

Step 5



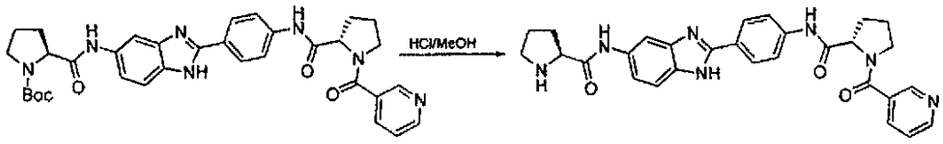
The product from step 4 (0.300 g, 0.657 mmol) was taken in MeOH (10 mL) and Pd/C (0.07 g) was added under N_2. The reaction was stirred for overnight at RT under H_2. The Pd/C was filtered through CELITE, and the filtrate was concentrated under reduced pressure to afford 234 mg of desired compound.

Step 6



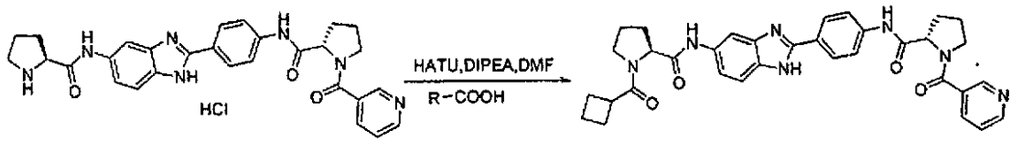
The product from step 5 (0.370 g, crude), *N*-Boc-proline (0.157 g, 1.27mmol), HATU (1.2 g, 3.18 mmol) and DIPEA (0.814 g, 6.36 mmol) were taken in DMF (10 mL) and stirred for overnight at RT. DMF was removed under reduced pressure, and the residue was extracted with DCM/water. The organic layer was washed with brine, dried ($NaSO_4$), concentrated and purified by column (DCM: MeOH/100:1) to afford 300 mg of targeted compound.

Step 7



The product from step 6 (0.600 g, 1.06 mmol) was stirred in MeOH/HCl (15 mL) for 1 hour at RT, and the solvent was removed under reduced pressure. The compound was dried at high vacuum to afford 370 mg of desired compound. ^{1}H NMR (MeOD) δ: 9.39 (s, 1H), 9.18-8.82 (m, 2H), 8.39-8.38 (m, 1H), 8.32-8.22 (m, 1H), 8.21-8.10 (m, 2H), 8.09-7.98 (m, 2H), 7.86-7.72 (m, 1H), 7.71-7.65 (m, 1H), 4.87-4.84 (t, J = 8.8Hz, 2H), 3.51-3.34 (m, 8H), 2.49-2.38 (m, 4H).

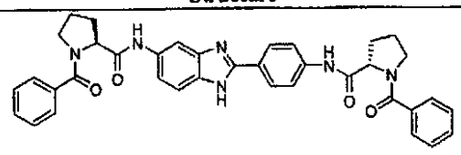
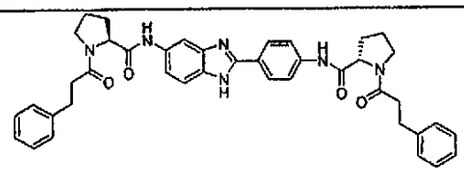
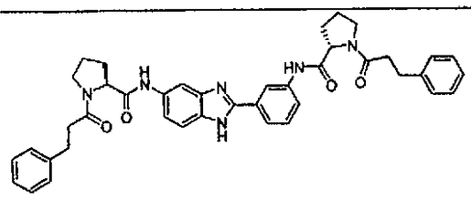
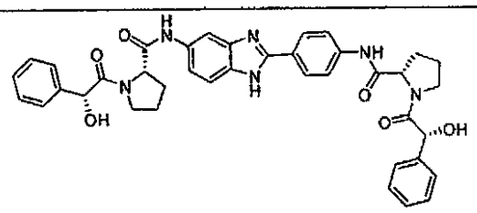
Step 8

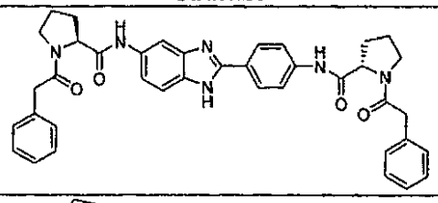
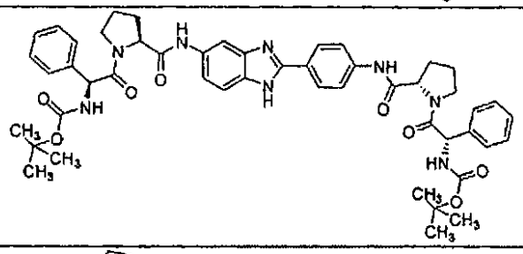
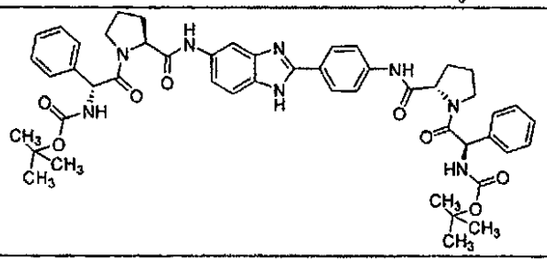


The product from step 7 (0.100 g, 0.191 mmol), cyclobutanecarboxylic acid (0.018 mg, 0.183 mmol), HATU (0.116 g, 0.305 mmol) and DIPEA (0.059 g, 0.416 mmol) were taken in DMF (5 mL) and stirred for overnight at RT. DMF was removed under reduced pressure, and the residue was extracted with DCM/water. The organic layer was washed with brine, dried ($NaSO_4$) and concentrated. The residue was purified by HPLC purification to afford 12 mg of the final product. ^{1}H NMR (MeOD) δ: 8.91 (s, 1H), 8.75 (s, 1H), 8.41 (s, 1H), 8.25 (s,1H), 7.96-7.95 (d, J = 5.2Hz, 4H), 7.73-7.67 (d, J = 3.2Hz, 2H), 7.52-7.51 (d, J = 3.2Hz, 1H), 4.54-4.82 (t, J = 3.6Hz, 2H), 3.63-3.46 (m, 4H), 2.48-2.46 (t, J = 2Hz, 1H), 2.34-2.29 (m, 6H), 2.18-2.10 (m, 4H), 2.08-2.02 (m, 4H).

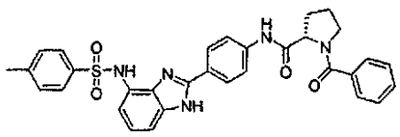
Examples 9-15

Compounds of Examples 9-15 were prepared in a similar manner to Example 8.

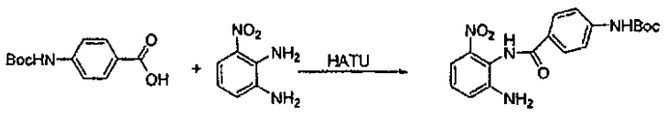
Example	Structure	MW	Name
9		626.721	(2*S*)-1-(phenylcarbonyl)-*N*-{4-[5-({[(2*S*)-1-(phenylcarbonyl)pyrrolidin-2-yl]carbonyl}amino)-1*H*-benzimidazol-2-yl]phenyl}pyrrolidine-2-carboxamide
10		682.83	(2*S*)-1-[(4*Z*,5*Z*)-4-ethylidenehept-5-enoyl]-*N*-{2-[4-({[(2*S*)-1-(3-phenylpropanoyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1*H*-benzimidazol-5-yl}pyrrolidine-2-carboxamide
11		682.83	(2*S*)-1-[(4*Z*,5*Z*)-4-ethylidenehept-5-enoyl]-*N*-{2-[3-({[(2*S*)-1-(3-phenylpropanoyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1*H*-benzimidazol-5-yl}pyrrolidine-2-carboxamide
12		686.774	(2*S*)-1-[(2*R*)-2-hydroxy-2-phenylacetyl]-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-hydroxy-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-benzimidazol-2-yl}phenyl)pyrrolidine-2-carboxamide

Example	Structure	MW	Name
13		654.776	(2*S*)-1-(phenylacetyl)-*N*-{4-[5-({[(2*S*)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl} amino)-1*H*-benzimidazol-2-yl]phenyl}pyrrolidine-2-carboxamide
14		885.041	*tert*-butyl {(1*S*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1*H*-benzimidazol-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
15		885.041	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1*H*-benzimidazol-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

Example 16 – Benzyl (2S)-2-{[4-(4-{[(4-methylphenyl)sulfonyl]amino}-1H-benzimidazol-2-yl)phenyl]carbamoyl}pyrrolidine-1-carboxylate

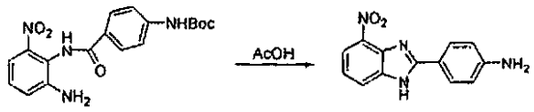


Step 1



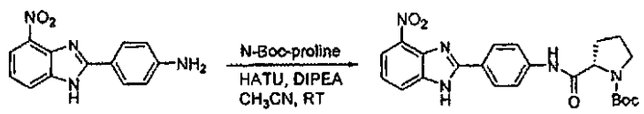
To a solution of *N*-Boc-p-aminobenzoic acid (1.86 g, 7.84 mmol) in DMF, 3-nitrophenylenediamine (1.0 g, 6.536 mmol), HOBt (0.875 g, 6.536 mmol) and EDCI (2.5 g, 9.804 mmol) were added, and reaction was stirred for overnight at RT. The excess of solvent was removed under reduced pressure, and the residue was diluted with DCM. The organic layer was washed with brine, dried ($NaSO_4$), filtered, concentrated and purified by column to obtain 400 mg of compound. MS m/z: 273 (M+1).

Step 2



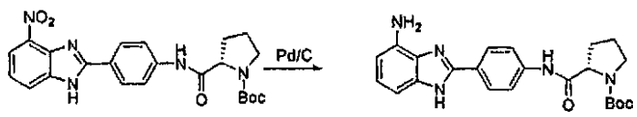
The compound from step 1 above (0.600 g, 1.611 mmol) and KOAc (0.158 g, 1.609 mmol) were taken in HOAc (9.3 mL). The reaction was stirred at 120°C for overnight, cooled to RT and poured into ice-water. The aqueous layer was extracted with DCM. The organic layer was washed with brine, dried ($NaSO_4$), filtered and concentrated to obtain 120 mg of the desired compound. MS m/z: 255 (M+1). ^{1}H NMR (DMSO) δ: 11.44 (s, 1H), 8.95-9.01 (m, 2H), 8.81-8.83 (d, J = 8.0Hz, 2H), 8.22-8.27 (m, 1H), 8.22-8.27 (m, 2H), 4.97 (s, 2H).

Step 3



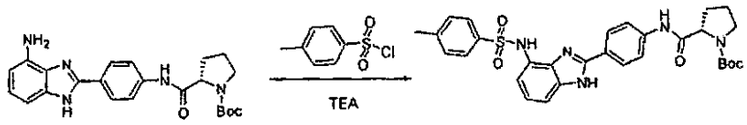
To a solution of the aniline (0.200 g, 0.787 mmol) in DMF, *N*-Boc-proline (0.186 g, 0.865 mmol), DIPEA (0.302 g, 2.361 mmol) and HATU (0.329 g, 0.865 mmol) were added. The reaction was stirred for overnight. The excess of solvent was removed under reduced pressure, and the residue was diluted with DCM. The organic layer was washed with brine, dried ($NaSO_4$), filtered, concentrated and purified by column to obtain 150 mg of the desired. MS m/z: 452 (M+1). ^{1}H NMR (MeOD) δ: 8.70-8.73 (m, 2H), 8.40-8.42 (d, J = 8Hz, 2H), 7.87-7.89 (d, J = 8Hz, 1H), 7.50-7.53 (m, 2H), 6.78-6.80 (d, J = 8Hz, 1H), 3.83 (s, 1H), 3.69-3.76 (m, 2H), 3.56-3.60 (m, 4H), 1.37-1.43 (m, 9H).

Step 4



To a solution of compound from step 3 above (0.200 g, 0.443 mmol), Pd/C (10 mg) was added under argon, and the reaction was stirred for 2 hours in H_2. The Pd/C was filtered and washed with MeOH for several times. The solvent was evaporated to obtain 180 mg of desired compound. MS m/z: 422 (M+1). ^{1}H NMR (MeOD) δ: 9.51 (s, 1H), 7.95-8.20 (m, 1H), 7.58-7.60 (m, 1H), 7.19-7.48 (m, 2H), 6.78-6.87 (m, 2H), 6.38 (s, 1H), 4.25-4.42 (m, 1H), 3.34-3.67 (m, 2H), 1.79-2.20 (m, 4H), 1.17-1.41 (m, 9H).

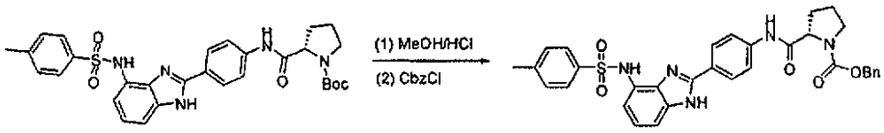
Step 5



To a solution of the compound from step 4 above (0.196 g, 0.465 mmol) in THF,

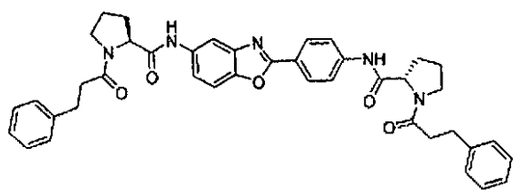
TEA (0.070 g, 0.693 mmol) and 4-methylbenzene-1-sulfonyl chloride (0.088 g, 0.461 mmol) were added drop wise at 0°C. The reaction was stirred for overnight, and the solvent was removed under reduced pressure. The residue was diluted with DCM and washed with brine. The organic layer was dried ($NaSO_4$), filtered and concentrated. The residue was purified by preparative TLC to afford 110 mg of desired compound. MS m/z: 576 (M+1). ^{1}H NMR (MeOD) δ: 7.98-8.00 (d, *J*= 8.0Hz, 2H), 7.78-7.80 (d, *J*= 8.0Hz, 2H), 7.66-7.68 (d, *J*= 8.0Hz, 2H), 7.26-7.28 (m, 11H), 7.19-7.21 (d, *J*= 8.0Hz, 2H), 7.07-7.09 (m, 2H), 4.36-4.38 (m, 1H), 3.55-3.58 (m, 2H), 2.32-2.35 (m, 4H), 1.89-2.11 (m, 3H), 1.50 (s, 9H).

Step 6

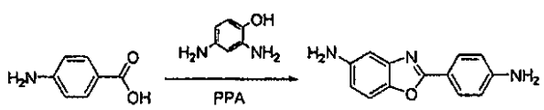


The product from step 5 above (0.180 g, 0.312 mmol) was stirred in MeOH/HCl (5.0 mL) for 1 hour at RT. The solvent was removed under reduced pressure and dried at high vacuum. It was used directly without any further purification. The residue was taken in DMF, benzoic acid (0.042 g, 0.344 mmol), DIPEA (0.320 g, 2.504 mmol) and HATU (0.143 g, 0.375 mmol) were added. The reaction was stirred for overnight at RT. The excess of solvent was removed under reduced pressure, and the residue was diluted with DCM. The organic layer was washed with brine, dried ($NaSO_4$), filtered, concentrated and purified by column to afford 40 mg of the final compound. MS m/z: 580 (M+1). ^{1}H NMR (MeOD) δ: 7.92-7.94 (d, *J*= 8.8Hz, 2H), 7.23-7.68 (m, 14H), 6.81-6.83 (d, *J*= 10Hz, 1H), 5.21 (s, 2H), 4.65-4.79 (m, 1H), 3.52-3.89 (m, 2H), 2.47-2.58 (m, 1H), 2.43 (s, 3H), 1.93-2.23 (m, 3H).

Example 17 – (2S)-1-(3-phenylpropanoyl)-N-{4-[5-({[(2S)-1-(3-phenylpropanoyl)pyrrolidin-2-yl]carbonyl}amino)-1,3-benzoxazol-2-yl]phenyl}pyrrolidine-2-carboxamide

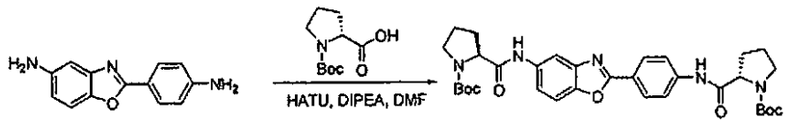


Step 1



p-Aminobenzoic acid (1.37 g, 10 mmol) and 2,4-diaminophenol (1.24 g, 10 mmol) were combined under argon and treated with 12 mL of PPA. The resulting solution was heated at 200°C for 30 minutes. The black solution was poured onto ice, and the resulting yellow solid was collected (1.12 g). ^{1}H-NMR (DMSO) δ: 10.2-10.5 (s, 2H), 8.10-8.20 (m, 4H), 7.10-7.80 (m, 3H). MS m/z: 226 (M+1).

Step 2



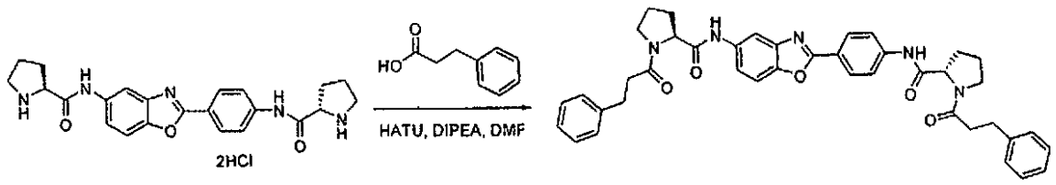
The product from step 1 above (0.100 g, 0.236 mmol), *N*-Boc-proline (0.098 g, 0.355 mmol), HATU (0.135 g, 0.355 mmol), TEA (0.100 g, 0.944 mmol) were taken in DCM (10 mL) and stirred overnight at RT. The reaction was diluted with DCM, and the organic layer was washed with water, brine, dried ($NaSO_4$), concentrated and purified by preparative TLC to afford 100 mg of desired compound. MS m/z: 620 (M+1).

Step 3



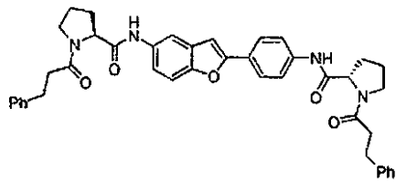
The product from step 2 above (0.100 g, 0.161 mmol) was stirred in MeOH/HCl (3.0 mL) for 1 hour at RT, and the solvent was removed under reduced pressure. The compound was dried at high vacuum to afford 80 mg of the desired compound. MS m/z: 420 (M+1).

Step 4

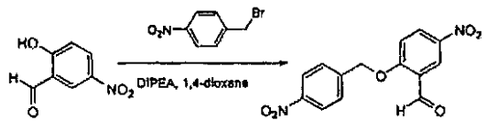


Compound from step 3 (0.080 g, 0.191 mmol), 3-phenylpropanoic acid (0.086 g, 0.574 mmol), HATU (0.218 g, 0.574 mmol), DIPEA (0.146 g, 1.146 mmol) were taken in DMF (3 mL) and stirred for overnight at RT. DMF was removed under reduced pressure, and the residue was extracted with DCM/water. The organic layer was washed with brine, dried ($NaSO_4$) and concentrated. The residue was purified by HPLC purification to afford 108 mg of target. ^{1}H NMR (DMSO) δ: 10.2-10.5 (s, 2H), 8.10-8.20 (m, 3H), 7.10-7.80 (m, 14H), 4.37-4.55 (m, 2H), 3.32-3.58 (m, 4H), 2.67-2.85 (m, 7H), 1.80-2.4 (m, 9H).

Example 18 – (2S)-1-(3-phenylpropanoyl)-N-{4-[5-({[(2S)-1-(3-phenylpropanoyl)pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl}pyrrolidine-2-carboxamide

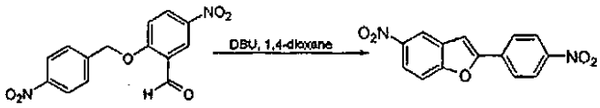


Step 1



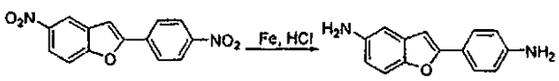
To a solution of 5-nitrosalicylaldehyde (1.0 g, 5.90 mmol) in 1,4-dioxane (10 mL), p-nitrobenzyl bromide (1.33 g, 6.15 mmol) and DIPEA (1.25 g, 9.70 mmol) were added, and the reaction was refluxed at 100°C for 2 hours. The reaction was cooled, and the solids were filtered, washed with EtOH and dried with high vacuum to afford the desired compound. MS m/z: 303 (M+1).

Step 2



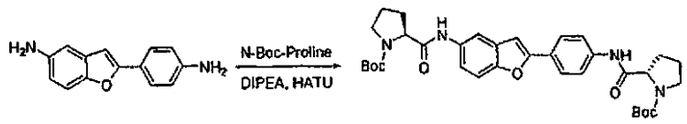
To a solution of the target compound from step 1 (1.5 g, 4.96 mmol) in 1, 4-dioxane (5 mL), DBU (0.9 g, 6.45 mmol) was added. The reaction was heated to 100°C for 3 hours, then cooled to RT, and the resulting solid was filtered off and sufficiently washed with EtOH to afford 927 mg of the desired compound. ^{1}H NMR (MeOD) δ: 8.66 (s, 1H), 8.37-8.39 (d, *J*= 8.0Hz, 2H), 8.30-8.32 (d, *J*= 8.0Hz, 1H), 8.18-8.21 (d, *J*= 12Hz, 2H), 7.78-7.80 (d, *J*= 8.0Hz, 1H), 7.70 (s, 1H).

Step 3



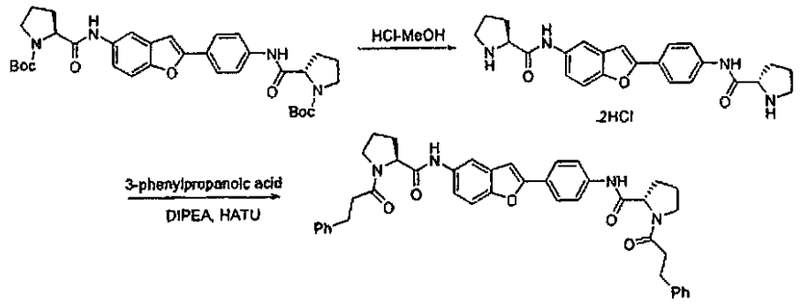
To a solution of the product from step 2 above (0.050 g, 0.176 mmol) in 1,4-dioxane (1.8 mL), water (1.8 mL), Fe (0.054 g) and HCl (1.1 μL) were added. The reaction was heated to 110°C for 3 hours. Then, the solid was filtered, and the organic layer was concentrated to afford 40 mg of the desired compound. ^{1}H NMR (MeOD) δ: 8.01-8.05 (m, 2H), 7.90-7.96 (m, 1H), 7.79 (s, 1H), 7.46-7.51 (m, 1H), 7.34 (s, 1H), 7.17-7.21 (m, 2H). MS m/z: 225 (M+1).

Step 4



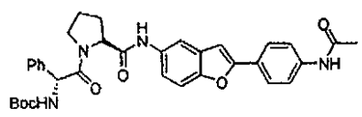
To a solution of the product from step 3 above (0.020 g, 0.089 mmol) in DCM (10 mL) *N*-Boc-proline (0.042 g, 0.196 mmol) and DIPEA (0.035 g, 0.267 mmol) were added. The reaction was stirred at RT for 5 minutes and then HATU (0.101 g, 0.267 mmol) was added. The reaction was stirred overnight and poured into brine and extracted with EtOAc. The organic layer was dried (Na_2SO_4), filtered and concentrated to afford 30 mg of the desired compound. MS m/z: 619 (M+1).

Step 5

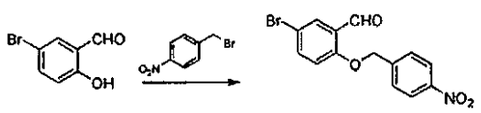


The product from step 4 (0.70 g, 1.13 mmol) was stirred in MeOH/HCl (20 mL) for 1 hour. The solvent was removed at high vacuum to afford the desired proline compound, which was used directly to the next step without further purification. 3-Phenylpropanoic acid (0.428 g, 2.85 mmol) were taken in DCM (30 mL) was reacted with the proline compound (0.500 g, 0.96 mmol) and DIPEA (0.9 g, 7.1 mmol). The reaction was stirred at RT for 5 minutes, and then HATU (1.0 g, 2.85 mmol) was added. The reaction was stirred overnight and poured into brine and extracted with EtOAc. The organic layer was dried (Na_2SO_4), concentrated and purified by HPLC to afford 30 mg of the desired compound. ^{1}H NMR ($CDCl_3$) δ: 9.85-9.87 (d, *J*= 8.0Hz, 2H), 7.86 (s, 1H), 7.42-7.44 (d, *J*= 8.8Hz, 2H), 7.46-7.48 (d, *J*= 8.8Hz, 2H), 7.03-7.31 (m, 9H), 6.90-6.99 (d, *J*= 3.6Hz, 1H), 6.58 (s, 1H), 4.71-4.82 (m, 2H), 3.62-3.71 (m, 2H), 3.43-3.50 (m, 2H), 2.95-3.05 (m, 4H), 2.63-2.88 (m, 4H), 2.21-2.43 (m, 4H), 1.87-2.14 (m, 4H). MS m/z: 683 (M+1).

Example 19 – N-{2-[4-(acetylamino)phenyl]-1-benzofuran-5-yl}-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}-L-prolinamide

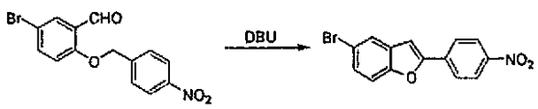


Step 1



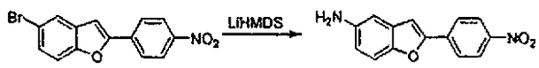
K_2CO_3 (68 g, 0.497 mol) was added to a solution of bromosalicylaldehyde (50 g, 0.248 mol) in DMF (300 ml). The resulting solution was stirred at RT for 1 hour, then to it was added compound 4-nitrobenzyl bromide (54 g, 0.25 mol). The reaction mixture was stirred for 30 minutes, filtered, and the filtrate was poured into water and extracted with EtOAc (3x). The combined organic layers were dried and concentrated. The product was recrystallized from dioxane to afford a white solid (50 g). ^{1}H NMR ($CDCl_3$) δ: 10.43 (s,1H), 8.24 (d, J = 4H), 7.51-7.58 (m, 2H), 7.37-7.42 (m, 4H), 7.31-7.36 (m, 6H), 5.52 (s, 1H), 4.57 (s, 2H), 3.90 (s, 2H), 3.34 (s, 2H), 2.06-2.15 (m, 6H), 1.86-1.88 (m, 1H), 1.41 (d, 18H).

Step 2



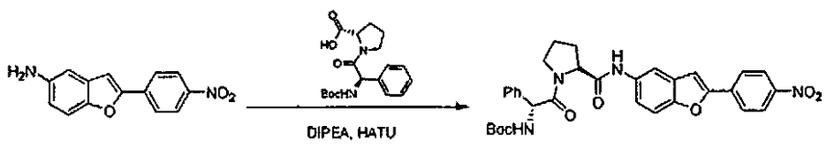
DBU (9 ml, 61.58 mmol) was added to a solution of the product from step 1 (10 g, 29.85 mmol) in dioxane (70 ml). The resulting solution was heated to reflux for 1 hour, cooled and filtered. The filter cake was washed with EtOAc and dried in air to afford a yellow solid (6.5 g).

Step 3



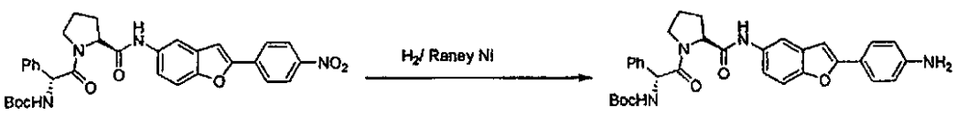
P^tBu_3 (1.93 ml, 0.32 mmol) was added to a solution of the product from step 2 (2 g, 6.3 mmol) and $Pd_2(dba)_3$ (0.29 g, 0.32 mmol) in THF (100 ml) under N_2. Then a solution of LiHMDS (18.9 ml, 18.9 mmol) was added dropwise. The resulting solution was heated to reflux for 3 hours and then cooled to RT. The reaction mixture was adjusted to pH = 1 using 1M HCl, then stirred for 0.5 hour. The reaction mixture was basified to pH = 8~9 using *aq.* saturated $NaHCO_3$, and extracted with EtOAc (3x). The combined organic layers were dried and concentrated. The residue was recrystallized from MeOH to afford the product as brown solid.

Step 4



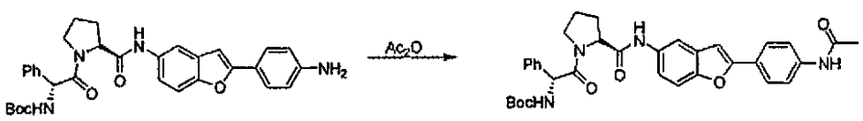
The mixture of the product from step 3 (500 mg, 2 mmol), R-Boc-Phg-L-Pro-OH (660 mg, 2.16 mmol), NMM (400 mg, 4 mmol) and DMF (30 ml) was stirred at RT for 30 minutes, then to it was added HATU (1.13 g, 3 mmol). The resulting mixture was stirred at RT overnight. The reaction mixture was diluted with water and filtered. The cake was washed with water and dried; the solid was used next step without purification.

Step 5



The product from step 4 (0.4 g, 1.3 mmol) in THF (10 ml) was hydrogenated using Raney Ni (0.2 mg) as the catalyst. After being stirred under H_2 atmosphere at RT overnight, the reaction slurry was filtered through CELITE, and the filtrate was concentrated under reduced pressure to afford 0.33 g of the desired compound.

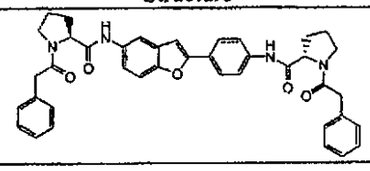
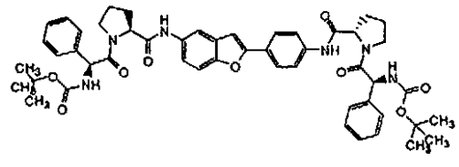
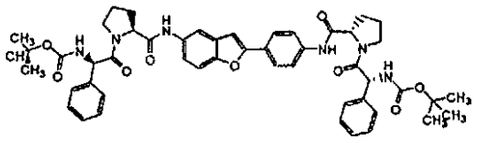
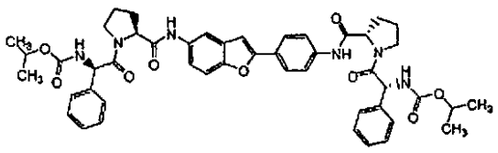
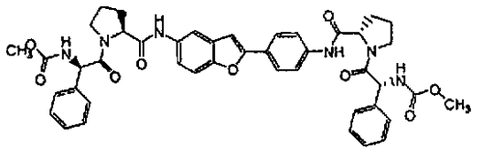
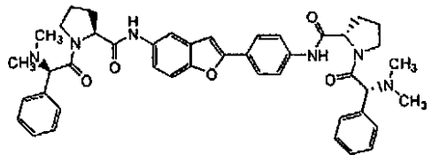
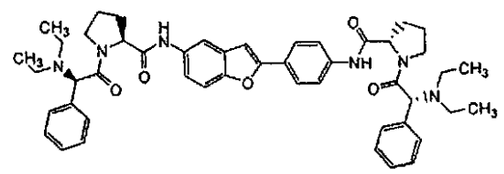
Step 6

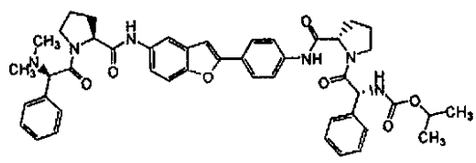
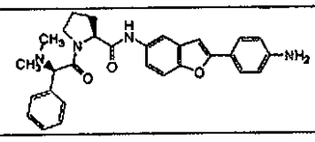
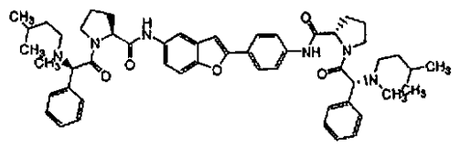
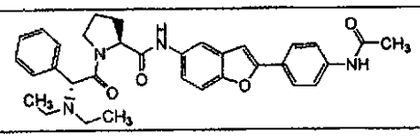
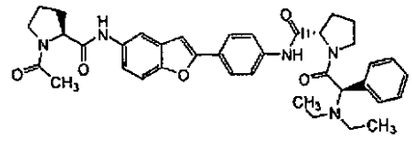
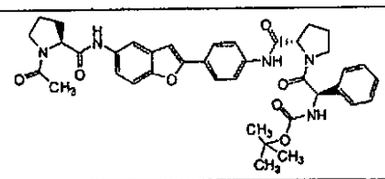
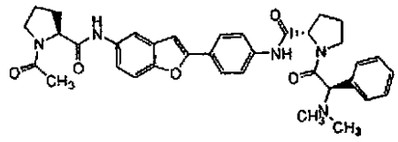
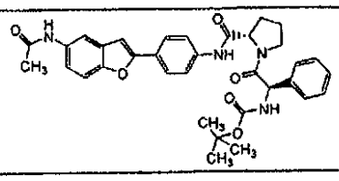


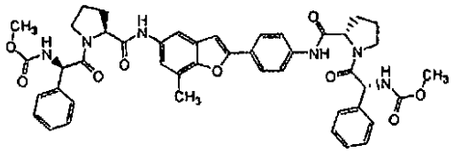
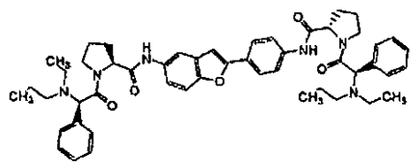
Ac_2O (18 mg, 0.18 mmol) was added to a solution of the aniline from step 5 (50 mg, 0.09 mmol) in THF (2 ml) at RT. The resulting solution was stirred at RT overnight, concentrated, and the residue was purified by RPLC to afford the desired product. ^{1}H NMR (acetone-*d6*) δ: 7.95 (s, 1 H,NH), 7.65-7.74 (m, 7 H, ArH), 7.40 –7.43 (m, 3 H, ArH), 7.30 –7.34 (m, 2 H, ArH), 7.01 (s, 1 H, ArH), 5.64 (s, 1 H, CH), 4.56-4.59 (m, 1 H, CH), 3.93-.3.99 (m, 1 H, CH_2), 3.27-3.42 (m, 2 H, CH_2), 3.02-3.17 (m, 3 H, CH_2), 1.98 (s, 3H, CH_3), 1.98- 1.95 (m, 4 H, CH_2), 1.22 (t, J = 7.2 Hz, 6 H, CH_3).

Examples 20-36

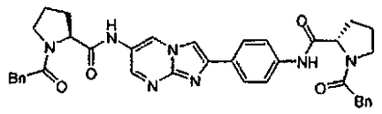
Compounds of Examples 20-36 were prepared in a similar manner as described in either Example 18 or Example 19.

Example	Structure	MW	Name
20		654.773	(2*S*)-1-(phenylacetyl)-*N*-{4-[5-({[(2*S*)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} pyrrolidine-2-carboxamide
21		885.039	*tert*-butyl {(1*S*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
22		885.039	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl] carbonyl}amino)-1-benzofuran-2-yl]phenyl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
23		856.984	propan-2-yl [(1*R*)-2-oxo-1-phenyl-2-{(2*S*)-2-[(4-{5-[({(2*S*)-1-[(2*R*)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl] pyrrolidin-2-yl}carbonyl)amino]-1-benzofuran-2-yl}phenyl) carbamoyl]pyrrolidin-1-yl}ethyl]carbamate
24		800.876	methyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
25		740.91	(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl} carbonyl)amino]-1-benzofuran-2-yl}phenyl)pyrrolidine-2-carboxamide
26		797.019	(2*S*)-1-[(2*R*)-2-(diethylamino)-2-phenylacetyl]-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl} carbonyl)amino]-1-benzofuran-2-yl}phenyl)pyrrolidine-2-carboxamide

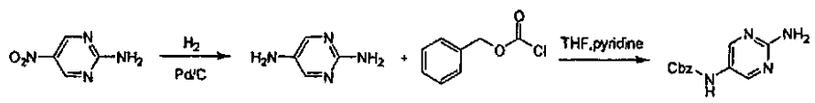
Example	Structure	MW	Name
27		798.947	propan-2-yl [(1*R*)-2-{(2*S*)-2-[(4-{5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1-benzofuran-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate
28		482.587	*N*-[2-(4-aminophenyl)-1-benzofuran-5-yl]-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-L-prolinamide
29		853.127	(2*S*)-1-{(2*R*)-2-[methyl(3-methylbutyl)amino]-2-phenylacetyl}-*N*-{4-[5-({[(2*S*)-1-{(2*R*)-2-[methyl(3-methylbutyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl}pyrrolidine-2-carboxamide
30		552.679	*N*-{2-[4-(acetylamino)phenyl]-1-benzofuran-5-yl}-1-[(2*R*)-2-(diethylamino)-2-phenylacetyl]-L-prolinamide
31		649.797	(2*S*)-1-acetyl-*N*-(2-{4-[({(2*S*)-1-[(2*R*)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1-benzofuran-5-yl)pyrrolidine-2-carboxamide
32		693.807	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-acetylpyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
33		621.743	(2*S*)-1-acetyl-*N*-(2-{4-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1-benzofuran-5-yl)pyrrolidine-2-carboxamide
34		596.689	*N*-{4-[5-(acetylamino)-1-benzofuran-2-yl]phenyl}-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}-L-prolinamide

Example	Structure	MW	Name
35		814.903	methyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-7-methyl-1-benzofuran-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
36		825.073	(2*S*)-1-{(2*R*)-2-[ethyl(propyl)amino]-2-phenylacetyl}-*N*-{4-[5-({[(2*S*)-1-{(2*R*)-2-[ethyl(propyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl}pyrrolidine-2-carboxamide

Example 37 – (2S)-1-(phenylacetyl)-N-{4-[6-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)imidazo[1,2-a]pyrimidin-2-yl]phenyl}pyrrolidine-2-carboxamide

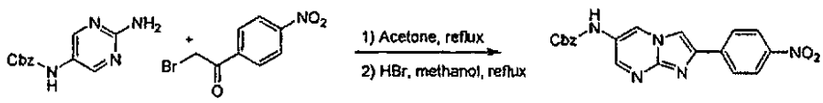


Step 1



A suspension of pyrimidine (280 mg, 2 mmol), Pd/C (15 mg, 0.1 mmol) in 40 mL EtOH was hydrogenated under 30 psi for 1 hour. The mixture was then filtered, and the filtrate was then concentrated to give the product (200 mg). The residue was dissolved in 20 ml THF and CbzCl (375 mg, 2.19 mmol) and pyridine (1 ml) were added. The mixture was stirred at RT for 1 hour, then the mixture was concentrated *in vacuo*, and the residue was extracted with EtOAc (2x), washed with H_2O (30 mL) and brine (30 mL), dried over anhydrous $NaSO_4$, concentrated *in vacuo* to give the desired compound as white powder (330 mg). MS (ESI) m/e ($M+H^+$): 245.

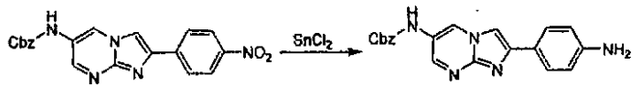
Step 2



A solution of the product from step 1 above (244 mg, 1.00 mmol) and 2-bromo-1-(4-nitrophenyl)ethanone (244 mg, 1 mmol) in 40 mL of acetone was heated to reflux and stirred for 6 hours. Then, the mixture was cooled to RT and filtered, and the filtrate was then dissolved

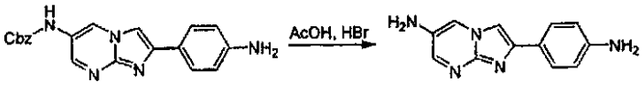
in 30 ml MeOH, and 0.5 ml HBr was added, the mixture was heated to reflux for another 3 hours; after that, the mixture was concentrated *in vacuo* to give the product as a pale yellow powder (120 mg). MS (ESI) m/e ($M+H^+$): 390.

Step 3



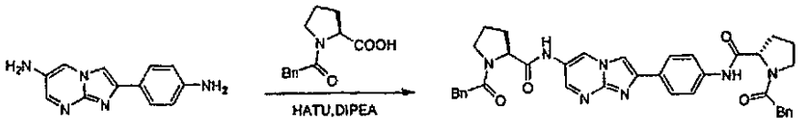
To the product from step 2 above (50mg, 0.128mmol) was dissolved in 10 mL CH_3OH was added $SnCl_2$ (144 mg, 0.64 mmol). The reaction mixture was stirred at RT for 30 minutes and then heated to reflux for 3 hours. MeOH was removed *in vacuo*, and the residue was purified (DCM/MeOH =50:1) to afford the desired compound (35mg). MS (ESI) m/e ($M+H^+$): 360.

Step 4



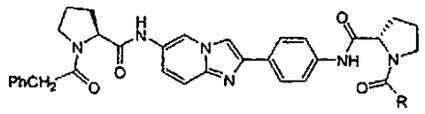
The compound from step 3 (35 mg, 0.1 mmol) was dissolved in 5 ml of HOAc, then HBr (1.5 ml) was added. The reaction mixture was heated to reflux and stirred for 6 hours, cooled and concentrated. The residue was extracted with EtOAc (2x), washed with *aq.* $NaHCO_3$ and water (30 mL) and brine (30 mL), dried over anhydrous $NaSo_4$. Concentration afforded the desired compound as a brown solid (16mg). MS (ESI) m/e ($M+H^+$): 226.

Step 5

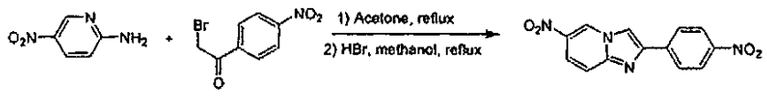


A mixture of the diamine product from step 4 above (16 mg, 0.071 mmol), *N*-phenylacetyl-L-proline (40mg, 0.170 mmol), DIPEA (36.9mg, 0.02 mmol) in CH_3CN (5 mL) was stirred at RT for 10 minutes, then HATU (54 mg, 0.142 mmol) was added. The mixture was stirred at RT overnight then the mixture was concentrated, and the residue was purified to give compound (15 mg). MS (ESI) m/e ($M+H^+$): 657. ^1H NMR (MeOD) δ: 9.45(s, 1H), 8.31(s, 1H), 8.05(s, 1H), 7.61~7.48 (m, 4H), 7.34~7.21 (m, 10H), 4.60~4.52 (m, 2H), 3.83~3.69 (m, 8H), 2.24~1.97(m, 8H).

Example 38 – (2S)-1-(phenylacetyl)-N-{4-[6-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)imidazo[1,2-a]pyridin-2-yl]phenyl}pyrrolidine-2-carboxamide

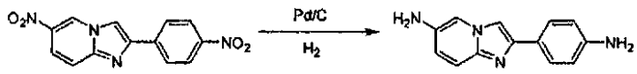


Step 1



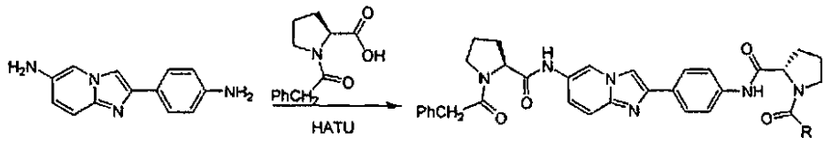
The mixture containing 2-amino-5-nitropyridine (1.39 g, 10 mmol) and p-nitro-alpha-bromoacetophenone (2.42g, 10 mmol) in 100 mL of acetone was heated at reflux for 12 hours. The solid was collected by filtration and then dissolved in 20 mL of MeOH and treated with a trace amount of HBr. The mixture was stirred at reflux for 1 hour, cooled and the solid was collected by filtration to give the desired (1.4 g). MS (m/z): 285 $(M+H)^+$.

Step 2



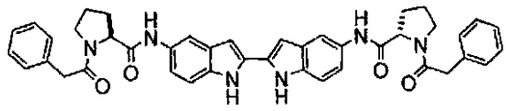
To a suspension of the product from step 1 above (0.7 g, 2.5 mmol) in MeOH (50 mL) was added 0.1 g of Pd/C (20%), and the suspension was stirred under 25 psi of H_2 at RT. After filtration, the filtrate was concentrated *in vacuo* to give the desired compound. MS (m/z): 225 $(M+H)^+$.

Step 3

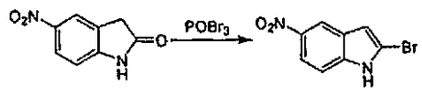


The mixture of the diamine from step 2 above (225 mg, 1 mmol), *N*-phenylacetylproline (1 mmol), DIPEA (5 mmol) and HATU (380 mg, 1 mmol) in 10 mL of MeCN was stirred at RT for 1 hour. The reaction mixture was concentrated, and the residue was purified by column chromatography to give the desired compound. ^1H NMR (MeOD) δ: 9.3 (s, 1H), 8.2 (s, 1H), 7.5-7.1 (m, 16H), 4.6 (m, 1H), 4.5 (m, 1H), 3.8 (m, 8H), 2.3-1.8 (m, 8H).

Example 39 – (2S,2'S)-N,N'-1H,1'H-2,2'-biindole-5,5'-diylbis[1-(phenylacetyl)pyrrolidine-2-carboxamide]

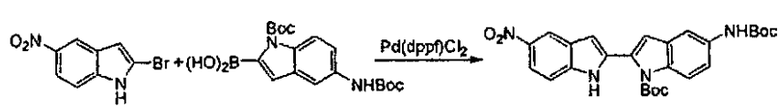


Step 1



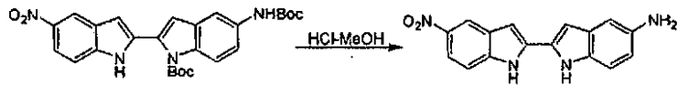
To a suspension of the lactam (10.0 g, 56 mmol) in 200 ml of 1,2-dichloroethane, was added $POBr_3$ (15.3g, 53.2 mmol) at RT. The resulting mixture was heated at reflux temperature in a 90°C oil bath for 0.5 hour (the reaction formed a copious amount of precipitate, and an oil bath was preferred over a heating mantle, as it provided gentle heating and avoided a darkening of the precipitate). The reaction was cooled just below reflux temperature, and imidazole (4.57 g, 62 mmol) was added in one portion. The resulting gummy suspension was heated at reflux temperature in an oil bath for another 2 hours. The reaction was cooled to RT, and 100 mL of ice-water was added. Solid $NaHCO_3$ (ca. 50 g) was added to the mixture until no further gas was evolved. The suspension was extracted with DCM (4x), and the combined DCM extracts were washed with 300 mL of brine. The DCM extracts were filtered through silica gel and concentrated to dryness to afford a crude product. The crude product was recrystallized from chloroform to give 5.41 g of the desired compound as a white solid. The filtrate was concentrated to dryness, and the residue was purified by flash column chromatography (30% EtOAc/Hex) to give an additional 2.6 g of desired product. MS (ESI) m/e ($M+H^+$): 242.

Step 2



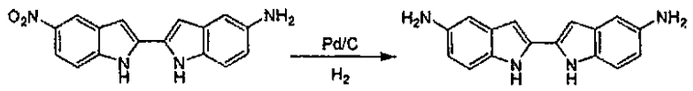
The mixture of compound from step 1 above (602.6 mg, 2.5 mmol), the indole boronic acid (1.034 g, 2.75mmol), $Pd(dppf)Cl_2$(183 mg, 0.25 mmol), Na_2CO_3 (530 mg, 5.0 mmol) in 5 mL dioxane-H_2O (5:1) was heated to reflux under N_2 atmosphere overnight. When reaction was complete the mixture was poured into water and extracted with DCM. The organic phase was dried over Na_2SO_4, concentrated, and the residue was purified to give compound the desired product. MS (ESI) m/e ($M+H^+$): 493.

Step 3



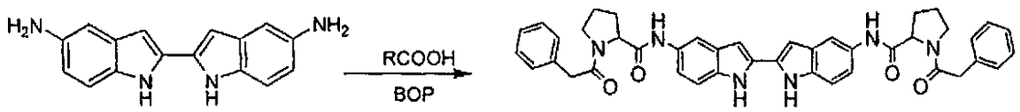
The product from step 2 (600 mg, 1.3 mmol) was added into HCl (30 ml, 3M in MeOH). Then the mixture stirred at RT for 2-3 hours. When reaction was complete, the mixture was concentrated to give the crude product (400 mg). MS (ESI) m/e ($M+H^+$): 293.

Step 4



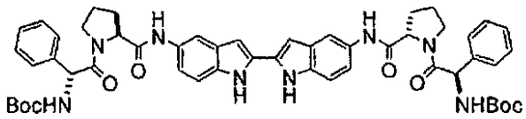
The product from step 3 (400 mg, 1.36 mmol) was dissolved in EtOAc and treated with Pd/C (100 mg, 20%). Then the mixture was stirred at RT overnight under H_2 atmosphere. When the reaction was complete, the Pd/C was filtered off, and the resulting solution was concentrated to give the crude product (300 mg). MS (ESI) m/e ($M+H^+$): 263.

Step 5



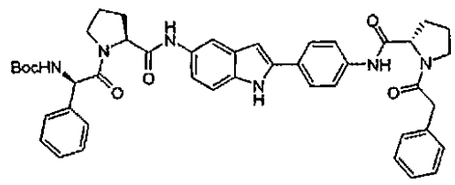
A solution containing (131 mg, 0.5 mmol) of the product from step 4, RCOOH (256.608 mg, 1.1 mmol), DIPEA (390 mg, 1.5 mmol) in CH_3CN (2 mL) was stirred at RT for 5 minutes, then HATU (418 mg, 1.1 mmol) was added into the mixture. The mixture was stirred at RT overnight. When reaction was complete, the mixture was concentrated, and the residue was purified to give the desired product. ^1H NMR (MeOD) δ: 7.15-7.75 (m, 18H), 4.51-4.59 (m, 2H), 3.56-3.80 (m, 10H), 2.37 (s, 3H), 1.97-2.30 (m, 8H). MS (ESI) m/e ($M+H^+$): 693.

Example 40 – di-tert-butyl (1H,1'H-2,2'-biindole-5,5'-diylbis{carbamoyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate

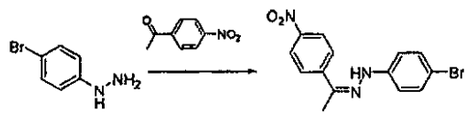


This compound was prepared using the similar method as Example 39, step 5 using N-Boc-R-Phg-L-Pro-OH. ^1H NMR (MeOD) δ: 6.78-7.78 (m, 18H), 5.49 (m, 2H), 4.55-4.58 (m, 2H), 3.94-3.97 (m, 3H), 2.37 (s, 3H), 1.87-2.14 (m, 8H), 1.40(s, 18H). MS (ESI) m/e ($M+H^+$):924.

***Example 41* – tert-*butyl* {(1R)-2-oxo-1-phenyl-2-[(2S)-2-({2-[4-({[(2S)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]ethyl}carbamate**

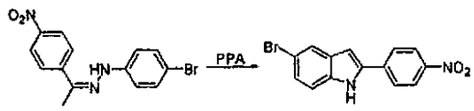


Step 1



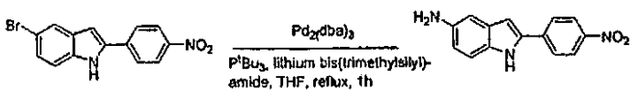
To a solution of 4-bromophenylhydrazine (2.5 g, 13.4 mmol) in acetic acid (19.5 mL) and EtOH (14.5 mL), 4-nitroacetophenone (1.66 g, 10.0 mmol) was added. The reaction was refluxed for 5 hours, and water (35 mL) was added. The resulting mixture was stirred for another 1 hour, and the resulting solid was filtered, washed with water to afford 3.1 g of the desired compound. ^{1}H NMR (MeOD) δ: 8.21-8.23 (d, *J* = 8.0Hz, 2H), 8.01-8.03 (d, *J* = 8.0Hz, 2H), 7.34-7.36 (d, *J* = 8.0Hz, 2H), 7.20-7.22 (d, *J* = 8.0Hz, 2H), 2.03 (s, 3H).

Step 2



The product from step 1 above (2.0 g, 6.0 mmol) was added into PPA (20 mL), and the mixture was stirred at 80°C for 1 hour before it was cooled in ice-bath, diluted with water/EtOAc (60/20 mL) and stirred for another 1 hour. The mixture was extracted with EtOAc and washed to yield the target. ^{1}H NMR (MeOD) δ: 8.28-8.30 (d, *J* = 8.0Hz, 2H), 7.97-7.99 (d, *J* = 8.0Hz, 2H), 7.72 (s, 1H), 7.33-7.35 (d, *J* = 8.0Hz, 1H), 7.24-7.26 (d, *J* = 8.0Hz, 1H), 7.02 (s, 1H).

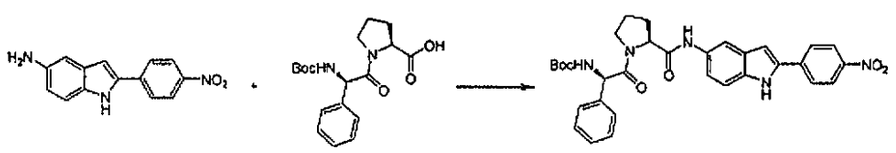
Step 3



An oven-dried argon-cooled round-bottom flask was charged with the indole from step 2 (2.0 g, 6.31 mmol) and 0.05 equivalents of $Pd_2(dba)_3$ in THF (100 mL). A solution of tri-*tert*-butyl phosphine (10 wt %) in hexane (1.93 mL, 0.63 mmol) was added followed by lithium

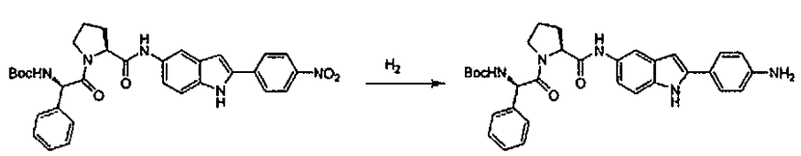
hexamethyldisilazane (1.0 M in THF) (18.9 mL, 18.9 mmol). The dark solution was heated to reflux overnight then cooled to RT. This mixture was poured into ice-cold aq 1.0 M HCl (70 mL) and stirred vigorously. Hexane was added, and stirring was continued for 30 minutes. The precipitate was filtered, washed with 20 mL of cold water and then 20 mL of THF:Hexanes (5:95) solution. The precipitate was washed with 200 mL of MeOH, and the filtrate was concentrated to give 1.5 g of the desired compound. MS m/z: 254 (M+1).

Step 4



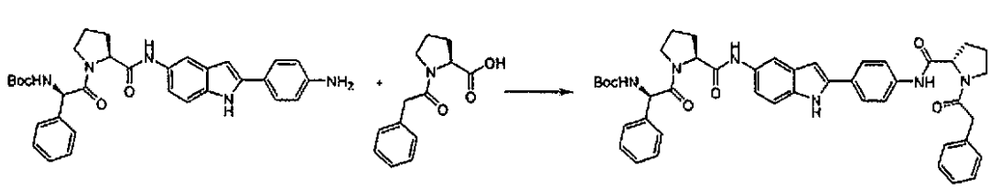
To a solution of the product from step 3 above (1 g, 3.9 mmol) in acetonitrile (20 mL) was added R-N-Boc-Phg-S-Pro-OH (1.4 g, 3.9 mmol), HATU (3 g, 7.8 mmol) and DIPEA (1 g, 7.8 mmol). The mixture was stirred at RT overnight. The solvent was distilled, and the residue was dissolved in EtOAc and washed with water. The organic layer was dried and concentrated *in vacuo*, and the residue was purified by column chromatography to give the desired compound (1.8 g). MS (ESI) m/e ($M+H^+$): 584.

Step 5



To a solution of compound from step 4 (300 mg, 0.51 mmol) in MeOH (10 mL) was added Pd/C (50 mg, 0.28 mmol). The mixture was stirred under H_2 atmosphere at RT for 1 hour. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give the desired compound (230 mg) as a yellow oil, which was used directly in next step. MS (ESI) m/e $(M+H)^+$: 554.

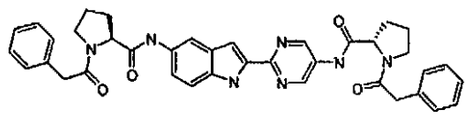
Step 6



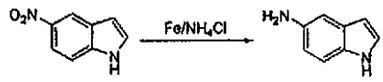
To a solution of the compound from step 5 (100 mg, 0.18 mmol) in acetonitrile (3 mL) was added compound *N*-phenylacetyl-L-proline (42 mg, 0.18 mmol), HATU (140 mg, 0.36 mmol) and DIPEA (46 mg, 0.36 mmol). The mixture was stirred at RT overnight then

concentrated, and the residue was purified by RPLC to give (60 mg). ^{1}H NMR ($CDCl_3$) δ: 9.62 (s, 1H), 9.08 (s, 1H), 7.84 (s, 1H), 7.45-7.09 (m, 15H), 6.52 (s, 1H), 5.67 (s, 1H), 5.49 (m, 1H), 4.72-4.51 (m, 2H), 3.82-3.48 (m, 5H), 3.20 (m, 1H), 2.15-1.72 (m, 8H), 1.43 (s, 9H). MS (ESI) m/e ($M+H^+$): 769.

Example 42 – (2S)-1-(phenylacetyl)-N-{2-[5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]pyrimidin-5-yl}pyrrolidine-2-carboxamide

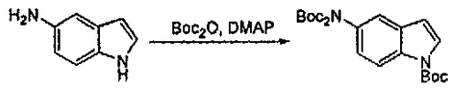


Step 1



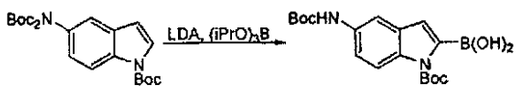
A mixture of 5-nitroindole (5 g, 30.9 mmol), Fe (8.6 g, 154 mmol), NH_4Cl (16.5 g, 309 mmol), EtOH (80 mL) and water (20 mL) was refluxed under N_2 protection for 2 hours. The mixture was cooled to RTand filtered. The filtrate was concentrated and dissolved in water. The mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2 two times. The combined organic phases were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated to yield the product (3.6 g). MS (ESI) m/e ($M+H^+$): 133. ^{1}H NMR (DMSO) δ: 10.55 (s, 1H), 7.12-7.06 (m, 2H), 6.68 (d, *J*=2.0 Hz, 1H), 6.48 (dd, *J*=8.4 Hz, 2.0 Hz, 1H), 6.12 (t, *J*=2.0 Hz, 1H), 4.39 (s, 2H).

Step 2



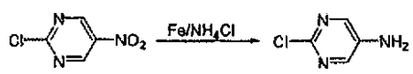
A mixture of 5-aminoindole (20 g, 76 mmol), DMAP (9.2 g, 38 mmol) THF (250 mL) and CH_3CN (100 mL) was cooled to 0°C Boc_2O (132 g, 304 mmol) was slowly added to the mixture. The reaction mixture was allowed to warm to RT and stirred over the weekend. The mixture was poured into water and exacted with CH_2Cl_2 three times. The organic phase was combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated, dissolved in CH_2Cl_2 and poured into PE and filtered. The solid was purified by column chromatography (PE/EA=20/1) to yield the product (23 g). ^{1}H NMR ($CDCl_3$): δ 8.05 (d, *J*=8.0 Hz, 1H), 7.56 (d, *J*=3.2 Hz, 1H), 7.28 (d, *J*=2.4 Hz, 1H), 7.03 (dd, *J*=8.8 Hz, 1.6 Hz, 1H), 1.63 (s, 9H), 1.36 (s, 18H).

Step 3



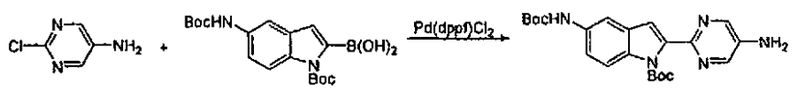
A mixture of the product from step 2 above (5.0 g, 11.6 mmol), (iPrO)$_3$B (17.5 mL, 92.8 mmol) and dry THF (100 mL) was cooled to 0°C LDA (prepared from nBuLi and iPr_2NH in THF, about 116 mmol) was slowly added to the mixture at 0°C. The mixture was allowed to warm to RT and stirred for 2 hours. The mixture was quenched by the addition of 1N HCl to pH=3 and extracted with CH_2Cl_2 three times. The combined organic phases were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by column chromatography (PE/CH_2Cl_2=1/1 to pure CH_2Cl_2 to CH_2Cl_2/acetone=10/1 to pure acetone) to afford the product (2.8g). ^{1}H NMR (DMSO) δ: 9.22 (s, 1H), 8.10 (s, 2H), 7.84 (d, J=9.2 Hz, 1H), 7.65 (s, 1H), 7.20 (dd, J=9.2 Hz, 2.0 Hz, 1H), 6.48 (d, 1H), 1.51 (s, 9H), 1.41 (s, 9H).

Step 4



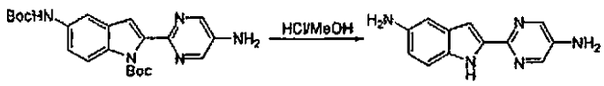
A mixture of the pyrimidine compound (0.3 g, 2 mmol), Fe powder (560 mg, 10 mmol), NH_4Cl (1.07 g, 20 mmol), EtOH (8 mL) and water (2 mL) was refluxed under N_2 overnight. The mixture was cooled to RT and filtered. The filtrate was concentrated and dissolved in water. The mixture was basified with Na_2CO_3 and extracted with CH_2Cl_2 two times. The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated to yield the product (120 mg). MS (ESI) m/e ($M+H^+$): 130. ^{1}H NMR (DMSO) δ: 7.99 (s, 2H), 5.73 (s, 2H).

Step 5



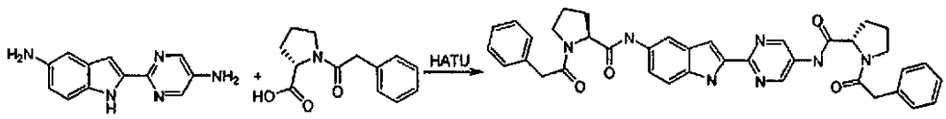
A mixture of the pyrimidine from step 4 (100 mg, 0.77 mmol), indole boronic acid from step 3 (290 mg, 0.77 mmol), Pd(dppf)Cl_2 (56 mg, 0.077 mmol), Na_2CO_3 (244 mg, 2.3 mmol), THF (20 mL) and H_2O (2 mL) was refluxed under N_2 overnight. The mixture was poured into water and extracted with CH_2Cl_2. The organic phase was combined, dried over Na_2SO_4 and filtered. The filtrate was purified by prep TLC (CH_2Cl_2/MeOH=20/1) to afford the product. MS (ESI) m/e ($M+H^+$): 426.

Step 6



A mixture of compound from step 5 above was added to a solution HCl in MeOH (4M) cooled with ice bath. The mixture was allowed to warm to RT and stirred overnight. The mixture was concentrated, dissolved in water, washed by CH_2Cl_2 and concentrated. The residue was directly used in the next step without further purification. MS (ESI) m/e ($M+H^+$): 226

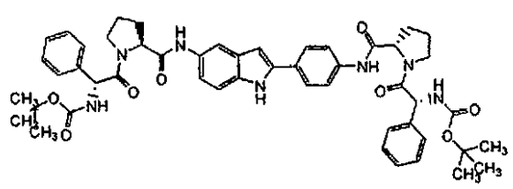
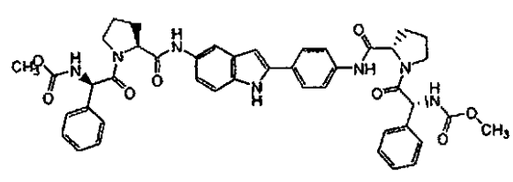
Step 7

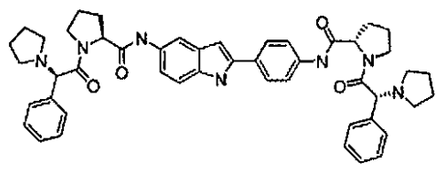
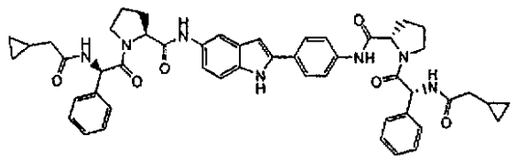
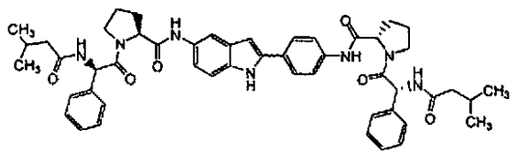
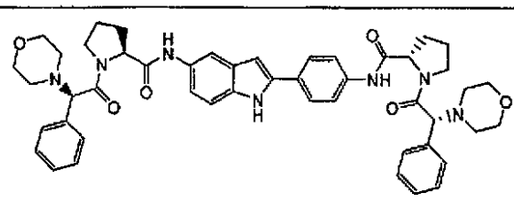
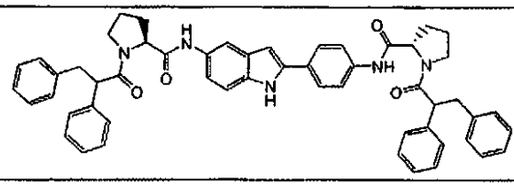
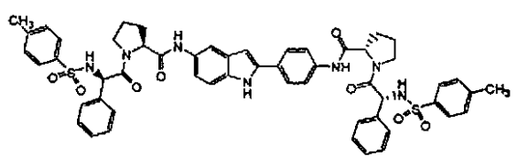
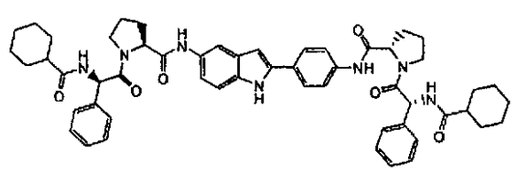


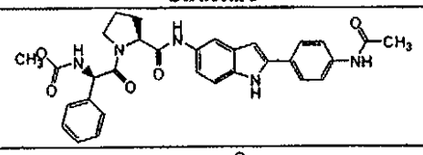
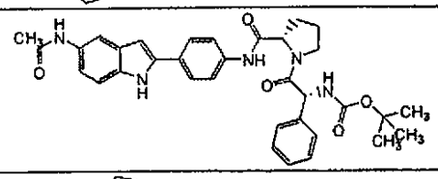
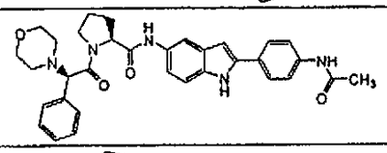
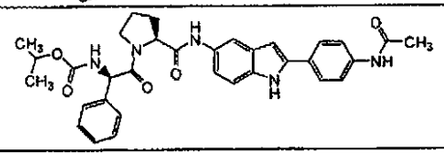
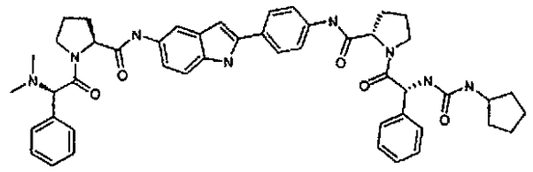
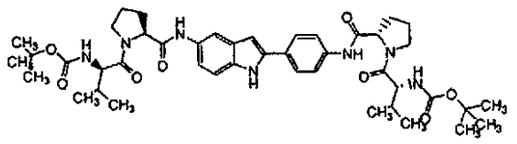
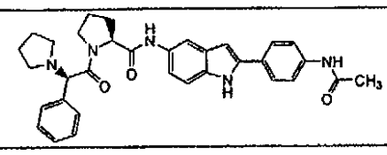
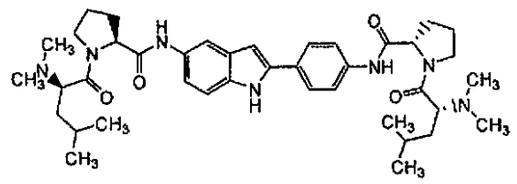
The product of step 6 above (0.22 mmol), *N*-phenylacetyl-L-proline (51 mg, 0.22 mmol), DIPEA (100 mg), and DMF (3 mL) was added HATU (84 mg, 0.22 mmol), and the mixture was stirred at RT overnight. The mixture was purified by RPLC to afford the product. MS (ESI) m/e ($M+H^+$): 656. ^1H NMR ($CDCl_3$) δ: 10.42 (s, 1H), 10.01 (s, 1H), 9.77 (s, 1H), 8.32 (s, 1H), 7.34-7.27 (m, 11H), 7.05-7.00 (m, 2H), 6.58 (d, *J*=8.0 Hz, 1H), 4.63-4.53 (m, 2H), 3.84-3.58 (m, 8H), 2.30-1.94 (m, 8H).

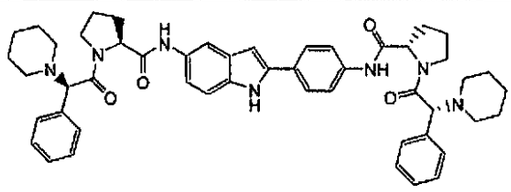
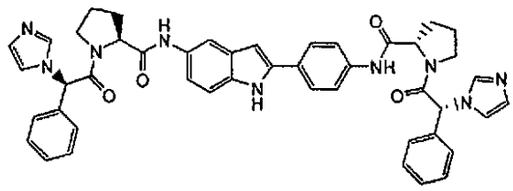
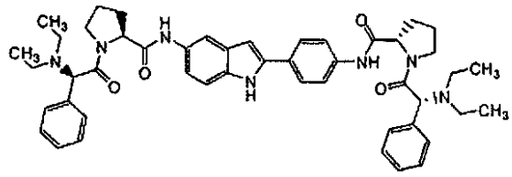
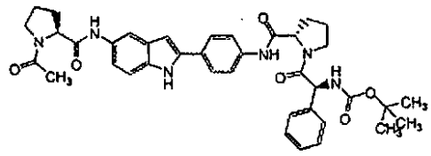
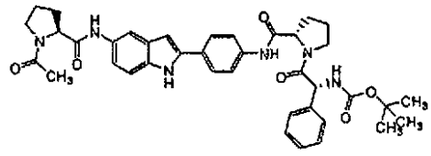
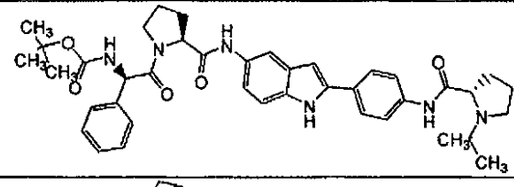
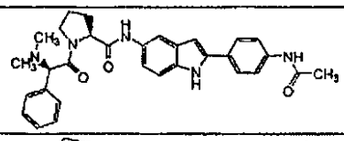
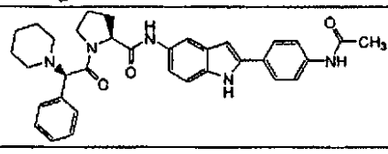
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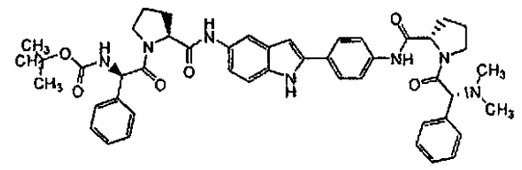
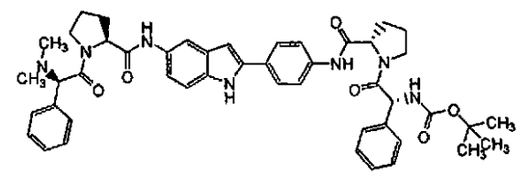
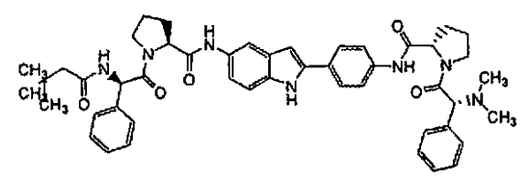
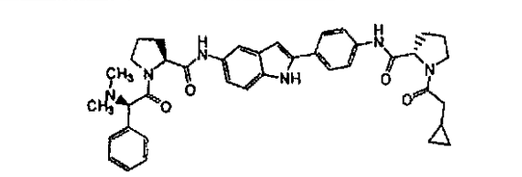
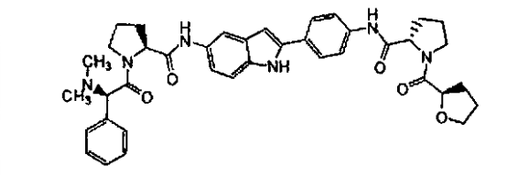
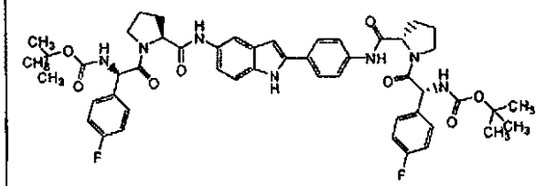
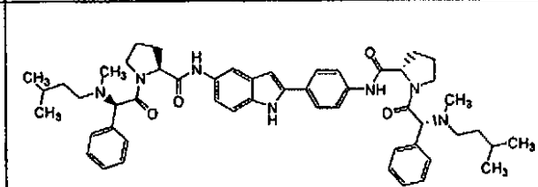
Compounds of Examples 43-87 were prepared in a similar manner as described in either Example 41 or Example 42.

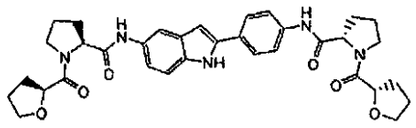
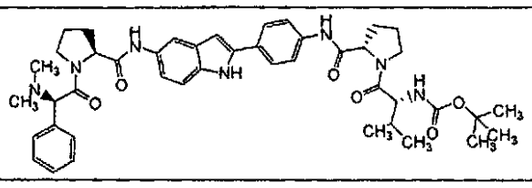
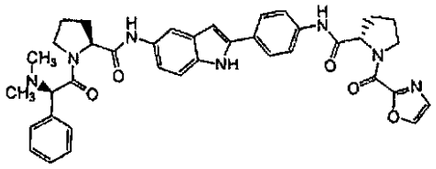
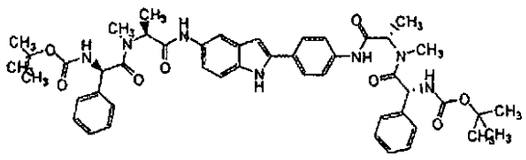
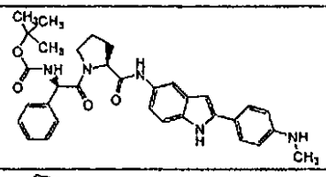
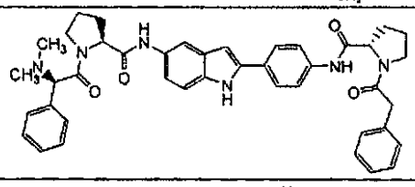
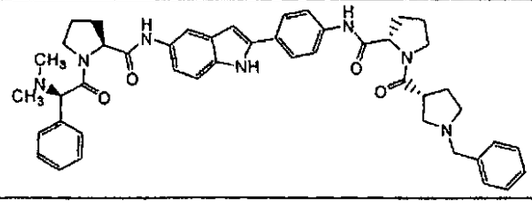
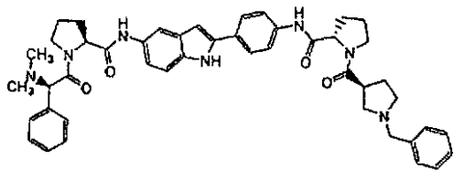
Example	Structure	MW	Name
43		884.054	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
44		799.891	methyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

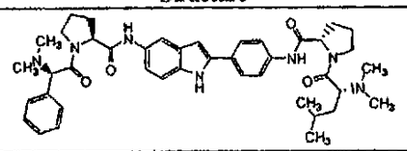
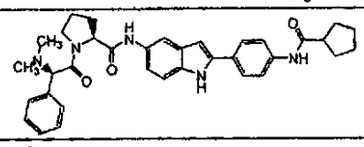
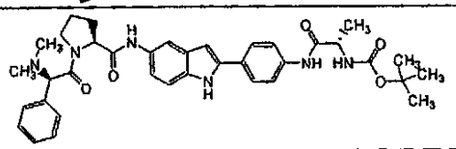
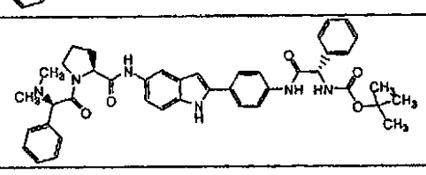
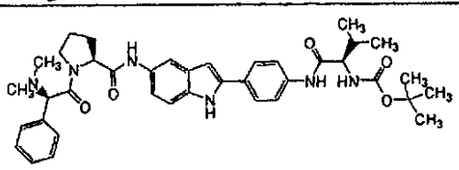
Example	Structure	MW	Name
45		792.002	(2*S*)-1-[(2*R*)-2-phenyl-2-(pyrrolidin-1-yl)acetyl]-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-phenyl-2-(pyrrolidin-1-yl)acetyl] pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl) pyrrolidine-2-carboxamide
46		848.023	(2*S*)-1-{(2*R*)-2-[(cyclopropylacetyl)amino]-2-phenylacetyl}-*N*-{4-[5-({[(2*S*)-1-{(2*R*)-2-[(cyclopropylacetyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl} pyrrolidine-2-carboxamide
47		852.055	(2*S*)-1-{(2*R*)-2-[(3-methylbutanoyl)amino]-2-phenylacetyl}-*N*-{4-[5-({[(2*S*)-1-{(2*R*)-2-[(3-methylbutanoyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl} pyrrolidine-2-carboxamide
48		824.001	(2*S*)-1-[(2*R*)-2-(morpholin-4-yl)-2-phenylacetyl]-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-(morpholin-4-yl)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)pyrrolidine-2-carboxamide
49		834.04	(2*S*)-1-(2,3-diphenylpropanoyl)-*N*-{4-[5-({[(2*S*)-1-(2,3-diphenylpropanoyl)pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}pyrrolidine-2-carboxamide
50		992.195	(2*S*)-1-[(2*R*)-2-{[(4-methylphenyl)sulfonyl]amino}-2-phenylacetyl]-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-{[(4-methylphenyl) sulfonyl]amino}-2-phenylacetyl] pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl) pyrrolidine-2-carboxamide
51		904.132	(2*S*)-1-{(2*R*)-2-[(cyclohexylcarbonyl)amino]-2-phenylacetyl}-*N*-{4-[5-({[(2*S*)-1-{(2*R*)-2-[(cyclohexylcarbonyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl} pyrrolidine-2-carboxamide

Example	Structure	MW	Name
52		553.623	methyl {(1*R*)-2-[(2*S*)-2-({2-[4-(acetylamino)phenyl]-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
53		595.704	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-(acetylamino)-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
54		565.678	*N*-{2-[4-(acetylamino)phenyl]-1*H*-indol-5-yl}-1-[(2*R*)-2-(morpholin-4-yl)-2-phenylacetyl]-L-prolinamide
55		581.677	propan-2-yl {(1*R*)-2-[(2*S*)-2-({2-[4-(acetylamino)phenyl]-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
56		817.953	(2*S*)-1-{(2*R*)-2-[(cyclopentylcarbamoyl)amino]-2-phenylacetyl}-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)pyrrolidine-2-carboxamide
57		816.019	*tert*-butyl {(2*R*)-1-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate
58		549.679	*N*-{2-[4-(acetylamino)phenyl]-1*H*-indol-5-yl}-1-[(2*R*)-2-phenyl-2-(pyrrolidin-1-yl)acetyl]-L-prolinamide
59		699.945	(2*S*)-1-[(2*R*)-2-(dimethylamino)-4-methylpentanoyl]-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-4-methylpentanoyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)pyrrolidine-2-carboxamide (non-preferred name)

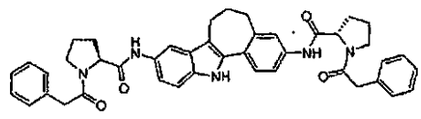
Example	Structure	MW	Name
60		820.056	(2*S*)-1-[(2*R*)-2-phenyl-2-(piperidin-1-yl)acetyl]-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-phenyl-2-(piperidin-1-yl)acetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)pyrrolidine-2-carboxamide
61		785.914	(2*S*)-1-[(2*R*)-2-(1*H*-imidazol-1-yl)-2-phenylacetyl]-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-(1*H*-imidazol-1-yl)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)pyrrolidine-2-carboxamide
62		796.034	(2*S*)-1-[(2*R*)-2-(diethylamino)-2-phenylacetyl]-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)pyrrolidine-2-carboxamide
63		692.822	*tert*-butyl {(1*S*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-acetylpyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
64		692.822	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-acetylpyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
65		692.866	*tert*-butyl {(1*R*)-2-oxo-1-phenyl-2-[(2*S*)-2-({2-[4-({[(2*S*)-1-(propan-2-yl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]ethyl}carbamate
66		523.64	*N*-{2-[4-(acetylamino)phenyl]-1*H*-indol-5-yl}-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-L-prolinamide
67		563.706	*N*-{2-[4-(acetylamino)phenyl]-1*H*-indol-5-yl}-1-[(2*R*)-2-phenyl-2-(piperidin-1-yl)acetyl]-L-prolinamide

Example	Structure	MW	Name
68		811.99	*tert*-butyl [(1*R*)-2-{(2*S*)-2-[(2-{4-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1*H*-indol-5-yl)carbamoyl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate
69		811.99	*tert*-butyl [(1*R*)-2-{(2*S*)-2-[(4-{5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl] pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl) carbamoyl] pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate
70		810.017	(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-*N*-{4-[5-({[(2*S*)-1-{(2*R*)-2-[(3,3-dimethylbutanoyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}pyrrolidine-2-carboxamide
71		660.823	(2*S*)-1-(cyclopropylacetyl)-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)pyrrolidine-2-carboxamide
72		676.823	(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-*N*-(2-{4-[({(2*S*)-1-[(2*R*)-tetrahydrofuran-2-ylcarbonyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1*H*-indol-5-yl)pyrrolidine-2-carboxamide
73		920.035	*tert*-butyl [(1*R*)-2-{(2*S*)-2-[(4-{5-[({(2*S*)-1-[(2R)-2-[(*tert*-butoxycarbonyl)amino]-2-(4-fluorophenyl)acetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-1-(4-fluorophenyl)-2-oxoethyl]carbamate
74		852.142	(2*S*)-1-{(2*R*)-2-[methyl(3-methylbutyl)amino]-2-phenylacetyl}-*N*-{4-[5-({[(2*S*)-1-{(2*R*)-2-[methyl(3-methylbutyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl} pyrrolidine-2-carboxamide

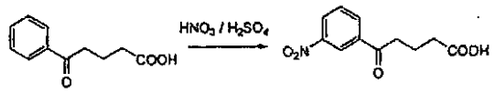
Example	Structure	MW	Name
75		613.72	(2*S*)-1-[(2*S*)-tetrahydrofuran-2-ylcarbonyl]-*N*-(4-{5-[({(2*S*)-1-[(2*S*)-tetrahydrofuran-2-ylcarbonyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)pyrrolidine-2-carboxamide
76		777.972	*N*-(*tert*-butoxycarbonyl)-D-valyl-*N*-{4-[5-({1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-L-prolyl}amino)-1*H*-indol-2-yl]phenyl}-L-prolinamide
77		673.778	(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-*N*-{2-[4-({[(2*S*)-1-(1,3-oxazol-2-ylcarbonyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1*H*-indol-5-yl}pyrrolidine-2-carboxamide
78		860.032	*tert*-butyl [(1*R*)-2-{[(2*S*)-1-({4-[5-({(2*S*)-2-[{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}(methyl)amino]propanoyl}amino)-1*H*-indol-2-yl]phenyl}amino)-1-oxopropan-2-yl](methyl)amino}-2-oxo-1-phenylethyl]carbamate
79		567.694	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({2-[4-(methylamino)phenyl]-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
80		696.857	(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-*N*-{2-[4-({[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1*H*-indol-5-yl}pyrrolidine-2-carboxamide
81		765.964	(2*S*)-1-{[(3*R*)-1-benzylpyrrolidin-3-yl]carbonyl}-N-(4-{5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)pyrrolidine-2-carboxamide
82		765.964	(2*S*)-1-{[(3*S*)-1-benzylpyrrolidin-3-yl]carbonyl}-*N*-(4-{5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)pyrrolidine-2-carboxamide

Example	Structure	MW	Name
83		719.935	*N,N*-dimethyl-D-leucyl-*N*-{4-[5-({1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-L-prolyl}amino)-1*H*-indol-2-yl]phenyl}-L-prolinamide
84		577.733	*N*-(2-{4-[(cyclopentylcarbonyl)amino]phenyl}-1*H*-indol-5-yl)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-L-prolinamide
85		652.8	*tert*-butyl [(2*S*)-1-({4-[5-({1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-L-prolyl}amino)-1*H*-indol-2-yl]phenyl}amino)-1-oxopropan-2-yl]carbamate
86		714.872	*tert*-butyl [(1*S*)-2-({4-[5-({1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-L-prolyl}amino)-1*H*-indol-2-yl]phenyl}amino)-2-oxo-1-phenylethyl]carbamate
87		680.855	*tert*-butyl [(2*R*)-1-({4-[5-({1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-L-prolyl}amino)-1*H*-indol-2-yl]phenyl}amino)-3-methyl-1-oxobutan-2-yl]carbamate

Example 88 – (2S,2'S)-N,N'-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole-3,9-diylbis[1-(phenylacetyl)pyrrolidine-2-carboxamide]

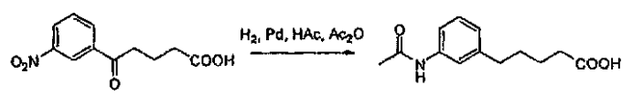


Step 1



To a mixture of HNO_3 (4 mL) and H_2SO_4 (2 mL) at 0°C was slowly added the above carboxylic acid (2 g, 10.4 mmol). The mixture was stirred under 0°C for 30 minutes. The resulting solution was poured into 20 mL of H_2O at 0°C, and the precipitate was filtered to give compound (2 g) as a yellow solid. MS (ESI) m/e ($M+H^+$): 238.

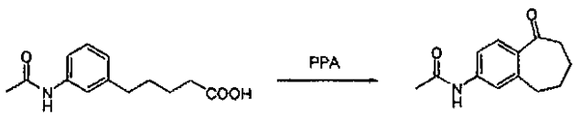
Step 2



To a mixture of HOAc (10 mL) and Ac_2O (3 mL) was added the nitro compound from step 1 (1 g, 4.3 mmol) and Pd/C (100 mg, 0.6 mmol). The mixture was stirred under H_2 for

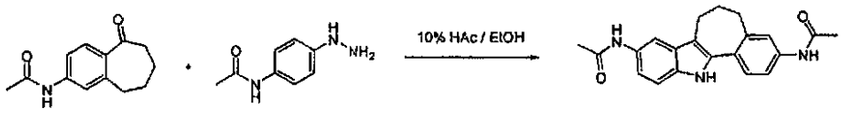
6 hours. The catalyst was filtered, and the filtrate was concentrated *in vacuo* to give the desired compound (1 g) as a brown solid. MS (ESI) m/e ($M+H^+$): 236.

Step 3



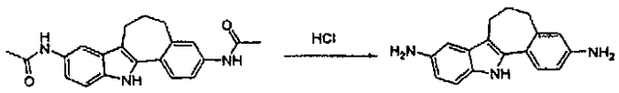
The compound from step 2 above (150 mg, 0.64 mmol) was slowly added to PPA (6 mL) at 100°C. The mixture was stirred for 3 hours. After cooling, the resulting solution was poured into 40 mL mixture of water and ice and extracted with DCM. The organic layer was concentrated to give the cyclic product (70 mg) as a brown solid. MS (ESI) m/e ($M+H^+$): 218.

Step 4



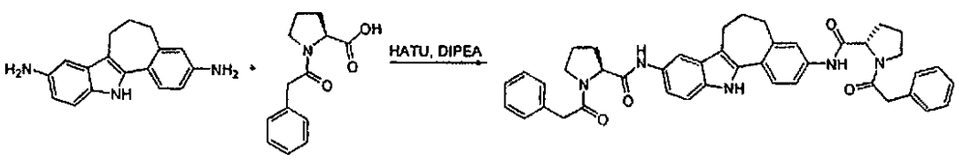
To a solution of the ketone from step 3 (140 mg, 0.65 mmol) in 10% HOAc/EtOH (10 mL) was added 4-acetamidophenylhydrazine (144 mg, 0.72 mmol). The mixture was stirred at reflux for 4 hours. After cooling, the resulting solution was concentrated *in vacuo*, washed with water and extracted by EtOAc. The organic layer was concentrated *in vacuo* to give the desired compound (200 mg) as a brown solid. MS (ESI) m/e ($M+H^+$): 348.

Step 5



To a solution of the product from step 4 above (200 mg, 0.57 mmol) in EtOH (10 mL) was added 6N HCl (2 mL, 12 mmol). The mixture was stirred at reflux overnight and cooled, and the resulting solution was concentrated then purified by silica gel flash chromatography (petroleum ether / ethyl acetate=5:1) to give the desired compound (150 mg) as a brown solid. MS (ESI) m/e ($M+H^+$): 264.

Step 6

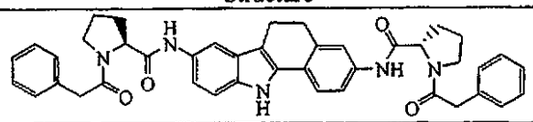
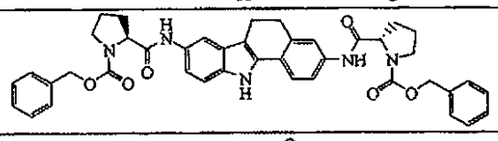
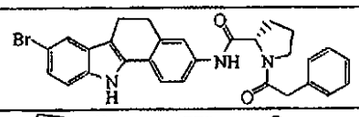
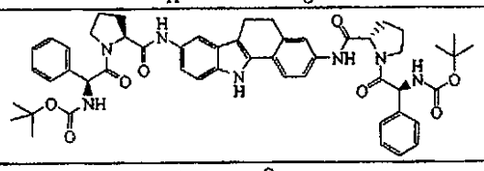
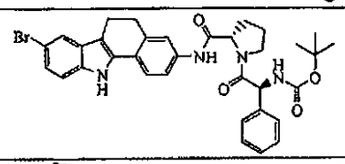
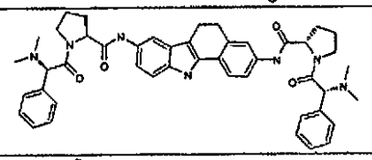
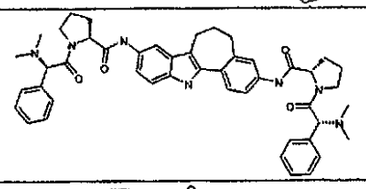
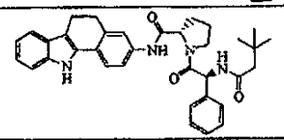
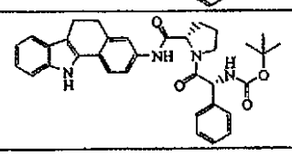


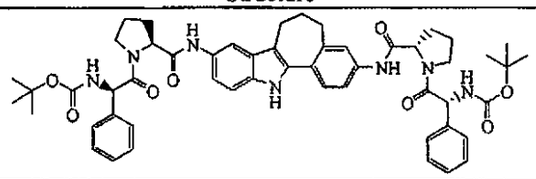
To a solution of the aniline from step 5 (40 mg, 0.15 mmol) in MeCN (5 mL) was added the proline analog (70 mg, 0.3 mol), HATU (250 mg, 0.6 mmol) and DIPEA (80 mg, 0.6

mmol). The mixture was stirred overnight. The resulting solution was purified by pre-HPLC to give the desired compound (10 mg) as a brown solid. ^{1}H NMR δ: 7.62-7.20 (m, 16H), 4.58-4.54 (m, 2H), 3.79-3.60 (m, 6H), 2.95 (m, 2H), 2.80 (m, 2H), 2.26-1.94 (m, 8H). MS (ESI) m/e ($M+H^+$): 694.

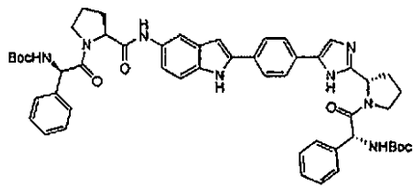
Examples 89-98

Compounds of Examples 89-98 were prepared in a similar manner as described in Example 88.

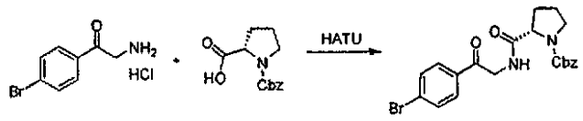
Example	Structure	MW	Name
89		679.826	(2*S*,2'*S*)-*N*,*N*'-6,11-dihydro-5*H*-benzo[a]carbazole-3,8-diylbis[1-(phenylacetyl)pyrrolidine-2-carboxamide]
90		711.825	dibenzyl (2*S*,2'*S*)-2,2'-(6,11-dihydro-5*H*-benzo[a]carbazole-3,8-diyldicarbamoyl) dipyrrolidine-1-carboxylate
91		528.453	*N*-(8-bromo-6,11-dihydro-5*H*-benzo[a]carbazol-3-yl)-1-(phenylacetyl)-L-prolinamide
92		910.092	di-*tert*-butyl (6,11-dihydro-5*H*-benzo[a]carbazole-3,8-diylbis {carbamoyl(2*S*)pyrrolidine-2,1-diyl[(1*S*)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate
93		643.586	*tert*-butyl [(1*S*)-2-{(2*S*)-2-[(8-bromo-6,11-dihydro-5*H*-benzo[a]carbazol-3-yl) carbamoyl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate
94		765.942	(2*S*,2'*S*)-*N*,*N*'-6,11-dihydro-5*H*-benzo[a]carbazole-3,8-diylbis{1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-carboxamide}
95		779.968	(2*S*,2'*S*)-*N*,*N*'-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta [1,2-b]indole-3,9-diylbis{1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-carboxamide}
96		562.718	*N*-(6,11-dihydro-5*H*-benzo[a]carbazol-3-yl)-1-{(2*S*)-2-[(3,3-dimethylbutanoyl)amino] -2-phenylacetyl}-L-prolinamide
97		564.69	*tert*-butyl {(1*R*)-2-[(2*S*)-2-(6,11-dihydro-5*H*-benzo[a]carbazol-3-ylcarbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

Example	Structure	MW	Name
98		924.119	di-*tert*-butyl (5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole-3,9-diylbis{carbamoyl(2*S*)pyrrolidine-2,1-diyl[(1*R*)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate

Example 99* – tert-*butyl {(1*R*)-2-[(2*S*)-2-(5-{4-[5-({[(2*S*)-1-{(2*R*)-2-[(tert-*butoxy carbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1*H*-*indol-2-yl]phenyl}-1*H*-*imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

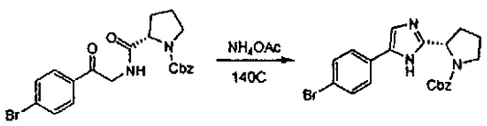


Step 1



HATU (20 g, 52.3 mmol) was added to a heterogeneous mixture of the amino ketone (12 g, 48.5 mmol) and L-Cbz-Pro (12.4 g, 50 mmol) in MeCN (156 mL). The mixture was cooled in an ice-water bath, and immediately afterward DIPEA (27 mL, 155 mmol) was added dropwise. After the addition of the base, the cooling bath was removed, and the reaction mixture was stirred for an additional 50 minutes. The volatile component was removed, and water (125 mL) was added to the resulting crude solid and stirred for about 1 hour. The off-white solid was filtered and washed with copious water, and dried *in vacuo* to provide the desired compound as a white solid (20.68 g). MS (ESI) m/e ($M+H^+$): 446.

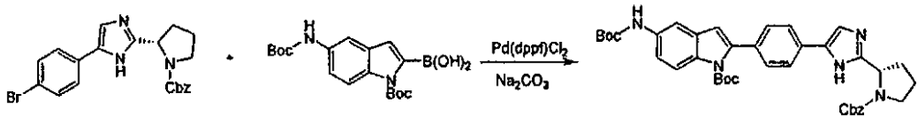
Step 2



A mixture of the product from step 1 above (12.8 g, 31.12 mmol) and NH_4OAc (12.0 g, 155.7 mmol) in xylenes (155 mL) was heated in a sealed tube at 160°C for 2 hours. The volatile component was removed *in vacuo*, and the residue was partitioned carefully between EtOAc and water, where by enough saturated $NaHCO_3$ solution was added so as to make the pH of the aqueous phase slightly basic after the shaking of the biphasic system. The layers were

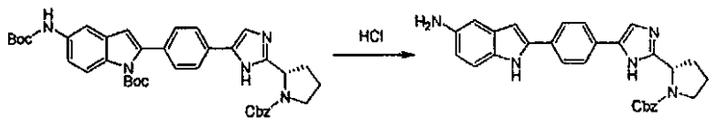
separated, and the aqueous layer was extracted with an additional EtOAc. The combined organic phase was washed with brine, dried, filtered, and concentrated *in vacuo* to yield a yellow solid. MS (ESI) m/e ($M+H^+$): 426. ^1H NMR ($CDCl_3$) δ: 7.31-7.52 (m, 9H), 7.17 (s, 1H), 5.12 ~ 5.20 (m, 2H), 5.00 ~ 5.01 (m, 1H), 3.50 ~ 3.52 (m, 2H), 2.96 ~ 2.97 (m, 1H), 1.97 ~ 2.17 (m, 3H).

Step 3



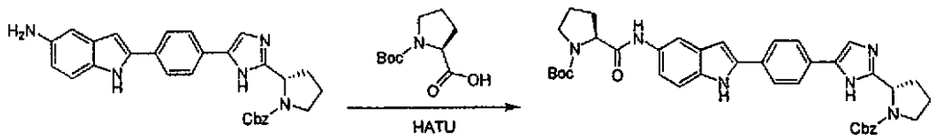
A mixture of the product from step 2 above (327 mg, 0.77 mmol), indole boronic acid from Example 42 (290 mg, 0.77 mmol), $Pd(dppf)Cl_2$ (56 mg, 0.077 mmol), Na_2CO_3 (244 mg, 2.3 mmol), THF (20 mL) and H_2O (2 mL) was refluxed under N_2 overnight. The mixture was poured into water and extracted with CH_2Cl_2. The organic phase was combined, dried over Na_2SO_4 and filtered to give the desired compound, which was used directly in the next step. MS (ESI) m/e ($M+H^+$): 678.

Step 4



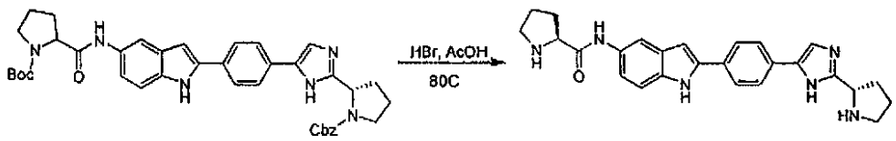
A solution of the product of step 3 in HCl/CH_3OH (5 N) was stirred for 3 hours. Concentration *in vacuo* afforded the crude product. MS (ESI) m/e ($M+H^+$): 478.

Step 5



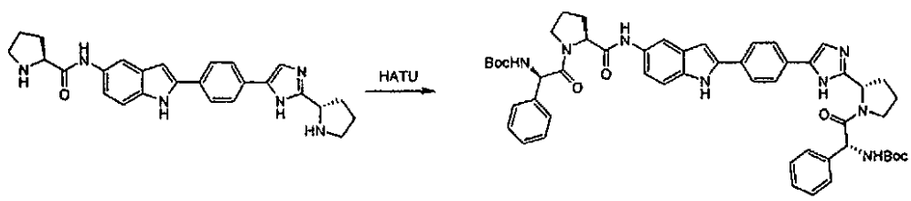
This reaction was carried out using the standard HATU-mediated coupling procedure described in step 1 between Boc-L-Pro-OH and the product from step 4 above. MS (ESI) m/e ($M+H^+$): 808. ^1H NMR (MeOD) δ: 8.95 (bs, 1H), 6.82 ~ 7.56 (m, 17H), 6.50 ~ 6.62 (m, 1H), 5.74 (bs, 1H), 5.38 ~ 5.39 (m, 1H), 4.91 ~ 5.08 (m, 2H), 4.66 (bs, 1H), 3.79 (bs, 1H), 3.40 ~ 3.54 (m, 2H), 3.19 (bs, 1H), 1.93 ~ 2.25 (m, 4H), 1.75 ~ 1.88 (m, 4H), 1.35 ~ 1.32 (m, 9H).

Step 6



To a solution of the product from step 5 (220mg, 0.3 mmol) in 20 mL of AcOH was added 3 mL of 48% HBr. The solution was heated to 80°C for 6 hours. The volatiles were removed *in vacuo*, and the residue was dissolved in DCM/i-PrOH (3:1), washed with saturated Na_2CO_3 and brine, dried and concentrated *in vacuo* to give a solid, which was used in the next step directly. MS (ESI) m/e ($M+H^+$): 441.

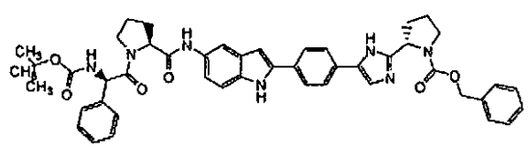
Step 7

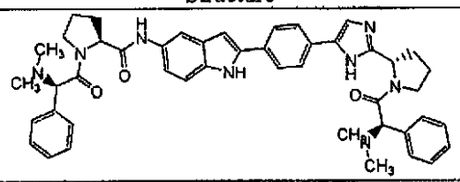
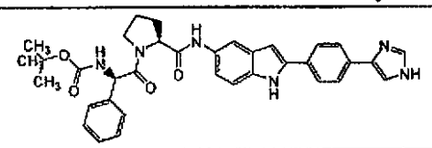
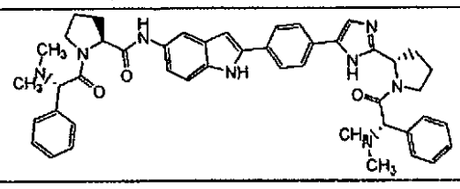
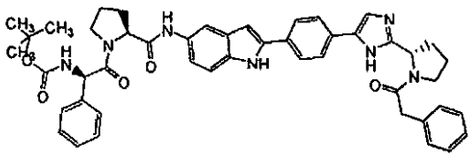
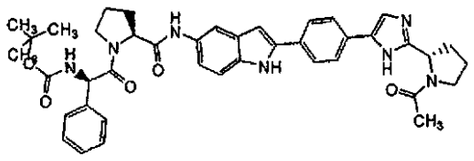
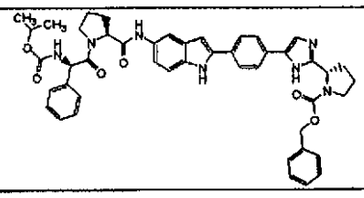
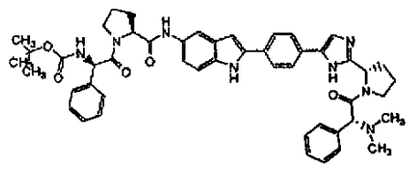
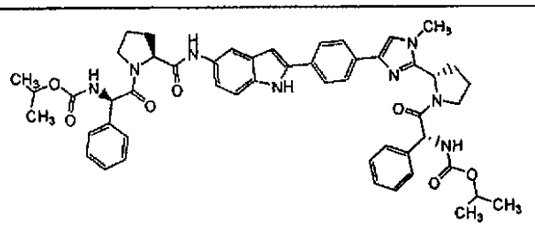


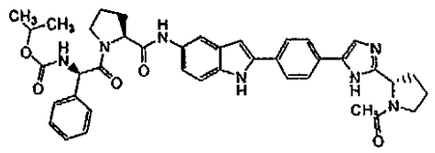
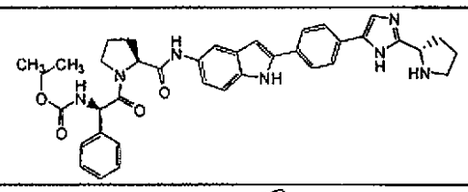
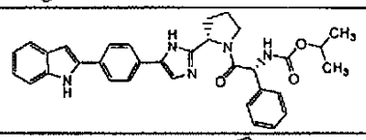
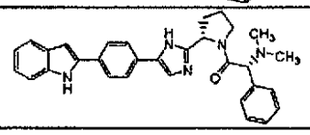
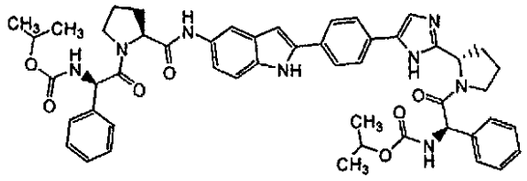
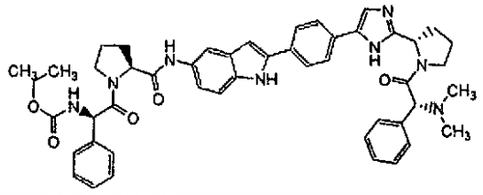
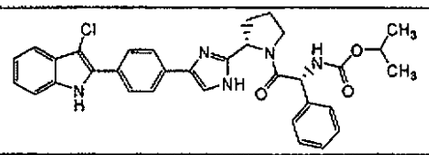
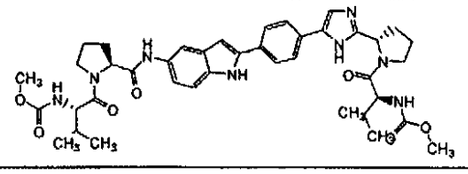
A cooled solution containing HATU (0.6 mmol), the diamine from step 6 above (132 mg, 0.3 mmol) and R-Boc-Pro (129 mg, 0.6 mmol) in MeCN (3 mL), was treated with DIPEA (2.4 mmol), added dropwise over 13 minutes. After the addition of the base was completed, the cooling bath was removed, and the reaction mixture was stirred for an additional 30 minutes. The volatile component was removed *in vacuo*; water was added to the resulting crude solid and stirred for about 1 hour. The off-white solid was filtered, washed with water, and dried *in vacuo* to provide the desired compound as a white solid. MS (ESI) m/e ($M+H^+$): 908. ^1H NMR (MeOD) δ: 7.66 ~ 7.84 (m, 6 H), 7.28 ~ 7.40 (m, 12H), 6.80 (s, 1H), 5.40 ~ 5.45 (m, 2H), 5.18 ~ 5.20 (m, 1H), 3.70 ~ 4.02 (m, 4 H), 1.80 ~ 2.12 (m, 8 H), 1.35 ~ 1.37 (m, 18 H).

Examples 100-116

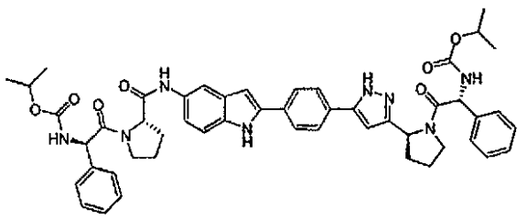
Compounds of Examples 100-116 were prepared in a similar manner as described in Example 99.

Example	Structure	MW	Name
100		807.958	benzyl (2*S*)-2-[5-(4-{5-[(1-{(2*R*)-2-[(*tert*-butoxycarbonyl) amino]-2-phenylacetyl}-L-prolyl)amino]-1*H*-indol-2-yl}phenyl)-1*H*-imidazol-2-yl]pyrrolidine-1-carboxylate

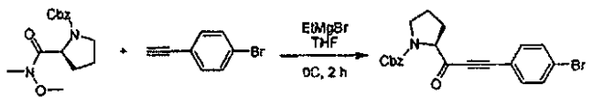
Example	Structure	MW	Name
101		762.963	1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-*N*-{2-[4-(2-{(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]-1*H*-indol-5-yl}-L-prolinamide
102		604.715	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({2-[4-(1*H*-imidazol-4-yl)phenyl]-1*H*-indol-5-yl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
103		762.963	1-[(2*S*)-2-(dimethylamino)-2-phenylacetyl]-N-{2-[4-(2-{(2*S*)-1-[(2*S*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]-1*H*-indol-5-yl}-L-prolinamide
104		791.958	*tert*-butyl {(1*R*)-2-oxo-1-phenyl-2-[(2*S*)-2-{[2-(4-{2-[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1*H*-indol-5-yl]carbamoyl}pyrrolidin-1-yl]ethyl}carbamate
105		715.86	*tert*-butyl{(1*R*)-2-[(2*S*)-2-{[2-(4-{2-[(2*S*)-1-acetylpyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1*H*-indol-5-yl]carbamoyl} pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
106		793.931	benzyl (2*S*)-2-(5-{4-[5-({1-[(2*R*)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]-L-prolyl}amino)-1*H*-indol-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidine-1-carboxylate
107		835.027	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({2-[4-(2-{(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
108		893.064	propan-2-yl [(1*R*)-2-{(2*S*)-2-[1-methyl-4-(4-{5-[({(2*S*)-1-[(2*R*)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl] pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate

Example	Structure	MW	Name
109		701.833	propan-2-yl {(1*R*)-2-[(2*S*)-2-{[2-(4-{2-[(2*S*)-1-acetylpyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1*H*-indol-5-yl]carbamoyl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
110		659.795	propan-2-yl {(1*R*)-2-oxo-1-phenyl-2-[(2*S*)-2-{[2-(4-{2-[(2S)-pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1*H*-indol-5-yl]carbamoyl}pyrrolidin-1-yl]ethyl}carbamate
111		547.663	propan-2-yl {(1*R*)-2-[(2*S*)-2-{5-[4-(1*H*-indol-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
112		489.626	(2*R*)-2-(dimethylamino)-1-[(2*S*)-2-{5-[4-(1*H*-indol-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-phenylethanone
113		879.037	propan-2-yl [(1*R*)-2-oxo-1-phenyl-2-{(2*S*)-2-[5-(4-{5-[({(2*S*)-1-[(2*R*)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}ethyl]carbamate
114		821	propan-2-yl {(1*R*)-2-[(2*S*)-2-({2-[4-(2-{(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
115		582.108	propan-2-yl {(1*R*)-2-[(2*S*)-2-{4-[4-(3-chloro-1*H*-indol-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
116		754.894	*N*-(methoxycarbonyl)-L-valyl-*N*-{2-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]-1*H*-indol-5-yl}-L-prolinamide

Example 117 – Propan-2-yl [(1R)-2-oxo-1-phenyl-2-{(2S)-2-{3-(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)-1H-pyrazol-5-yl]pyrrolidin-1-yl}ethyl]carbamate

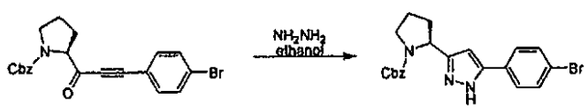


Step 1



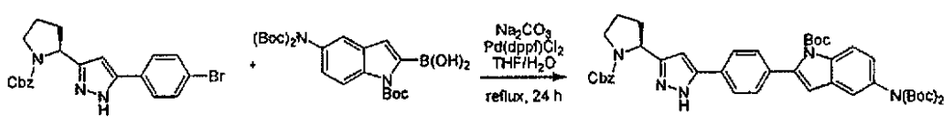
A solution of 4-bromophenylacetylene (5.0g, 27.6mmol) in THF (100mL) at 0°C was treated a solution of EtMgBr (3M in THF, 9.84mL, 29.5mmol). After 10 minutes, the cooling bath was removed, and the mixture was allowed to stir at RT for 3 hours. The reaction mixture was then cooled to 0°C and added to the Weinreb amide of Z-proline (6.10g, 20.9 mmol) in THF (50mL). The reaction mixture was warmed to RT for 48 hours. The reaction mixture was quenched with saturated NH_4Cl and diluted with EtOAc/H_2O. The aqueous phase was back-extracted with EtOAc (2x), and the combined organic layers were washed (H_2O, brine), dried (Na_2SO_4), and filtered. The solvent was removed, and the residue was purified by silica gel (PE: EA=10:1-4:1) to give the product (7.0g) as a cream-colored solid. ^1H NMR ($CDCl_3$) δ: 7.37 ~ 7.47 (m, 2 H), 7.10 ~ 7.30 (m, 7 H), 4.98 ~ 5.32 (m, 2 H), 4.32 ~ 4.47 (m, 1 H), 3.45 ~ 3.61 (m, 2 H), 2.15 ~ 2.27 (m, 1 H), 2.03 ~ 2.12 (m, 1 H), 1.76 ~ 193 (m, 2 H). MS (ESI) m/e ($M+H^+$): 413.

Step 2



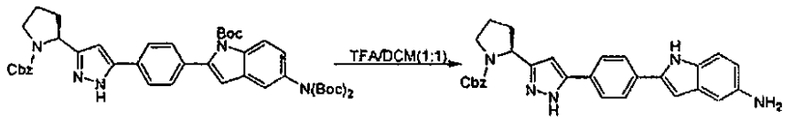
A mixture of the product from step 1 (7.0g, 17 mmol) and hydrazine hydrate (85%, 1.6 mL) in EtOH (50 mL) was heated at 80°C for 16 hours. The reaction mixture was cooled and concentrated to afford the desired product (6.7g). MS (ESI) m/e ($M+H^+$): 426.

Step 3



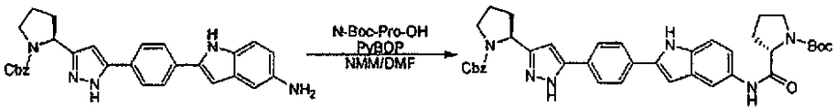
A mixture of the product from step 2 above (0.77 mmol), indole boronic acid from Example 42 (290 mg, 0.77 mmol), $Pd(dppf)Cl_2$ (56 mg, 0.077 mmol), Na_2CO_3 (244 mg, 2.3 mmol), THF (20 mL) and H_2O (2 mL) was refluxed under N_2 overnight. The mixture was poured into water and extracted with CH_2Cl_2, dried over Na_2SO_4 and filtered to give the desired compound, which was used directly in the next step. MS (ESI) m/e ($M+H^+$): 678.

Step 4



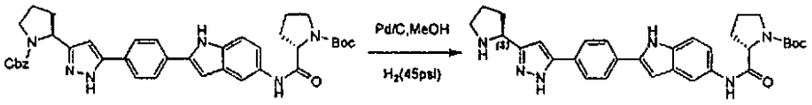
A solution of the product from step 3 above (339 mg, 0.5 mmol) was dissolved in 3 mL of DCM and cooled to 0°C. After the addition of 3 mL of TFA, the reaction mixture was warmed to RT and stirred for 3 hours. Removal of the solvent left the desired product as an oil, which was used directly in the next reaction. MS (ESI) m/e ($M+H^+$): 378.

Step 5



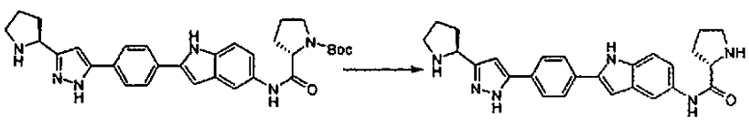
A solution containing PyBOP (0.3 mmol), the amine from step 4 above (132 mg, 0.3 mmol) and N-Boc-L-Pro-OH (62 mg, 0.3 mmol) in DMF (2 mL) was treated with *N*-methylmorpholine (1.2 mmol). The reaction mixture was stirred for 3 hours, diluted with EtOAc and washed with water (5x). The organic phase was dried and concentrated then chromatographed by RPLC to afford the desired compound. MS (ESI) m/e ($M+H^+$): 675.

Step 6



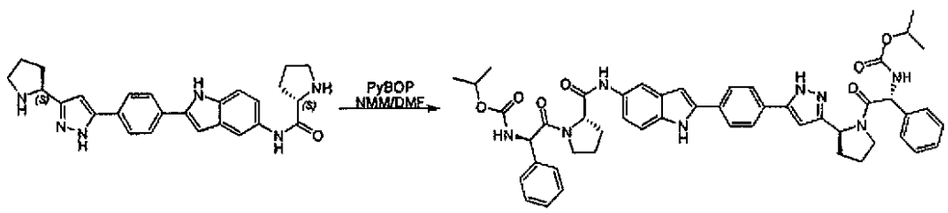
The product from step 5 (100 mg, 0.15 mmol) was dissolved in MeOH and treated with 20 mg of 20% $Pd(OH)_2$ then hydrogenated at 45 psi for 4 hours. The catalyst was removed by filtration through CELITE, and the filtrate was evaporated to leave the desired product. MS (ESI) m/e ($M+H^+$): 541.

Step 7



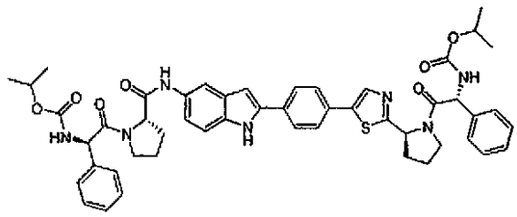
A solution of the product from step 6 above was dissolved in 2 mL of DCM and 2 mL of TFA. The reaction mixture was stirred for 3 hours before the solvent was evaporated to give the desired product as an oil, which was used directly in the next reaction. MS (ESI) m/e ($M+H^+$): 441.

Step 8

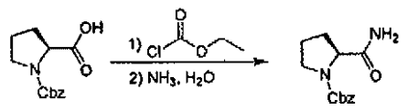


A solution containing PyBOP (0.6 mmol), the diamine from step 7 above (132 mg, 0.3 mmol) and R-i-Proc-Phg-OH (125 mg, 0.6 mmol) in DMF (5 mL) was treated with *N*-methylmorpholine (2.4 mmol). The reaction mixture was stirred for 3 hours, diluted with 20 mL of EtOAc and washed with water (5x). The organic phase was dried and concentrated then chromatographed by RPLC to afford the desired compound. ^{1}H NMR (MeOD) δ: 7.70 ~ 7.80(m, 4H), 7.05 ~ 7.55(m, 14H), 6.80 ~ 7.00(m, 1H), 5.10 ~ 5.50(m, 3H), 4.40 ~ 4.65(m, 2H), 3.25 ~ 4.00(m, 4H), 1.70 ~ 2.40(m, 9H), 1.05 ~ 1.20(m, 12H). MS (ESI) m / e ($M+H^+$): 880.

Example 118 – Propan-2-yl [(1R)-2-oxo-1-phenyl-2-{(2S)-2-[5-(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}ethyl]carbamate



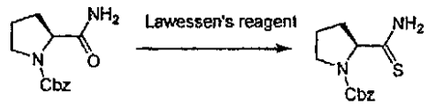
Step 1



Ethyl chloroformate (12 mL, 125 mmol) in 180 mL of THF was added drop-wise to a cooled solution (-5°C) of compound Z-Pro-OH (13.8 g, 55.5 mmol), TEA (7.71 mL, 55.5 mmol). The resulting slurry was stirred for 20 minutes at -5°C before saturated NH_4OH (15 mL) was added. The solution was stirred at RT for 18 hours, volatiles were removed, and the residue was taken up in EtOAc (180 mL). The undissoloved white precipitate was filtered off and rinsed

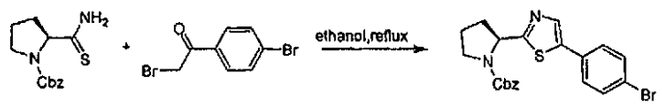
with EtOAc (100 mL). The organic layers were dried over Na_2SO_4 and concentrated *in vacuo* to give the desired product (13.5 g) as off-white amorphous solid. MS (ESI) m/e ($M+H^+$): 249.

Step 2



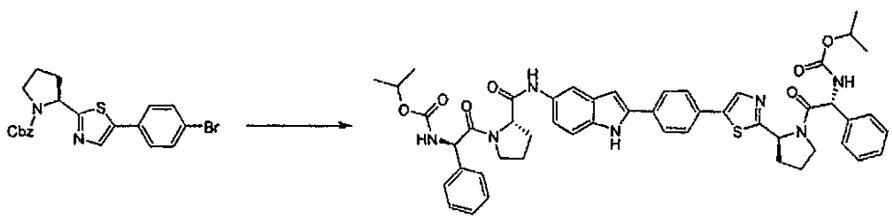
Lawesson's reagent (16.1 g, 39.9 mmol) was added to a stirred slurry of the amide (18 g, 72.6 mmol) in PhMe (200 mL) at RT. The reaction mixture was heated to 100°C for 3 hours before the solvent was removed. The residue was purified by flash SiO_2 chromatography (DCM/MeOH=1:0-20:1) to afford the product (18 g). MS (ESI) m/e ($M+H^+$): 265.

Step 3



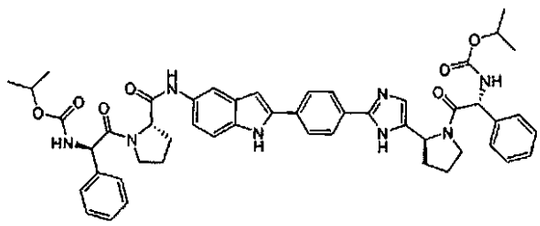
A mixture of the thioamide from step 2 (10.0 g, 37.8 mmol) and the bromoacetophenone (10.0 g, 35.9 mmol) in EtOH (100 mL) was heated at 90°C for 150 minutes. The reaction mixture was cooled and concentrated, and the residue was purified by SiO_2 chromatography to afford the product (11 g). MS (ESI) m/e ($M+H^+$): 444.

Step 4

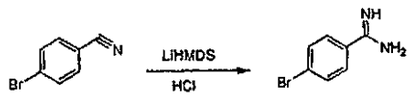


The product from step 3 above can be converted to the final compounds using the same procedure as described in Example 117, steps 4-8. ^1H NMR (MeOD) δ: 7.00 ~ 8.10(m, 19H), 5.40 ~ 5.60(m, 3H), 4.50 ~ 4.70(m, 1H), 3.45 ~ 4.10(m, 4H), 3.35 ~ 3.40(m, 1H), 1.80 ~ 2.6(m, 9H), 1.05 ~ 1.30(m, 12H). MS (ESI) m / e ($M+H^+$): 897.

Example 119 – propan-2-yl [(1R)-2-oxo-1-phenyl-2-{(2S)-2-[2-(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)-1H-imidazol-5-yl]pyrrolidin-1-yl}ethyl]carbamate

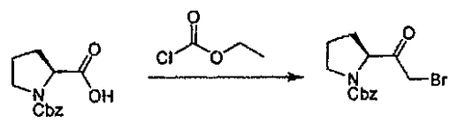


Step 1



To a solution of 4-bromobenzonitrile (1.82 g, 10 mmol) in anhydrous THF (50 mL) was added LiHMDS (2N, 15 mmol) under N_2 atmosphere at RT, and the mixture was stirred for 1 hour. After quenching with 1N HCl, the reaction mixture was heated at reflux for 5 minutes. The precipitate was collected by filtration and then dried *in vacuo* to give the desired compound (1.9 g). ^{1}H NMR (DMSO) δ: 7.74 (d, 2H, *J*=8.2 Hz), 7.62 (d, 2H, *J*=8.2 Hz) 6.43 (br, 3H).

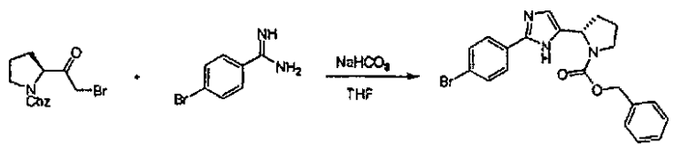
Step 2



To a solution of Cbz-Pro-OH (2.9986 g, 12.0 mmol) in THF (100 mL) was added TEA (1.7 mL, 12.2 mmol). The solution was cooled to -25°C and ethyl chloroformate (1.6 mL, 12.3 mmol) was added. The resulting solution was stirred at RT for 1hour. The precipitate was removed by filtration, and the filtrate was used in next step without purification. A solution of 0.5 M diazomethane was added to the above reaction mixture. The sample was stirred at -10°C for 1 hour. The reaction mixture was concentrated to one half of its original volume and washed once with saturated $NaHCO_3$ (50 mL). The organic layer was dried over $MgSO_4$ and filtered. The crude materiàl was adsorbed onto silica gel and purified by flash chromatography (40 g SiO_2, 0-50% ethyl acetate in hexanes) to give the diazoketone (2.29 g). ^{1}H NMR ($CDCl_3$) δ: 7.32 (m, 5H) 5.13 (m, 2H), 4.61 (m, 1H), 3.81, 4.03, 4.17 (s, AB quartet, 2H, *J*=4.0 Hz), 3.58 (m, 2H), 1.88-2.09, 2.17-2.38 (2, br m, 4H).

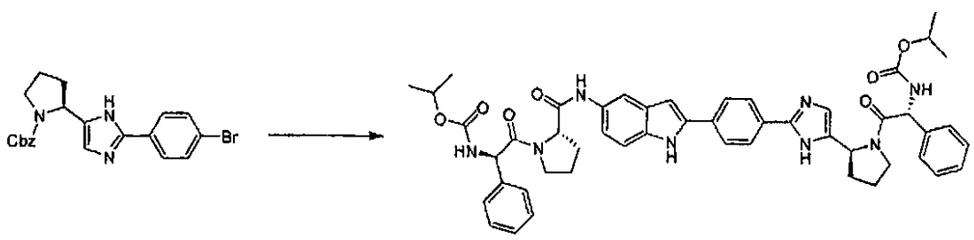
To a solution of the *N*-carbobenzyloxy-L-proline diazoketone (1.0 g, 3.6 mmol) in anhydrous diethyl ether (10 mL) was added a saturated solution of HBr in diethyl ether until N_2 evolution ceased. The solution was stirred for about 1 hour at about 25°C, then washed with saturated $NaHCO_3$, water and brine. The crude material was purified by silica gel column chromatography and eluted with 40% ethyl acetate in pentane to obtain the bromoketone (0.49 g) as clear oil. ^{1}H NMR ($CDCl_3$; mixture of cis-trans amide rotamers) δ: 7.35 (m, 5H), 5.28 (t, 1H), 5.17 (m, 2H), 4.32 (m, 1H), 3.58 (m, 2H), 1.84-2.30 (br m, 4H).

Step 3



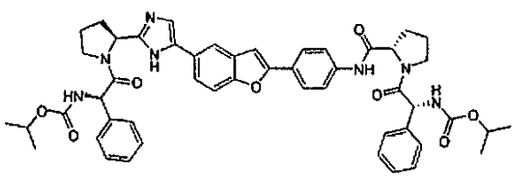
To a mixture of bromoketone (3.25 g, 10 mmol) and the amidine (1.97 g, 10 mol) in THF (100 mL) was added $NaHCO_3$ (1.7 g, 20 mmol), and the suspension was stirred at reflux for 12 hours. The reaction was cooled, concentrated and chromatographed to give compound 7 (0.425 g). MS (ESI) m/e ($M+H^+$): 426, 428.

Step 4

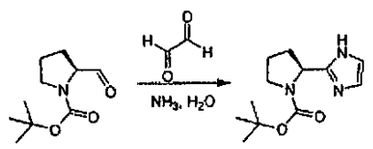


The product from step 3 above can be converted to the final compounds using the same procedure as described in Example 117, steps 4-8. ^{1}H NMR (MeOD) δ: 7.7-8.0 (m, 5H), 7.3-7.5 (m, 10H), 6.9-7.1 (m, 3H), 6.8 (d, *J*=4.8Hz, 10H), 5.4-5.6 (m, 2H), 5.2-5.3 (m, 1H), 4.8 (s, 2H), 4.5-4.7 (m, 10H), 4.0 (d, *J*=2.4Hz, 1H), 3.7 (d, *J*=4.84Hz, 1H), 3.1-3.3 (m, 1H), 2.3-2.5 (m, 1H), 1.8-2.2 (m, 1H), 1.1-1.4 (m, 12H). MS (ESI) m/e ($M+H^+$): 880.

Example 120 – 1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]-N-{4-[5-(2-{(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1-benzofuran-2-yl]phenyl}-L-prolinamide

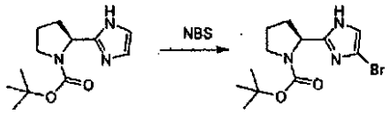


Step 1



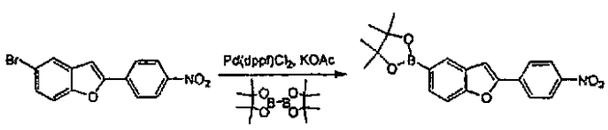
Glyoxal (2.0 mL of 40% in water) was added dropwise to a MeOH solution of NH_4OH (32 mL) and (*S*)-Boc-prolinal (8.564 g, 42.98 mmol), then the whole was stirred at ambient temperature for 19 hours. The volatile component was removed *in vacuo*, and the residue was purified by a flash chromatography (silica gel, ethyl acetate) followed by a recrystallization (ethyl acetate) to provide compound as a white fluffy solid (4.43 g). ^{1}H NMR (DMSO) δ: 11.68/11.59 (br s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 4.76 (m, 1H), 3.48 (m, 1H), 3.35-3.29 (m, 1H), 2.23-1.73 (m, 4H), 1.39/1.15 (s, 9H).

Step 2



NBS (838.4 mg, 4.71 mmol) was added in batches over 15 minutes to a cooled (ice/water) CH_2Cl_2 (20 mL) solution of imidazole (1.06 g, 4.50 mmol). The reaction mixture was stirred for 75 minutes and concentrated. The crude material was purified by RPLC to separate the mono bromide from its dibromo analog and the starting material. The HPLC elute was neutralized with excess NH_3/MeOH, and the volatile component was removed *in vacuo*. The residue was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted with water. The combined organic phase was dried ($MgSO_4$), filtered, and concentrated to provide compound as a white solid (374 mg). ^{1}H NMR (DMSO) δ: 12.12 (br s, 1H), 7.10 (m, 1H), 4.70 (m, 1H), 3.31 (m, 1H; overlapped with water signal), 2.25-1.73 (m, 4H), 1.39/1.17 (s, 3.8H + 5.2H).

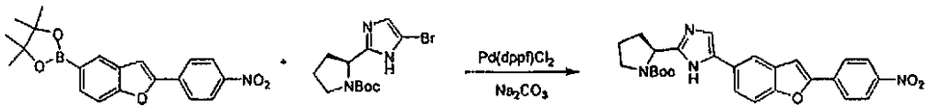
Step 3



To a mixture of the benzofuran from Example 19, step 1 (15 g, 0.05 mol), bis(pinacolato)diboron (25.4 g, 0.1 mol), $Pd(dppf)Cl_2$ (1 g), KOAc (0.1 mol) in dioxane (500 mL) was stirred at reflux under N_2 atmosphere for 2 hours. Concentration of the reaction mixture left a residue that was chromatographed to give the desired compound (12 g). ^{1}H NMR

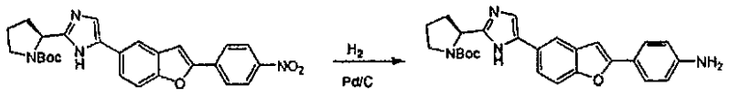
(DMSO) δ: 8.28 (d, *J*=8.8 Hz, 2H), 8.10 (s, 1H), 7.95 (d, *J*=8.8 Hz, 2H), 7.72 (d, *J*=8.8 Hz, 1H), 7.43 (d, *J*=8.8 Hz, 1H), 7.05 (s, 1H).

Step 4



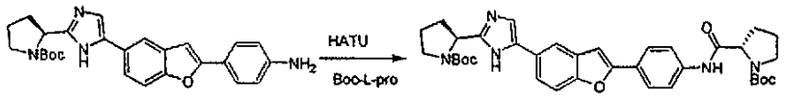
This reaction was conducted in a similar manner to that described in Example 117. MS (ESI) m/e ($M+H^+$): 475.

Step 5



The product from step 4 (475 mg, 1.0 mmol) was dissolved in EtOH and treated with 20 mg of 10% Pd/C then hydrogenated over 5 hours. The catalyst was removed by filtration through CELITE, and the filtrate was evaporated to leave the desired product. MS (ESI) m/e ($M+H^+$): 445.

Step 6



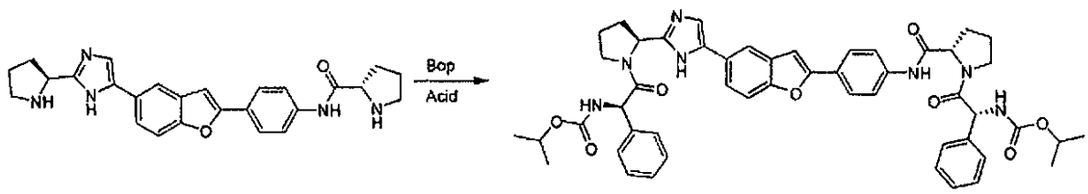
A solution containing HATU (1.0 mmol), the amine from step 5 above (445 mg, 1.0 mmol) and *N*-Boc-L-Pro-OH (215 mg, 1.0 mmol) in MeCN (10mL) was treated with DIPEA (1.2 mmol). The reaction mixture was stirred for 3 hours, diluted with EtOAc and washed with water (5x). The organic phase was dried and concentrated then chromatographed by silica gel chromatography (EtOAc) to afford the desired compound. MS (ESI) m/e ($M+H^+$): 642.

Step 7



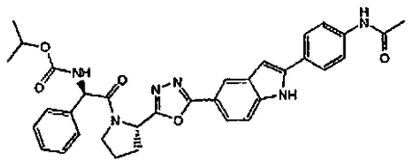
A solution of the product from step 6 above was dissolved in 2 mL of DCM and 2 mL of TFA. The reaction mixture was stirred for 3 hours before the solvent was evaporated to give the desired product as an oil, which was used directly in the next reaction. MS (ESI) m/e ($M+H^+$): 442.

Step 8



A solution containing BOP reagent (222 mg, 0.5 mmol), the diamine from step 7 above (112 mg, 0.25 mmol) and R-*i*-Proc-Phg-OH (125 mg, 0.6 mmol) in DMF (5 mL) was treated with *N*-methylmorpholine (2.4 mmol). The reaction mixture was stirred for 3 hours, diluted with 20 mL of EtOAc and washed with water (5x). The organic phase was dried and concentrated, then chromatographed by RPLC to afford the desired compound. ^{1}H NMR (MeOD) δ: 6.8-7.9 (m, 19H), 5.1-5.5 (m, 3H), 4.5 (m, 1H), 3.5-4.04 (m, 2H), 1.6-2.5 (m, 9H), 0.9-1.3(m, 12H). MS (ESI) m/e (M+H$^+$): 880.

Example 121 – propan-2-yl {(1R)-2-[(2S)-2-(5-{2-[4-(acetylamino)phenyl]-1H-indol-5-yl}-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

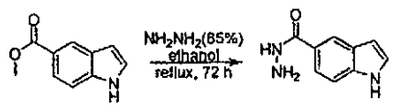


Step 1



A mixture of 5-carboxyindole (32.2 g, 0.2 mol), $NaHCO_3$ (53.36 g, 0.64 mol), methyl iodide (122.22 g, 0.86 mol) in 60 mL of DMF were stirred at RT for 2 days. Water and EtOAc are added, and the organic layer was washed with bicarbonate solution, dried and concentrated to obtain 5-(methoxycarbonyl)indole. ^{1}H NMR (DMSO) δ: 11.44 (s, 1H), 8.22 (s, 1H), 7.68(d, J = 8.4 Hz, 1H), 7.37 ~ 7.47 (m, 2 H), 6.56(d, J = 2.0 Hz, 1H), 3.80 (s, 3H). MS (ESI) m/e (M+H$^+$): 176.

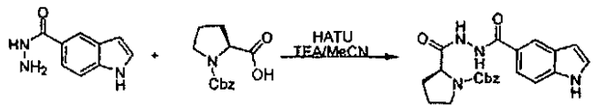
Step 2



A mixture of the ester (28 g, 0.16 mmol) and NH_2NH_2 (85%, 50 mL) in ethanol (200 mL) was heated at reflux for 48 hours. The reaction mixture was concentrated, and the

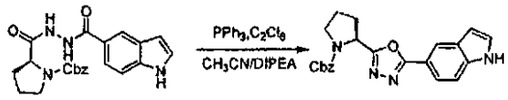
residue was purified by column chromatography (5% MeOH / DCM) to give compound (25 g). ^{1}H NMR (DMSO) δ: 11.27 (s, 1H), 9.54 (s, 1H), 8.06 (s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.37 (d, J = 8.8 Hz, 2H), 4.42 (s, 1H), 6.48 (s, 2H), 3.32 (s, 1H). MS (ESI) m/e ($M+H^+$): 176.

Step 3



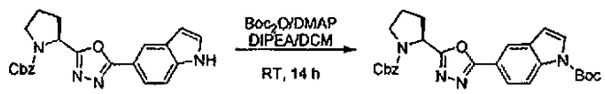
The product from step 3 above was coupled using a standard HATU amide bond forming procedure. MS (ESI) m/e ($M+H^+$): 407.

Step 4



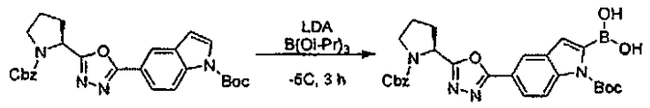
To a suspension of the product from step 3 above (100 g, 0.25 mol), PPh_3 (98.4 g, 0.375 mol) and DIPEA (96.7 g, 0.75mol) in CH_3CN (500 mL) at RT was added C_2Cl_6 (82.8 g, 0.35 mol). The reaction was stirred at RT for 1.5 hours, and the solvent was removed, and the residue was portioned with EtOAc/H_2O. The layers were separated, the aqueous phase was re-extracted with EtOAc (2X), and the combined organic layers were removed *in vacuo*, and the residue purified by column chromatography (5% MeOH/DCM) to give compound 4 (55 g). MS (ESI) m/e ($M+H^+$): 389

Step 5



Di-*tert*-butyl dicarbonate (30.7 g, 142 mmol) was added drop wise to a solution of indole (55.0 g, 142 mmol), DMAP (2.0 g) and DIPEA (18.3 g, 142 mmol) in 50 mL of DCM at 0°C. The reaction was allowed to stir to RT overnight before it was concentrated, and the residue purified by prep TLC (PE/EA=2:1). MS (ESI) m/e ($M+H^+$): 489.

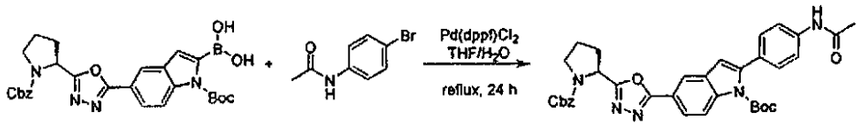
Step 6



A mixture of compound indole from step 5 (977 mg, 2 mmol), (iPrO)$_3$B (3.0 g, 16 mmol) and dry THF (100 mL) was cooled to 0°C. LDA (prepared from n-BuLi and iPr$_2$NH in THF, about 8 mmol) was slowly added and the mixture was allowed to warm to RT over 2 hours.

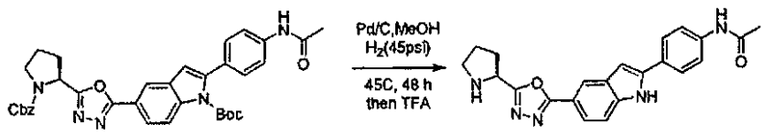
The mixture was quenched by 1N HCl to pH=3 and extracted with CH_2Cl_2 three times. The combined organic phases were combined, dried over Na_2SO_4 and filtered. The filtrate was concentrated and purified by column chromatography (PE/DCM=1/1 to pure CH_2Cl_2 to CH_2Cl_2/acetone=10/1 to pure acetone) to afford the product 8 (0.5 g).

Step 7



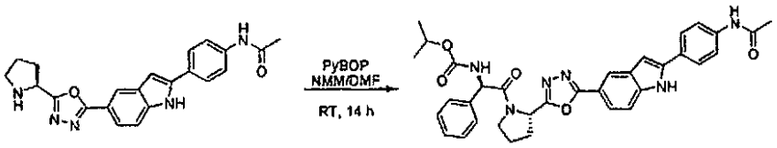
A mixture of the product from step 6 (0.38 mmol), indole boronic acid from Example 42 (145 mg, 0.38 mmol), $Pd(dppf)Cl_2$ (28 mg, 0.038 mmol), Na_2CO_3 (122 mg, 1.15 mmol), THF (10 mL) and H_2O (1 mL) was refluxed under N_2 overnight. The mixture was poured into water and extracted with CH_2Cl_2. The organic phase was combined, dried over Na_2SO_4 and filtered to give the desired compound, which was used directly in the next step. MS (ESI) m/e ($M+H^+$): 622.

Step 8



The product from step 7 (0.15 mmol) was dissolved in MeOH and treated with 20 mg of 20% $Pd(OH)_2$ then hydrogenated at 45 psi for 4 hours. The catalyst was removed by filtration through CELITE, and the filtrate was evaporated then dissolved in 1 mL of DCM then treated with 1 mL of TFA. After stirring for 2 hours, the mixture was evaporated and the residue was used directly in the next reaction without further purification. MS (ESI) m/e ($M+H^+$): 488.

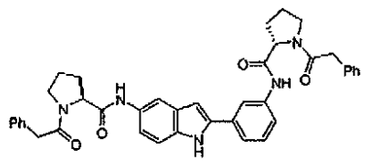
Step 9



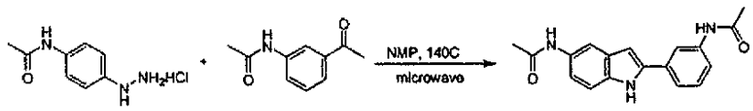
A solution containing PyBOP (44 mg, 0.1 mmol), the amine from step 8 above (49 mg, 0.1 mmol) and R-*i*-Proc-Phg-OH (21 mg, 0.1 mmol) in DMF (1 mL) was treated with *N*-methylmorpholine (0.6 mmol). The reaction mixture was stirred for 3 hours, diluted with EtOAc and washed with water (five times). The organic phase was dried and concentrated, then chromatographed by RPLC to afford the desired compound. ^1H NMR (MeOD): δ7.90 ~ 8.35(m,

1H), 7.70 ~ 7.85(m, 2H), 7.60 ~ 7.70(m, 2H), 7.20 ~ 7.52(m, 7H), 6.55 ~ 7.20(m, 1H), 5.50 ~ 5.60(m, 1H), 5.30 ~ 5.50(m, 1H), 4.75 ~ 4.85(m, 1H), 3.70 ~ 4.10(m, 1H), 3.35 ~ 3.50(m, 1H), 1.95 ~ 2.50(m, 7H), 1.10 ~ 1.30(m, 6H). MS (ESI) m / e ($M+H^+$): 607.

Example 122 – (2S)-1-(phenylacetyl)-N-{3-[5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}pyrrolidine-2-carboxamide

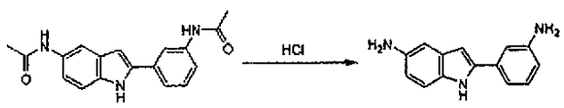


Step 1



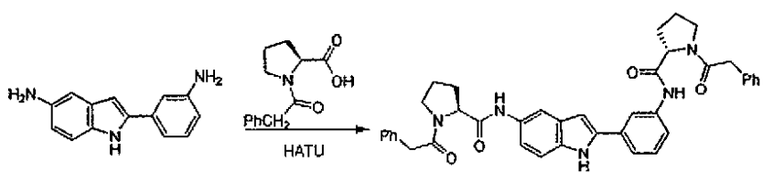
A solution of the hydrazine (1 g, 5 mmol) and 3-acetylacetanilide (0.88 g, 5 mmol) in NMP (5 ml) was heated at 150°C under microwave for 10 minutes. The solution was poured into water and extracted with EtOAc three times. The organic layer was washed with water, dried over sodium sulfate and then concentrated *in vacuo*. The residue was purified by RPLC to give the desired compound. MS (m/z): 308 $(M+H)^+$.

Step 2



To aqueous HCl (4N, 5 mL) was added the product from step 1 above (300 mg, 1 mmol), and the mixture was heated at reflux for 1 hour. The reaction mixture was cooled and concentrated, and the residue was purified by RPLC to give compound (200 mg). MS (m/z): 224 $(M+H)^+$.

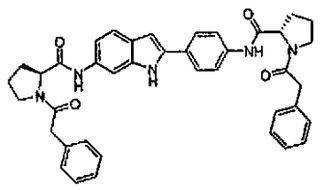
Step 3



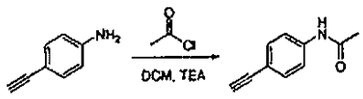
To a solution of the compound from step 2 above (35 mg, 0.148 mmol) in MeCN (5 mL) were added *N*-phenylacetyl-L-proline (15 mg, 0.0673 mmol), DIPEA (26 mg, 0.202 mmol) and HATU (56 mg, 0.148 mmol). The reaction was stirred overnight and concentrated, and the residue was purified by RPLC to give the desired product (15 mg).. MS (ESI) m/e

(M+H$^+$): 654. ^{1}H NMR (MeOD) δ: 8.0 (m, 1H), 7.7(m, 1H), 7.6-7.1 (m, 14H), 6.7 (m, 1H), 4.6 (m, 2H), 3.9-3.5 (m, 9H), 2.4-1.7 (m, 8H).

Example 123 – (2S)-1-(phenylacetyl)-N-{4-[6-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}pyrrolidine-2-carboxamide

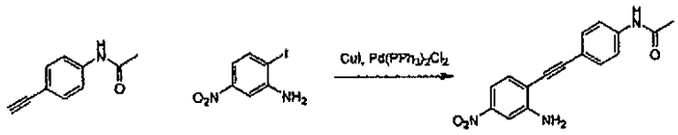


Step 1



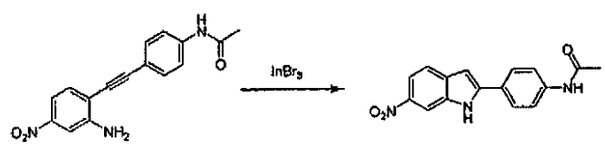
To a stirred solution of 4-ethynylaniline (1 g, 8.5 mmol) in DCM (60 ml) was added acetyl chloride (0.8 g, 10 mmol) and TEA (1.7 g, 17 mmol). The mixture was stirred for 3 hours. The resulting solution was washed with water, 1 N HCl and brine. The organic layer was concentrated *in vacuo* to give the desired product (900 mg), which was used in next step without purification. MS (ESI) m/e (M+H$^+$): 160.

Step 2



To a stirred solution of 4-ethynylacetanilide (800 mg, 3.1 mmol) in anhydrous THF (6 ml) was added compound 2 (0.5 g, 3.1 mmol), $PdCl_2(PPh)_3$ (33 mg, 0.05 mmol), CuI (10 mg, 0.05 mmol) and TEA (2 mL). The mixture was protected from light and stirred at RT overnight. The resulting solution was concentrated *in vacuo*, and the residue was washed with DCM to give the desired compound (300 mg) as a yellow solid. MS (ESI) m/e (M+H$^+$): 296.

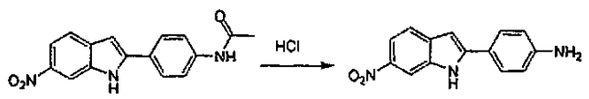
Step 3



To a stirred solution of compound from step 2 above (200 mg, 0.68 mmol) in toluene (2 ml) was added $InBr_3$ (2 mg, 0.004 mmol). The mixture was stirred at reflux for 3 hours. The resulting solution was washed with water and extracted with EtOAc. The combined

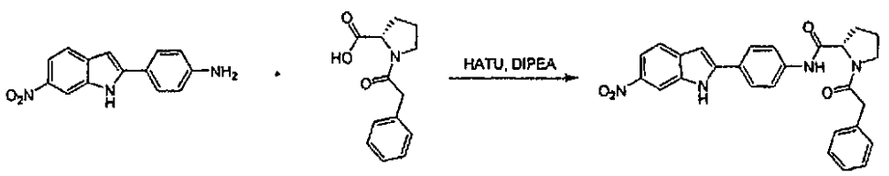
organic layers were dried over sodium sulfate, concentrated *in vacuo* to give the desired indole (170 mg) as a brown solid. MS (ESI) m/e ($M+H^+$): 296.

Step 4



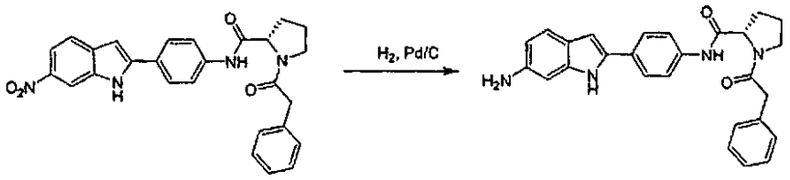
To a stirred solution of the product from step 3 above (100 mg, 0.34 mmol) in EtOH (5 ml) was added 3N HCl (1 mg). The mixture was stirred at reflux overnight. The resulting solution was concentrated *in vacuo* to give the desired aniline (80 mg) as a brown solid. MS (ESI) m/e ($M+H^+$): 254.

Step 5



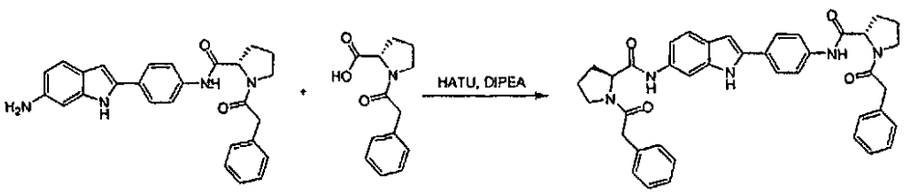
To a solution of the aniline from step 4 (50 mg, 0.2 mmol) in acetonitrile (5 mL) was added *N*-phenylacetyl-L-proline (56 mg, 0.2 mol), HATU (167 mg, 0.4 mmol) and DIPEA (100 mg, 0.8 mmol). The mixture was stirred overnight. The resulting solution was purified by RPLC to give the desired compound (40 mg) as a brown solid. MS (ESI) m/e ($M+H^+$): 469.

Step 6



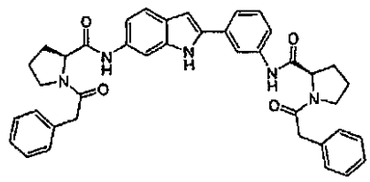
To a solution of the nitro compound (40 mg, 0.08 mmol) in THF (2 mL) was added Pd/C (20 mg, 0.1 mmol). The mixture was stirred under H_2 atmosphere for 1 hour. After replacement of H_2 with N_2, the Pd/C was filtered off, and the filtrate was evaporated *in vacuo* to give the desired aminoindole (40 mg) as a brown solid. MS (ESI) m/e ($M+H^+$): 439.

Step 7

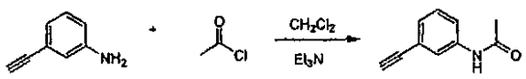


To a solution of the product from step 6 above (40 mg, 0.1 mmol) in acetonitrile (5 mL) was added *N*-phenylacetyl-L-proline (23 mg, 0.1 mmol), HATU (70 mg, 0.2 mmol) and DIPEA (25 mg, 0.2 mmol). The mixture was stirred overnight. The resulting solution was purified by RPLC to give the desired compound (15 mg) as a brown solid. ^{1}H NMR (MeOD) δ: 7.81 (m, 1H), 7.70 (d, *J*=8.6 Hz, 2H), 7.60 (d, *J*=8.4 Hz, 2H), 7.39 (m, 1H), 7.30-7.28 (m, 10H), 6.96 (m, 1H), 6.69 (s, 1H), 4.63-4.50 (m, 2H), 3.78-3.60 (m, 8H), 2.23-1.92 (m, 8H). MS (ESI) m/e (M+H$^+$): 654.

Example 124 – (2S)-1-(phenylacetyl)-N-{3-[6-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}pyrrolidine-2-carboxamide

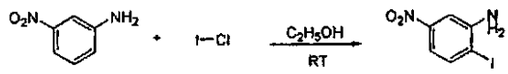


Step 1



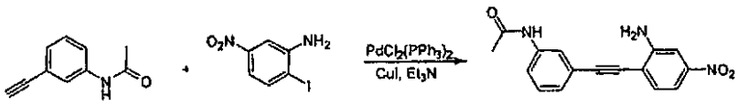
To a solution of 3-ethynylaniline (1.17 g, 10 mmol) and 1.5 ml Et_3N in 40 mL DCM was added dropwise acetyl chloride (1 g, 13 mmol). The reaction mixture was stirred at RT for 1 hour. After that, the solvents were evaporated, and the residue was extracted with EtOAc (100 mL), washed with water (50 mL) and brine (50 mL), dried over anhydrous $NaSO_4$, and concentrated *in vacuo* to afford 3-ethynylacetanilide (1.5 g). MS (ESI) m/e (M+H$^+$): 160.

Step 2



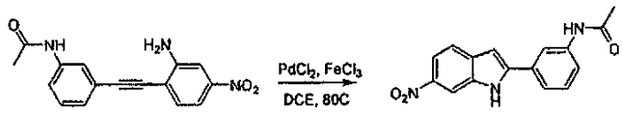
3-nitroaniline (6.9 g, 0.05 mmol) was dissolved in 150ml ethanol, iodine chloride (8.1 g, 0.05 mmol) added with dropwise. The reaction mixture was stirred at RT for 4 hours. After that, the solvents were evaporated, and the residue was extracted with EtOAc (100 mL), washed with water (50 mL) and brine (50 mL), dried over anhydrous $NaSO_4$. After concentrated *in vacuo*, the residue was purified by column chromatography (PE/EtOAc =40:1→20:1) to afford the desired product (8.9 g). MS (ESI) m/e (M+H$^+$): 265.

Step 3



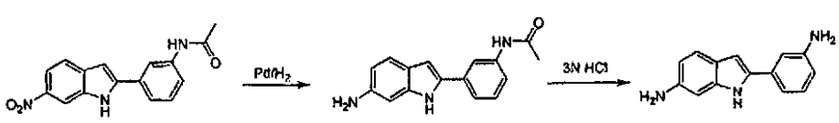
3-Ethynylacetanilide (480 mg, 3 mmol) and 2-iodo-5-introaniline (800 mg, 3 mmol) were dissolved in anhydrous THF (30 mL), $PdCl_2(PPh_3)_2$ (105 mg,0.15 mmol) and CuI (28.5 mg,0.15 mmol) Et_3N(1 ml) was added sequentially. The reaction mixture was protected by N_2 and stirred at RT for overnight. After that, the solvents were evaporated, and the residue was extracted with EtOAc (50x2 mL), washed with water (40 mL) and brine (30 mL), dried over anhydrous $NaSO_4$. After concentrated *in vacuo*, the residue was purified by column chromatography (DCM/MeOH =50:1→20:1) to afford the desired product (620 mg). MS (ESI) m/e ($M+H^+$): 296.

Step 4



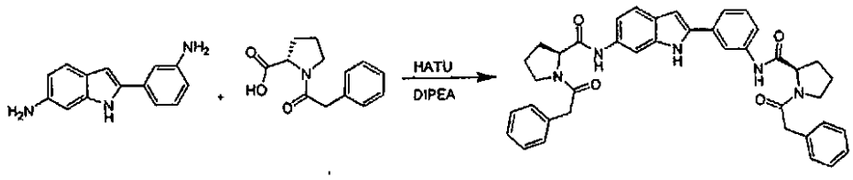
To a solution of the product from step 3 (295 mg, 1.0 mol) in DCE (15 mL) was added $PdCl_2$ (9 mg, 0.05 mmol) and $FeCl_3$ (8 mg, 0.05 mmol). The reaction mixture was heated at 80°C for 2 hours. The reaction was cooled, and the solvents were evaporated, and the residue was extracted with EtOAc (2x), washed with water (30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4. After concentrated *in vacuo*, the residue was purified by Prep-TLC (DCM/MeOH =50:1) to afford the desired product (240 mg). MS (ESI) m/e ($M+H^+$): 296. ^1H NMR (DMSO) δ: 0.12 (s, 1 H), 8.25 (d, *J*= 8.0 Hz, 2 H), 7.45~7.94 (m, 6 H), 7.03 (s, 1 H), 2.10 (s, 3 H).

Step 5



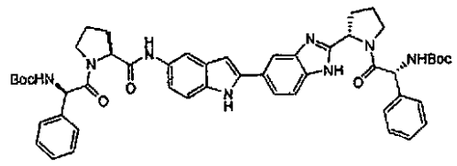
A suspension of the product from step 4 (200 mg, 0.67 mmol), Pd/C (10 mg, 0.034 mmol) in 40 mL EtOH was under H_2 protection and stirred for 1 hour. The mixture was then filtered, and the filtrate was then concentrated to give the product (160 mg). The residue was dissolved in 20 ml 3N HCl, the mixture was stirred at 80°C for 1 hour. It was cooled to RT, concentrated *in vacuo* and the residue was purified to give desired compound (120 mg) as a brown solid. MS (m/z) ($M+H^+$): 224

Step 6

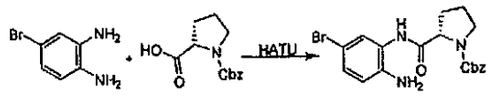


The mixture of compound 10 (50 mg, 0.224 mmol), *N*-phenylacetyl-L-proline (110 mg, 0.45 mmol), DIPEA (88mg, 0.7 mmol) in CH_3CN (5 mL) was stirred at RT for 5 minutes, then HATU (82 mg, 0.54 mmol) was added to it. The mixture was stirred at RT overnight. When reaction completed, the mixture was concentrated *in vacuo*, the residue was purified by chromatography on silica gel to give the desired target (70 mg). MS (ESI) m/e ($M+H^+$): 654 ^1H NMR (MeOD): δ 7.95 (d, J= 8.0 Hz, 2 H), 7.86~7.21 (m, 13 H), 6.98 (d, J= 8.0 Hz, 1 H), 6.72 (s, 1 H), 4.57(m,2H), 3.53 (m, 3 H), 2.02~2.31 (m, 8 H).

Example 125 – tert-butyl [(1R)-2-{(2S)-2-[(2-{2-[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl) amino]-2-phenylacetyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1H-indol-5-yl)carbamoyl] pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate

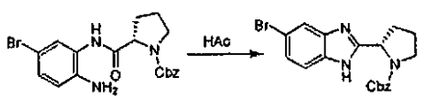


Step 1



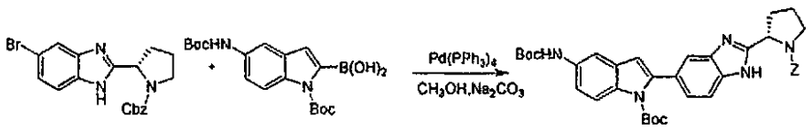
The mixture of 4-bromo-1,2-phenylenediamine (3.1 g, 16 mmol), L-proline (4.3 g, 16 mmol), DIPEA (3 ml) in MeCN (100 mL) was stirred at RT for 5 minutes, then HATU (6 g, 17 mmol) was added. The mixture was stirred at RT overnight. When reaction completed, the mixture was concentrated, the residue was washed with water (100 mL) and extracted with EtOAc (three times), washed with brine (50 mL), dried over anhydrous Na_2SO_4. The residue purified by was purified by column chromatography (DCM/MeOH = 100:1→50:1) to afford the desired compound (5.0 g). MS (ESI) m/e ($M+H^+$): (418,420).

Step 2



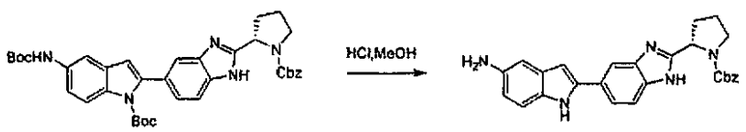
The product from step 1 (5 g, 7.2 mmol) was dissolved in 50 mL acetic acid .The reaction mixture was stirred at 100°C for 4 hours. The mixture was cooled, and the acetic acid was removed *in vacuo*. The residue was purified by column chromatography (DCM/MeOH = 150:1→100:1) to afford the desired compound (3.8 g). MS (ESI) m/e ($M+H^+$): (400,402).

Step 3



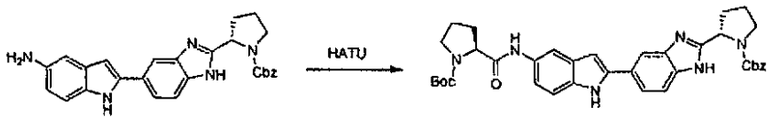
A suspension of the product from step 3 (1.2 g, 3 mmol), 1,5-bis-Boc-5-aminoindole-2-boronic acid (1.2 g, 3 mmol), $Pd(PPh_3)_4$ (240 mg), Na_2CO_3 (1 g, 9 mmol) and H_2O (3 mL) in 30 mL of THF under N_2 protection was reacted with refluxed at 75°C overnight. The mixture was filtered, and the filtrate was washed with 50 mL of water and extracted with 100ml EtOAc and dried over anhydrous Na_2SO_4. Removal of the solvent and column chromatography (CH_2Cl_2/MeOH = 250:1→200:1) afforded the desired compound (500 mg). MS (ESI) m/e (M+H+): 652

Step 4



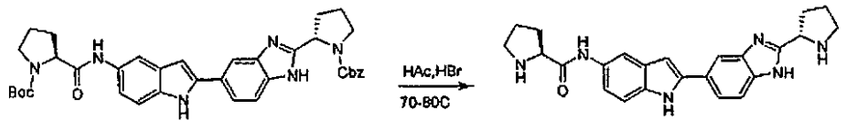
The product from step 3 (500 mg, 0.9 mmol) was stirred in MeOH/HCl (20 mL) for 16 hours. The solvent was removed under reduced pressure and the residue was dried at high vacuum. MS (ESI) m/e ($M+H^+$): 452.

Step 5



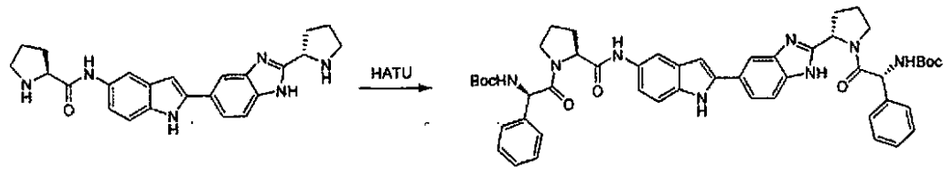
The mixture of aniline from step 4 (450 mg, 1 mmol), (*S*)-*N*-Boc proline (215mg 1mmol), DIPEA (0.4 mL) in CH_3CN (10 mL) was stirred at RT for 10 minutes, then HATU (400 mg, 1.1 mmol) was added. The mixture was stirred at RT overnight, concentrated, and the residue was purified by column chromatography (CH_2Cl_2 / MeOH = 250:1→200:1). MS (ESI) m/e ($M+H^+$): 649.

Step 6



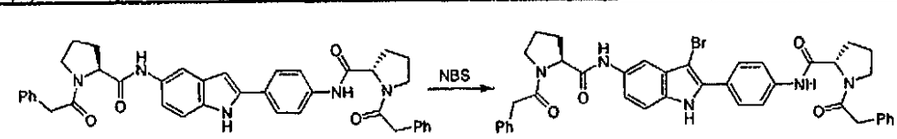
The product from step 5 (290 mg, 0.45 mmol) was dissolved in 5 mL of acetic acid and HBr (1mL) was added. The reaction mixture was heated to 70-80°C and stirred for 4 hours. The mixture was cooled to RT and concentrated *in vacuo*. The residue was extracted with EtOAc (2x), washed with aq $NaHCO_3$ and water (30 mL) and brine (30 mL), dried over anhydrous sodium sulfate. Evaporation of the solvent afforded the desired compound as brown solid (160 mg). MS (ESI) m/e ($M+H^+$): 415.

Step 7



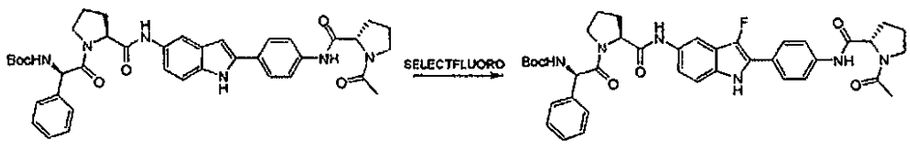
A mixture of the product from step 6 (100 mg, 0.24 mmol), (*R*)-*N*-Boc-Phg (120 mg, 0.48 mmol), DIPEA (0.4 mL) in CH_3CN (10 mL) was stirred at RT for 10 minutes, then HATU (200 mg, 0.5 mmol) was added. The mixture was stirred at RT overnight then concentrated, and the residue was purified by RPLC to afford the desired compound (54 mg). MS (ESI) m/e ($M+H^+$): 882. ^1H NMR (MeOD) δ: 7.96~7.69(m, 4H), 7.49~6.84(m, 13H), 5.50~5.40(m, 2H), 4.06~3.94 (m, 2H), 2.27~1.88 (m, 8H), 1.37 (s, 18H).

Example 126 – (2S)-N-{4-[3-bromo-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)pyrrolidine-2-carboxamide



To a solution of the indole (1 equiv) in 5 mL of THF was added NBS (278 mg, 1 mmol) at RT, and the mixture was stirred for 1 hour. Concentration of the solvent and purification of the residue by RPLC afforded the targeted halogenated compounds. ^1H NMR (MeOD) δ: 7.9-7.5 (m, 5H), 7.4-7.0 (m, 12H), 5.2-4.9 (m, 2H), 4.4 (m, 2H), 3.8-3.5 (m, 6H), 2.5-1.8 (m, 8H).

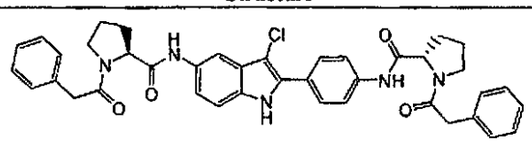
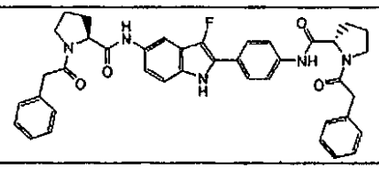
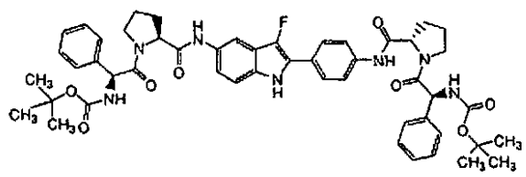
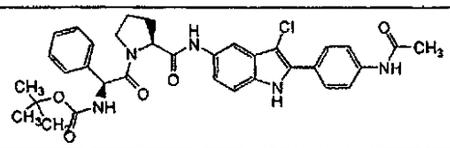
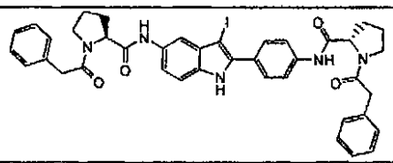
***Example 127* – tert-*butyl* {(1S)-2-[(2S)-2-({2-[4-(acetylamino)phenyl]-3-fluoro-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate**

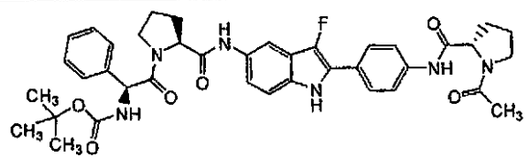
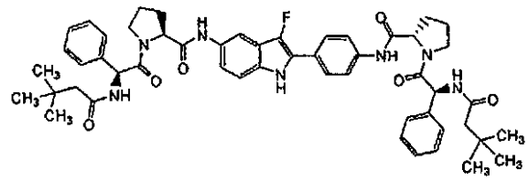
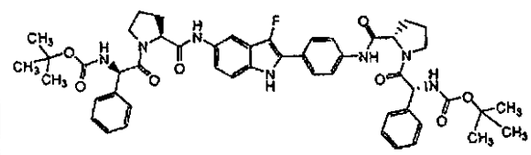
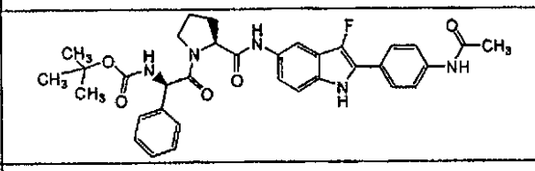
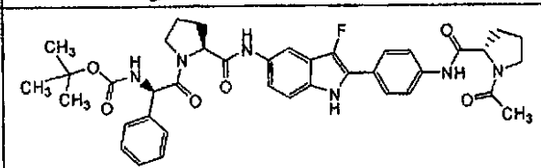
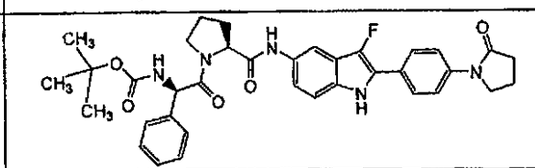
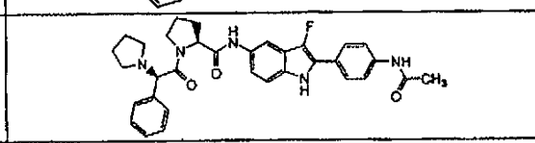
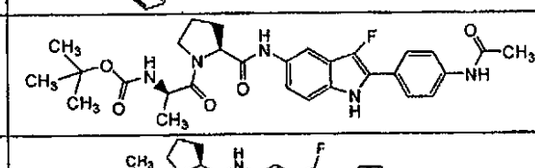
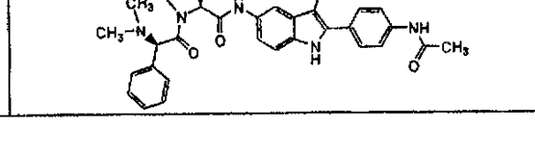


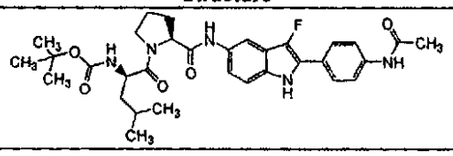
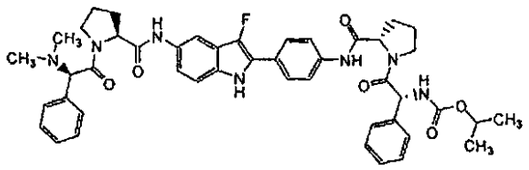
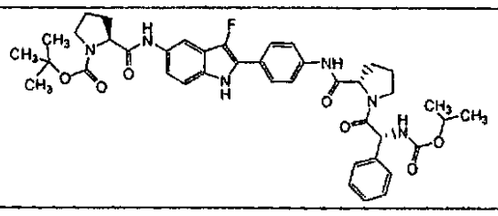
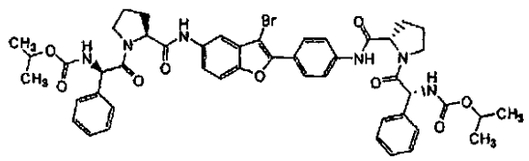
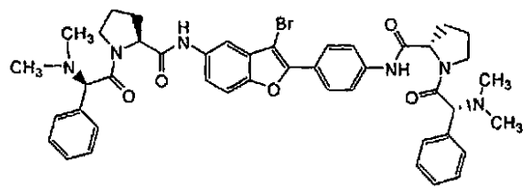
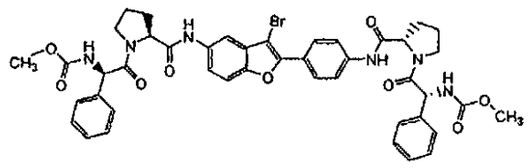
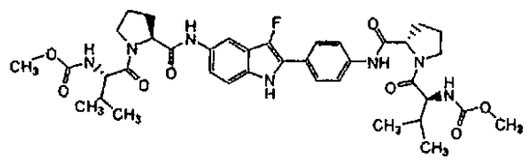
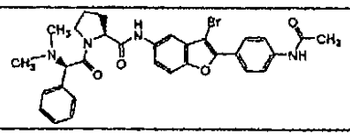
To a solution of the indole (1 equiv.) in acetonitrile/DMSO (5 ml, 1:1) was added SELECTFLUORO (1 equiv.) at 0°C. The mixture was stirred at RT for 3 3 hours before it was concentrated, and the residue purified with RPLC. ^{1}H NMR (MeOD) δ: 7.9-7.c8 (m, 3H), 7.8-7.7 (m, 2H), 7.5-7.3 (m, 6H), 7.3 (m, 1H), 5.5 (s, 1H), 4.6-4.5 (m, 2H), 4.0-3.9 (m, 1H), 3.8 (m, 1H), 3.7 (m, 1H), 2.4-2.3 (m, 1H), 2.2-2.1 (m, 7H), 2.1-2.0 (m, 3H), 2.0-1.9 (m, 1H), 1.4 (m, 9H). MS (m/z): 711 $(M+H)^+$.

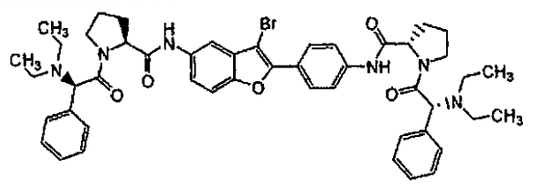
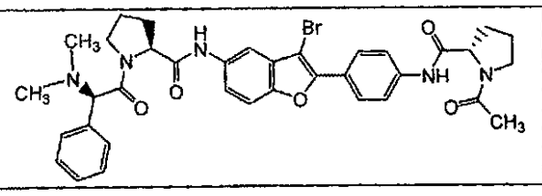
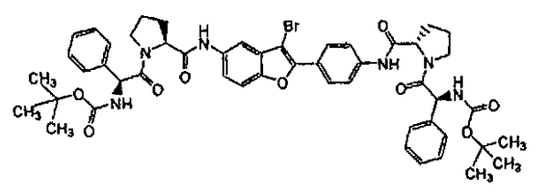
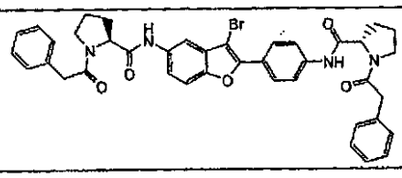
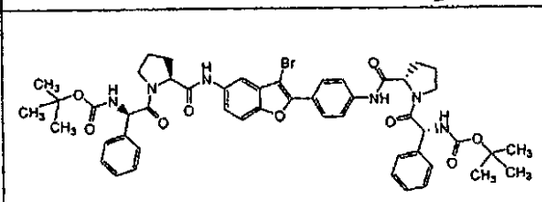
Examples 128-154

Compounds of Examples 128-154 can be prepared by direct halogenation of the indole or benzofuran compounds in a similar manner as described in either Example 126 or Example 127.

Example	Structure	MW	Name
128		688.233	(2*S*)-*N*-{4-[3-chloro-5-({[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide
129		671.778	(2*S*)-*N*-{4-[3-fluoro-5-({[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide
130		902.044	*tert*-butyl {(1*S*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2S)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-fluoro-1*H*-indol-2-yl]phenyl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
131		630.15	*tert*-butyl {(1*S*)-2-[(2*S*)-2-({2-[4-(acetylamino)phenyl]-3-chloro-1*H*-indol-5-yl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
132		779.684	(2*S*)-*N*-{4-[3-iodo-5-({[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl] carbonyl}amino)-1*H*-indol-2-yl] phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide

Example	Structure	MW	Name
133		710.813	*tert*-butyl {(1*S*)-2-[(2*S*)-2-({2-[4-({[(2*S*)-1-acetylpyrrolidin-2-yl]carbonyl}amino)phenyl]-3-fluoro-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
134		898.1	(2*S*)-1-{(2*S*)-2-[(3,3-dimethylbutanoyl)amino]-2-phenylacetyl}-*N*-{4-[5-({[(2*S*)-1-{(2*S*)-2-[(3,3-dimethylbutanoyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-fluoro-1*H*-indol-2-yl]phenyl}pyrrolidine-2-carboxamide
135		902.044	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-fluoro-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
136		613.695	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({2-[4-(acetylamino)phenyl]-3-fluoro-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
137		710.813	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({2-[4-({[(2S)-1-acetylpyrrolidin-2-yl]carbonyl}amino)phenyl]-3-fluoro-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
138		639.733	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({3-fluoro-2-[4-(2-oxopyrrolidin-1-yl)phenyl]-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
139		567.669	*N*-{2-[4-(acetylamino)phenyl]-3-fluoro-1*H*-indol-5-yl}-1-[(2*R*)-2-phenyl-2-(pyrrolidin-1-yl)acetyl]-L-prolinamide
140		551.623	*N*-(*tert*-butoxycarbonyl)-D-alanyl-*N*-{2-[4-(acetylamino)phenyl]-3-fluoro-1*H*-indol-5-yl}-L-prolinamide
141		541.631	*N*-{2-[4-(acetylamino)phenyl]-3-fluoro-1*H*-indol-5-yl}-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-L-prolinamide

Example	Structure	MW	Name
142		593.705	*N*-(*tert*-butoxycarbonyl)-D-leucyl-*N*-{2-[4-(acetylamino)phenyl]-3-fluoro-1*H*-indol-5-yl}-L-prolinamide
143		815.953	propan-2-yl [(1*R*)-2-{(2*S*)-2-[(4-{5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-3-fluoro-1*H*-indol-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate)
144		754.866	*tert*-butyl (2*S*)-2-[(3-fluoro-2-{4-[({(2*S*)-1-[(2*R*)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1*H*-indol-5-yl)carbamoyl]pyrrolidine-1-carboxylate
145		935.88	propan-2-yl [(1*R*)-2-{(2*S*)-2-[(4-{3-bromo-5-[({(2*S*)-1-[(2*R*)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]-1-benzofuran-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate
146		819.806	(2*S*)-*N*-(4-{3-bromo-5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1-benzofuran-2-yl}phenyl)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-carboxamide
147		879.772	methyl {(1*R*)-2-[(2*S*)-2-({4-[3-bromo-5-({[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
148		749.847	methyl {(2*S*)-1-[(2*S*)-2-({4-[3-fluoro-5-({[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate
149		603.521	*N*-{2-[4-(acetylamino)phenyl]-3-bromo-1-benzofuran-5-yl}-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]-L-prolinamide

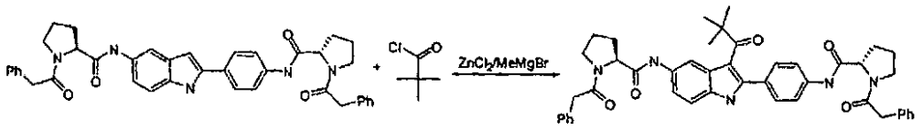
Example	Structure	MW	Name
150		875.915	(2*S*)-*N*-(4-{3-bromo-5-[({(2*S*)-1-[(2*R*)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1-benzofuran-2-yl}phenyl)-1-[(2*R*)-2-(diethylamino)-2-phenylacetyl]pyrrolidine-2-carboxamide
151		700.639	(2*S*)-1-acetyl-*N*-(4-{3-bromo-5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1-benzofuran-2-yl}phenyl)pyrrolidine-2-carboxamide
152		963.935	*tert*-butyl {(1*S*)-2-[(2*S*)-2-({4-[3-bromo-5-({[(2*S*)-1-{(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate)
153		733.669	(2*S*)-*N*-{4-[3-bromo-5-({[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl}-1-(phenylacetyl)pyrrolidine-2-carboxamide
154		963.935	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[3-bromo-5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

Example 155 – (2S)-N-{4-[3-cyano-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)pyrrolidine-2-carboxamide



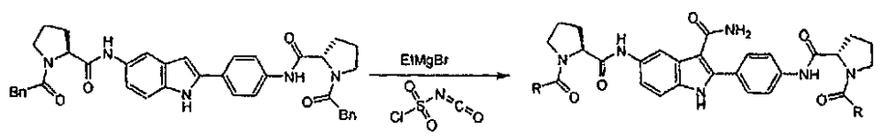
A mixture of the bromo compound from Example 126 (150 mg, 0.2 mmol), CuCN (50 mg, 0.6 mmol) and DMF (3 mL) was refluxed under N_2 protection overnight. The mixture was purified by RPLC to afford the product. MS (ESI) m/e ($M+H^+$): 679. ^1H NMR ($CDCl_3$) δ: 7.73-7.70 (m, 4H), 7.38-7.29 (m, 4H), 7.21-7.04 (m, 6H), 4.63-4.60 (m, 1H), 4.49-4.47 (m, 1H), 3.81-3.59 (m, 4H), 2.48-1.97 (m, 8H).

Example 156 – (2S)-N-{4-[3-(2,2-dimethylpropanoyl)-5-({[(2S)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)pyrrolidine-2-carboxamide



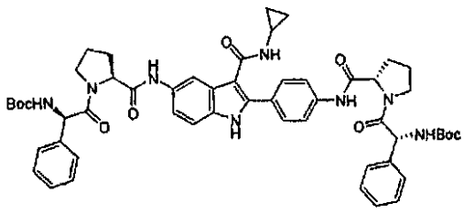
To a stirred solution of the indole (50 mg, 0.076 mmol) in CH_2Cl_2 (5 mL) was added anhydrous $ZnCl_2$ (54 mg, 0.4mmol) then MeMgBr (3.0 M in Et_2O, 0.4 mL, 0.4 mmol). The resulting suspension was stirred for 10 minutes at RT and then cooled to 0°C at an ice bath. A solution of pivaloyl chloride (14 mg) in CH_2Cl_2 (0.2 mL) was added to the mixture. The reaction mixture was allowed to warm to RT and stirred overnight. The reaction mixture was quenched by saturated aqueous NH_4Cl and exacted with CH_2Cl_2 3 times. The organic layers were combined, dried over anhydrous Na_2SO_4 and filtered. The filtrate was concentrated and purified by RPLC to yield the product. MS (ESI) m/e ($M+H^+$): 738. ^1H NMR (MeOD) δ: 7.69-7.63 (m, 3H), 7.44-7.41 (m, 2H), 7.31-7.21 (m, 12H), 4.55-4.52 (m, 2H), 3.76-3.59 (m, 8H), 2.26-1.94 (m, 8H).

Example 157 – 5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-2-[4-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-indole-3-carboxamide

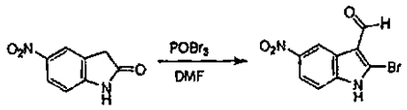


To a solution of the indole (653 mg, 1 mmol) in THF 10 (mL) was added EtMgBr (2 mL, 6 mmol), and the mixture was stirred at RT for 30 minutes. Thereto was added chlorosulfonyl isocyanate (140 mg, 1 mmol), and the mixture was stirred at RT for 20 minutes. Then, DMF (146 mg, 2 mmol) was added to the above mixture, and the stirring continued for 20 minutes. After adding aqueous NaOH (2N, 1mL), the resulting solution was heated at reflux for 5 minutes. Concentration *in vacuo*, the residue was purified with RPLC to give (67 mg). ^1H NMR (MeOD) δ: 8.0 (s, 1H), 7.6 (m, 4H), 7.1-7.4 (m, 12H), 4.5 (m, 4H), 3.5-3.7 (m, 8H), 2.5-2.0 (m, 6H).

Example 158 – **tert-*butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-(cyclopropylcarbamoyl)-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate***



Step 1



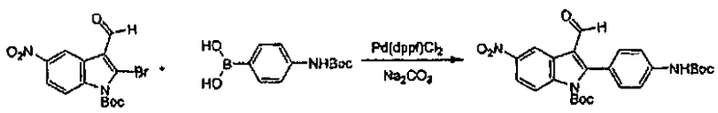
To a solution of $POBr_3$ (113.2 g, 0.4 mol) in DCE (1 L) was added DMF (14.6 g, 0.2 mol) dropwise under ice bath, and the mixture was stirred at RT for 30 minutes. Thereto was added nitro compound (17.8 g, 0.1 mol), and the mixture was stirred at reflux for 4 hours. The precipitate was collected by filtration and then washed with water and MeOH. The solid was dried *in vacuo* to give the desired compound (13.5 g). ^{1}H NMR (DMSO) δ: 13.6 (s, 1H), 9.8 (s, 1H), 8.8 (s, 1H), 8.1 (d, *J*=9.2 Hz, 1H), 7.6 (d, *J*=9.2 Hz, 1H).

Step 2



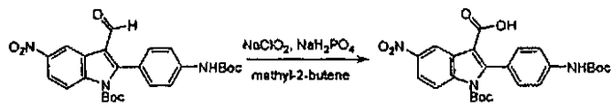
To a solution of the aldehyde from step 1 (13.5 g, 0.05 mol) in DCM (100 mL) was added DMAP (0.6 g, 0.005 mol), TEA (10.1 g, 0.1mol) and $(Boc)_2O$ (21.8 g, 0.1 mol), and the mixture was stirred at RT overnight. The mixture was concentrated, and the residue was purified by column chromatography to give the desired compound (14.7 g). ^{1}H NMR ($CDCl_3$) δ: 9.8 (s, 1H), 8.8 (s, 1H), 8.1 (d, *J*=9.2 Hz, 1H), 7.6 (d, *J*=9.2 Hz, 1H), 1.4 (s, 9H).

Step 3



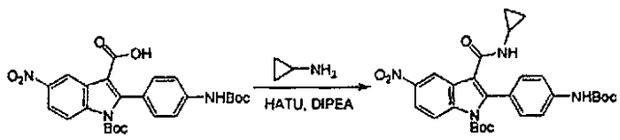
The Suzuki coupling procedure was the same as described in Example 117, step 3. MS (m/z): 482 $(M+H)^+$.

Step 4



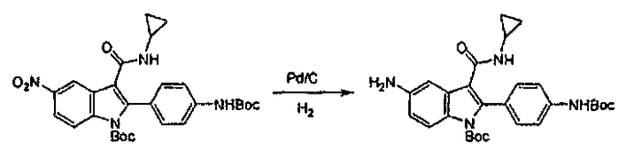
To a solution of compound from step 3 (2.4 g, 5 mmol) in pH 3.5 phosphate buffer (24 mL) and *t*-BuOH (30 mL) was added 2-methyl-2-butene (10 mL) and sodium chlorate (0.89 g, 10 mmol). The reaction was stirred at RT for 16 hours and then extracted with DCM (3x). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to give the desired carboxylic acid (2.3 g). MS (m/z): 498 $(M+H)^+$.

Step 5



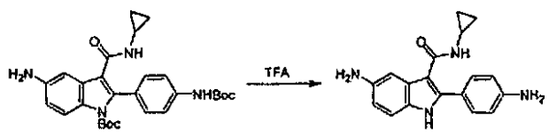
The mixture of compound from step 4 (1 mmol), cyclopropyl amine (1 mmol), HATU (1 mmol) and DIPEA (5 mmol) in DCM was stirred at RT overnight. Concentration and purification of the residue by RPLC gave the desired compound (0.8 mmol). MS (m/z): 538 $(M+H)^+$.

Step 6



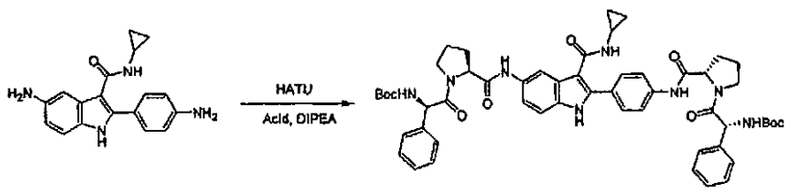
To a solution of the amide from step 5 (0.8 mmol) in MeOH (10 mL) was added Pd/C (100 mg) and the mixture was stirred under H_2 at RT for 1 hour. The Pd/C was removed by filtration, and the filtrate was concentrated to give the desired compound (0.7 mmol). MS (m/z): 507 $(M+H)^+$.

Step 7



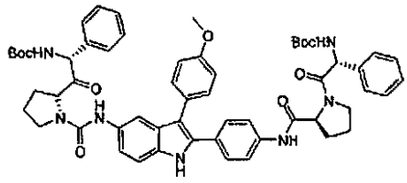
To a solution of compound from step 6 (0.7 mmol) in DCM (5 mL) was added TFA (2 mL), and the mixture was stirred at RT overnight. The solution was concentrated, and the residue was used in next step without purification. MS (m/z): 307 $(M+H)^+$.

Step 8

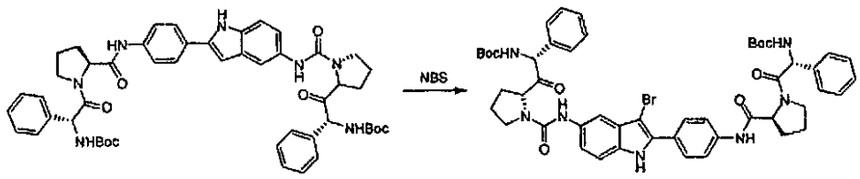


The coupling procedure was the same as used in Example 72, step 7. ^{1}H NMR (MeOD) δ: 6.9-7.9 (m, 17H), 5.2-5.5 (m, 2H), 4.4-4.5 (m, 2H), 3.5-3.9 (m, 3H), 2.7-2.8 (m, 1H), 1.7-2.2 (m, 8H), 1.4 (s, 18H), 1.2 (m, 1H), 0.4-0.8 (m, 4H). MS (m/z): 967 $(M+H)^+$.

Example 159 – **tert-*butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxy-carbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-(4-methoxyphenyl)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate***

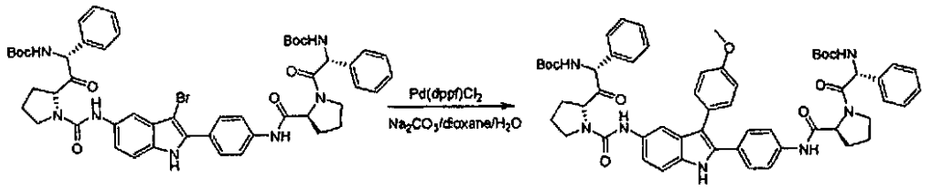


Step 1



NBS (103 mg, 0.5769 mmol) was added in portions to the solution of the indole (510 mg, 0.5769 mmol) in 20 mL of THF, the mixture was stirred at RT for 1 hour, then concentrated. The residue was purified by Prep-HPLC to afford the desired compound (500 mg). MS (ESI) m/e $(M+H^+)$: 962.

Step 2

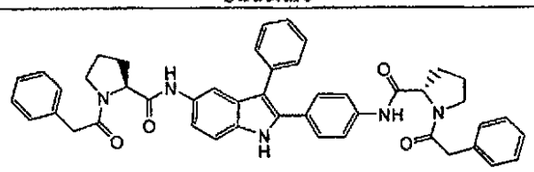
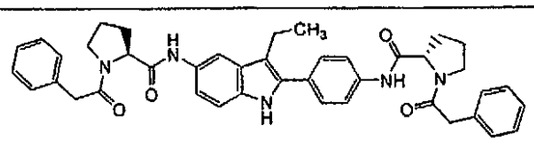
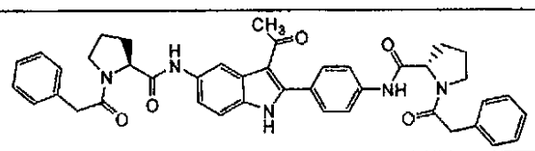
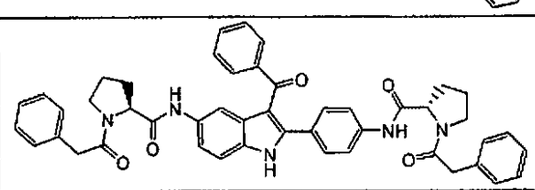
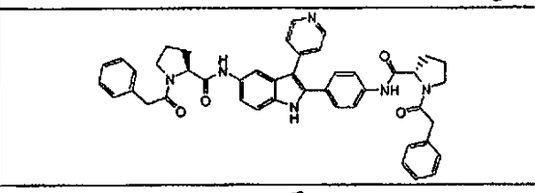
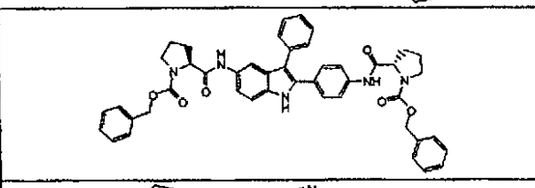
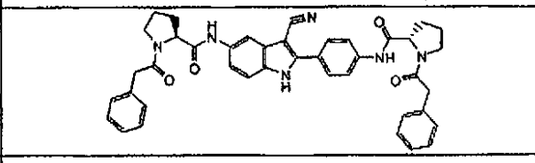
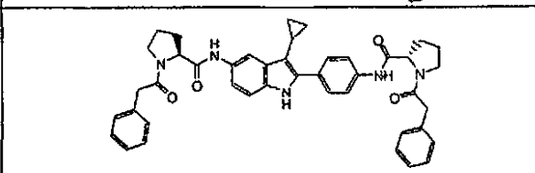


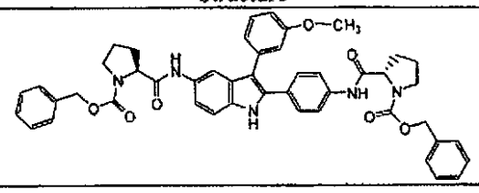
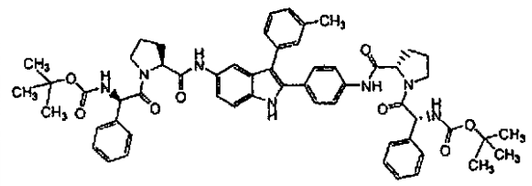
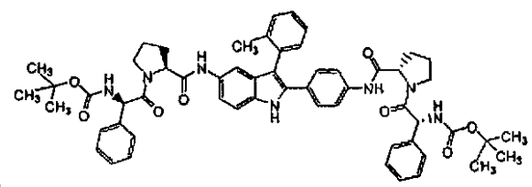
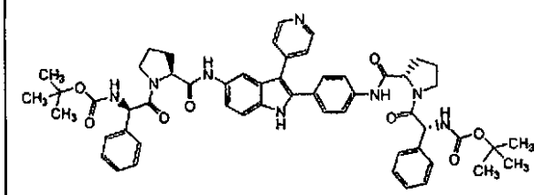
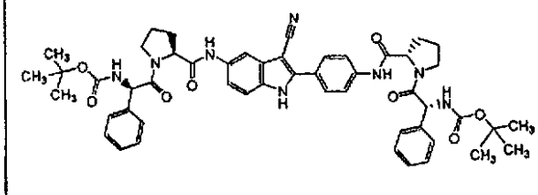
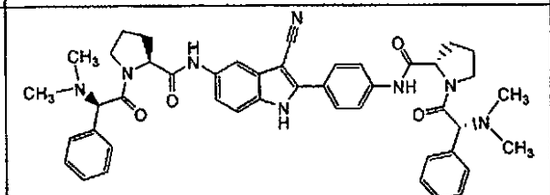
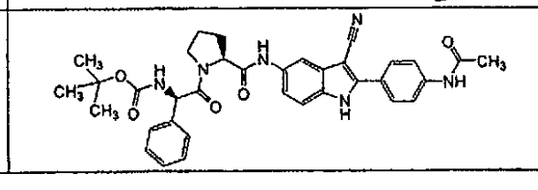
The mixture of the product from step 1 above (100 mg, 0.104 mmol), 4-methoxy-phenylboronic acid (24 mg, 0.1558 mmol), $Pd(dppf)Cl_2$ (7.6 mg, 0.0104 mmol), Na_2CO_3 (3.3 mg, 0.0312 mmol) in 10 mL of dioxane and 2 mL of water was heated to reflux under N_2 atmosphere overnight. The mixture was cooled and concentrated, then the residue was purified

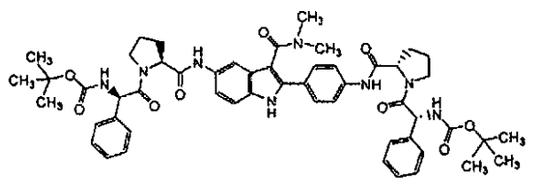
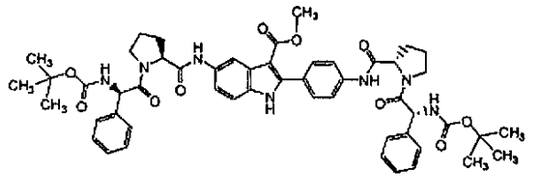
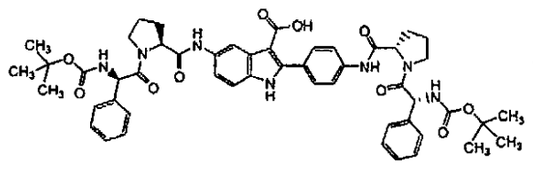
by RPLC to give the desired product (30 mg). ^{1}H NMR (MeOD) δ: 7.71~7.54 (m, 3H), 7.42~7.26 (m, 16H), 6.96~6.92 (m, 3H), 5.45 (s, 2H), 4.53~4.50 (m, 2H), 3.92~3.81 (m, 5H), 2.08~1.84 (m, 8H), 1.42~1.32 (m, 18H). MS (ESI) m/e ($M+H^+$): 991.

Examples 160-177

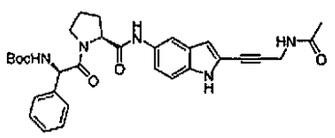
Compounds of Examples 160-177 were prepared in a similar manner as described in Examples 155-159.

Example	Structure	MW	Name
160		729.887	(2*S*)-1-(phenylacetyl)-*N*-{4-[3-phenyl-5-({[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}pyrrolidine-2-carboxamide
161		681.842	(2*S*)-*N*-{4-[3-ethyl-5-({[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide
162		695.826	(2*S*)-*N*-{4-[3-acetyl-5-({[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide
163		757.897	(2*S*)-1-(phenylacetyl)-*N*-{4-[5-({[(2*S*)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl}amino)-3-(phenylcarbonyl)-1*H*-indol-2-yl]phenyl}pyrrolidine-2-carboxamide
164		730.874	(2S)-1-(phenylacetyl)-*N*-{2-[4-({[(2*S*)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl} amino)phenyl]-3-(pyridin-4-yl)-1*H*-indol-5-yl}pyrrolidine-2-carboxamide
165		761.886	benzyl (2*S*)-2-[(4-{5-[({(2*S*)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}carbonyl)amino]-3-phenyl-1*H*-indol-2-yl}phenyl) carbamoyl]pyrrolidine-1-carboxylate
166		678.798	(2*S*)-*N*-{4-[3-cyano-5-({[(2*S*)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide
167		693.853	(2*S*)-*N*-{4-[3-cyclopropyl-5-({[(2*S*)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl}amino)-1*H*-indol-2-yl]phenyl}-1-(phenylacetyl)pyrrolidine-2-carboxamide

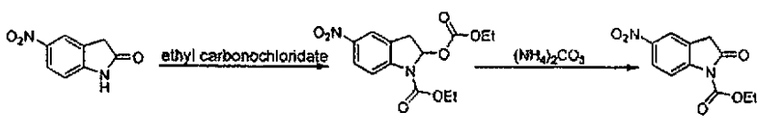
Example	Structure	MW	Name
168		791.912	benzyl (2*S*)-2-[(4-{5-[({(2*S*)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}carbonyl)amino]-3-(3-methoxyphenyl)-1*H*-indol-2-yl}phenyl)carbamoyl]pyrrolidine-1-carboxylate
169		974.18	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-(3-methylphenyl)-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
170		974.18	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-(2-methylphenyl)-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
171		961.14	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({2-[4-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)phenyl]-3-(pyridin-4-yl)-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
172		909.064	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-cyano-1*H*-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
173		764.936	(2*S*)-*N*-(4-{3-cyano-5-[({(2*S*)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1*H*-indol-2-yl}phenyl)-1-[(2*R*)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-carboxamide
174		620.714	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({2-[4-(acetylamino)phenyl]-3-cyano-1*H*-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

Example	Structure	MW	Name
175		955.133	*tert*-butyl {(1*R*)-2-[(2*S*)-2-({4-[5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-(dimethylcarbamoyl)-1*H*-indol-2-yl]phenyl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
176		942.091	methyl 5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-2-[4-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)phenyl]-1*H*-indole-3-carboxylate
177		928.064	5-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-2-[4-({[(2*S*)-1-{(2*R*)-2-[(*tert*-butoxycarbonyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino) phenyl]-1*H*-indole-3-carboxylic acid

Example 178 – **tert-*butyl {(1R)-2-[(2S)-2-({2-[3-(acetylamino)prop-1-yn-1-yl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate***

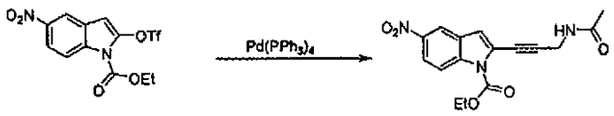


Step 1



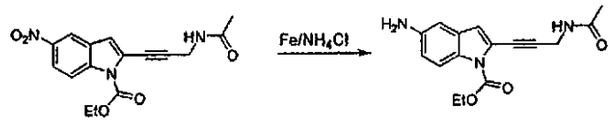
Ethyl carbonochloridate (3 mL) was added to the nitro lactam (2.0 g, 11.2 mmol), and the mixture was stirred for 3 hours before being concentrated to give the crude product. MS (ESI) m/e (M+H+): 325. The crude product was dissolved in DMF (25 mL), then $(NH_4)_2CO_3$ (1.5 g) was added, and the mixture was stirred overnight. The mixture was evaporated and the residue was poured into ice-water and extracted with DCM, and the organics were dried. The solvent was removed, and the residue was purified by chromatography on silica gel to give the desired compound as a white solid. MS (ESI) m/e ($M+H^+$): 251.

Step 2



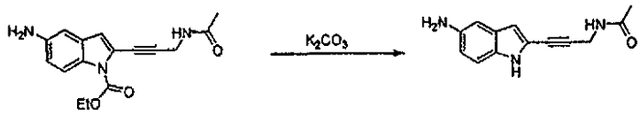
The mixture of the triflate (382 mg, 1.0 mmol), *N*-(prop-2-ynyl)acetamide (97 mg, 1.0 mmol), Et_3N (3 mL) in CH_3CN(3 mL) was stirred at RT for 3 hours. The mixture was concentrated, and the residue was purified by chromatography on silica gel to give compound target compound (254 mg). MS (ESI) m/e ($M+H^{+}$): 330.

Step 3



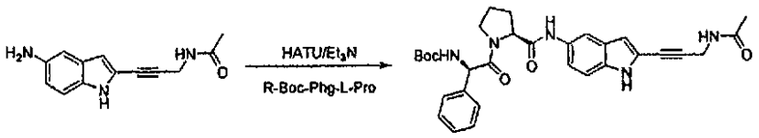
A solution of the nitro compound from step 2 above (165 mg, 0.50 mmol) in absolute EtOH (3 mL) was added Fe power (280 mg, 2.5 mmol) and NH_4Cl (535 mg, 5.0 mmol). The mixture was stirred at 70°C for 2 hours, cooled and poured into ice/water (50ml). The mixture was extracted with EtOAc (200 ml), and the organic phase was combined and washed with brine, dried and concentrated to yield the crude product (150mg). MS (ESI) m/z :(M+H) 300.

Step 4



To a solution of the aniline from step 3 (150 mg, 0.50 mmo) in absolute EtOH (3 mL) was added K_2CO_3 (138 mg, 1.0 mmol), and the mixture was stirred at RT for 12 hours. The reaction mixture was poured into water (10 mL), extracted with EtOAc (20 mL), and the organic phases were combined and washed with brine, dried over $MgSO_4$ and concentrated to yield the crude product (113mg). MS (ESI) m/z :(M+H+) 228.

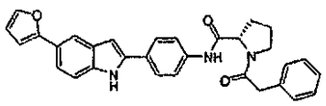
Step 5



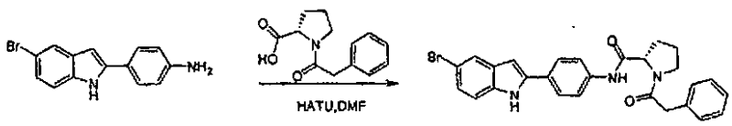
The mixture of the indole (113 mg, 0.5 mmol), R-Boc-Phg-L-Pro-OH (175 mg, 0.5 mmol), DIPEA (115 mg, 1.0mmol) in MeCN (2 mL) was stirred at RT for 5 minutes, then HATU (190 mg, 0.5 mmol) was added into the mixture. The mixture was stirred at RT overnight

then concentrated. The residue was purified by RPLC to give the desired compound (110 mg). ^{1}H NMR (MeOD) δ: 1.37 (s, 9H), 1.96 ~ 2.14 (m, 7H), 3.92 ~ 3.94 (m, 2H), 4.51 ~ 4.54 (m, 1H), 5.41 (s, 1H), 6.56 (s, 1H), 7.20 ~ 7.43 (m, 7H), 7.72 (s, 1H). MS (ESI) m/z :(M+H+) 576.

Example 179 – N-{4-[5-(furan-3-yl)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)-L- prolinamide

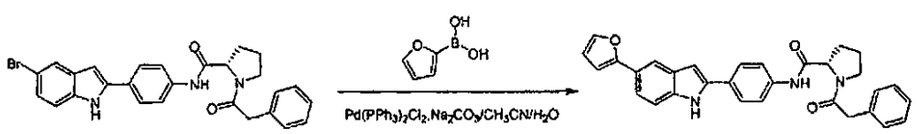


Step 1



The mixture of the indole from Example 41 (1.6 mg, 5.575 mmol), 1-phenylacetyl pyrrolidine-2-carboxylic acid (1.3 g, 5.575 mmol), DIPEA (1.45 g, 11.15 mmol) in DMF (50 mL) was stirred at RT for 30 minutes, then HATU (2.54 g, 6.689 mmol) was added. The mixture was stirred at RT overnight, concentrated *in vacuo*, and the residue was purified by chromatography on silica gel to give the desired product (2.3 g). MS (ESI) m/e ($M+H^+$): 504.

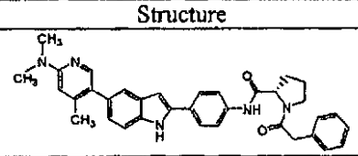
Step 2

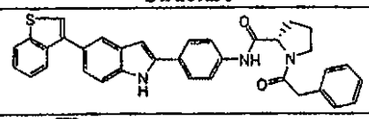
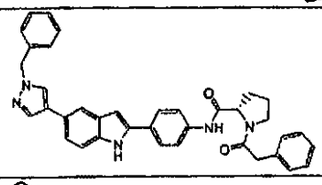
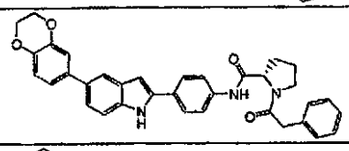
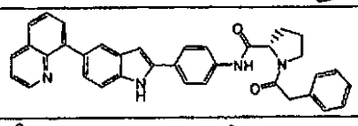
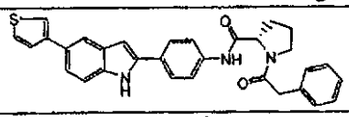
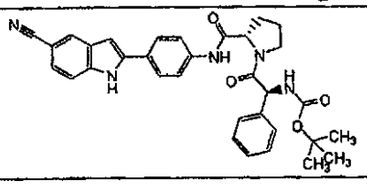
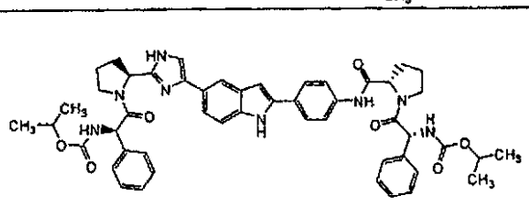
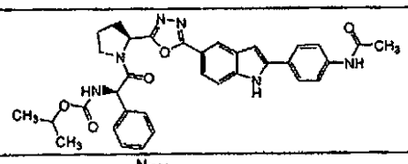
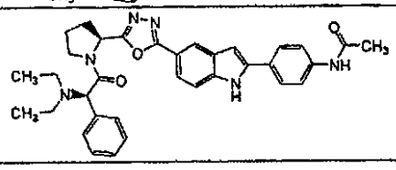
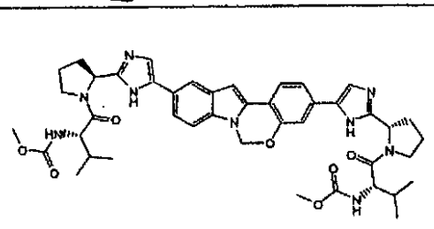


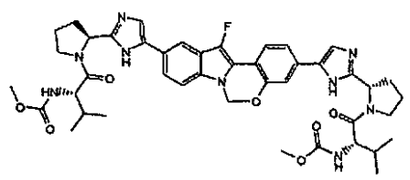
A suspension of the product from step 1 above (18 mg, 0.03583 mmol), furan-2-boronic acid (6 mg, 0.05374 mmol), $Pd(PPh_3)_2Cl_2$ (1.4 mg), Na_2CO_3 (7.6 mg, 0.07166 mmol) and H_2O (0.15 mL) in 0.5 mL of acetonitrile under N_2 protection was heated at 150°C for 10 mintues in a microwave reactor. The mixture was cooled, filtered and washed with 10 mL of DCM. The solvents were removed, and the residue was purified by HPLC to give the desired product. ^{1}H NMR (MeOD) δ: 7.79~7.74 (m, 3H), 7.67~7.62 (m, 3H), 7.50 (s, 1H), 7.37~7.22 (m, 6H), 6.78~6.75 (m, 2H), 4.57~4.55 (m, 1H), 3.78~3.61 (m, 4H), 2.24~1.99 (m, 4H).

Examples 180-189b

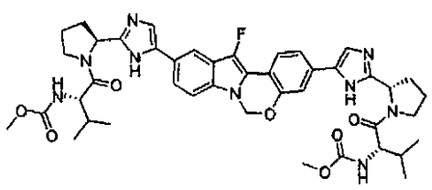
Compounds of Examples 180-189b were prepared in a similar manner as described in Example 179.

Example	Structure	MW	Name
180		557.701	*N*-(4-{5-[6-(dimethylamino)-4-methylpyridin-3-yl]-1*H*-indol-2-yl}phenyl)-1-(phenylacetyl)-L-prolinamide

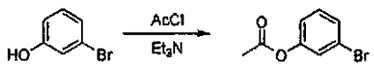
Example	Structure	MW	Name
181		555.704	*N*-{4-[5-(1-benzothiophen-3-yl)-1*H*-indol-2-yl]phenyl}-1-(phenylacetyl)-L-prolinamide
182		579.708	*N*-{4-[5-(1-benzyl-1*H*-pyrazol-4-yl)-1*H*-indol-2-yl]phenyl}-1-(phenylacetyl)-L-prolinamide
183		557.655	*N*-{4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-1*H*-indol-2-yl]phenyl}-1-(phenylacetyl)-L-prolinamide
184		550.666	1-(phenylacetyl)-*N*-{4-[5-(quinolin-8-yl)-1*H*-indol-2-yl]phenyl}-L-prolinamide
185		505.644	1-(phenylacetyl)-*N*-{4-[5-(thiophen-3-yl)-1*H*-indol-2-yl]phenyl}-L-prolinamide
186		563.662	*tert*-butyl {(1*S*)-2-[(2*S*)-2-{[4-(5-cyano-1*H*-indol-2-yl)phenyl]carbamoyl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
187		879.037	propan-2-yl [(1*R*)-2-oxo-1-phenyl-2-{(2*S*)-2-[4-(2-{4-[({(2*S*)-1-[(2*R*)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1*H*-indol-5-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}ethyl]carbamate
188		606.687	propan-2-yl {(1*R*)-2-[(2*S*)-2-(5-{2-[4-(acetylamino)phenyl]-1*H*-indol-5-yl}-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
189		576.704	*N*-{4-[5-(5-{(2*S*)-1-[(2*R*)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1,3,4-oxadiazol-2-yl)-1*H*-indol-2-yl]phenyl}acetamide
189a		806.9	methyl [(2*S*)-1-{(2*S*)-2-[5-(10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}indolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example	Structure	MW	Name
189b		824.9	methyl [(2*S*)-1-{(2*S*)-2-[5-(12-fluoro-10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}indolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 189b (Alternative Procedure: Methyl [(2S)-1{(2S)-2-[5-(12-fluoro-10-{2-[(2S)-1-{(2s)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}indolo[1,2-c][1,3]benzoxazin-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

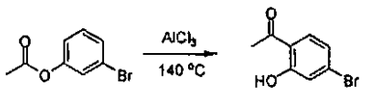


Step 1



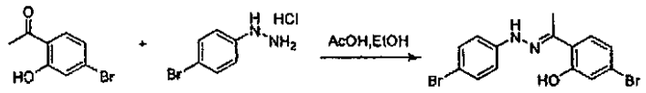
To a solution of compound 3-bromophenol (51 g, 0.3 mol) and Et_3N (36 g, 0.36 mol) in 500 mL of DCM was added dropwise acetyl chloride (26 g, 0.33 mol) in an ice-water bath. The mixture was stirred at RT for 30 minutes. The mixture was washed with 1 N HCl, saturated Na_2CO_3 and brine, dried over Na_2SO_4 and concentrated *in vacuo* to give a oil (62 g).

Step 2



$AlCl_3$ (40 g, 0.3 mol) was slowly added to the product from step 1 (21.5 g, 0.1 mol) in an ice-water bath. The mixture was stirred at 140°C for 2 hours. After cooling to 60-70°C, the mixture was slowly poured into an ice water. The resulting solution was extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography to give the desired compound (14 g). MS (ESI) m / e ($M+H^+$): 214.

Step 3



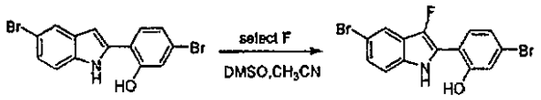
A mixture of the ketone obtained in step 2 (4.2 g, 20 mmol) and 4-bromophenyl hydrazine hydrochloride (4.4 g, 20 mmol) in AcOH and EtOH (1:10, 100 mL) was heated to reflux for 6 hours. The solvent was removed *in vacuo* to give a solid, which was used in the next step without further purification (9.2 g crude). MS (ESI) m / e ($M+H^+$): 383.

Step 4



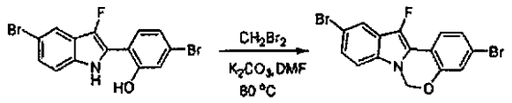
A mixture of product from step 3 (9.2 g) in PPA was heated to 80°C for 2 hours. After cooling to RT, the mixture was poured into ice water. The resulting solution was extracted with DCM. The combined organic phases were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography to give the desired indole (4.8 g). MS (ESI) m / e ($M+H^+$): 368.

Step 5



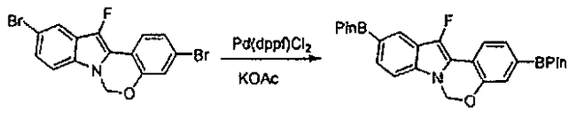
To a mixture of the indole from step 4 (6 g, 16.3 mmol) in DMSO/CH_3CN (1:1, 24 mL) was added SELECTFLUOR® (5.8 g, 16.3 mmol) in portion at RT. The mixture was stirred for an additional 1 hour at RT, and the mixture was purified by HPLC to give a solid (1.0 g). MS (ESI) m / e ($M+H^+$):386.

Step 6



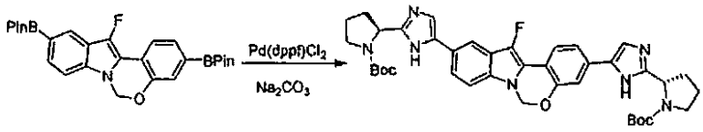
A mixture of the compound from step 5 (650 mg, 1.63 mmol), CH_2Br_2 (1.5 g, 8.62 mmol) and K_2CO_3 (1.2 g, 8.7 mmol) in DMF (32.5 mL) was stirred for 5 hours at 80°C. Then the mixture was evaporated *in vacuo*. The residue was diluted with EA and water. The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo* to give a solid, which was directly used to next step without further purification (610 mg). MS (ESI) m / e ($M+H^+$):396.

Step 7



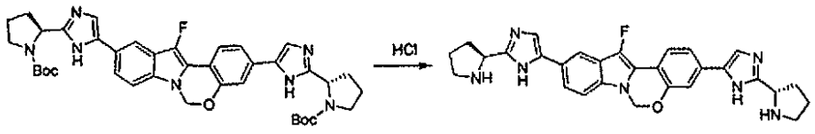
To a solution of the product from step 6 (1 mmol) in 1,4-dioxane was added bis pinacol borate (1.1 mmol) and $Pd(dppf)Cl_2$ (0.02 mmol) and KOAc (2 mmol). The reaction mixture was stirred under N_2 and heated to 110°C for 3 hours. After that, the solvent was removed under vacuum, and the residue was purified by column chromatography to afford the product. MS (ESI) m / e ($M+H^+$):492.

Step 8



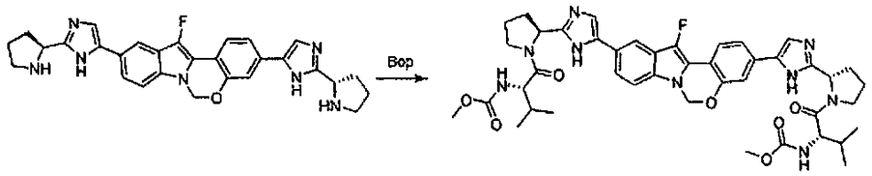
A suspension of the boronate from above (2 mmol), *tert*-butyl 2-(2-bromo-1*H*-imidazol-5-yl) pyrrolidine-1-carboxylate (2.4 mmol), $Pd(dppf)Cl_2$ (200 mg), Na_2CO_3 (3 mmol) and in THF/H_2O (10:1, 33 mL) was refluxed at 75°C overnight under N_2 protection. The mixture was cooled and filtered, and the filtrate was washed with water (50 mL) and extracted with EtOAc (100 mL), washed with brine and dried over anhydrous sodium sulfate. After concentrated *in vacuo*, the residue was purified by column chromatography to afford the desired compound. MS (ESI) m / e ($M+H^+$):710.

Step 9



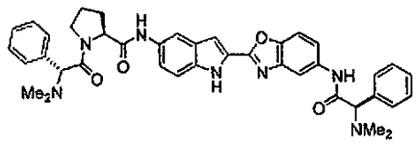
The protected proline from above (1.3 mmol) was added to HCl/CH_3OH (10 mL, 3M). The mixture was stirred at RT for 2-3 hours before the mixture was concentrated to give the crude product, which was used in the next step without further purification. MS (ESI) m / e ($M+H^+$):510

Step 10

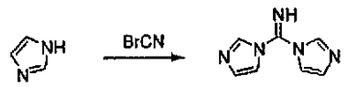


To a mixture of the crude product from step 9 (1.0 mmol), (*S*)-2-(methoxycarbonylamino)-3-methylbutanoic acid (2.0 mmol) and DIPEA (8 mmol) in CH_3CN (10 mL) was added BOP (2.2 mmol). The resulting mixture was stirred at RT. After LCMS showed the starting material to be consumed, the mixture was filtered, and the filtrate was purified by HPLC to give the desired compound as a white solid. MS (ESI) m / e ($M+H^+$):825. ^1H NMR (MeOD): δ 7.83 - 7.85 (m, 3 H), 7.72 (s, 1 H), 7.53 (s, 2 H), 7.46 - 7.48 (m, 1 H), 7.42 (s, 1 H), 5.92 (s, 2 H), 5.20 - 5.22 (m, 2 H), 4.20 - 4.23 (m, 2 H), 4.06 - 4.09 (m, 2 H), 3.86 - 3.88 (m, 2 H), 3.61 (s, 6 H), 2.50 - 2.52 (m, 2 H), 1.96 - 2.20 (m, 8 H), 0.90 - 0.98 (m, 12 H).

Example 190: (2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-N-(2-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1,3-benzoxazol-2-yl}-1H-indol-5-yl)pyrrolidine-2-carboxamide

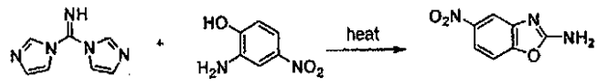


Step 1



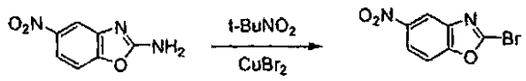
To a solution of imidazole (13.6 g, 0.2 mol) in 1L of DCM was added BrCN (7.4 g, 66 mmol), and the mixture was heated at reflux for 30 minutes. The mixture was cooled to RT, and the white precipitate removed by filtration, and the filtrate concentrated to 100 mL then cooled to 0°C for 2 days. The crystallized solid was filtered and washed with cold DCM, then dried *in vacuo* to give the desired product (8.8 g) as a white solid.

Step 2



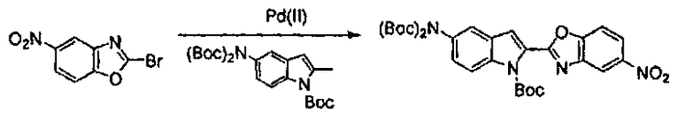
A solution containing the product from step 1 (8.36g, 54.2 mmol) and 2-amino-4-nitrophenol (8.74g, 54.2 mmol) in anhydrous THF (200 mL) was allowed to reflux under N_2 for 14 hours. The mixture was cooled to RT, filtered, and the precipitate was washed with THF (cold) then dried *in vacuo* to afford the desired product (9.0g), as a yellow solid. MS (ESI) m/e ($M+H^+$): 180. ^1H NMR (DMSO) δ: 7.85 ~ 7.96(m, 3 H), 7.52(d, J = 8.8 Hz, 1H).

Step 3



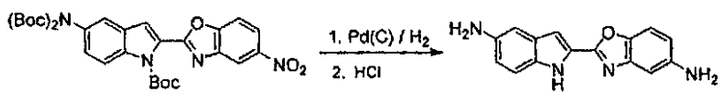
To a suspension of the product from step 2 (3.58 g, 20 mmol) in acetonitrile (300 mL) was added $CuBr_2$ (8.96 g, 40 mmol). The solution became dark green and *t*-butyl nitrite (4.12 g, 40 mmol) was added RT over 5 minutes, whereupon the mixture heated at 45°C for 2 hours. The reaction mixture was poured into water (800 mL) and DCM (800 mL), and the phases were separated. The aqueous phase was extracted with DCM (3 X 800 mL), dried with Na_2SO_4 and evaporated to afford the crude product. Purification by column chromatography afforded the desired product. MS (ESI) m/e ($M+H^+$): 243/245. ^1H NMR (DMSO) δ: 8.71 (s, 1 H), 8.42(d, J = 9.2 Hz, 1H), 8.10 (d, J = 9.2 Hz, 1H).

Step 4



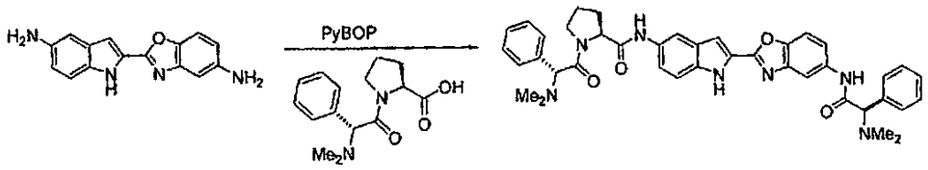
The mixture of compound from step 3 above (603 mg, 2.5 mmol), the indole boronic acid from Example 42 (1.0 g, 2.75mmol), $Pd(dppf)Cl_2$ (183 mg, 0.25 mmol), Na_2CO_3 (530 mg, 5.0 mmol) in 5 mL dioxane-H_2O (5:1) was heated to reflux under N_2 atmosphere overnight. When reaction was complete, the mixture was poured into water and extracted with DCM. The organic phase was dried over Na_2SO_4 and concentrated, and the residue was purified to give compound the desired product. MS (ESI) m/e ($M+H^+$): 596.

Step 5



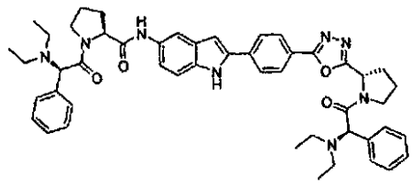
The product from step 4 (596 mg, 1.0 mmol) was dissolved in EtOAc and treated with Pd/C (100 mg, 20%). Then, the mixture was stirred at RT overnight under H_2 atmosphere. When the reaction was complete, the Pd/C was filtered off, and the resulting solution was concentrated to give the crude product MS (ESI) m/e ($M+H^+$): 565. This material was covered with 5 mL of 3M HCl, and the mixture was stirred at RT for 2 hours. Evaporation of the solvent afforded the desired product, which was used directly without further purification. MS (ESI) m/e ($M+H^+$): 265.

Step 6

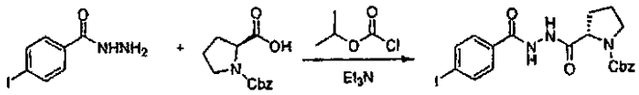


The compound was coupled using the procedure similar to that which was described in Example 40 starting from 265 mg (1.0 mmol) of the product from step 5. ^{1}H NMR (MeOD) δ: 8.12(s, 1H), 7.97(d, J=2Hz, 1H), 7.30 ~ 7.70 (m, 15H), 5.30 ~ 5.35 (m, 2H), 4.51 ~ 4.60 (m, 2H), 3.85 ~ 3.95(m, 2H), 3.15 ~ 3.25(m, 2H), 3.06(s, 3H), 2.54(s, 6H), 1.80 ~ 2.30(m, 8H). MS (ESI) m / e (M+H$^+$): 781.

Example 191: 1-[(2R)-2-(diethylamino)-2-phenylacetyl]-N-{2-[4-(5-{(2S)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1,3,4-oxadiazol-2-yl)phenyl]-1H-indol-5-yl}-L-prolinamide

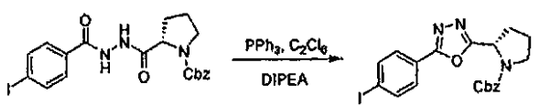


Step 1



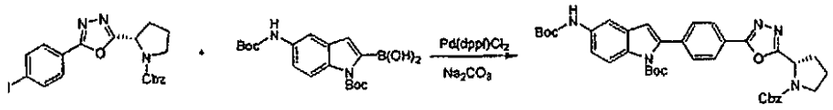
To a solution of N-Cbz-L-Pro (14.9 g, 0.06 mol) and TEA (8.08 g, 0.08 mol) in 100 mL of DCM added dropwise isopropyl chloroformate (8.05 g, 0.066 mol) at 0°C. After addition, the solution was continued to stir for 1 hour before the hydrazide (13.0 g, 0.05 mol) was added, and the mixture was continued to stir for another 1 hour. The solvent was evaporated *in vacuo*, and the residue was recrystallized from EtOH to give a white solid (22.1 g). ^{1}H NMR (DMSO) δ: 10.47 (s, 1H), 10.03 (s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.62 (d, J = 8.0 Hz, 2H), 7.31 ~ 7.61 (m, 5H), 4.91 ~ 5.14 (m, 2 H), 4.26 ~ 4.35 (m, 1 H), 3.30 ~ 3.4 (m, 2 H), 1.95 ~ 2.19 (s, 4 H). MS (ESI) m/e (M+H$^+$): 494.

Step 2



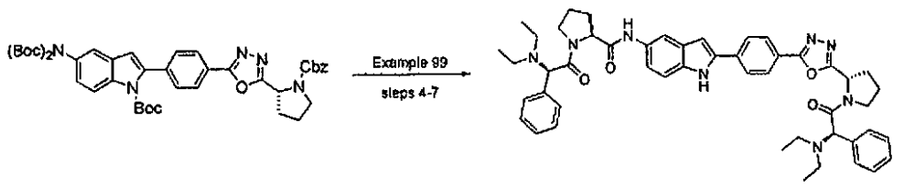
To a solution of the product from step 1 (2.1 g, 4.26 mmol), DIPEA (2.3 mL, 17.7 mmol) and PPh_3 (1.71 g, 6.5 mmol) in 20 mL of MeCN was added hexchloroethane (1.41 g, 5.97 mmol), and the mixture was stirred at RT for 1.5 hours. The solvent was evaporated, and the residue was purified by chromatography to give a white solid (1.75 g). MS (ESI) m/e ($M+H^+$): 494.

Step 3



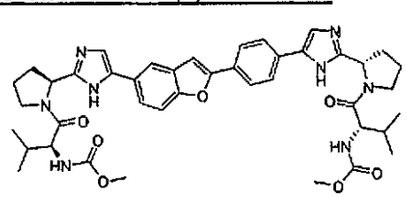
A mixture of the product from step 2 above (494 mg, 1.0 mmol), indole boronic acid from Example 42 (377 mg, 1.0 mmol), $Pd(dppf)Cl_2$ (73 mg, 0.10 mmol), Na_2CO_3 (318 mg, 3.0 mmol), THF (25 mL) and H_2O (5 mL) was refluxed under N_2 overnight. The mixture was poured into water and extracted with CH_2Cl_2. The organic phase was combined, dried over Na_2SO_4 and filtered to give the desired compound, which was used directly in the next step. MS (ESI) m/e ($M+H^+$): 680.

Step 4

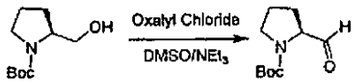


Following the procedure described in Example 99, steps 4-7, the oxadiazole from step 3 above was converted to the desired product. ^1H NMR (MeOD) δ: 8.09 (d, J = 8.8 Hz, 2H), 7.99 (d, J= 8.8 Hz, 2H), 7.83 (s, 1H), 7.66 ~ 7.68 (m, 4H), 7.55 ~ 7.58 (m, 6H), 7.38 ~ 7.40 (m, 1H), 7.22 ~ 7.24 (m, 1H), 6.98 (s, 1H), 5.39 (s, 1H), 5.37 ~ 5.39 (m, 2H), 4.52 ~ 4.54 (m, 1H), 4.12 ~ 4.14 (m, 1H), 3.94 ~ 3.96 (m, 1H), 3.10 ~ 3.41 (m, 8H), 2.72 ~ 2.76 (m, 2H), 1.84 ~ 2.24 (m, 8H), 1.34 ~ 1.41 (m, 6H), 1.16 ~ 1.19 (m, 6H). MS (ESI) m/e ($M+H^+$): 821.

Example 192: Methyl {(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(methoxy- carbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

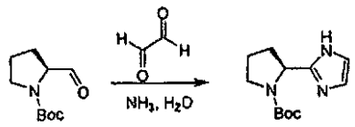


Step 1



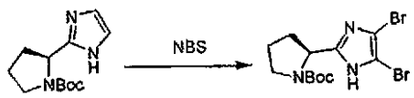
A 2 L, 3-necked round bottomed flask equipped with an overhead stir and a N_2 inlet was charged with a solution of oxalyl chloride (130 mL, 0.26 mol) in DCM (250 mL). The solution was cooled to -78°C, and a solution of DMSO (20 mL, 0.28 mol) in DCM (30 mL) was added dropwise. After 30 minutes, a solution of (*S*)-*N*-Boc-prolinol (40 g, 0.20 mol) in DCM (200 mL) was added dropwise. After 30 minutes, TEA (140 mL, 1.00 mol) was added to the solution, and the flask was transferred to an ice/water bath and stirred for another 30 minutes. The reaction mixture was diluted with DCM (200 mL) and washed successively with H_2O, 1M HCl, saturated $NaHCO_3$, and brine. The DCM layer was dried over Na_2SO_4, filtered, and concentrated to afford crude (*S*)-2-formyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (40 g) as an oil, which was used without further purification.

Step 2



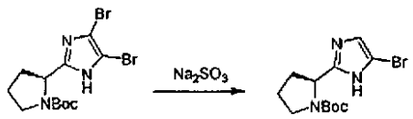
Glyoxal (2.0 mL of 40% in water) was added dropwise over 11 minutes to a methanol solution of NH_4OH (32 mL) and (*S*)-Boc-prolinal (8.564 g, 42.98 mmol) and stirred at ambient temperature for 19 hours. The volatile components were removed *in vacuo*, and the residue was purified by a flash silica gel chromatography (EtOAc) followed by a recrystallization (EtOAc) to provide the desired compound as a white fluffy solid (4.43 g). ^1H NMR (DMSO) δ: 11.68, 11.59 (br s, 1H), 6.94 (s, 1H), 6.76 (s, 1H), 4.76 (m, 1H), 3.48 (m, 1H), 3.35-3.29 (m, 1H), 2.23-1.73 (m, 4H), 1.39/1.15 (s, 9H). MS (ESI) m/e ($M+H^+$): 238.

Step 3



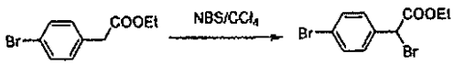
To a suspension of the compound from step 2 (140 g, 0.59 mol) in THF (2000 ml) was added NBS (200 g, 1.1 mol). The mixture was stirred at RT under N_2 protection overnight before the solvent was removed, and the residue was purified by chromatography on silica gel to give 230 g of the desired dibromo compound. MS (ESI) m/e ($M+H^+$): 396.

Step 4



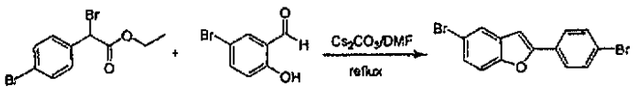
To a suspension of compound from step 3 (230 g, 0.58 mol) in EtOH/H_2O (3000 ml) was added Na_2SO_3 (733 g, 5.8 mol). The resulting mixture was stirred under reflux overnight. After cooling to RT, the mixture was extracted by DCM and concentrated under vacuum. The resulting residue was purified by chromatography on silica gel to give the desired bromo imidazole target. MS (ESI) m/e ($M+H^+$): 317.

Step 5



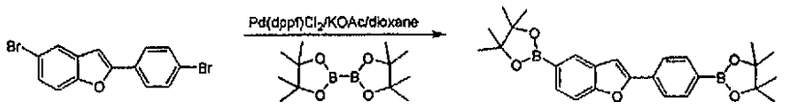
To a stirred solution of ethyl 4-bromophenylacetate (50 g, 205.8 mmol) in CCl_4 (500 mL) was added NBS (38 g, 214.7 mmol), then 48% aqueous HBr (4 drops). After the addition, the solution was stirred overnight at 80°C under argon. Then the reaction was cooled to RT, filtered, and concentrated. The resulting oil was directly used the next step.

Step 6



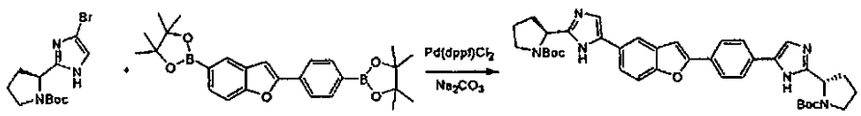
To a solution of the compound from step 5 (2 g, 6.2 mmol) in DMF (20 mL) was added 5-bromosalicylaldehyde (1.21 g, 6.0 mmol) and Cs_2CO_3 (2 g, 12.3 mmol) under N_2 protection. The resulting suspension was stirred for 5 hours at 160°C, then cooled and treated with water. The resulting precipitate was filtered, and the filtrate cake was dried *in vacuo* to give the desired compound, which was used directly in next step.

Step 7



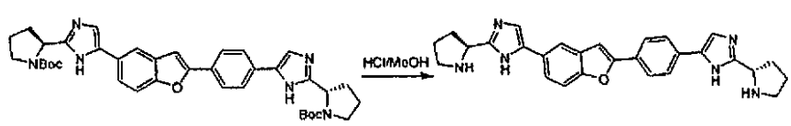
A suspension of the product from step 6 above (4.43 g, 12.58 mmol), bis(pincolato)diboron (8.31 g, 32.72 mmol), AcOK (3.72 g, 37.7 mmol) and $Pd(dppf)Cl_2$ (921 mg, 1.26 mmol) in dioxane (100 mL) was heated to reflux for 4 hours under N_2. The mixture was concentrated, the residue was partitioned between H_2O and DCM, and the aqueous phase was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, concentrated. The residue was purified by chromatography on silica gel to afford the desired compound (5 g).

Step 8



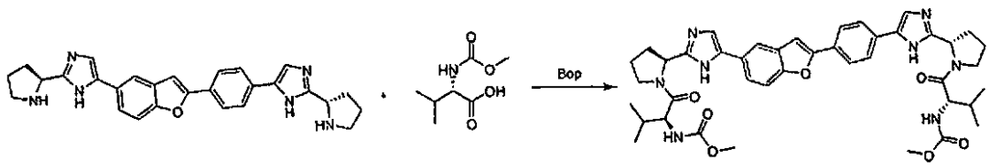
A suspension of the product from step 4 (5 mmol), the boronate ester from step 7 (2 mmol), $Pd(dppf)Cl_2$ (146 mg, 0.2 mmol), and Na_2CO_3 (636 mg, 6 mmol) were refluxed in THF/H_2O (10:1, 33 mL) overnight under N_2 protection. The mixture was cooled and filtered, and the filtrate was washed with water (50 mL) then extracted with EtOAc (100 mL), washed with brine and dried over anhydrous sodium sulfate. The solution was concentrated and the resulting residue was purified by column chromatography (PE / EA = 8:1→5:1) to afford the desired compound. MS (ESI) m/z $(M+H)^+$:641).

Step 9



The product from step 8 (1.3 mmol) was added into 3M HCl/CH_3OH (20 mL) and the mixture was stirred at RT for 2 to 3 hours. The mixture was concentrated, and the crude product was used directly in the next step without further purification. MS (ESI) m/z $(M+H)^+$: 441.

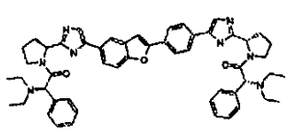
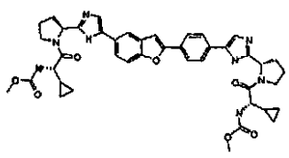
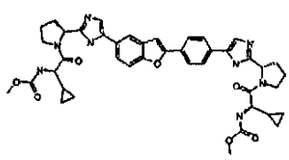
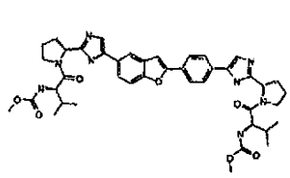
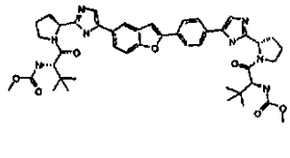
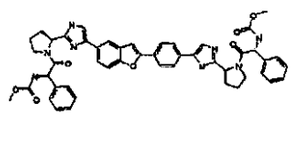
Step 10

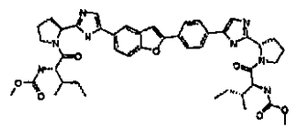
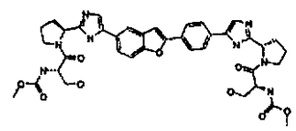
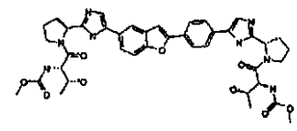
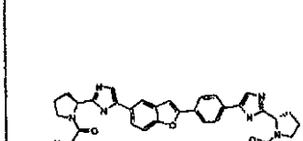


To a mixture of the product from step 9 (1 mmol), *N*-Moc-L-valine (2.1 mmol) and DIPEA (0.4 mL) in DMF (3 mL) was added BOP reagent (2.2 mmol). The resulting mixture was stirred at RT for 16 hours. The solution was subjected directly to RPLC to afford the desired compound. ^1H NMR (MeOD) δ: 7.7-8.1 (m, 10 H), 7.4 (m, 1 H), 5.3 (m, 2 H), 4.3 (m, 2 H), 4.1 (d, *J* =4.8Hz, 2 H), 3.9 (m, 2 H), 3.7 (m, 6 H), 2.6 (d, *J* =4.8 Hz, 2 H), 2.0-2.4 (m, 8 H), 1.3-1.4 (m, 2 H), 0.9-1.0 (m, 12 H). MS (ESI) m/z $(M+H)^+$: 780.

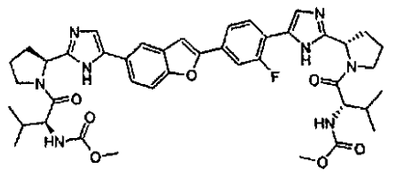
Examples 193-202

Compounds of Examples 193-202 were prepared in a similar manner as described in Example 192.

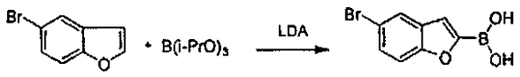
Example	Structure	^{1}H NMR	M+1	Name
193		(MeOD) δ: 7.2-8.1 (m, 20 H), 5.2-5.6 (m, 4 H), 3.9-4.2 (m, 2 H), 3.1 (m, 2 H), 2.6 (m, 8 H), 1.9-2.5 (m, 8 H), 1.0-1.5 (m, 12 H).	844	(2*R*)-2-(diethylamino)-1-[(2*S*)-2-(5-{4-[5-(2-{(2*S*)-1-[(2*R*)-2-(diethylamino)-2-phenylacetyl] pyrrolidin-2-yl}-1*H*-imidazol-5-yl)-1-benzofuran-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-2-phenylethanone
194		(MeOD) δ: 8.0-8.1 (m, 3 H), 7.7-7.9 (m, 6 H), 7.4 (d, J=2.4Hz, 1 H), 5.3 (d, J=5.6 Hz, 2 H), 4.1 (m, 2 H), 3.9 (m, 4 H), 3.7 (m, 6 H), 2.5-2.6 (m, 2 H), 2.1-2.3 (m, 6 H), 1.1-1.2 (m, 2 H), 0.4-0.6 (m, 9 H).	775	Methyl {(1*S*)-1-cyclopropyl-2-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-cyclopropyl-2-[(methoxycarbonyl)amino]acetyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxoethyl}carbamate
195		(MeOD) δ: 7.7-8.1 (m, 9 H), 7.4(m, 16 H), 5.3-5.4 (m, 2 H), 3.5-4.1 (m, 12 H), 2.6 (d, *J* =4.8 Hz, 26 H), 2.2 (d, *J* =4.8 Hz, 6 H), 1.1-1.2 (m, 2 H), 0.4-0.7 (m, 8 H).	775	Methyl {(1*R*)-1-cyclopropyl-2-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-cyclopropyl-2-[(methoxycarbonyl)amino]acetyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl}-2-oxoethyl}carbamate
196		(MeOD) δ: 7.8-7.9 (m, 5 H), 7.1-7.6 (m, 5 H), 5.6-5.7 (m, 1 H), 5.2 (d, J =4.8 Hz, 1 H), 4.0-4.2 (m, 3 H), 3.6-3.8 (m, 8 H), 2.0-2.5 (m, 10 H), 1.6 (d, J =4.8 Hz, 1 H), 1.3 (m, 1 H), 0.8-1.1 (m, 11 H), 0.4 (m, 26 H).	780	Methyl {(2*R*)-1-[(2*S*)-2-{5-[2-(4-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1-benzofuran-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate
197		(MeOD), δ 8.10(d, J =4 Hz, 2 H), 8.01(s, 1 H), 7.94(s, 1 H), 7.87(d , J =2 Hz, 2 H), 7.84(m, 1 H), 7.73(d, J =4 Hz, 1 H), 7.44(m, 1 H), 5.25(m, 2 H), 4.33(m, 2 H), 4.16(m, 2 H), 3.89(m, 2 H), 3.67(s, 6 H), 2.58(m, 2 H), 2.20(m, 6 H), 0.97(m, 18 H)	806	Methyl {(2*S*)-1-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate
198		(MeOD) δ: 7.6-8.1 (m, 9 H), 7.3-7.5 (m, 11 H), 7.2 (m, 1 H), 5.4-5.5 (m, 2 H), 5.3 (m, 2 H), 4.1 (d, J =4.8 Hz, 2 H), 3.7 (d, J =2.4 Hz, 6 H), 1.9-2.4 (m, 8 H)	848	Methyl {(1*R*)-2-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

Example	Structure	^{1}H NMR	M+1	Name
199		(MeOD) δ 8.08(d, J =4 Hz, 2 H), 8.04(s, 1 H), 7.89(d, 3 H), 7.78(m , 1 H), 7.77 (m, 2 H), 7.42(m,1 H), 5.34(t, J =4 Hz, 2 H), 4.42(d, J =4Hz, 2 H), 4.10(s, 2 H), 3.82(m, 2 H), 3.79(m, 3 H), 3.64(s, 3 H), 2.57(m, 2 H), 2.20(m, 6 H), 1.88(m, 2 H), 1.48(m, 2 H), 1.32(m, 2 H), 0.97(m, 12 H).	806	Methyl {(2*S*,3*R*)-1-[(2*S*)-2-(5-{2-[4-(2-{(2*S*)-1-[*N*-(methoxycarbonyl)-L-alloisoleucyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)phenyl]-1-benzofuran-5-yl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate
200		(MeOD) δ: 7.6-8.1 (m, 9 H), 7.4 (m, 6 H), 5.4 (m, 2 H), 4.6 (m, 2 H), 3.5-4.1 (m, 13 H), 2.5-2.7 (m, 6 H), 2.3 (m, 5 H).	755	Methyl {(2*S*)-3-hydroxy-1-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*S*)-3-hydroxy-2-[(methoxycarbonyl) amino]propanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-1-oxopropan-2-yl}carbamate
201		(MeOD), δ 8.04(d, J =4 Hz, 2 H), 7.97(s, 1H), 7.84(d, J =2 Hz, 2 H), 7.81(m, 1 H), 7.76(m, 1 H), 7.64(d, J =4 Hz, 2 H), 7.38(m, 1 H), 5.29(m, 2 H), 4.49(m, 2 H), 4.15(m, 2 H), 3.97(m, 1 H), 3.92(m, 1 H), 3.66(m, 6 H), 2.63(m, 1 H), 2.60(m, 1 H), 2.54(m, 2 H), 2.16-2.22(m, 6 H), 1.16 (d, J =2 Hz, 6 H).	783	Methyl {(2*S*,3*R*)-3-hydroxy-1-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*S*,3*R*)-3-hydroxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate
202		(MeOD), δ 8.05(d, J =4 Hz, 2 H), 7.97(s, 1 H), 7.84(d, 1 H), 7.81(d , J =2 Hz, 2 H), 7.76(m, 1 H), 7.64(d, J =4Hz, 2 H), 7.39(m, 1 H), 5.25(m, 2 H), 4.45(m, 2 H), 4.03(m, 2 H), 3.84(m, 2 H), 3.85(m, 2 H), 3.64(s, 6 H), 2.55(m, 2 H), 2.22(m, 6 H), 1.70(m, 2 H), 1.51(m, 4 H), 0.98(m, 12 H)	806	Methyl {(2*S*)-1-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-4-methylpentanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-4-methyl-1-oxopentan-2-yl}carbamate

Example 203: Methyl {(2S)-1-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl} carbamate

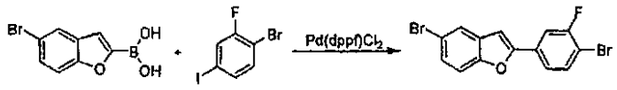


Step 1



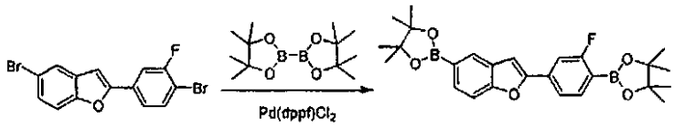
To a solution of 5-bromobenzofuran (3.9 g, 20 mmol) in dry THF (30 mL) cooled to -78°C under N_2-protected LDA (prepared from n-BuLi and iPr_2NH in THF (~30 mmol)) was slowly added. The mixture was stirred at the same temperature for 30 minutes, then tri*iso*propylborate (5.64 g, 30 mmol) was added to the mixture. The mixture was allowed to warm to RT and stirred for 2 hours. The mixture was then quenched with 1N HCl to pH=3 and extracted with EtOAc. The combined organic phases were combined, dried and filtered. The filtrate was concentrated to afford the desired product (4.3 g). MS (ESI) m/e ($M+H^+$): 241.

Step 2



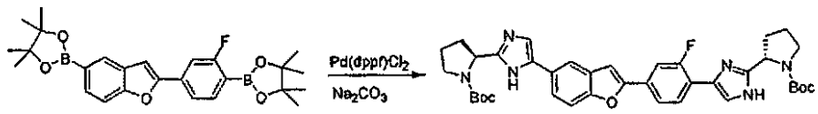
A suspension of the boronic acid from step 1 (1.44 mg, 6.0 mmol), 2-fluoro-4-iodobromobenzene (1.8 g, 6.0 mmol), $Pd(dppf)Cl_2$ (600 mg), Na_2CO_3 (954 mg, 9.0 mmol) and in THF/H_2O (9:1, 100 mL) was refluxed at 75°C overnight under N_2 protection. The mixture was cooled and filtered. The filtrate was washed with water (150 mL) and extracted with EtOAc (200 mL), washed with brine and dried over anhydrous sodium sulfate. The solution was evaporated and the residue was purified by column chromatography (PE / EA = 8:1→5:1) to afford the desired compound. MS (ESI) m/e ($M+H^+$): 370.

Step 3



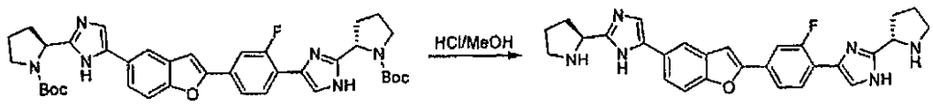
To a solution of the product from step 2 (1.85 g, 5 mmol), bis(pinacolato)diboron (2.54 g, 10 mmol) and $Pd(dppf)Cl_2$ (80 mg) and KOAc (0.98 g, 10 mmol) were dissolved in 1,4-dioxane (30 mL), and the reaction mixture was heated at 110°C for 16 hours. The solvent was evaporated, and the residue was purified by column chromatography with silica gel elution with PE to afford the desired product as white solid (1.95 g). MS (ESI) m/e ($M+H^+$): 465.

Step 4



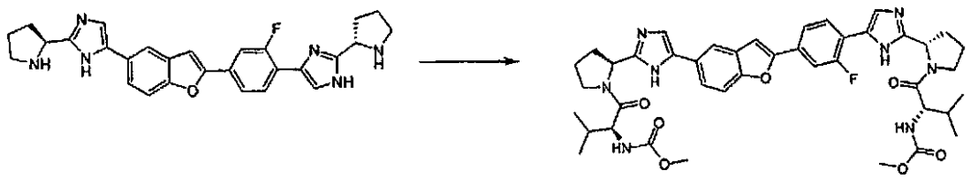
A suspension of the bromoimidazole from Example 192 (5 mmol), the boronate ester from step 3 (2 mmol), $Pd(dppf)Cl_2$ (146 mg, 0.2 mmol) and Na_2CO_3 (636 mg, 6 mmol) was refluxed in THF/H_2O (10:1, 33 mL) overnight under N_2 protection. The mixture was cooled and filtered, and the filtrate was washed with water (50 mL) and extracted with EtOAc (100 mL), washed with brine and dried over anhydrous sodium sulfate. The solution was concentrated, and the resulting residue was purified by column chromatography (PE / EtOAc = 8:1) to afford the desired compound. MS (ESI) m/e ($M+H^+$): 683.

Step 5



The product from step 4 (682 mg, 1.0 mmol) was treated with 3M HCl/CH_3OH (10 mL) and the mixture was stirred at RT for 3 hours. The reaction mixture was concentrated, and the crude product was used directly in the next step without further purification. MS (ESI) m/e ($M+H^+$): 483.

Step 6

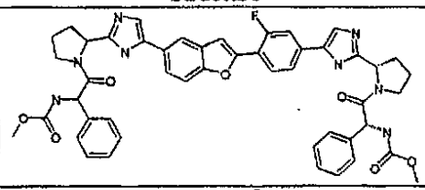
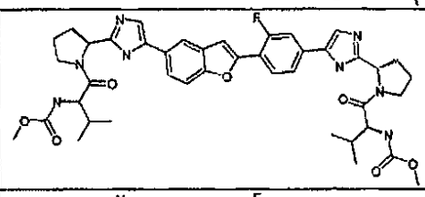
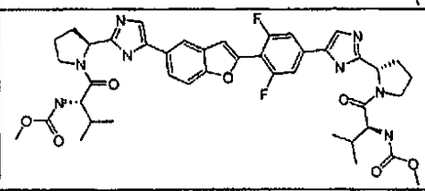
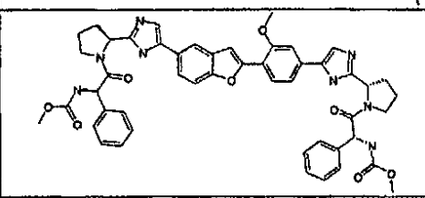
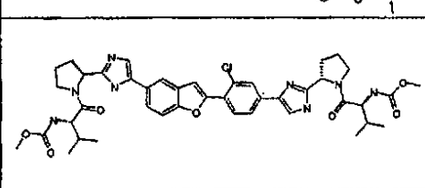
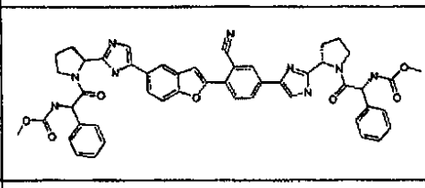
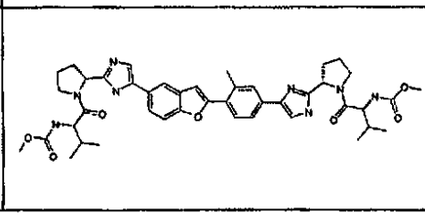


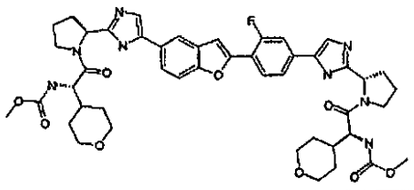
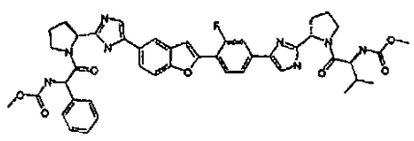
To a mixture of the product from step 5 (482 mg, 1.0 mmol), *N*-Moc-L-valine (2.1 mmol) and DIPEA (0.4 mL) in DMF (3 mL) was added BOP reagent (977 mg, 2.2 mmol). The resulting mixture was stirred at RT for 16 hours. The solution was subjected directly to RPLC to afford the desired compound as white solid (40 mg). ^1H NMR (MeOD) δ: 7.99 (s,1 H), 7.89-7.80 (m, 5 H), 7.72-7.67 (m, 2 H), 7.47 (s, 1 H), 5.27-5.22 (m, 2 H), 4.22 (d, 2 H), 4.09 (d, 2 H),

3.89-3.84 (m, 2 H), 3.64 (s, 6 H), 2.55-2.02 (m, 10 H), 0.92 (d, 6 H), 0.88 (d, 6 H). MS (ESI) m/e ($M+H^+$): 797.

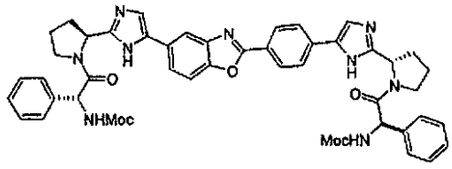
Examples 204-212

Compounds of Examples 204-212 were prepared in a similar manner as described in Example 203.

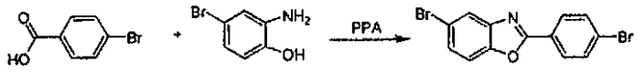
Example	Structure	M+1	Name
204		866	Methyl {(1*R*)-2-[(2*S*)-2-{5-[3-fluoro-4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
205		797	Methyl {(2*S*)-1-[(2*S*)-2-{5-[3-fluoro-4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate
206		816	Methyl {(2*S*)-1-[(2*S*)-2-{5-[2-(2,6-difluoro-4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1-benzofuran-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate
207		878	Methyl {(1*R*)-2-[(2*S*)-2-{5-[3-methoxy-4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
208		814	Methyl {(2*S*)-1-[(2*S*)-2-{5-[2-(2-chloro-4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)-1-benzofuran-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate
209		873	Methyl {(1*R*)-2-[(2*S*)-2-{4-[3-cyano-4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate
210		794	Methyl {(2*S*)-1-[(2*S*)-2-{5-[2-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-2-methylphenyl)-1-benzofuran-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example	Structure	M+1	Name
211			Methyl [(1*S*)-2-[(2*S*)-2-(5-{3-fluoro-4-[5-(2-{(2*S*)-1-[(2*S*)-2-[(methoxycarbonyl)amino]-2-(tetrahydro-2*H*-pyran-4-yl)acetyl]pyrrolidin-2-yl}-1*H*-imidazol-5-yl)-1-benzofuran-2-yl]phenyl}-1*H*-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-(tetrahydro-2*H*-pyran-4-yl)ethyl]carbamate
212		832	Methyl {(2*S*)-1-[(2*S*)-2-{4-[3-fluoro-4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate

Example 213: Methyl {(1R)-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,3-benzoxazol-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate

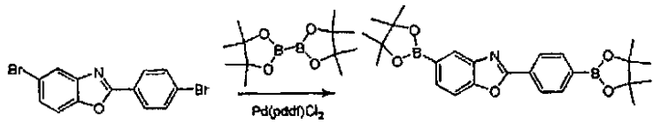


Step 1



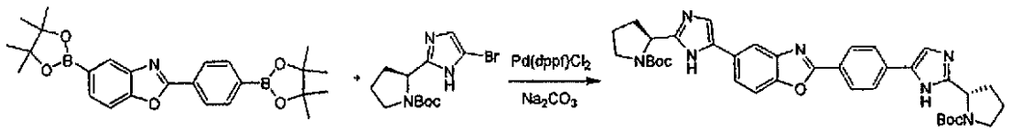
4-Bromobenzoic acid (20 g, 0.1 mol) and 2-amino-4-bromophenol (18.8 g, 0.1 mol) were added into polyphosphoric acid (250 mL), and the mixture was stirred at 140°C for 90 minutes. After cooling in an ice-bath, the reaction mixture was diluted with water (4000 mL) and neutralized with NaOH. The resulting solid was filtered off and dried to afford the desired benzoxazole. MS (ESI) m/e ($M+H^+$): 354.

Step 2



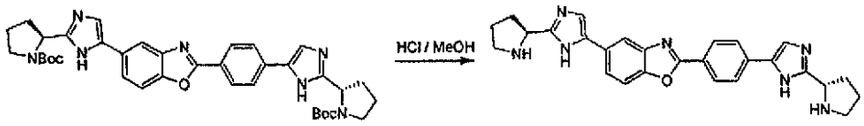
A suspension of the product from step 1 above (10.6 g, 30 mmol), bis(pinacolato)diboron (30.3 g, 120 mmol), KOAc (7.6 g, 78 mmol) and $Pd(dppf)Cl_2$ (1.1 g, 1.5 mmol) in dioxane (300 ml) was stirred at 100°C under N_2 protection overnight. The reaction mixture was cooled and concentrated, then chromatographed on silica gel gave the product compound. MS (ESI) m/e ($M+H^+$): 366.

Step 3



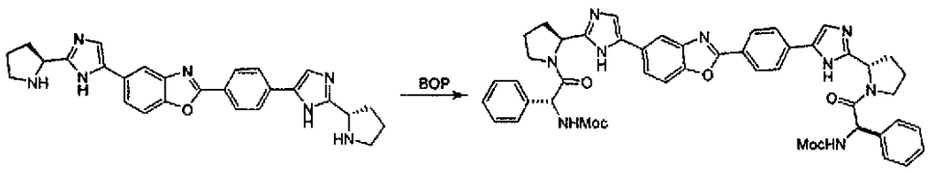
A suspension of the product from step 2 (1.2 g, 2.6 mmol), bromoimidazole from Example 192 (2 g, 6.3 mmol), Na_2CO_3 (1.3 g, 12 mmol) and $Pd(dppf)Cl_2$ (220 mg, 0.3 mmol) in THF/H_2O (36 ml) was stirred at 100°C under N_2 protection overnight. The reaction mixture was concentrated and purified by chromatography on silica gel to give the desired compound. MS (ESI) m/e ($M+H^+$): 666.

Step 4



A solution of the product from step 3 (400 mg, 0.6 mmol) in HCl/MeOH (20 ml) was stirred at ambient temperature for 3 hours, then concentrated and dried under high vacuum to give to desired product. MS (ESI) m/e ($M+H^+$): 466.

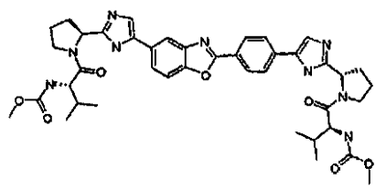
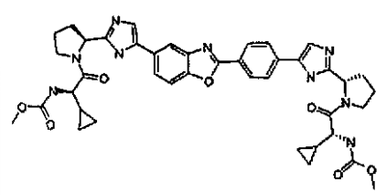
Step 5



To a mixture of the product from step 4 (233 mg, 0.5 mmol), *N*-Moc-D-Phg (1.1 mmol) and DIPEA (0.2 mL) in DMF (3 mL) was added BOP reagent (488 mg, 1.1 mmol). The resulting mixture was stirred at RT for 16 hours before the solution was subjected directly to RPLC to afford the desired compound. ^1H NMR (MeOD) δ: 8.4 (d, *J*=8.4 Hz, 2 H), 8.2 (s, 1 H), 8.0 (m, 3 H), 7.9 (m, 3 H), 7.5-7.4 (m, 10 H), 5.5 (s, 2 H), 5.3 (m, 2 H), 4.1-4.0 (m, 2 H), 3.6 (d, *J*=2.8 Hz, 6 H), 3.3 (m, 1 H), 3.3-3.1 (m, 1 H), 2.5-2.3 (m, 2 H), 2.2-2.1 (m, 4 H), 2.0 (m, 2 H). MS (ESI) m / e ($M+H^+$): 780.

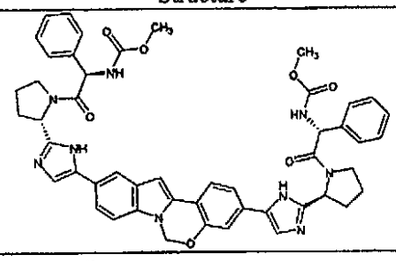
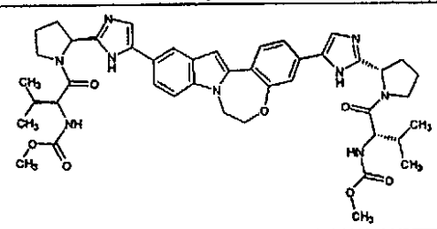
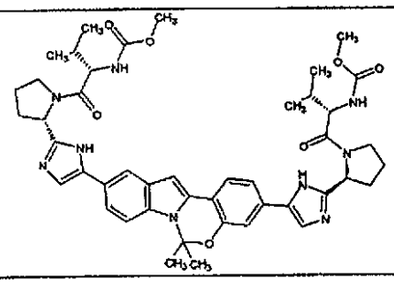
Examples 214-215

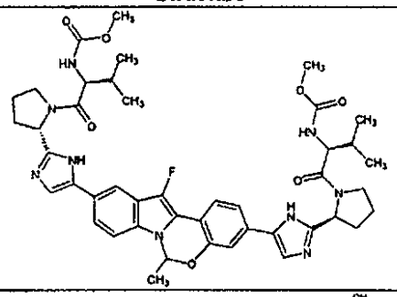
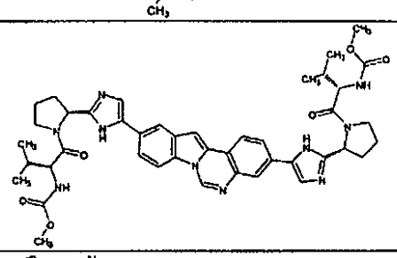
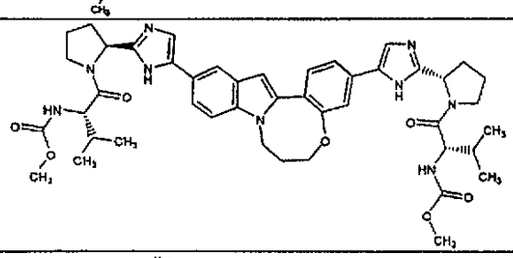
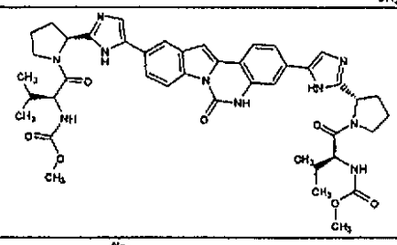
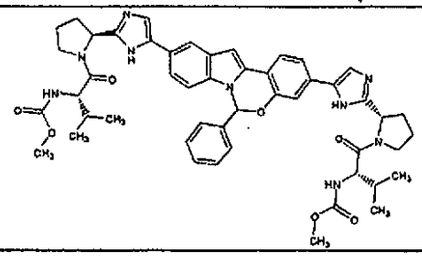
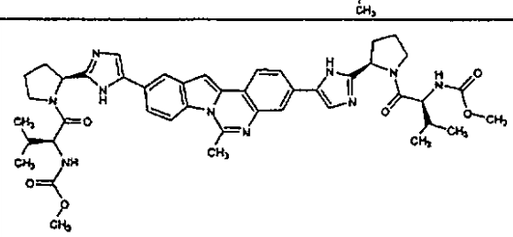
Compounds of Examples 214-215 were prepared in a similar manner as described in Example 213.

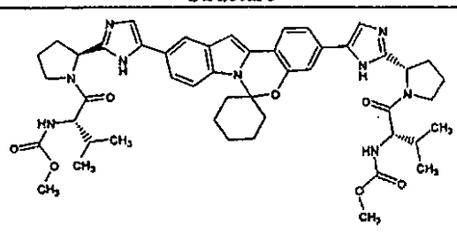
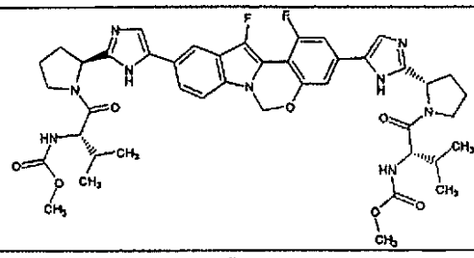
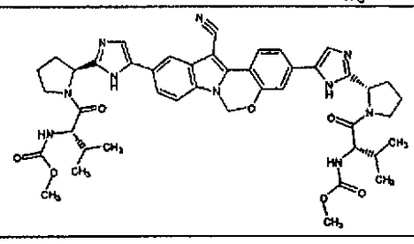
Example	Structure	^{1}H NMR	M+1	Name
214		(MeOD) δ: 8.4 (d, *J*=8.4 Hz, 2 H), 8.1 (s, 1 H), 7.9 (m, 3 H), 7.8 (m, 2 H), 7.7 (m, 1 H), 5.3 (m, 2 H), 4.2 (m, 2 H), 4.1-4.0 (m, 2 H), 3.9-3.8 (m, 2 H), 3.6 (s, 2 H), 2.6 (m, 2 H), 2.3 (m, 2 H), 2.2 (m, 4 H), 2.0 (m, 2 H), 0.9 (m, 12 H).	848	Methyl {(2*S*)-1-[(2*S*)-2-{5-[2-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1,3-benzoxazol-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate
215		(MeOD) δ: 8.4 (d, *J*=6.8 Hz, 2 H), 8.2-8.1 (s, 1 H), 8.0 (m, 3 H), 7.9-7.8 (m, 3 H), 5.3 (m, 2 H), 4.1-4.0 (m, 2 H), 4.0 (m, 2 H), 3.9-3.8 (m, 2 H), 3.7 (m, 6 H), 2.6 (m, 2 H), 2.4-2.1 (m, 6 H), 1.3-1.1 (m, 2 H), 0.7-0.6 (m, 3 H), 0.6-0.5 (m, 3 H), 0.4 (m, 2 H).	776	Methyl {(1*R*)-1-cyclopropyl-2-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*R*)-2-cyclopropyl-2-[(methoxycarbonyl) amino]acetyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1,3-benzoxazol-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxoethyl}carbamate

Examples 216-227

Compounds of Examples 216-227 were prepared in a similar manner as described in Example 189b (Alternative Procedure).

Example	Structure	M+1	Name
216		875	dimethyl (indolo[1,2-c][1,3]benzoxazine-3,10-diylbis{1*H*-imidazole-5,2-diyl(2*S*)pyrrolidine-2,1-diyl[(1*R*)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate
217		821	methyl [(2*S*)-1-{(2*S*)-2-[5-(11-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-6,7-dihydroindolo[1,2-d][1,4] benzoxazepin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate
218		835	methyl [(2*S*)-1-{(2*S*)-2-[5-(3-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-6,6-dimethylindolo[1,2-c][1,3] benzoxazin-10-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example	Structure	M+1	Name
219		839	methyl [(2*S*)-1-{(2*S*)-2-[5-(12-fluoro-10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-6-methylindolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate
220		804	methyl [(2*S*)-1-{(2*S*)-2-[5-(3-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}indolo[1,2-c]quinazolin-10-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate
221		835	methyl [(2*S*)-1-{(2*S*)-2-[5-(12-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-7,8-dihydro-6*H*-indolo[1,2-e][1,5]benzoxazocin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate
222		820	methyl [(2*S*)-1-{(2*S*)-2-[5-(3-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-6-oxo-5,6-dihydroindolo[1,2-c]quinazolin-10-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate
223		883	methyl [(2*S*)-1-{(2*S*)-2-[5-(10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-6-phenylindolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate
224		818	methyl [(2*S*)-1-{(2*S*)-2-[5-(3-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-6-methylindolo[1,2-c]quinazolin-10-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example	Structure	M+1	Name
225		875.1	methyl [(2*S*)-1-{(2*S*)-2-[5-(10'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}spiro[cyclohexane-1,6'-indolo[1,2-c][1,3]benzoxazin]-3'-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate
226		842	methyl [(2*S*)-1-{(2*S*)-2-[5-(1,12-difluoro-10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}indolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate
227		832	methyl [(2*S*)-1-{(2*S*)-2-[5-(12-cyano-10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}indolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate

Example 228 – Measuring Compound Inhibitory Potency

Measurement of inhibition by compounds was performed using the HCV replicon system. Several different replicons encoding different HCV genotypes or mutations were used. In addition, potency measurements were made using different formats of the replicon assay, including different ways of measurements and different plating formats. *See* Jan M. Vrolijk *et al.*, *A replicons-based bioassay for the measurement of interferons in patients with chronic hepatitis C*, 110 J. VIROLOGICAL METHODS 201 (2003); Steven S. Carroll *et al.*, *Inhibition of Hepatitis C Virus RNA Replication by 2'-Modified Nucleoside Analogs*, 278(14) J. BIOLOGICAL CHEMISTRY 11979 (2003). However, the underlying principles are common to all of these determinations, and are outlined below.

Stable neomycin phosphotransferase encoding replicon-harboring cell lines were used, so all cell lines were maintained under G418 selection prior to the assay. In some cases, the cell lines encoded a luciferase:Neor fusion and could be assayed either directly by determination of RNA copy number, or indirectly through measurement of the luciferase activity.

To initiate an assay, replicon cells were plated in the presence of a dilution series of test compound in the absence of G418. Typically, the assays were performed in a 96-well

plate format for manual operation, or a 384-well plate in an automated assay. Replicon cells and compound were incubated for 24 to 72 hours. At the end of the assay, cells are washed free of media and compound and then lysed. Luciferase activity was measured using a conventional luciferase assay. EC_{50} determinations were calculated as a percent of a DMSO control by fitting the data to a four parameter fit function.

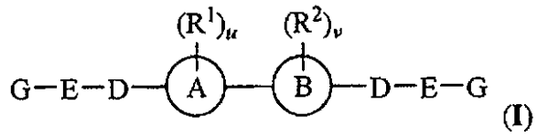
The activity table below provides representative data illustrating observed activity against genotype 1b.

Activity Table			
Example	EC_{50} (nM)	Example	EC_{50} (nM)
2	9	105	0.08
6	200	107	0.04
14	10	116	0.065
15	0.045	119	0.013
19	25	125	0.016
26	0.063	129	0.7
30	26	130	0.05
39	0.24	131	17
40	0.026	137	0.009
41	0.05	138	8.5
42	14	144	0.036
45	0.02	155	0.9
49	0.072	158	0.5
58	0.97	159	0.002
60	0.13	169	0.004
62	0.067	178	317
72	0.17	186	0.015
94	0.006	189a	0.15
95	0.01	189b	0.001
96	0.015	190	0.067
99	0.038	191	0.02
100	0.031	192	0.002
101	0.5	193	0.05
102	8.3	203	0.004
103	5.7	213	0.009

It will be appreciated that various of the above-discussed and other features and functions, or alternatives thereof, may be desirably combined into many other different systems or applications. It will also be appreciated that various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein, also intended to be encompassed by the following claims, may be subsequently made by those skilled in the art.

WHAT IS CLAIMED IS:

1. A compound having structural formula (I):



(I)

and/or a pharmaceutically acceptable salt thereof, wherein:

(A) is chosen from the group consisting of 9-membered bicyclic aryl ring systems that contain from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and that are substituted on C or N atoms by *u* substituents R^1,

each R^1 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-(CH_2)_{0-6}C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, and C_{3-8}cycloalkyl,

u is from 0 to 4,

each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, $-O-C_{1-6}$alkyl and C_{3-8}cycloalkyl, and

each R^{3a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

(B) is a group chosen from the group consisting of

(a) -C≡C- and

(b) aryl ring systems B' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems B' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by *v* substituents R^2,

each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})COR^4$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, $-N(R^{4a})SO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4,

v is from 0 to 4,

each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

R^1 and R^2 may be taken together with (A) and (B) to form a 5- to 9-membered carbocyclic ring containing 1 or 2 heteroatoms independently chosen from the group consisting of N, O and S;

each D is a group independently chosen from the group consisting of:

(a) a single bond,

(b) $-C(O)N(R^5)-$,

(c) $-N(R^5)C(O)-$, and

(d) a 5- or 6-membered aryl ring system D' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by from 0 to 2 substituents R^5,

each R^5 is independently chosen from the group consisting of hydrogen, halogen, $-OR^6$, -CN, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, C_{1-6}alkyl substituted by from 0 to 3 R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 R^6, and

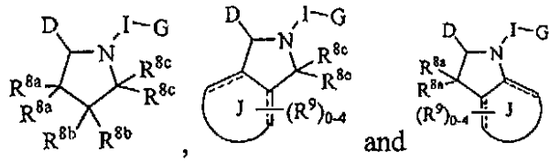
each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each E is a group independently chosen from the group consisting of:

(a) a single bond,

(b) $-(C(R^7)_2)_{0-2}NR^7C(O)O_{0-1}-$, and

(c) a pyrrolidinyl derivative chosen from the group consisting of:



I is a bivalent group chosen from -C(O)-, -CO_2- and -C(O)N(R^7)-,

J is a fused ring system chosen from the group consisting of 3- to 7-membered carbocycles and 5- or 6-membered aryl rings containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by substituents R^9,

each R^{8a} is independently chosen from the group consisting of hydrogen, halogen, -OH, -OC_{1-6}alkyl and C_{1-6}alkyl, or two R^{8a} may be taken together to form oxo,

each R^{8b} is independently chosen from the group consisting of hydrogen, halogen, -OH, -OC_{1-6}alkyl and C_{1-6}alkyl, or two R^{8b} may be taken together to form oxo,

each R^{8c} is independently chosen from the group consisting of hydrogen and C_{1-6}alkyl,

or any two groups selected from R^{8a}, R^{8b} and R^{8c} may be taken together to form a spiro-bicyclic or bridged bicyclic ring;

each R^9 is independently chosen from the group consisting of hydrogen, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NH-C_{1-6}alkyl and -NHC(O)-C_{1-6}alkyl,

each R^7 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and phenyl, and the C_{1-6}alkyl and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl and -S-C_{1-6}alkyl; and

each G is independently chosen from the group consisting of:

(a) hydrogen,

(b) -OR^{10a},

(c) -CN,

(d) -CO_2R^{10a},

(e) -C(O)N(R^{10})$_2$,

(f) -SR^{10a},

(g) $-S(O)R^{10a}$,

(h) $-S(O_2)R^{10a}$,

(i) $-N(R^{10})_2$,

(j) $-N(R^{10})SO_2R^{10a}$,

(k) $-NCO_2R^{10a}$,

(l) $-NC(O)N(R^{10})_2$,

(m) C_{1-6}alkyl having 0 to 4 substituents R^{11},

each R^{11} is independently chosen from the group consisting of:

(i) -OH,

(ii) $-N(R^{10})_2$,

(iii) $=NR^{10}$,

(iv) $-O-C_{1-6}$alkyl,

(v) $-C(O)R^{10}$,

(vi) $-S-C_{1-6}$alkyl,

(vii) $-SO_2-C_{1-6}$alkyl,

(viii) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl having from 0 to 3 substituents chosen from R^{10}, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-OR^{10a}$, -CN, $-C(O)R^{10}$, $-CO_2R^{10a}$, $-C(O)N(R^{10})_2$, $-SR^{10a}$, $-S(O)R^{10a}$, $-S(O_2)R^{10a}$, $-N(R^{10})SO_2R^{10a}$, $-NCO_2R^{10a}$, $-NC(O)N(R^{10})_2$ and $-N(R^{10})_2$, or two R^{12} are taken together to form oxo, and

(ix) 5- or 6-membered aryl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, $-O-C_{1-6}$alkyl and 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

(n) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{10} on N or C atoms; and

(o) aryl ring systems G' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems G' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by 0 to 3 substitutents R^{10};

each R^{10} is independently chosen from the group consisting of

(i) hydrogen,

(ii) -CN,

(iii) C_{1-6}alkyl,

(iv) -O-C_{0-6}alkyl,

(v) -S-C_{0-6}alkyl,

(vi) C_{1-6}alkyl-O-R^{14},

(vii) -C(O)R^{14},

(viii) -CO_2R^{14},

(ix) -SO_2R^{14},

(x) -$N(R^{14})_2$,

(xi) -$N(R^{14})SO_2R^{14}$,

(xii) -NCO_2R^{14},

(xiii) -$NC(O)N(R^{14})_2$, and

(xiv) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

or two R^{10} may be taken together to form oxo;

each R^{10a} is independently chosen from the group consisting of

(i) hydrogen,

(ii) -CN,

(iii) C_{1-6}alkyl,

(iv) C_{1-6}alkyl-O-R^{14},

(v) -C(O)R^{14},

(vi) -CO_2R^{14},

(vii) -SO_2R^{14},

(x) -$N(R^{14})_2$,

(xi) -$N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

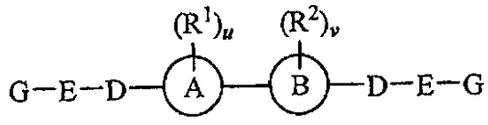
(xiii) $-NC(O)N(R^{14})_2$, and

(xiv) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

and two R^{10} or R^{10a} groups can be taken together with the N to which they are attached to form a ring, which may be substituted by from 0 to 3 substituents R^{14}, and

each R^{14} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-(CH_2)_{0-3}C_{3-8}$cycloalkyl and phenyl.

2. A compound having structural formula (I):



(I)

and/or a pharmaceutically acceptable salt thereof, wherein:

(A) is chosen from the group consisting of 9-membered bicyclic aryl ring systems that contain from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and that are substituted on C or N atoms by ***u*** substituents R^1,

each R^1 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, $-O-C_{1-6}$alkyl and $-S-C_{1-6}$alkyl,

u is from 0 to 4,

each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, $-O-C_{1-6}$alkyl and C_{3-8}cycloalkyl, and

each R^{3a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

(B) is a group chosen from the group consisting of

(a) -C≡C- and

(b) aryl ring systems B' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems B' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by v substituents R^2,

each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})COR^4$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, $-N(R^{4a})SO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4,

v is from 0 to 4,

each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

R^1 and R^2 may be taken together with (A) and (B) to form a 5- to 9-membered carbocyclic ring containing 1 or 2 heteroatoms independently chosen from the group consisting of N, O and S;

each D is a group independently chosen from the group consisting of:

(a) a single bond,

(b) $-C(O)N(R^5)-$,

(c) $-N(R^5)C(O)-$, and

(d) a 5- or 6-membered aryl ring system D' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by from 0 to 2 substituents R^5,

each R^5 is independently chosen from the group consisting of hydrogen, halogen, $-OR^6$, -CN, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, C_{1-6}alkyl substituted by from 0 to 3 R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 R^6, and

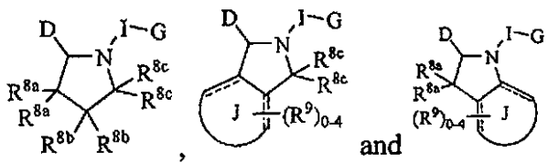
each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each E is a group independently chosen from the group consisting of:

(a) a single bond,

(b) $-(C(R^7)_2)_{0-2}NR^7C(O)O_{0-1}-$, and

(c) a pyrrolidinyl derivative chosen from the group consisting of:



and

I is a bivalent group chosen from -C(O)-, $-CO_2-$ and $-C(O)N(R^7)-$,

J is a fused ring system chosen from the group consisting of 3- to 7-membered carbocycles and 5- or 6-membered aryl rings containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by substituents R^9,

each R^{8a} is independently chosen from the group consisting of hydrogen, halogen, -OH, $-OC_{1-6}$alkyl and C_{1-6}alkyl, or two R^{8a} may be taken together to form oxo,

each R^{8b} is independently chosen from the group consisting of hydrogen, halogen, -OH, $-OC_{1-6}$alkyl and C_{1-6}alkyl, or two R^{8b} may be taken together to form oxo,

each R^{8c} is independently chosen from the group consisting of hydrogen and C_{1-6}alkyl,

or any two groups selected from R^{8a}, R^{8b} and R^{8c} may be taken together to form a spiro-bicyclic or bridged bicyclic ring;

each R^9 is independently chosen from the group consisting of hydrogen, halogen, C_{1-6}alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-NH-C_{1-6}$alkyl and $-NHC(O)-C_{1-6}$alkyl,

each R^7 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and phenyl, and the C_{1-6}alkyl and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, C_{1-6}alkyl, $-O-C_{1-6}$alkyl and $-S-C_{1-6}$alkyl; and

each G is independently chosen from the group consisting of:

(a) hydrogen,

(b) $-OR^{10a}$,

(c) -CN,

(d) $-CO_2R^{10a}$,

(e) $-C(O)N(R^{10})_2$,

(f) $-SR^{10a}$,

(g) $-S(O)R^{10a}$,

(h) $-S(O_2)R^{10a}$,

(i) $-N(R^{10})_2$,

(j) $-N(R^{10})SO_2R^{10a}$,

(k) $-NCO_2R^{10a}$,

(l) $-NC(O)N(R^{10})_2$,

(m) C_{1-6}alkyl having 0 to 4 substituents R^{11},

each R^{11} is independently chosen from the group consisting of:

(i) -OH,

(ii) $-N(R^{10})_2$,

(iii) $=NR^{10}$,

(iv) $-O-C_{1-6}$alkyl,

(v) $-C(O)R^{10}$,

(vi) $-S-C_{1-6}$alkyl,

(vii) $-SO_2-C_{1-6}$alkyl,

(viii) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl having from 0 to 3 substituents chosen from R^{10}, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, $-OR^{10a}$, -CN, $-C(O)R^{10}$, $-CO_2R^{10a}$, $-C(O)N(R^{10})_2$, $-SR^{10a}$, $-S(O)R^{10a}$, $-S(O_2)R^{10a}$, $-N(R^{10})SO_2R^{10a}$, $-NCO_2R^{10a}$, $-NC(O)N(R^{10})_2$ and $-N(R^{10})_2$, or two R^{12} are taken together to form oxo, and

(ix) 5- or 6-membered aryl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group

consisting of hydrogen, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl and 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

(n) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{10} on N or C atoms; and

(o) aryl ring systems G' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems G' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by 0 to 3 substitutents R^{10};

each R^{10} is independently chosen from the group consisting of

(i) hydrogen,

(ii) -CN,

(iii) C_{1-6}alkyl,

(iv) -O-C_{0-6}alkyl,

(v) -S-C_{0-6}alkyl,

(vi) C_{1-6}alkyl-O-R^{14},

(vii) -C(O)R^{14},

(viii) -CO_2R^{14},

(ix) -SO_2R^{14},

(x) -N(R^{14})$_2$,

(xi) -N(R^{14})SO_2R^{14},

(xii) -NCO_2R^{14},

(xiii) -NC(O)N(R^{14})$_2$, and

(xiv) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

or two R^{10} may be taken together to form oxo;

each R^{10a} is independently chosen from the group consisting of

(i) hydrogen,

(ii) -CN,

(iii) C_{1-6}alkyl,

(iv) C_{1-6}alkyl-O-R^{14},

(v) $-C(O)R^{14}$,

(vi) $-CO_2R^{14}$,

(vii) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

(xiii) $-NC(O)N(R^{14})_2$, and

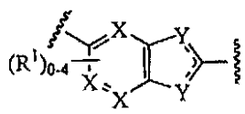
(xiv) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

and two R^{10} or R^{10a} groups can be taken together with the N to which they are attached to form a ring, which may be substituted by from 0 to 3 substituents R^{14}, and

each R^{14} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-(CH_2)_{0-3}C_{3-8}$cycloalkyl and phenyl.

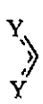
3. The compound according to claim 1 or 2, wherein

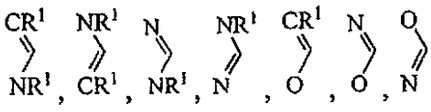
said (A) is chosen from the group consisting of:



, where

each X is independently chosen from the group consisting of CR^1 and N,



is chosen from the group consisting of 

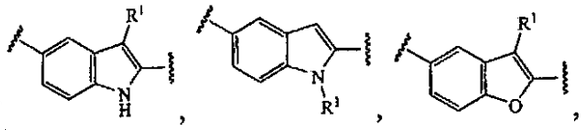
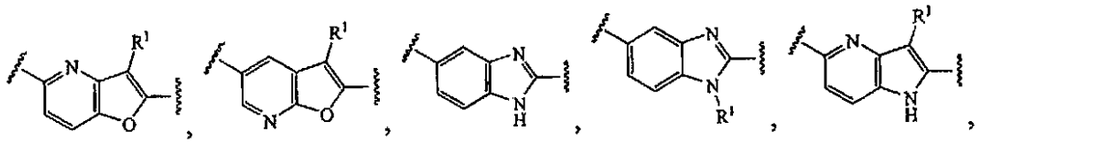
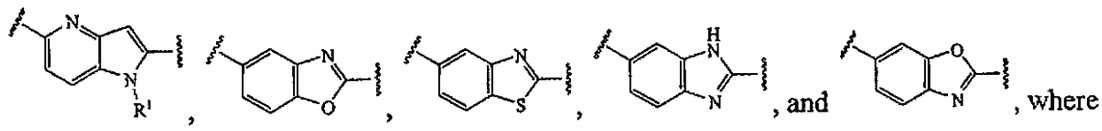
and  ,

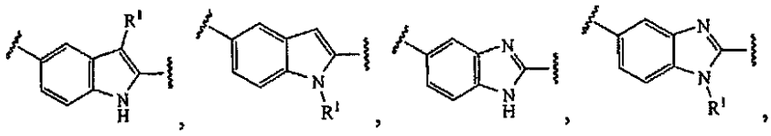
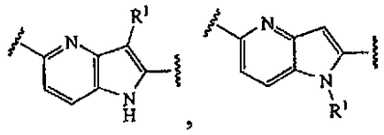
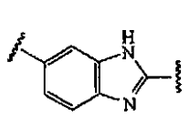
each R^1 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently

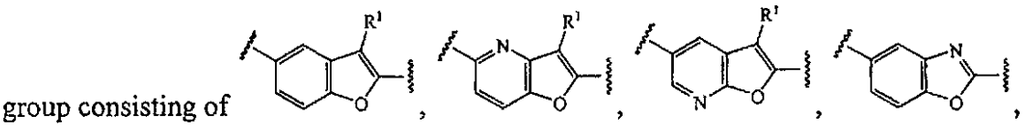
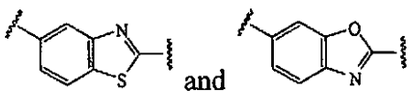
chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, $-O-C_{1-6}$alkyl and $-S-C_{1-6}$alkyl,

each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, $-O-C_{1-6}$alkyl and C_{3-8}cycloalkyl, and

each R^{3a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl.

4. The compound according to any one of claims 1-3, wherein said Ⓐ is chosen from the group consisting of  ,  ,  , and , where said Ⓐ is substituted by from 0 to 3 additional R^1.

5. The compound according to claim 4, wherein said Ⓐ is chosen from the group consisting of  ,  , and  , where said Ⓐ is substituted by from 0 to 3 additional R^1.

6. The compound according to claim 4, wherein said (A) is chosen from the group consisting of  , and  , where said (A) is substituted by from 0 to 3 additional R^1.

7. The compound according to any one of claims 1-6, wherein each R^1 is chosen from the group consisting of hydrogen, halogen, -CN and C_{1-6}alkyl.

8. The compound according to claim 7, wherein each R^1 is chosen from the group consisting of hydrogen, fluorine and -CN.

9. The compound according to any one of claims 1-8, wherein

said (B) is chosen from the group consisting of -C≡C-, phenyl, pyridinyl, pyrazinyl, pyrimidyl, 1,2,4-triazinyl, pyridazinyl, thiazyl and 9-membered bicyclic ring systems that contain from 1 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

v is from 0 to 4,

each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})CO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, $-N(R^{4a})SO_2R^{4a}$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4,

each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl, and

each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl.

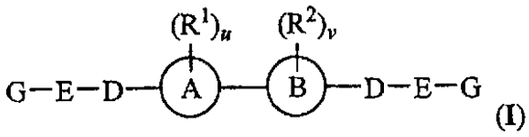
10. The compound according to claim 9, wherein

said (B) is phenyl,

v is from 0 to 2, and

each R^2 is independently chosen from the group consisting of fluorine, chlorine, -OH, $-CH_3$, $-OCH_3$ and -CN.

11. A compound having structural formula (I):



(I)

and/or a pharmaceutically acceptable salt thereof, wherein:

(A) is chosen from the group consisting of 9-membered bicyclic aryl ring systems that contain from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and that are substituted on C or N atoms by u substituents R^1,

each R^1 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-(CH_2)_{0-6}C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, $-O-C_{1-6}$alkyl, $-S-C_{1-6}$alkyl, and C_{3-8}cycloalkyl,

u is from 0 to 4,

each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, $-O-C_{1-6}$alkyl and C_{3-8}cycloalkyl, and

each R^{3a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

(B) is a group chosen from the group consisting of

(a) -C≡C- and

(b) aryl ring systems B' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems B' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by v substituents R^2,

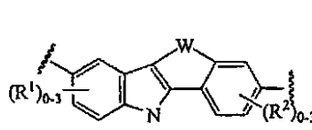
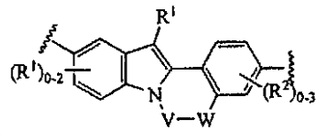
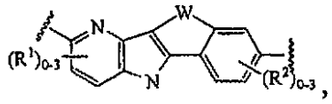
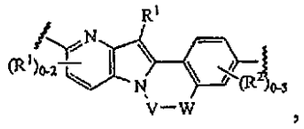
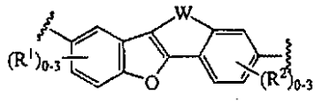
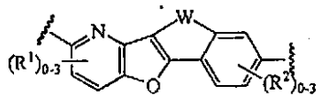
each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})COR^4$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, $-N(R^{4a})SO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4,

v is from 0 to 4,

each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

wherein said (A) and said (B) are taken together with one said substituent R^1 and one said substituent R^2 to form a 5- to 9-membered carbocyclic ring containing 1 or 2 heteroatoms independently chosen from the group consisting of N, O and S, represented by a group chosen from the group consisting of:

W is chosen from the group consisting of $-(CH_2)_{1-3}-$, $-(CH_2)_{0-2}NH(CH_2)_{0-2}-$, $-(CH_2)_{0-2}N(C_{1-6}alkyl)(CH_2)_{0-2}-$, $-(CH_2)_{0-2}O(CH_2)_{0-2}-$ and $-(CH_2)_{0-2}C(O)(CH_2)_{0-2}-$, where W is substituted by from 0 to 4 R^w, where each R^w is independently selected from C_{1-6}alkyl and C_{3-8}cycloalkyl;

V is chosen from the group consisting of -C(O)- and $-CH_2-$, and where V is $-CH_2-$, V is substituted by from 0 to 2 R^v, where each R^v is independently selected from the group consisting of C_{1-6}alkyl and C_{3-8}cycloalkyl;

each D is a group independently chosen from the group consisting of:

(a) a single bond,

(b) $-C(O)N(R^5)-$,

(c) $-N(R^5)C(O)-$, and

(d) a 5- or 6-membered aryl ring system D' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by from 0 to 2 substituents R^5,

each R^5 is independently chosen from the group consisting of hydrogen, halogen, $-OR^6$, $-CN$, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, C_{1-6}alkyl substituted by from 0 to 3 R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 R^6, and

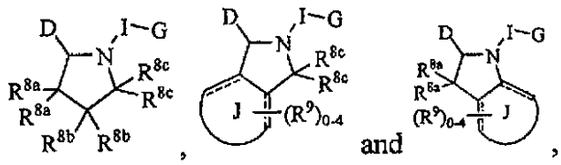
each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each E is a group independently chosen from the group consisting of:

(a) a single bond,

(b) $-(C(R^7)_2)_{0-2}NR^7C(O)O_{0-1}-$, and

(c) a pyrrolidinyl derivative chosen from the group consisting of:



I is a bivalent group chosen from $-C(O)-$, $-CO_2-$ and $-C(O)N(R^7)-$,

J is a fused ring system chosen from the group consisting of 3- to 7-membered carbocycles and 5- or 6-membered aryl rings containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by substituents R^9,

each R^{8a} is independently chosen from the group consisting of hydrogen, halogen, -OH, $-OC_{1-6}$alkyl and C_{1-6}alkyl, or two R^{8a} may be taken together to form oxo,

each R^{8b} is independently chosen from the group consisting of hydrogen, halogen, -OH, $-OC_{1-6}$alkyl and C_{1-6}alkyl, or two R^{8b} may be taken together to form oxo,

each R^{8c} is independently chosen from the group consisting of hydrogen and C_{1-6}alkyl,

or any two groups selected from R^{8a}, R^{8b} and R^{8c} may be taken together to form a spiro-bicyclic or bridged bicyclic ring;

each R^9 is independently chosen from the group consisting of hydrogen, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -NH-C_{1-6}alkyl and -NHC(O)-C_{1-6}alkyl,

each R^7 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and phenyl, and the C_{1-6}alkyl and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl and -S-C_{1-6}alkyl; and

each G is independently chosen from the group consisting of:

(a) hydrogen,

(b) $-OR^{10a}$,

(c) -CN,

(d) $-CO_2R^{10a}$,

(e) $-C(O)N(R^{10})_2$,

(f) $-SR^{10a}$,

(g) $-S(O)R^{10a}$,

(h) $-S(O_2)R^{10a}$,

(i) $-N(R^{10})_2$,

(j) $-N(R^{10})SO_2R^{10a}$,

(k) $-NCO_2R^{10a}$,

(l) $-NC(O)N(R^{10})_2$,

(m) C_{1-6}alkyl having 0 to 4 substituents R^{11},

each R^{11} is independently chosen from the group consisting of:

(i) -OH,

(ii) $-N(R^{10})_2$,

(iii) $=NR^{10}$,

(iv) -O-C_{1-6}alkyl,

(v) $-C(O)R^{10}$,

(vi) -S-C_{1-6}alkyl,

(vii) $-SO_2$-C_{1-6}alkyl,

(viii) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0

to 3 substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl having from 0 to 3 substituents chosen from R^{10}, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -OR^{10a}, -CN, -$C(O)R^{10}$, -CO_2R^{10a}, -$C(O)N(R^{10})_2$, -SR^{10a}, -$S(O)R^{10a}$, -$S(O_2)R^{10a}$, -$N(R^{10})SO_2R^{10a}$, -NCO_2R^{10a}, -$NC(O)N(R^{10})_2$ and-$N(R^{10})_2$, or two R^{12} are taken together to form oxo, and

(ix) 5- or 6-membered aryl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl, -O-C_{1-6}alkyl and 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

(n) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{10} on N or C atoms; and

(o) aryl ring systems G' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems G' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by 0 to 3 substitutents R^{10};

each R^{10} is independently chosen from the group consisting of

(i) hydrogen,

(ii) -CN,

(iii) C_{1-6}alkyl,

(iv) -O-C_{0-6}alkyl,

(v) -S-C_{0-6}alkyl,

(vi) C_{1-6}alkyl-O-R^{14},

(vii) -$C(O)R^{14}$,

(viii) -CO_2R^{14},

(ix) -SO_2R^{14},

(x) -$N(R^{14})_2$,

(xi) -$N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

(xiii) $-NC(O)N(R^{14})_2$, and

(xiv) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

or two R^{10} may be taken together to form oxo;

each R^{10a} is independently chosen from the group consisting of

(i) hydrogen,

(ii) -CN,

(iii) C_{1-6}alkyl,

(iv) C_{1-6}alkyl-O-R^{14},

(v) $-C(O)R^{14}$,

(vi) $-CO_2R^{14}$,

(vii) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

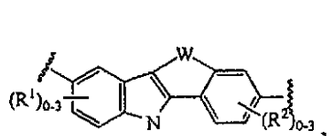
(xiii) $-NC(O)N(R^{14})_2$, and

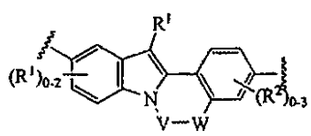
(xiv) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

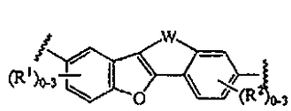
and two R^{10} or R^{10a} groups can be taken together with the N to which they are attached to form a ring, which may be substituted by from 0 to 3 substituents R^{14}, and

each R^{14} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, C_{3-8}cycloalkyl, $-(CH_2)_{0-3}C_{3-8}$cycloalkyl and phenyl.

12. The compound according to claim 11, wherein said (A) and said (B), taken together with one said substituent R^1 and one said substituent R^2, are represented by a group chosen from the group consisting of:

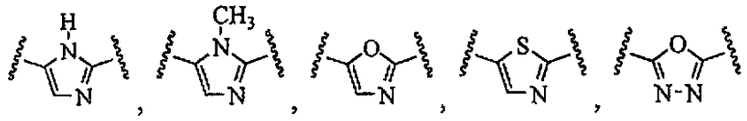
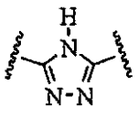


,


, and


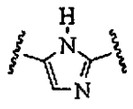
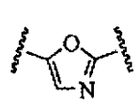
.

13. The compound according to claim 12, wherein W is chosen from the group consisting of -CH_2-, -NH-, -N(C_{1-6}alkyl)-, -C(O)-, -CH_2NH-, -CH_2N(C_{1-6}alkyl)-, -CH_2CH_2-, -C(O)CH_2-, -CH_2C(O)-, -CH_2O-, -$CH_2CH_2CH_2$-, -C(O)CH_2CH_2-, -CH_2C(O)CH_2-, -CH_2OCH_2-, -CH_2CH_2C(O)-, -CH_2CH_2O-, -CH_2CH_2NH-, -CH_2CH_2N(C_{1-6}alkyl)-, -CH_2NHCH_2-, -CH_2N(C_{1-6}alkyl)CH_2-, -NHCH_2CH_2-, and -N(C_{1-6}alkyl)CH_2CH_2-.

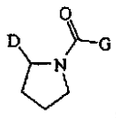
14. The compound according to any one of claims 1-13, wherein each D is independently chosen from the group consisting of a single bond, -C(O)N(R^5)-, -NR^5C(O)-,  , and  , where

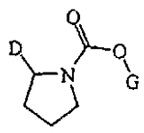
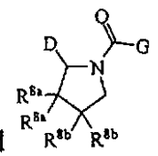
R^5 is independently chosen from the group consisting of hydrogen, halogen, -OR^6, -CN, -CO_2R^6, -C(O)N(R^6)$_2$, -N(R^6)$_2$, -N(R^6)COR^6, -SR^6, -S(O)R^6, -S(O_2)R^6, -N(R^6)SO_2R^6, -NCO_2R^6, -NC(O)N(R^6)$_2$, C_{1-6}alkyl substituted by from 0 to 3 substituents R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 substituents R^6, and

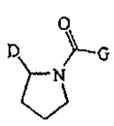
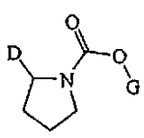
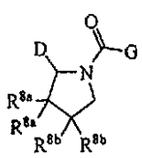
each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl.

15. The compound according to claim 14, wherein each D is independently chosen from the group consisting of  and  .

16. The compound according to any one of claims 1-15, wherein each E is independently chosen from the group consisting of a single bond, -CH_2NHC(O)-, -CH_2N(CH_3)C(O)-, -C(CH_3)HNHC(O)-, -C(CH_3)HN(CH_3)C(O)-, -C(CH_3)$_2$NHC(O)-, -C(CH_3)$_2$N(CH_3)C(O)-, -CH_2NHC(O)O-, -CH_2N(CH_3)C(O)O-, -C(CH_3)HNHC(O)O-,

-C(CH$_3$)HN(CH$_3$)C(O)O-, -C(CH$_3$)$_2$NHC(O)O-, -C(CH$_3$)$_2$N(CH$_3$)C(O)O-,  ,

 and  where one of R^{8a} and R^{8b} is -OH or fluorine.

17. The compound according to claim 16, wherein each E is independently chosen from the group consisting of a single bond,  ,  and  where one of R^{8a} and R^{8b} is -OH or fluorine.

18. The compound according to any one of claims 1-17, wherein each G is independently chosen from the group consisting of:

(a) C_{1-6}alkyl having 0 to 4 substituents R^{11},

(b) 3- to 8-membered carbocycles containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S, and having from 0 to 3 substitutents R^{10} on N or C atoms; and

(c) aryl ring systems G' chosen from the group consisting of:

(i) 5- to 7-membered monocyclic ring systems and

(ii) 8- to 10-membered bicyclic ring systems,

and the aryl ring systems G' containing from 0 to 4 heteroatoms independently chosen from the group consisting of N, O and S, and substituted on C or N atoms by 0 to 3 substitutents R^{10}.

19. The compound according to any one of claims 1-17, wherein each G is independently chosen from the group consisting of

(a) hydrogen,

(b) -CN,

(c) C_{1-5}alkyl having 1 to 3 substituents R^{11},

each R^{11} is independently chosen from the group consisting of -OH, $-NH_2$, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, =NH, $=NCH_3$, -C(O)H, -C(O)OH, $-C(O)CH_3$, $-C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl, and oxacyclohexyl, phenyl, pyridinyl, pyrimidinyl and pyrrolyl, where

the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl are substituted by from 0 to 2 substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl and -S-C_{1-6}alkyl; and

the phenyl, pyridinyl, pyrimidinyl and pyrrolyl are substituted by from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl and 3- to 8-membered cycloalkyl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

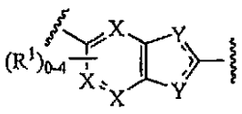
(d) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl having from 0 to 3 substitutents R^{10} on N or C atoms, said R^{10} independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, phenyl and benzyl, and

(e) aryl ring systems G' chosen from the group consisting of: phenyl, pyridinyl and 9-membered bicyclic ring systems containing from 0 to 2 heteroatoms independently chosen from the group consisting of N and O.

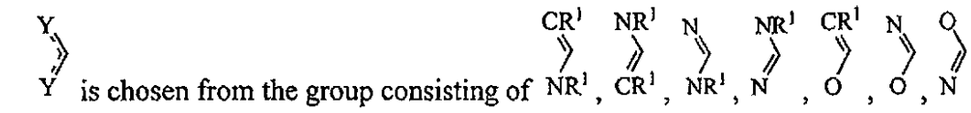
20. The compound according to claim 19, wherein each G is independently chosen from the group consisting of C_{1-4}alkyl having 1 to 2 substituents R^{11}, wherein each R^{11} is independently chosen from the group consisting of -OH, $-NH_2$, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-C(O)OCH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl, oxacyclohexyl, phenyl, pyridinyl, pyrimidinyl and pyrrolyl.

21. The compound according to claim 1 or 2, wherein

said (A) is chosen from the group consisting of:


, where

each X is independently chosen from the group consisting of CR^1 and N,


is chosen from the group consisting of
and ,

each R^1 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, $-O-C_{1-6}$alkyl and $-S-C_{1-6}$alkyl,

each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, $-O-C_{1-6}$alkyl and C_{3-8}cycloalkyl, and

each R^{3a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

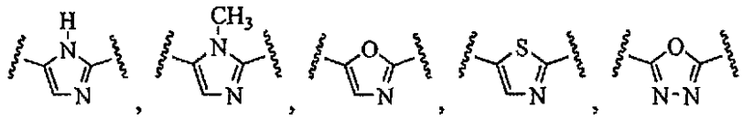
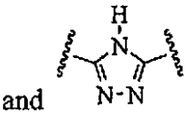
said (B) is chosen from the group consisting of $-C\equiv C-$, phenyl, pyridinyl, pyrazinyl, pyrimidyl, 1,2,4-triazinyl, pyridazinyl, thiazyl and 9-membered bicyclic ring systems that contain from 1 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

v is from 0 to 4,

each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})CO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, $-N(R^{4a})SO_2R^{4a}$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4,

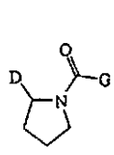
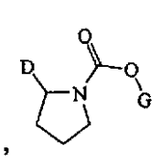
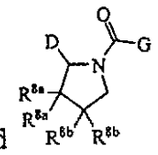
each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl, and

each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

wherein each D is independently chosen from the group consisting of a single bond, -C(O)N(R^5)-, -NR^5C(O)-,  ,  and , where

R^5 is independently chosen from the group consisting of hydrogen, halogen, -OR^6, -CN, -CO_2R^6, -C(O)N(R^6)$_2$, -N(R^6)$_2$, -N(R^6)COR^6, -SR^6, -S(O)R^6, -$S(O_2)R^6$, -N(R^6)SO_2R^6, -NCO_2R^6, -NC(O)N(R^6)$_2$, C_{1-6}alkyl substituted by from 0 to 3 substituents R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 substituents R^6, and

each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

wherein each E is independently chosen from the group consisting of a single bond, -CH_2NHC(O)-, -CH_2N(CH_3)C(O)-, -C(CH_3)HNHC(O)-, -C(CH_3)HN(CH_3)C(O)-, -C(CH_3)$_2$NHC(O)-, -C(CH_3)$_2$N(CH_3)C(O)-, -CH_2NHC(O)O-, -CH_2N(CH_3)C(O)O-, -C(CH_3)HNHC(O)O-, -C(CH_3)HN(CH_3)C(O)O-, -C(CH_3)$_2$NHC(O)O-, -C(CH_3)$_2$N(CH_3)C(O)O-,  ,  and  where one of R^{8a} and R^{8b} is -OH or fluorine;

wherein each G is independently chosen from the group consisting of

(a) hydrogen,

(b) -CN,

(c) C_{1-5}alkyl having 1 to 3 substituents R^{11},

each R^{11} is independently chosen from the group consisting of -OH, -NH_2, -NCH_3H, -N(CH_3)$_2$, -N(CH_2CH_3)$_2$, =NH, =NCH_3, -C(O)H, -C(O)OH, -C(O)CH_3, -C(O)OCH_3, -NHC(O)H, -NHC(O)OH, -NHC(O)CH_3, -NHC(O)OCH_3, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl, and oxacyclohexyl, phenyl, pyridinyl, pyrimidinyl and pyrrolyl, where

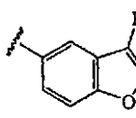
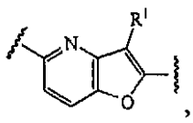
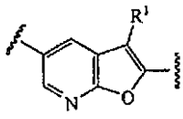
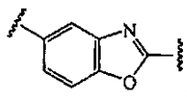
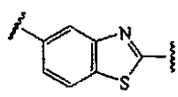
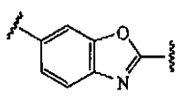
the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl are substituted by from 0 to 2 substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl and -S-C_{1-6}alkyl; and

the phenyl, pyridinyl, pyrimidinyl and pyrrolyl are substituted by from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl and 3- to 8-membered cycloalkyl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

(d) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl having from 0 to 3 substitutents R^{10} on N or C atoms, said R^{10} independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, phenyl and benzyl, and

(e) aryl ring systems G' chosen from the group consisting of: phenyl, pyridinyl and 9-membered bicyclic ring systems containing from 0 to 2 heteroatoms independently chosen from the group consisting of N and O.

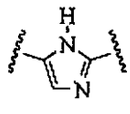
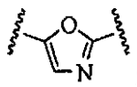
22. The compound according to claim 1 or claim 2, wherein

said (A) is chosen from the group consisting of  ,  ,  ,  ,  and  , where said (A) is substituted by from 0 to 3 additional R^1;

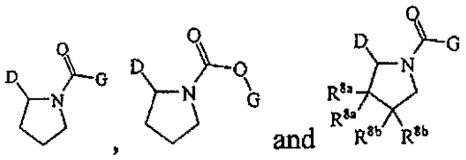
said (B) is phenyl;

v is from 0 to 2;

each R^2 is independently chosen from the group consisting of fluorine, chlorine, -OH, -CH_3, -OCH_3 and -CN;

each D is independently chosen from the group consisting of  and  ;

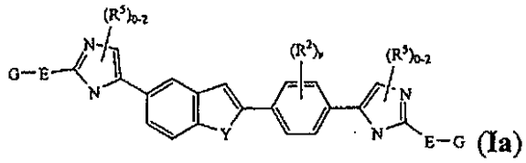
each E is independently chosen from the group consisting of a single bond,



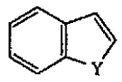
where one of R^{8a} and R^{8b} is -OH or fluorine; and

each G is independently chosen from the group consisting of C_{1-4}alkyl having 1 to 2 substituents R^{11}, wherein each R^{11} is independently chosen from the group consisting of -OH, -NH_2, -NCH_3H, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, -$C(O)OCH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl, oxacyclohexyl, phenyl, pyridinyl, pyrimidinyl and pyrrolyl.

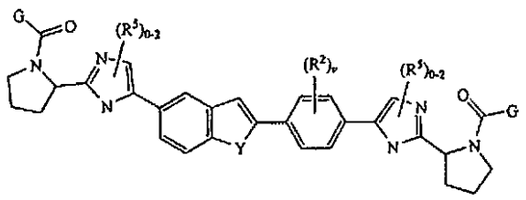
23. The compound according to any one of claims 1-22, wherein the compound having structural formula (**I**) is a compound having structural formula (**Ia**):



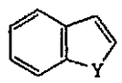
(**Ia**)

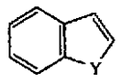
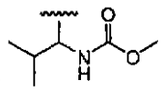
or a pharmaceutically acceptable salt thereof, wherein said  is substituted by ***u*** substituents R^1, and Y is selected from the group consisting of O and NR^1.

24. The compound according to according to claim 23, wherein the compound having structural formula (**Ia**) is a compound having structural formula (**Ib**):

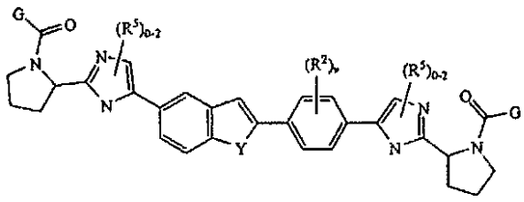


(**Ib**)

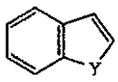
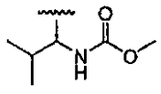
or a pharmaceutically acceptable salt thereof, wherein said  is substituted by ***u*** substituents R^1, and Y is selected from the group consisting of O and NR^1.

25. The compound according to according to claim 24, wherein said  is substituted by u substituents R^1, Y is O, and both instances of G are  .

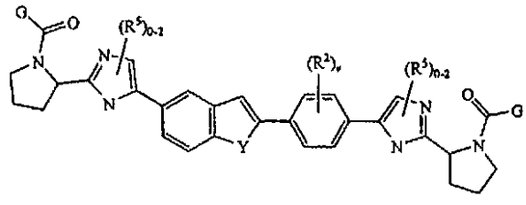
26. The compound according to according to claim 1 or claim 2, wherein the compound having structural formula (**Ia**) is a compound having structural formula (**Ib**):



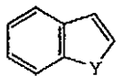
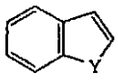
(**Ib**)

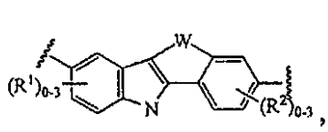
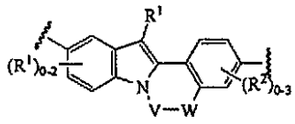
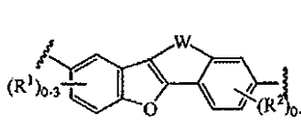
or a pharmaceutically acceptable salt thereof, wherein said  is substituted by u substituents R^1, Y is O, and both instances of G are  .

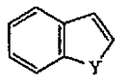
27. The compound according to according to any one of claims 1-23, wherein the compound having structural formula (**Ia**) is a compound having structural formula (**Ib**):

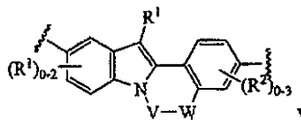
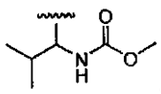


(**Ib**)

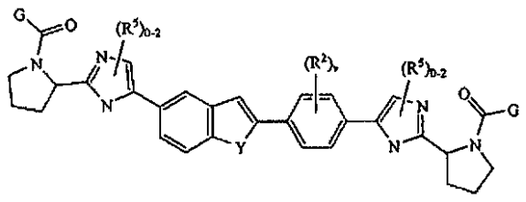
or a pharmaceutically acceptable salt thereof, wherein said  is substituted by u substituents R^1, and said  and said  , taken together with one said substituent R^1 and one said substituent R^2, are represented by a group chosen from the group consisting of:

 ,  , and  .

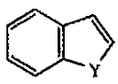
28. The compound according to according to claim 27, wherein said  and said  , taken together with one said substituent R^1 and one said substituent R^2, are represented by

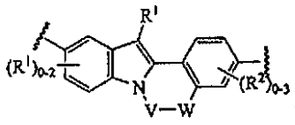
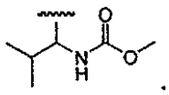
 wherein V is $-CH_2-$, W is $-(CH_2)_{0-2}O(CH_2)_{0-2}-$, R^1 is fluorine, and both instances of G are  .

29. The compound according to according to claim 1 or claim 11, wherein the compound having structural formula (**Ia**) is a compound having structural formula (**Ib**):



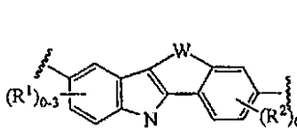
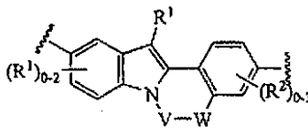
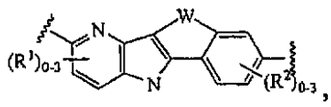
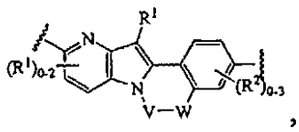
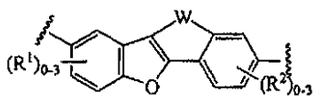
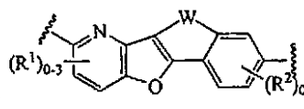
(**Ib**)

or a pharmaceutically acceptable salt thereof, wherein said  and said  , taken together with one said substituent R^1 and one said substituent R^2, are represented by

 wherein V is $-CH_2-$, W is $-(CH_2)_{0-2}O(CH_2)_{0-2}-$, R^1 is fluorine, and both instances of G are  .

30. The compound according to claim 1 or claim 11, wherein

said  and said  , taken together with one said substituent R^1 and one said substituent R^2, are represented by a group chosen from the group consisting of:






and

, where

W is chosen from the group consisting of $-(CH_2)_{1-3}-$, $-(CH_2)_{0-2}NH(CH_2)_{0-2}-$, $-(CH_2)_{0-2}N(C_{1-6}alkyl)(CH_2)_{0-2}-$, $-(CH_2)_{0-2}O(CH_2)_{0-2}-$ and $-(CH_2)_{0-2}C(O)(CH_2)_{0-2}-$, where W is substituted by from 0 to 4 R^w, where each R^w is independently selected from C_{1-6}alkyl and C_{3-8}cycloalkyl; and

V is chosen from the group consisting of -C(O)- and $-CH_2-$, and where V is $-CH_2-$, V is substituted by from 0 to 2 R^v, where each R^v is independently selected from the group consisting of C_{1-6}alkyl and C_{3-8}cycloalkyl;

each R^1 is independently chosen from the group consisting of hydrogen, halogen, $-OR^3$, -CN, $-C(O)R^3$, $-CO_2R^3$, $-C(O)N(R^{3a})_2$, $-SR^3$, $-S(O)R^3$, $-S(O_2)R^3$, $-N(R^{3a})_2$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^3$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})COR^3$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, C_{3-8}carbocycle containing from 0 to 3 heteroatoms chosen from N, O and S, and phenyl, and the C_{1-6}alkyl, C_{3-8}carbocycle and phenyl are substituted by from 0 to 3 substitutents independently chosen from the group consisting of hydrogen, halogen, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, C_{1-6}alkyl, $-O-C_{1-6}$alkyl and $-S-C_{1-6}$alkyl,

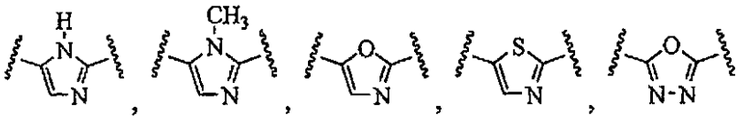
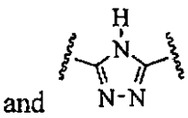
each R^3 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl, -OH, $-O-C_{1-6}$alkyl and C_{3-8}cycloalkyl, and

each R^{3a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

each R^2 is independently chosen from the group consisting of hydrogen, halogen, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})CO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, $-N(R^{4a})SO_2R^{4a}$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, C_{1-6}alkyl substituted by from 0 to 4 R^4 and C_{3-8}cycloalkyl substituted by from 0 to 4 R^4,

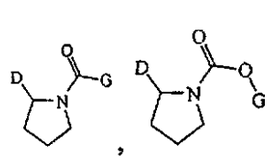
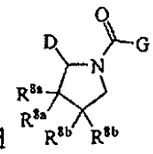
each R^4 is independently chosen from the group consisting of hydrogen, -OH, C_{1-6}alkyl and C_{3-8}cycloalkyl, and

each R^{4a} is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

wherein each D is independently chosen from the group consisting of a single bond, $-C(O)N(R^5)-$, $-NR^5C(O)-$,  ,  and , where

R^5 is independently chosen from the group consisting of hydrogen, halogen, $-OR^6$, -CN, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, C_{1-6}alkyl substituted by from 0 to 3 substituents R^6 and C_{3-8}cycloalkyl substituted by from 0 to 3 substituents R^6, and

each R^6 is independently chosen from the group consisting of hydrogen, C_{1-6}alkyl and C_{3-8}cycloalkyl;

wherein each E is independently chosen from the group consisting of a single bond, $-CH_2NHC(O)-$, $-CH_2N(CH_3)C(O)-$, $-C(CH_3)HNHC(O)-$, $-C(CH_3)HN(CH_3)C(O)-$, $-C(CH_3)_2NHC(O)-$, $-C(CH_3)_2N(CH_3)C(O)-$, $-CH_2NHC(O)O-$, $-CH_2N(CH_3)C(O)O-$, $-C(CH_3)HNHC(O)O-$, $-C(CH_3)HN(CH_3)C(O)O-$, $-C(CH_3)_2NHC(O)O-$, $-C(CH_3)_2N(CH_3)C(O)O-$,  and  where one of R^{8a} and R^{8b} is –OH or fluorine;

wherein each G is independently chosen from the group consisting of

(a) hydrogen,

(b) -CN,

(c) C_{1-5}alkyl having 1 to 3 substituents R^{11},

each R^{11} is independently chosen from the group consisting of -OH, $-NH_2$, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, =NH, $=NCH_3$, -C(O)H, -C(O)OH, $-C(O)CH_3$, $-C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl, and oxacyclohexyl, phenyl, pyridinyl, pyrimidinyl and pyrrolyl, where

the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl are substituted by from 0 to 2

substitutents R^{12} on N or C atoms, and each R^{12} is independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl and -S-C_{1-6}alkyl; and

the phenyl, pyridinyl, pyrimidinyl and pyrrolyl are substituted by from 0 to 3 substitutents R^{13} on N or C atoms, and each R^{13} is independently selected from the group consisting of hydrogen, halogen, C_{1-6}alkyl and 3- to 8-membered cycloalkyl containing from 0 to 3 heteroatoms independently chosen from the group consisting of N, O and S,

(d) cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, pyranyl, pyrrolidinyl, piperidinyl, oxacyclopentyl and oxacyclohexyl having from 0 to 3 substitutents R^{10} on N or C atoms, said R^{10} independently selected from the group consisting of hydrogen, halogen, carboxy, C_{1-6}alkyl, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, phenyl and benzyl, and

(e) aryl ring systems G' chosen from the group consisting of: phenyl, pyridinyl and 9-membered bicyclic ring systems containing from 0 to 2 heteroatoms independently chosen from the group consisting of N and O.

31. A compound according to claim 1, claim 2 or claim 11, chosen from the group consisting of:

N-{4-[5-(acetylamino)-1H-pyrrolo[3,2-b]pyridin-2-yl]phenyl}-1-(phenylacetyl)-L-prolinamide;

(2S)-1-(phenylacetyl)-N-{2-[4-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-pyrrolo[3,2-b]pyridin-5-yl}pyrrolidine-2-carboxamide;

benzyl (2S)-2-[(2-{4-[({(2S)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1H-pyrrolo[3,2-b]pyridin-5-yl)carbamoyl]pyrrolidine-1-carboxylate;

tert-butyl {(1S)-2-[(2S)-2-{[4-(5-bromo-1H-pyrrolo[3,2-b]pyridin-2-yl)phenyl]carbamoyl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-N-{3-chloro-2-[4-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-pyrrolo[2,3-c]pyridin-5-yl}-1-(phenylacetyl)pyrrolidine-2-carboxamide;

(2S)-N-{3-chloro-2-[4-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-pyrrolo[2,3-b]pyridin-5-yl}-1-(phenylacetyl)pyrrolidine-2-carboxamide;

N-[4-(3-oxo-7-{2-oxo-2-[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]ethyl}-3,7-dihydroimidazo[1,2-a]pyrazin-2-yl)phenyl]-1-(phenylacetyl)-L-prolinamide;

(2S)-1-(cyclobutylcarbonyl)-N-{2-[4-({[(2S)-1-(pyridin-3-ylcarbonyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-benzimidazol-5-yl}pyrrolidine-2-carboxamide;

(2S)-1-(phenylcarbonyl)-N-{4-[5-({[(2S)-1-(phenylcarbonyl)pyrrolidin-2-yl]carbonyl}amino)-1H-benzimidazol-2-yl]phenyl}pyrrolidine-2-carboxamide;

(2S)-1-[(4Z,5Z)-4-ethylidenehept-5-enoyl]-N-{2-[4-({[(2S)-1-(3-phenylpropanoyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-benzimidazol-5-yl}pyrrolidine-2-carboxamide;

(2S)-1-[(4Z,5Z)-4-ethylidenehept-5-enoyl]-N-{2-[3-({[(2S)-1-(3-phenylpropanoyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-benzimidazol-5-yl}pyrrolidine-2-carboxamide;

(2S)-1-[(2R)-2-hydroxy-2-phenylacetyl]-N-(4-{5-[({(2S)-1-[(2R)-2-hydroxy-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-benzimidazol-2-yl}phenyl)pyrrolidine-2-carboxamide;

(2S)-1-(phenylacetyl)-N-{4-[5-({[(2S)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl} amino)-1H-benzimidazol-2-yl]phenyl}pyrrolidine-2-carboxamide;

tert-butyl {(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2S)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1H-benzimidazol-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1H-benzimidazol-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

benzyl (2S)-2-{[4-(4-{[(4-methylphenyl)sulfonyl]amino}-1H-benzimidazol-2-yl)phenyl]carbamoyl}pyrrolidine-1-carboxylate;

(2S)-1-(3-phenylpropanoyl)-N-{4-[5-({[(2S)-1-(3-phenylpropanoyl)pyrrolidin-2-yl]carbonyl}amino)-1,3-benzoxazol-2-yl]phenyl}pyrrolidine-2-carboxamide;

(2S)-1-(3-phenylpropanoyl)-N-{4-[5-({[(2S)-1-(3-phenylpropanoyl)pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl}pyrrolidine-2-carboxamide;

N-{2-[4-(acetylamino)phenyl]-1-benzofuran-5-yl}-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}-L-prolinamide;

(2S)-1-(phenylacetyl)-N-{4-[5-({[(2S)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} pyrrolidine-2-carboxamide;

tert-butyl {(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2S)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl] carbonyl}amino)-1-benzofuran-2-yl]phenyl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

propan-2-yl [(1R)-2-oxo-1-phenyl-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl] pyrrolidin-2-yl}carbonyl)amino]-1-benzofuran-2-yl}phenyl) carbamoyl]pyrrolidin-1-yl}ethyl]carbamate;

methyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-N-(4-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl} carbonyl)amino]-1-benzofuran-2-yl}phenyl)pyrrolidine-2-carboxamide;

(2S)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]-N-(4-{5-[({(2S)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl} carbonyl)amino]-1-benzofuran-2-yl}phenyl)pyrrolidine-2-carboxamide;

propan-2-yl [(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl} carbonyl)amino]-1-benzofuran-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate;

N-[2-(4-aminophenyl)-1-benzofuran-5-yl]-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-L-prolinamide;

(2S)-1-{(2R)-2-[methyl(3-methylbutyl)amino]-2-phenylacetyl}-N-{4-[5-({[(2S)-1-{(2R)-2-[methyl(3-methylbutyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} pyrrolidine-2-carboxamide;

N-{2-[4-(acetylamino)phenyl]-1-benzofuran-5-yl}-1-[(2R)-2-(diethylamino)-2-phenylacetyl]-L-prolinamide;

(2S)-1-acetyl-N-(2-{4-[({(2S)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1-benzofuran-5-yl)pyrrolidine-2-carboxamide;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-acetylpyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-1-acetyl-N-(2-{4-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1-benzofuran-5-yl)pyrrolidine-2-carboxamide;

N-{4-[5-(acetylamino)-1-benzofuran-2-yl]phenyl}-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}-L-prolinamide;

methyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-7-methyl-1-benzofuran-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-1-{(2R)-2-[ethyl(propyl) amino]-2-phenylacetyl}-N-{4-[5-({[(2S)-1-{(2R)-2-[ethyl(propyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} pyrrolidine-2-carboxamide;

(2S)-1-(phenylacetyl)-N-{4-[6-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)imidazo[1,2-a]pyrimidin-2-yl]phenyl}pyrrolidine-2-carboxamide;

(2S)-1-(phenylacetyl)-N-{4-[6-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)imidazo[1,2-a]pyridin-2-yl]phenyl}pyrrolidine-2-carboxamide;

(2S,2'S)-N,N'-1H,1'H-2,2'-biindole-5,5'-diylbis[1-(phenylacetyl)pyrrolidine-2-carboxamide];

di-tert-butyl (1H,1'H-2,2'-biindole-5,5'-diylbis{carbamoyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate;

tert-butyl {(1R)-2-oxo-1-phenyl-2-[(2S)-2-({2-[4-({[(2S)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]ethyl}carbamate;

(2S)-1-(phenylacetyl)-N-{2-[5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]pyrimidin-5-yl}pyrrolidine-2-carboxamide;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

methyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-1-[(2R)-2-phenyl-2-(pyrrolidin-1-yl)acetyl]-N-(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-(pyrrolidin-1-yl)acetyl] pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl) pyrrolidine-2-carboxamide;

(2S)-1-{(2R)-2-[(cyclopropylacetyl)amino]-2-phenylacetyl}-N-{4-[5-({[(2S)-1-{(2R)-2-[(cyclopropylacetyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl} pyrrolidine-2-carboxamide;

(2S)-1-{(2R)-2-[(3-methylbutanoyl)amino]-2-phenylacetyl}-N-{4-[5-({[(2S)-1-{(2R)-2-[(3-methylbutanoyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl} pyrrolidine-2-carboxamide;

(2S)-1-[(2R)-2-(morpholin-4-yl)-2-phenylacetyl]-N-(4-{5-[({(2S)-1-[(2R)-2-(morpholin-4-yl)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)pyrrolidine-2-carboxamide;

(2S)-1-(2,3-diphenylpropanoyl)-N-{4-[5-({[(2S)-1-(2,3-diphenylpropanoyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}pyrrolidine-2-carboxamide;

(2S)-1-[(2R)-2-{[(4-methylphenyl)sulfonyl]amino}-2-phenylacetyl]-N-(4-{5-[({(2S)-1-[(2R)-2-{[(4-methylphenyl) sulfonyl]amino}-2-phenylacetyl] pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl) pyrrolidine-2-carboxamide;

(2S)-1-{(2R)-2-[(cyclohexylcarbonyl)amino]-2-phenylacetyl}-N-{4-[5-({[(2S)-1-{(2R)-2-[(cyclohexylcarbonyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl} pyrrolidine-2-carboxamide;

methyl {(1R)-2-[(2S)-2-({2-[4-(acetylamino)phenyl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-(acetylamino)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

N-{2-[4-(acetylamino)phenyl]-1H-indol-5-yl}-1-[(2R)-2-(morpholin-4-yl)-2-phenylacetyl]-L-prolinamide;

propan-2-yl {(1R)-2-[(2S)-2-({2-[4-(acetylamino)phenyl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-1-{(2R)-2-[(cyclopentylcarbamoyl)amino]-2-phenylacetyl}-N-(4-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)pyrrolidine-2-carboxamide;

tert-butyl {(2R)-1-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

N-{2-[4-(acetylamino)phenyl]-1H-indol-5-yl}-1-[(2R)-2-phenyl-2-(pyrrolidin-1-yl)acetyl]-L-prolinamide;

(2S)-1-[(2R)-2-(dimethylamino)-4-methylpentanoyl]-N-(4-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-4-methylpentanoyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)pyrrolidine-2-carboxamide;

(2S)-1-[(2R)-2-phenyl-2-(piperidin-1-yl)acetyl]-N-(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-(piperidin-1-yl)acetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)pyrrolidine-2-carboxamide;

(2S)-1-[(2R)-2-(1H-imidazol-1-yl)-2-phenylacetyl]-N-(4-{5-[({(2S)-1-[(2R)-2-(1H-imidazol-1-yl)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)pyrrolidine-2-carboxamide;

(2S)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]-N-(4-{5-[({(2S)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)pyrrolidine-2-carboxamide;

tert-butyl {(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-acetylpyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-acetylpyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-oxo-1-phenyl-2-[(2S)-2-({2-[4-({[(2S)-1-(propan-2-yl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]ethyl}carbamate;

N-{2-[4-(acetylamino)phenyl]-1H-indol-5-yl}-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-L-prolinamide;

N-{2-[4-(acetylamino)phenyl]-1H-indol-5-yl}-1-[(2R)-2-phenyl-2-(piperidin-1-yl)acetyl]-L-prolinamide;

tert-butyl [(1R)-2-{(2S)-2-[(2-{4-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1H-indol-5-yl)carbamoyl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate;

tert-butyl [(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl] pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl) carbamoyl] pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate;

(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-N-{4-[5-({[(2S)-1-{(2R)-2-[(3,3-dimethylbutanoyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}pyrrolidine-2-carboxamide;

(2S)-1-(cyclopropylacetyl)-N-(4-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)pyrrolidine-2-carboxamide;

(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-N-(2-{4-[({(2S)-1-[(2R)-tetrahydrofuran-2-ylcarbonyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1H-indol-5-yl)pyrrolidine-2-carboxamide;

tert-butyl [(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(4-fluorophenyl)acetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)carbamoyl]pyrrolidin-1-yl}-1-(4-fluorophenyl)-2-oxoethyl]carbamate;

(2S)-1-{(2R)-2-[methyl(3-methylbutyl)amino]-2-phenylacetyl}-N-{4-[5-({[(2S)-1-{(2R)-2-[methyl(3-methylbutyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl} pyrrolidine-2-carboxamide;

(2S)-1-[(2S)-tetrahydrofuran-2-ylcarbonyl]-N-(4-{5-[({(2S)-1-[(2S)-tetrahydrofuran-2-ylcarbonyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)pyrrolidine-2-carboxamide;

N-(tert-butoxycarbonyl)-D-valyl-N-{4-[5-({1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-L-prolyl}amino)-1H-indol-2-yl]phenyl}-L-prolinamide;

(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-N-{2-[4-({[(2S)-1-(1,3-oxazol-2-ylcarbonyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-indol-5-yl}pyrrolidine-2-carboxamide;

tert-butyl [(1R)-2-{[(2S)-1-({4-[5-({(2S)-2-[{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}(methyl)amino]propanoyl}amino)-1H-indol-2-yl]phenyl}amino)-1-oxopropan-2-yl](methyl)amino}-2-oxo-1-phenylethyl]carbamate;

tert-butyl {(1R)-2-[(2S)-2-({2-[4-(methylamino)phenyl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-N-{2-[4-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-indol-5-yl}pyrrolidine-2-carboxamide;

(2S)-1-{[(3R)-1-benzylpyrrolidin-3-yl]carbonyl}-N-(4-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)pyrrolidine-2-carboxamide;

(2S)-1-{[(3S)-1-benzylpyrrolidin-3-yl]carbonyl}-N-(4-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)pyrrolidine-2-carboxamide;

N,N-dimethyl-D-leucyl-N-{4-[5-({1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-L-prolyl}amino)-1H-indol-2-yl]phenyl}-L-prolinamide;

N-(2-{4-[(cyclopentylcarbonyl) amino]phenyl}-1H-indol-5-yl)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-L-prolinamide;

tert-butyl [(2S)-1-({4-[5-({1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-L-prolyl}amino)-1H-indol-2-yl]phenyl}amino)-1-oxopropan-2-yl]carbamate;

tert-butyl [(1S)-2-({4-[5-({1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-L-prolyl}amino)-1H-indol-2-yl]phenyl}amino)-2-oxo-1-phenylethyl]carbamate;

tert-butyl [(2R)-1-({4-[5-({1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-L-prolyl}amino)-1H-indol-2-yl]phenyl}amino)-3-methyl-1-oxobutan-2-yl]carbamate;

(2S,2'S)-N,N'-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole-3,9-diylbis[1-(phenylacetyl)pyrrolidine-2-carboxamide];

(2S,2'S)-N,N'-6,11-dihydro-5H-benzo[a]carbazole-3,8-diylbis[1-(phenylacetyl)pyrrolidine-2-carboxamide];

dibenzyl (2S,2'S)-2,2'-(6,11-dihydro-5H-benzo[a]carbazole-3,8-diyldicarbamoyl) dipyrrolidine-1-carboxylate;

N-(8-bromo-6,11-dihydro-5H-benzo[a]carbazol-3-yl)-1-(phenylacetyl)-L-prolinamide;

di-tert-butyl (6,11-dihydro-5H-benzo[a]carbazole-3,8-diylbis {carbamoyl(2S)pyrrolidine-2,1-diyl[(1S)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate;

tert-butyl [(1S)-2-{(2S)-2-[(8-bromo-6,11-dihydro-5H-benzo[a]carbazol-3-yl) carbamoyl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate;

(2S,2'S)-N,N'-6,11-dihydro-5H-benzo[a]carbazole-3,8-diylbis{1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-carboxamide};

(2S,2'S)-N,N'-5,6,7,12-tetrahydrobenzo[6,7]cyclohepta [1,2-b]indole-3,9-diylbis{1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-carboxamide};

N-(6,11-dihydro-5H-benzo[a]carbazol-3-yl)-1-{(2S)-2-[(3,3-dimethylbutanoyl)amino] -2-phenylacetyl}-L-prolinamide;

tert-butyl {(1R)-2-[(2S)-2-(6,11-dihydro-5H-benzo[a]carbazol-3-ylcarbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

di-tert-butyl (5,6,7,12-tetrahydrobenzo[6,7]cyclohepta[1,2-b]indole-3,9-diylbis {carbamoyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate;

tert-butyl {(1R)-2-[(2S)-2-(5-{4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxy carbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

benzyl (2S)-2-[5-(4-{5-[(1-{(2R)-2-[(tert-butoxycarbonyl) amino]-2-phenylacetyl}-L-prolyl)amino]-1H-indol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidine-1-carboxylate;

1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-N-{2-[4-(2-{(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)phenyl]-1H-indol-5-yl}-L-prolinamide;

tert-butyl {(1R)-2-[(2S)-2-({2-[4-(1H-imidazol-4-yl)phenyl]-1H-indol-5-yl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

1-[(2S)-2-(dimethylamino)-2-phenylacetyl]-N-{2-[4-(2-{(2S)-1-[(2S)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)phenyl]-1H-indol-5-yl}-L-prolinamide;

tert-butyl {(1R)-2-oxo-1-phenyl-2-[(2S)-2-{[2-(4-{2-[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-indol-5-yl]carbamoyl}pyrrolidin-1-yl]ethyl}carbamate;

tert-butyl{(1R)-2-[(2S)-2-{[2-(4-{2-[(2S)-1-acetylpyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-indol-5-yl]carbamoyl} pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

benzyl (2S)-2-(5-{4-[5-({1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]-L-prolyl}amino)-1H-indol-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidine-1-carboxylate;

tert-butyl {(1R)-2-[(2S)-2-({2-[4-(2-{(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)phenyl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

propan-2-yl [(1R)-2-{(2S)-2-[1-methyl-4-(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl] pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate;

propan-2-yl {(1R)-2-[(2S)-2-{[2-(4-{2-[(2S)-1-acetylpyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-indol-5-yl]carbamoyl} pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

propan-2-yl {(1R)-2-oxo-1-phenyl-2-[(2S)-2-{[2-(4-{2-[(2S)-pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1H-indol-5-yl]carbamoyl}pyrrolidin-1-yl]ethyl}carbamate;

propan-2-yl {(1R)-2-[(2S)-2-{5-[4-(1H-indol-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2R)-2-(dimethylamino)-1-[(2S)-2-{5-[4-(1H-indol-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-phenylethanone;

propan-2-yl [(1R)-2-oxo-1-phenyl-2-{(2S)-2-[5-(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl] amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)-1H-imidazol-2-yl] pyrrolidin-1-yl}ethyl]carbamate;

propan-2-yl {(1R)-2-[(2S)-2-({2-[4-(2-{(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl] pyrrolidin-2-yl}-1H-imidazol-5-yl)phenyl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

propan-2-yl {(1R)-2-[(2S)-2-{4-[4-(3-chloro-1H-indol-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

N-(methoxycarbonyl)-L-valyl-N-{2-[4-(2-{(2S)-1-[N-(methoxycarbonyl)-L-valyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)phenyl]-1H-indol-5-yl}-L-prolinamide;

propan-2-yl [(1R)-2-oxo-1-phenyl-2-{(2S)-2-[3-(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)-1H-pyrazol-5-yl]pyrrolidin-1-yl}ethyl]carbamate;

propan-2-yl [(1R)-2-oxo-1-phenyl-2-{(2S)-2-[5-(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)-1,3-thiazol-2-yl]pyrrolidin-1-yl}ethyl]carbamate;

propan-2-yl [(1R)-2-oxo-1-phenyl-2-{(2S)-2-[2-(4-{5-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)-1H-imidazol-5-yl]pyrrolidin-1-yl}ethyl]carbamate;

1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]-N-{4-[5-(2-{(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)-1-benzofuran-2-yl]phenyl}-L-prolinamide;

propan-2-yl {(1R)-2-[(2S)-2-(5-{2-[4-(acetylamino)phenyl]-1H-indol-5-yl}-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-1-(phenylacetyl)-N-{3-[5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}pyrrolidine-2-carboxamide;

(2S)-1-(phenylacetyl)-N-{4-[6-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}pyrrolidine-2-carboxamide;

(2S)-1-(phenylacetyl)-N-{3-[6-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}pyrrolidine-2-carboxamide;

tert-butyl [(1R)-2-{(2S)-2-[(2-{2-[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl) amino]-2-phenylacetyl}pyrrolidin-2-yl]-1H-benzimidazol-5-yl}-1H-indol-5-yl)carbamoyl] pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate;

(2S)-N-{4-[3-bromo-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)pyrrolidine-2-carboxamide;

tert-butyl {(1S)-2-[(2S)-2-({2-[4-(acetylamino)phenyl]-3-fluoro-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-N-{4-[3-chloro-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide;

(2S)-N-{4-[3-fluoro-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide;

tert-butyl {(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2S)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-fluoro-1H-indol-2-yl]phenyl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1S)-2-[(2S)-2-({2-[4-(acetylamino)phenyl]-3-chloro-1H-indol-5-yl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-N-{4-[3-iodo-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl] carbonyl}amino)-1H-indol-2-yl] phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide;

tert-butyl {(1S)-2-[(2S)-2-({2-[4-({[(2S)-1-acetylpyrrolidin-2-yl]carbonyl}amino)phenyl]-3-fluoro-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-1-{(2S)-2-[(3,3-dimethylbutanoyl)amino]-2-phenylacetyl}-N-{4-[5-({[(2S)-1-{(2S)-2-[(3,3-dimethylbutanoyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino)-3-fluoro-1H-indol-2-yl]phenyl} pyrrolidine-2-carboxamide;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-fluoro-1H-indol-2-yl]phenyl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({2-[4-(acetylamino)phenyl]-3-fluoro-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({2-[4-({[(2S)-1-acetylpyrrolidin-2-yl]carbonyl}amino)phenyl]-3-fluoro-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({3-fluoro-2-[4-(2-oxopyrrolidin-1-yl)phenyl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

N-{2-[4-(acetylamino)phenyl]-3-fluoro-1H-indol-5-yl}-1-[(2R)-2-phenyl-2-(pyrrolidin-1-yl)acetyl]-L-prolinamide;

N-(tert-butoxycarbonyl)-D-alanyl-N-{2-[4-(acetylamino)phenyl]-3-fluoro-1H-indol-5-yl}-L-prolinamide;

N-{2-[4-(acetylamino)phenyl]-3-fluoro-1H-indol-5-yl}-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-L-prolinamide;

N-(tert-butoxycarbonyl)-D-leucyl-N-{2-[4-(acetylamino)phenyl]-3-fluoro-1H-indol-5-yl}-L-prolinamide;

propan-2-yl [(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl} carbonyl)amino]-3-fluoro-1H-indol-2-yl}phenyl)carbamoyl] pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate);

tert-butyl (2S)-2-[(3-fluoro-2-{4-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl] amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1H-indol-5-yl)carbamoyl] pyrrolidine-1-carboxylate;

propan-2-yl [(1R)-2-{(2S)-2-[(4-{3-bromo-5-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl]amino}acetyl] pyrrolidin-2-yl}carbonyl)amino]-1-benzofuran-2-yl}phenyl) carbamoyl] pyrrolidin-1-yl}-2-oxo-1-phenylethyl]carbamate;

(2S)-N-(4-{3-bromo-5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1-benzofuran-2-yl}phenyl)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidine-2-carboxamide;

methyl {(1R)-2-[(2S)-2-({4-[3-bromo-5-({[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

methyl {(2S)-1-[(2S)-2-({4-[3-fluoro-5-({[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

N-{2-[4-(acetylamino)phenyl]-3-bromo-1-benzofuran-5-yl}-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-L-prolinamide;

(2S)-N-(4-{3-bromo-5-[({(2S)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl} carbonyl)amino]-1-benzofuran-2-yl}phenyl)-1-[(2R)-2-(diethylamino)-2-phenylacetyl] pyrrolidine-2-carboxamide;

(2S)-1-acetyl-N-(4-{3-bromo-5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl] pyrrolidin-2-yl}carbonyl)amino]-1-benzofuran-2-yl}phenyl) pyrrolidine-2-carboxamide;

tert-butyl {(1S)-2-[(2S)-2-({4-[3-bromo-5-({[(2S)-1-{(2S)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate);

(2S)-N-{4-[3-bromo-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl] carbonyl}amino)-1-benzofuran-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide;

tert-butyl {(1R)-2-[(2S)-2-({4-[3-bromo-5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-1-benzofuran-2-yl]phenyl} carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-N-{4-[3-cyano-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)pyrrolidine-2-carboxamide;

(2S)-N-{4-[3-(2,2-dimethylpropanoyl)-5-({[(2S)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)pyrrolidine-2-carboxamide;

5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-2-[4-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-indole-3-carboxamide;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-(cyclopropylcarbamoyl)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxy-carbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-(4-methoxyphenyl)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-1-(phenylacetyl)-N-{4-[3-phenyl-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}pyrrolidine-2-carboxamide;

(2S)-N-{4-[3-ethyl-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide;

(2S)-N-{4-[3-acetyl-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide;

(2S)-1-(phenylacetyl)-N-{4-[5-({[(2S)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl}amino)-3-(phenylcarbonyl)-1H-indol-2-yl]phenyl}pyrrolidine-2-carboxamide;

(2S)-1-(phenylacetyl)-N-{2-[4-({[(2S)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl} amino)phenyl]-3-(pyridin-4-yl)-1H-indol-5-yl}pyrrolidine-2-carboxamide;

benzyl (2S)-2-[(4-{5-[({(2S)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}carbonyl)amino]-3-phenyl-1H-indol-2-yl}phenyl) carbamoyl]pyrrolidine-1-carboxylate;

(2S)-N-{4-[3-cyano-5-({[(2S)-1-(phenylacetyl)pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl) pyrrolidine-2-carboxamide;

(2S)-N-{4-[3-cyclopropyl-5-({[(2S)-1-(phenylacetyl) pyrrolidin-2-yl]carbonyl}amino)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)pyrrolidine-2-carboxamide;

benzyl (2S)-2-[(4-{5-[({(2S)-1-[(benzyloxy)carbonyl]pyrrolidin-2-yl}carbonyl)amino]-3-(3-methoxyphenyl)-1H-indol-2-yl}phenyl)carbamoyl]pyrrolidine-1-carboxylate;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-(3-methylphenyl)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-(2-methylphenyl)-1H-indol-2-yl]phenyl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({2-[4-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)phenyl]-3-(pyridin-4-yl)-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-cyano-1H-indol-2-yl]phenyl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

(2S)-N-(4-{3-cyano-5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1H-indol-2-yl}phenyl)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl] pyrrolidine-2-carboxamide;

tert-butyl {(1R)-2-[(2S)-2-({2-[4-(acetylamino)phenyl]-3-cyano-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

tert-butyl {(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-3-(dimethylcarbamoyl)-1H-indol-2-yl]phenyl}carbamoyl) pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

methyl 5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-2-[4-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)phenyl]-1H-indole-3-carboxylate;

5-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]carbonyl}amino)-2-[4-({[(2S)-1-{(2R)-2-[(tert-butoxycarbonyl) amino]-2-phenylacetyl} pyrrolidin-2-yl]carbonyl}amino) phenyl]-1H-indole-3-carboxylic acid;

tert-butyl {(1R)-2-[(2S)-2-({2-[3-(acetylamino)prop-1-yn-1-yl]-1H-indol-5-yl}carbamoyl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

N-{4-[5-(furan-3-yl)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)-L- prolinamide;

N-(4-{5-[6-(dimethylamino)-4-methylpyridin-3-yl]-1H-indol-2-yl}phenyl)-1-(phenylacetyl)-L-prolinamide;

N-{4-[5-(1-benzothiophen-3-yl)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)-L-prolinamide;

N-{4-[5-(1-benzyl-1H-pyrazol-4-yl)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)-L-prolinamide;

N-{4-[5-(2,3-dihydro-1,4-benzodioxin-6-yl)-1H-indol-2-yl]phenyl}-1-(phenylacetyl)-L-prolinamide;

1-(phenylacetyl)-N-{4-[5-(quinolin-8-yl)-1H-indol-2-yl]phenyl}-L-prolinamide;

1-(phenylacetyl)-N-{4-[5-(thiophen-3-yl)-1H-indol-2-yl]phenyl}-L-prolinamide;

tert-butyl {(1S)-2-[(2S)-2-{[4-(5-cyano-1H-indol-2-yl)phenyl] carbamoyl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

propan-2-yl [(1R)-2-oxo-1-phenyl-2-{(2S)-2-[4-(2-{4-[({(2S)-1-[(2R)-2-phenyl-2-{[(propan-2-yloxy)carbonyl] amino}acetyl]pyrrolidin-2-yl}carbonyl)amino]phenyl}-1H-indol-5-yl)-1H-imidazol-2-yl] pyrrolidin-1-yl}ethyl]carbamate;

propan-2-yl {(1R)-2-[(2S)-2-(5-{2-[4-(acetylamino)phenyl]-1H-indol-5-yl}-1,3,4-oxadiazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

N-{4-[5-(5-{(2S)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1,3,4-oxadiazol-2-yl)-1H-indol-2-yl]phenyl}acetamide;

methyl [(2S)-1-{(2S)-2-[5-(10-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}indolo[1,2-c] [1,3]benzoxazin-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(12-fluoro-10-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}indolo[1,2-c] [1,3]benzoxazin-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]-N-(2-{5-[({(2S)-1-[(2R)-2-(dimethylamino)-2-phenylacetyl]pyrrolidin-2-yl}carbonyl)amino]-1,3-benzoxazol-2-yl}-1H-indol-5-yl)pyrrolidine-2-carboxamide;

1-[(2R)-2-(diethylamino)-2-phenylacetyl]-N-{2-[4-(5-{(2S)-1-[(2R)-2-(diethylamino)-2-phenylacetyl]pyrrolidin-2-yl}-1,3,4-oxadiazol-2-yl)phenyl]-1H-indol-5-yl}-L-prolinamide;

methyl {(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(methoxy- carbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

(2R)-2-(diethylamino)-1-[(2S)-2-(5-{4-[5-(2-{(2S)-1-[(2R)-2-(diethylamino)-2-phenylacetyl] pyrrolidin-2-yl}-1H-imidazol-5-yl)-1-benzofuran-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-phenylethanone;

methyl {(1S)-1-cyclopropyl-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-cyclopropyl-2-[(methoxycarbonyl)amino]acetyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxoethyl}carbamate;

methyl {(1R)-1-cyclopropyl-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-cyclopropyl-2-[(methoxycarbonyl)amino]acetyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxoethyl}carbamate;

methyl {(2R)-1-[(2S)-2-{5-[2-(4-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-benzofuran-5-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoyl} pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate;

methyl {(1R)-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

methyl {(2S,3R)-1-[(2S)-2-(5-{2-[4-(2-{(2S)-1-[N-(methoxycarbonyl)-L-alloisoleucyl]pyrrolidin-2-yl}-1H-imidazol-5-yl)phenyl]-1-benzofuran-5-yl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-3-methyl-1-oxopentan-2-yl}carbamate;

methyl {(2S)-3-hydroxy-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-3-hydroxy-2-[(methoxycarbonyl) amino]propanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-1-oxopropan-2-yl}carbamate;

methyl {(2S,3R)-3-hydroxy-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S,3R)-3-hydroxy-2-[(methoxycarbonyl)amino]butanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-1-oxobutan-2-yl}carbamate;

methyl {(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-4-methylpentanoyl} pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-4-methyl-1-oxopentan-2-yl}carbamate;

methyl {(2S)-1-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl} carbamate;

methyl {(1R)-2-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

methyl {(2S)-1-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2S)-1-[(2S)-2-{5-[2-(2,6-difluoro-4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1-benzofuran-5-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(1R)-2-[(2S)-2-{5-[3-methoxy-4-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl) amino]-2-phenylacetyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

methyl {(2S)-1-[(2S)-2-{5-[2-(2-chloro-4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}phenyl)-1-benzofuran-5-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(1R)-2-[(2S)-2-{4-[3-cyano-4-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

methyl {(2S)-1-[(2S)-2-{5-[2-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-4-yl}-2-methylphenyl)-1-benzofuran-5-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl [(1S)-2-[(2S)-2-(5-{3-fluoro-4-[5-(2-{(2S)-1-[(2S)-2-[(methoxycarbonyl)amino]-2-(tetrahydro-2H-pyran-4-yl)acetyl]pyrrolidin-2-yl}-1H-imidazol-5-

yl)-1-benzofuran-2-yl]phenyl}-1H-imidazol-2-yl)pyrrolidin-1-yl]-2-oxo-1-(tetrahydro-2H-pyran-4-yl)ethyl]carbamate;

methyl {(2S)-1-[(2S)-2-{4-[3-fluoro-4-(5-{2-[(2S)-1-{(2R)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(1R)-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2 [(methoxy-carbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,3-benzoxazol-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

methyl {(2S)-1-[(2S)-2-{5-[2-(4-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1H-imidazol-5-yl}phenyl)-1,3-benzoxazol-5-yl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(1R)-1-cyclopropyl-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-cyclopropyl-2-[(methoxycarbonyl) amino]acetyl} pyrrolidin-2-yl]-1H-imidazol-5-yl}-1,3-benzoxazol-2-yl)phenyl]-1H-imidazol-2-yl}pyrrolidin-1-yl]-2-oxoethyl}carbamate;

dimethyl (indolo[1,2-c][1,3]benzoxazine-3,10-diylbis{1H-imidazole-5,2-diyl(2S)pyrrolidine-2,1-diyl[(1R)-2-oxo-1-phenylethane-2,1-diyl]})biscarbamate;

methyl [(2S)-1-{(2S)-2-[5-(11-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-6,7-dihydroindolo[1,2-d][1,4] benzoxazepin-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-6,6-dimethylindolo[1,2-c][1,3] benzoxazin-10-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(12-fluoro-10-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-6-methylindolo[1,2-c][1,3]benzoxazin-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}indolo[1,2-c]quinazolin-10-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(12-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-7,8-dihydro-6H-indolo[1,2-

e][1,5]benzoxazocin-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-6-oxo-5,6-dihydroindolo[1,2-c]quinazolin-10-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(10-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-6-phenylindolo[1,2-c][1,3]benzoxazin-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}-6-methylindolo[1,2-c]quinazolin-10-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(10'-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}spiro [cyclohexane-1,6'-indolo[1,2-c][1,3]benzoxazin]-3'-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(1,12-difluoro-10-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}indolo[1,2-c][1,3]benzoxazin-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2S)-1-{(2S)-2-[5-(12-cyano-10-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1H-imidazol-5-yl}indolo[1,2-c][1,3]benzoxazin-3-yl)-1H-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate; and

pharmaceutically acceptable salts thereof.

32. A compound according to claim 1 or claim 2, chosen from the group consisting of:

methyl {(2*S*)-1-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxy- carbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*R*)-1-[(2*S*)-2-{5-[2-(4-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1-benzofuran-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-4-methylpentanoyl} pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-4-methyl-1-oxopentan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[3-fluoro-4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl} carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[3-fluoro-4-(5-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[2-(2,6-difluoro-4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}phenyl)-1-benzofuran-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[2-(2-chloro-4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}phenyl)-1-benzofuran-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate;

methyl {(1*R*)-2-[(2*S*)-2-{4-[3-cyano-4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(methoxycarbonyl)amino]-2-phenylacetyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-1-benzofuran-2-yl)phenyl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-2-oxo-1-phenylethyl}carbamate;

methyl {(2*S*)-1-[(2*S*)-2-{5-[2-(4-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-4-yl}-2-methylphenyl)-1-benzofuran-5-yl]-1*H*-imidazol-2-yl}pyrrolidin-1-yl]-3-methyl-1-oxobutan-2-yl}carbamate; and

pharmaceutically acceptable salts thereof.

33. A compound according to claim 1 or claim 11, chosen from the group consisting of:

methyl [(2*S*)-1-{(2*S*)-2-[5-(12-fluoro-10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}indolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2*S*)-1-{(2*S*)-2-[5-(3-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-6,6-dimethylindolo[1,2-c][1,3] benzoxazin-10-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2*S*)-1-{(2*S*)-2-[5-(12-fluoro-10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-6-methylindolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2*S*)-1-{(2*S*)-2-[5-(10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}-6-phenylindolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2*S*)-1-{(2*S*)-2-[5-(10'-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl) amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}spiro [cyclohexane-1,6'-indolo[1,2-c][1,3]benzoxazin]-3'-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2*S*)-1-{(2*S*)-2-[5-(1,12-difluoro-10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}indolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate;

methyl [(2*S*)-1-{(2*S*)-2-[5-(12-cyano-10-{2-[(2*S*)-1-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}pyrrolidin-2-yl]-1*H*-imidazol-5-yl}indolo[1,2-c][1,3]benzoxazin-3-yl)-1*H*-imidazol-2-yl]pyrrolidin-1-yl}-3-methyl-1-oxobutan-2-yl]carbamate; and

pharmaceutically acceptable salts thereof.

34. A pharmaceutical composition comprising an effective amount of the compound according to any one of claims 1-33, and a pharmaceutically acceptable carrier.

35. The pharmaceutical composition according to claim 34, further comprising a second therapeutic agent selected from the group consisting of HCV antiviral agents, immunomodulators, and anti-infective agents.

36. The pharmaceutical composition according to claim 34, further comprising a second therapeutic agent selected from the group consisting of HCV protease inhibitors and HCV NS5B polymerase inhibitors.

37. A use of the compound according to any one of claims 1-33 in the preparation of a medicament for preventing and/or treating infection by HCV in a subject in need thereof.

38. A method of treating a patient infected with HCV comprising the step of administering an amount of the compound according to any one of claims 1-33 effective to prevent and/or treat infection by HCV in a subject in need thereof.

39. A method of treating a patient infected with HCV comprising the step of administering an amount of the compound according to any one of claims 1-33 effective to inhibit HCV viral replication and/or viral production.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/28653

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/18; A61K 31/16 (2010.01)
USPC - 514/613
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)
USPC - 514/613

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/265.1, 427, 563, 630 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (PGPB,USPT,USOC,EPAB,JPAB); Google
Search Terms Used:
polycyclic fused rings hcv inhibitor, viramidine, benzofuran, tetracycle

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2006/0019974 A1 (MEDERSKI et al.) 26 January 2006 (26.01.2006) para [0001]-[0016]	1-3 and 21 --- 22, 26, 32
X -- Y	US 2007/0049593 A1 (OKA et al.) 01 March 2007 (01.03.2007) para [0042]-[0051]	11-13, 30-31 --- 29, 33
Y	US 2007/0185175 A1 (LIU et al.) 09 August 2007 (09.08.2007) para [0008]-[0089]	22, 26, 29, 32, 33
Y	US 2006/0258682 A1 (LIAO et al.) 16 November 2006 (16.11.2006) para [0003]-[0047]	26

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

* 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 application or patent 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
02 May 2010 (02.05.2010)	12 MAY 2010

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/28653

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.: 4-10, 14-20, 23-25, 27-28 and 34-39
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

2. ☐ As all searchable claims could be searched without effort justifying 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.:

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.

TÍTULO DE LA SOLICITUD

INHIBIDORES DE LA REPLICACIÓN DEL VIRUS DE LA HEPATITIS C

CAMPO DE LA INVENCIÓN

La presente descripción se refiere a compuestos antivirales que son útiles como inhibidores de la replicación del virus de la hepatitis C (VHC). Se espera que los compuestos actúen sobre la proteína NS5A (5A no estructural) del VHC. También se proporcionan composiciones que comprenden dichos compuestos, el uso de dichos compuestos para tratar la infección por el VHC y/o reducir la probabilidad o gravedad de los síntomas de la infección por VHC, procedimientos para inhibir la función de la proteína NS5A no estructural y procedimientos para inhibir la replicación viral y/o la producción viral del VHC.

ANTECEDENTES DE LA INVENCIÓN

La infección por el virus de la hepatitis C (VHC) es un importante problema de salud que conduce a enfermedad hepática crónica, tal como cirrosis y carcinoma hepatocelular, en un número sustancial de individuos afectados. Los tratamientos actuales para la infección por VHC incluyen inmunoterapia con interferón □ recombinante solo o junto con el análogo de nucleósido ribavirina.

Varias enzimas codificadas viralmente son dianas putativas para la intervención terapéutica, incluyendo una metaloproteasa (NS2-3), una serina proteasa (NS3, restos de aminoácidos 1-180), una helicasa (NS3, longitud completa), un cofactor de la proteasa NS3 (NS4A), una proteína de membrana (NS4B), una metaloproteína de cinc (NS5A) y una polimerasa de ARN dependiente de ARN (NS5B).

Una diana identificada para la intervención terapéutica es la proteína NS5A no estructural del VHC, que se describe, por ejemplo, en Seng-Lai Tan & Michael G. Katze, *How Hepatitis C Virus Counteracts the Interferon Response: The Jury Is Still Out on NS5A,* 284 VIROLOGY 1-12 (2001); y en Kyu-Jin Park *et al., Hepatitis C Virus NS5A Protein Modulates c-Jun N-terminal Kinase through Interaction with Tumor Necrosis Factor Receptor-associated Factor 2,* 278(33) J. BIO. CHEM. 30711 (2003). Una proteína no estructural, NS5A es un componente básico para la replicación y el conjunto viral. Las mutaciones en la NS5A en o cerca de sitios conocidos de fosforilación pueden afectar a la capacidad de replicación de alto nivel en los sistemas de cultivo celular, sugiriendo una función importante de la fosforilación de NS5A en la eficacia de la replicación vírica. Los inhibidores de la fosforilación de la NS5A pueden conducir a una replicación de ARN vírico reducida.

NS5A es una metaloproteína de cinc organizada en tres dominios discretos. NS5A se localiza en el sitio asociado a membrana de la síntesis de ARN mediante un ancla de hélice □ anfipática N-terminal. La estructura de cristal del dominio I demuestra que la NS5A puede existir

en forma de un dímero, con un gran surco de unión a ARN putativo localizado en la interfaz de los monómeros. Timothy L. Tellinghuisen *et al., Structure of the cinc-binding domain of an essential component of the hepatitis C viral replicase,* 435(7040) NATURE 374 (2005). Robert A. Love *et al., Crystal Structure of a Novel Dimeric Form of NS5A Domain I Protein From Hepatitis C Virus,* 89(3) J. VIROLOGY 4395-403 (2009). Se cree que la interacción de la NS5A con el ARN es crítica para la función de esta proteína en la replicación del ARN. Todavía no se ha obtenido información estructural para los dominios II o III. Un mapeo genético reciente ha mostrado que aunque algunos residuos del dominio II son esenciales para la replicación de ARN, muchas partes del dominio II y todas las del dominio III son prescindibles. Timothy L. Tellinghuisen *et al., Identification of Residues Required for RNA Replication en Domains II and III of the Hepatitis C Virus NS5A Protein,* J. VIROLOGY 1073 (2008). Las mutaciones construidas en el dominio III dan como resultado un virus que puede mantener la replicación de ARN, pero que produce valoraciones inferiores del virus infeccioso en el cultivo celular, demostrando una segunda función distinta para la NS5A después de que haya ocurrido la replicación de ARN. Timothy L. Tellinghuisen *et al., Regulation of Hepatitis C Virion Production via Phosphorylation of the NS5A Protein,* 4(3) PLOS PATHOGENS e1000032 (2008); Nicole Appel *et al., Mutational Analysis of Hepatitis C Virus Nonstructural Protein 5A: Potential Role of Differential Phosphorylation in RNA Replication and Identification of a Genetically Flexible Domain,* 79(5) J. VIROLOGY 3187 (2005). La NS5A, a diferencia de las demás proteínas no estructurales, puede trans-complementarse, coherente con funciones fuera de la replicasa viral. Se ha descrito la interacción de la NS5A con numerosas rutas de señalización de huésped (Michael J. Gale Jr. *et al., Evidence That Hepatitis C Virus Resistance to Interferon Is Mediated through Repression of the PKR Protein Kinase by the Nonstructural 5A Protein,* 230 VIROLOGY 217 (1997); Andrew Macdonald & Mark Harris, *Hepatitis C virus NS5A: tales of a promiscuous protein,* 85 J. GEN. VIROLOGY 2485 (2004).), sugiriendo que esta proteína puede modificar el entorno celular huésped en un estado favorable para el virus, acontecimientos que pueden requerir una forma de la NS5A disociada del complejo de replicación.

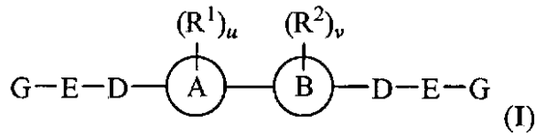
Existe la clara necesidad desde hace tiempo de desarrollar terapias eficaces para el tratamiento de la infección por VHC. Específicamente, existe la necesidad de desarrollar compuestos que sean útiles para tratar pacientes infectados por VHC y compuestos que inhiban selectivamente la replicación viral del VHC.

SUMARIO DE LA INVENCIÓN

La presente descripción se refiere a nuevos compuestos de fórmula **(I)** y/o sales farmacéuticamente aceptables, hidratos, solvatos, profármacos o isómeros de los mismos. Estos compuestos son útiles, como compuestos o sus sales farmacéuticamente aceptables (cuando sea apropiado), en la inhibición de la proteína NS5A (5A no estructural) del VHC (virus de la hepatitis

C), la prevención o tratamiento de uno o más de los síntomas de la infección por VHC, la inhibición de la replicación viral de VHC y/o la producción viral del VHC, y/o como ingredientes de composiciones farmacéuticas. Como ingredientes de composiciones farmacéuticas, estos compuestos, que incluyen referencia a hidratos y solvatos de dichos compuestos, y su sales pueden ser el principal agente terapéutico activo, y, cuando sea apropiado, pueden combinarse con otros agentes terapéuticos, incluyendo pero sin limitación, otros antivirales del VHC, anti-infecciosos, inmunomoduladores, antibióticos o vacunas.

Más particularmente, la presente descripción se refiere a un compuesto de fórmula **(I)**:



(I)

y/o una sal farmacéuticamente aceptable del mismo, en la que:

(A) se elige entre el grupo que consiste en sistemas de anillos arilo bicíclicos de 9 miembros que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que están sustituidos en los átomos de C o N con ***u*** sustituyentes R^1,

cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{3a}, -CN, -$(CH_2)_{0-6}C(O)R^3$, -CO_2R^{3a}, -$C(O)N(R^{3a})_2$, -SR^{3a}, -$S(O)R^{3a}$, -$S(O_2)R^{3a}$, -$(CH_2)_{0-6}N(R^{3a})_2$, -$N(R^{3a})SO_2R^{3a}$, -$N(R^{3a})CO_2R^{3a}$, -$N(R^{3a})C(O)R^3$, -$N(R^{3a})COR^{3a}$, -$N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-6}, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, -OR^{3a}, -CN, -CO_2R^{3a}, -$C(O)N(R^{3a})_2$, -$N(R^{3a})_2$, -$N(R^{3a})CO_2R^{3a}$, -SR^{3a}, -$S(O)R^{3a}$, -$S(O_2)R^{3a}$, -$N(R^{3a})SO_2R^{3a}$, -$N(R^{3a})CO_2R^{3a}$, -$N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6} y cicloalquilo C_{3-8},

u es de 0 a 4,

cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

(B) es un grupo elegido entre el grupo que consiste en

(a) -C≡C- y

(b) sistemas de anillos arilo B' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo B' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con *v* sustituyentes R^2,

cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{4a}, -CN, -CO_2R^{4a}, -$C(O)R^{4a}$, -$C(O)N(R^{4a})_2$, -$N(R^{4a})_2$, -$N(R^{4a})COR^4$, -$N(R^{4a})CO_2R^{4a}$, -$N(R^{4a})C(O)N(R^{4a})$, -$N(R^{4a})SO_2R^{4a}$, -SR^{4a}, -$S(O)R^{4a}$, -$S(O_2)R^{4a}$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4,

v es de 0 a 4,

cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada R^{4a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

R^1 y R^2 pueden tomarse junto con (A) y (B) para formar un anillo carbocíclicos de 5 a 9 miembros que contiene 1 ó 2 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S;

cada D es un grupo independientemente elegidos entre el grupo que consiste en:

(a) un enlace sencillo,

(b) -$C(O)N(R^5)$-,

(c) -$N(R^5)C(O)$-, y

(d) un sistema de anillos arilo de 5 ó 6 miembros D' que contiene de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 2 sustituyentes R^5,

cada R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^6, -CN, -CO_2R^6, -$C(O)N(R^6)_2$, -$N(R^6)_2$, -$N(R^6)COR^6$, -SR^6, -$S(O)R^6$, -$S(O_2)R^6$, -$N(R^6)SO_2R^6$, -NCO_2R^6, -$NC(O)N(R^6)_2$, alquilo C_{1-6} sustituido con 0 a 3 R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 R^6, y

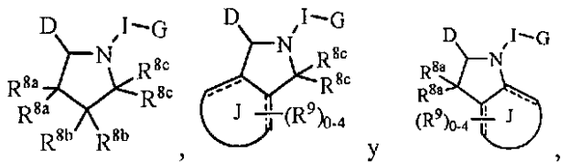
cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada E es un grupo independientemente elegidos entre el grupo que consiste en:

(a) un enlace sencillo,

(b) -$(C(R^7)_2)_{0-2}NR^7C(O)O_{0-1}$-, y

(c) un derivado de pirrolidinilo elegido entre el grupo que consiste en:



I es un grupo bivalente elegido entre -C(O)-, -CO_2- y -C(O)N(R^7)-,

J es un sistema de anillos condensado elegido entre el grupo que consiste en carbociclos de 3 a 7 miembros y anillos arilo de 5 ó 6 miembros que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con sustituyentes R^9,

cada R^{8a} se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OH, -Oalquilo C_{1-6} y alquilo C_{1-6}, o dos R^{8a} pueden tomarse juntos para formar oxo,

cada R^{8b} se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OH, -Oalquilo C_{1-6} y alquilo C_{1-6}, o dos R^{8b} pueden tomarse juntos para formar oxo,

cada R^{8c} se elige independientemente entre el grupo que consiste en hidrógeno y alquilo C_{1-6},

o dos grupos cualquiera seleccionados entre R^{8a}, R^{8b} y R^{8c} pueden tomarse juntos para formar un anillo espiro-bicíclico o bicíclico puenteado;

cada R^9 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, -NH-alquilo C_{1-6} y -NHC(O)-alquilo C_{1-6},

cada R^7 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y fenilo, y el alquilo C_{1-6} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

cada G se elige independientemente entre el grupo que consiste en:

(a) hidrógeno,

(b) -OR^{10a},

(c) -CN,

(d) -CO_2R^{10a},

(e) -C(O)N(R^{10})$_2$,

(f) -SR^{10a},

(g) -S(O)R^{10a},

(h) -S(O_2)R^{10a},

(i) -N(R^{10})$_2$,

(j) -N(R^{10})SO_2R^{10a}, (k) -NCO_2R^{10a}, (l) -NC(O)N(R^{10})$_2$,

(m) alquilo C_{1-6} que tiene de 0 a 4 sustituyentes R^{11},

cada R^{11} se elige independientemente entre el grupo que consiste en:

(i) -OH,

(ii) $-N(R^{10})_2$,

(iii) $=NR^{10}$,

(iv) -O-alquilo C_{1-6},

(v) $-C(O)R^{10}$,

(vi) -S-alquilo C_{1-6},

(vii) $-SO_2$-alquilo C_{1-6},

(viii) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{12} en los átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} que tiene de 0 a 3 sustituyentes elegidos entre R^{10}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, $-OR^{10a}$, -CN, $-C(O)R^{10}$, $-CO_2R^{10a}$, $-C(O)N(R^{10})_2$, $-SR^{10a}$, $-S(O)R^{10a}$, $-S(O_2)R^{10a}$, $-N(R^{10})SO_2R^{10a}$, $-NCO_2R^{10a}$, $-NC(O)N(R^{10})_2$ y $-N(R^{10})_2$, o dos R^{12} se toman juntos para formar oxo, y

(ix) arilo de 5 ó 6 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tiene de 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6} y carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

(n) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C; y

(o) sistemas de anillos arilo G' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo G' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 3 sustituyentes R^{10};

cada R^{10} se elige independientemente entre el grupo que consiste en

(i) hidrógeno,

(ii) -CN,

(iii) alquilo C_{1-6},

(iv) -O-alquilo C_{0-6},

(v) -S-alquilo C_{0-6},

(vi) alquil C_{1-6}-O-R^{14},

(vii) $-C(O)R^{14}$,

(viii) $-CO_2R^{14}$,

(ix) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

(xiii) $-NC(O)N(R^{14})_2$, y

(xiv) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

o dos R^{10} pueden tomarse juntos para formar oxo;

cada R^{10a} se elige independientemente entre el grupo que consiste en

(i) hidrógeno,

(ii) -CN,

(iii) alquilo C_{1-6},

(iv) alquil C_{1-6}-O-R^{14},

(v) $-C(O)R^{14}$,

(vi) $-CO_2R^{14}$,

(vii) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

(xiii) $-NC(O)N(R^{14})_2$, y

(xiv) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

y dos grupos R^{10} o R^{10a} pueden tomarse junto con el N al que están unidos para formar un anillo, que puede estar sustituido con 0 a 3 sustituyentes R^{14}, y

cada R^{14} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-8}, $-(CH_2)_{0-3}$cicloalquilo C_{3-8} y fenilo.

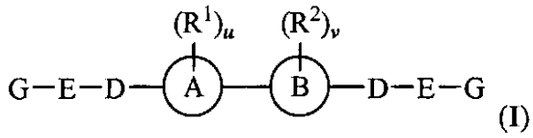
La presente invención también incluye composiciones farmacéuticas que contienen un compuesto de la presente invención y procedimientos de preparación de dichas composiciones farmacéuticas. La presente invención incluye adicionalmente procedimientos para tratar o reducir la probabilidad o gravedad de infección por VHC, procedimientos para inhibir la función de la proteína NS5A y procedimientos para inhibir la replicación viral y/o la producción viral del VHC.

Otras realizaciones, aspectos y características de la presente invención se describen adicionalmente en o serán evidentes a partir de la siguiente descripción, ejemplos y reivindicaciones adjuntas.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

La presente invención incluye los compuestos de fórmula **(I)** anteriores, y sales farmacéuticamente aceptables de los mismos. Los compuestos de fórmula **(I)** son inhibidores NS5A del VHC.

Una primera realización de la invención se refiere a compuestos que tienen la fórmula estructural **(I)**:



(I)

y/o una sal farmacéuticamente aceptable de los mismos, en la que:

(A) se elige entre el grupo que consiste en sistemas de anillos arilo bicíclicos de 9 miembros que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que están sustituidos en los átomos de C o N con ***u*** sustituyentes R^1,

cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-6}, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6},

u es de 0 a 4,

cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

(B) es un grupo elegido entre el grupo que consiste en

(a) $-C\equiv C-$ y $\equiv$

(b) sistemas de anillos arilo B' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo B' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con *v* sustituyentes R^2,

cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{4a}, -CN, -CO_2R^{4a}, -$C(O)N(R^{4a})_2$, -$N(R^{4a})_2$, -$N(R^{4a})COR^4$, -$N(R^{4a})CO_2R^{4a}$, -$N(R^{4a})C(O)N(R^{4a})$, -$N(R^{4a})SO_2R^{4a}$, -SR^{4a}, -$S(O)R^{4a}$, -$S(O_2)R^{4a}$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4,

v es de 0 a 4,

cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada R^{4a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

R^1 y R^2 pueden tomarse junto con (A) y (B) para formar un anillo carbocíclicos de 5 a 9 miembros que contiene 1 ó 2 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S;

cada D es un grupo independientemente elegidos entre el grupo que consiste en:

(a) un enlace sencillo,

(b) -$C(O)N(R^5)$-,

(c) -$N(R^5)C(O)$-, y

(d) un sistema de anillos arilo de 5 ó 6 miembros D' que contiene de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S; y están sustituidos en los átomos de C o N con 0 a 2 sustituyentes R^5,

cada R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^6, -CN, -CO_2R^6, -$C(O)N(R^6)_2$, -$N(R^6)_2$, -$N(R^6)COR^6$, -SR^6, -$S(O)R^6$, -$S(O_2)R^6$, -$N(R^6)SO_2R^6$, -NCO_2R^6, -$NC(O)N(R^6)_2$, alquilo C_{1-6} sustituido con 0 a 3 R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 R^6, y

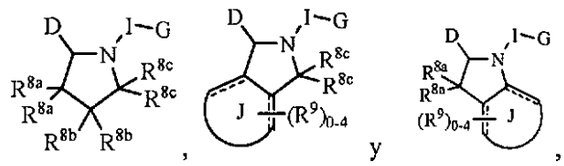
cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada E es un grupo independientemente elegidos entre el grupo que consiste en:

(a) un enlace sencillo,

(b) -$(C(R^7)_2)_{0-2}NR^7C(O)O_{0-1}$-, y

(c) un derivado de pirrolidinilo elegido entre el grupo que consiste en:



I es un grupo bivalente elegido entre -C(O)-, $-CO_2-$ y $-C(O)N(R^7)-$,

J es un sistema de anillos condensado elegido entre el grupo que consiste en carbociclos de 3 a 7 miembros y anillos arilo de 5 ó 6 miembros que contiene de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con sustituyentes R^9,

cada R^{8a} se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OH, -Oalquilo C_{1-6} y alquilo C_{1-6}, o dos R^{8a} pueden tomarse juntos para formar oxo,

cada R^{8b} se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OH, -Oalquilo C_{1-6} y alquilo C_{1-6}, o dos R^{8b} pueden tomarse juntos para formar oxo,

cada R^{8c} se elige independientemente entre el grupo que consiste en hidrógeno y alquilo C_{1-6},

o dos grupos cualquiera seleccionados entre R^{8a}, R^{8b} y R^{8c} pueden tomarse juntos para formar un anillo espiro-bicíclico o bicíclico puenteado;

cada R^9 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, -NH-alquilo C_{1-6} y -NHC(O)-alquilo C_{1-6},

cada R^7 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y fenilo, y el alquilo C_{1-6} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

cada G se elige independientemente entre el grupo que consiste en:

(a) hidrógeno,

(b) $-OR^{10a}$,

(c) -CN,

(d) $-CO_2R^{10a}$,

(e) $-C(O)N(R^{10})_2$,

(f) $-SR^{10a}$,

(g) $-S(O)R^{10a}$,

(h) $-S(O_2)R^{10a}$,

(i) $-N(R^{10})_2$,

(j) $-N(R^{10})SO_2R^{10a}$, (k) $-NCO_2R^{10a}$, (l) $-NC(O)N(R^{10})_2$,

(m) alquilo C_{1-6} que tiene de 0 a 4 sustituyentes R^{11},

cada R^{11} se elige independientemente entre el grupo que consiste en:

(i) -OH,

(ii) $-N(R^{10})_2$,

(iii) $=NR^{10}$,

(iv) -O-alquilo C_{1-6},

(v) $-C(O)R^{10}$,

(vi) -S-alquilo C_{1-6},

(vii) $-SO_2$-alquilo C_{1-6},

(viii) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{12} en los átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} que tiene de 0 a 3 sustituyentes elegidos entre R^{10}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, $-OR^{10a}$, -CN, $-C(O)R^{10}$, $-CO_2R^{10a}$, $-C(O)N(R^{10})_2$, $-SR^{10a}$, $-S(O)R^{10a}$, $-S(O_2)R^{10a}$, $-N(R^{10})SO_2R^{10a}$, $-NCO_2R^{10a}$, $-NC(O)N(R^{10})_2$ y $-N(R^{10})_2$, o dos R^{12} se toman juntos para formar oxo, y

(ix) arilo de 5 ó 6 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tiene de 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6} y carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

(n) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C; y

(o) sistemas de anillos arilo G' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo G' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 3 sustituyentes R^{10};

cada R^{10} se elige independientemente entre el grupo que consiste en

(i) hidrógeno,

(ii) -CN,

(iii) alquilo C_{1-6},

(iv) -O-alquilo C_{0-6},

(v) -S-alquilo C_{0-6},

(vi) alquil C_{1-6}-O-R^{14},

(vii) $-C(O)R^{14}$,

(viii) $-CO_2R^{14}$,

(ix) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

(xiii) $-NC(O)N(R^{14})_2$, y

(xiv) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

o dos R^{10} pueden tomarse juntos para formar oxo;

cada R^{10a} se elige independientemente entre el grupo que consiste en

(i) hidrógeno,

(ii) -CN,

(iii) alquilo C_{1-6},

(iv) alquil C_{1-6}-O-R^{14},

(v) $-C(O)R^{14}$,

(vi) $-CO_2R^{14}$,

(vii) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

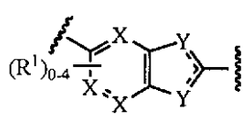
(xiii) $-NC(O)N(R^{14})_2$, y

(xiv) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

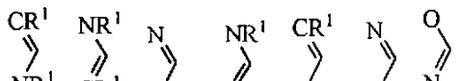
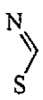
y dos grupo R^{10} o R^{10a} pueden tomarse junto con el N al que están unidos para formar un anillo, que puede estar sustituido con 0 a 3 sustituyentes R^{14}, y

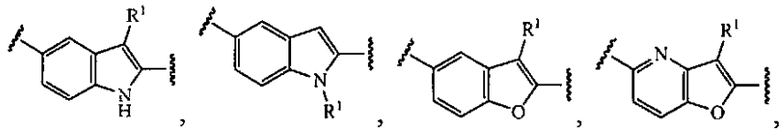
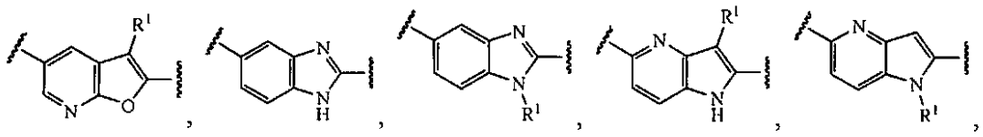
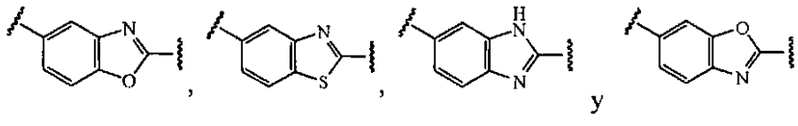
cada R^{14} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-8}, $-(CH_2)_{0-3}$cicloalquilo C_{3-8} y fenilo. En esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior.

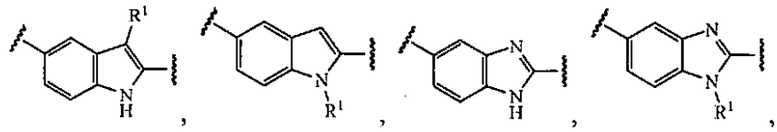
En una segunda realización de la invención, (A) se elige entre el grupo que consiste en

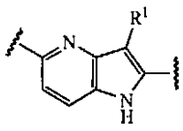
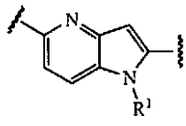
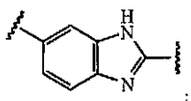
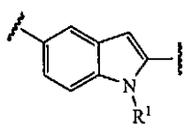


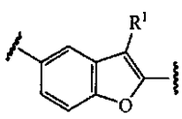
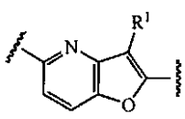
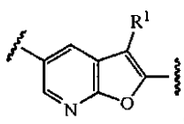
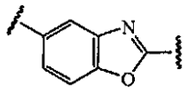
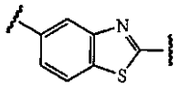
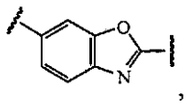
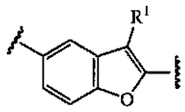
, en la que cada X se elige independientemente entre el grupo que consiste

en CR^1 y N,  se elige entre el grupo que consiste en  , y  , cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-6}, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3A})_2$, $-N(R^{3A})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}, cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8}. En todos los aspectos de esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior o en la primera realización anterior.

En un primer aspecto de la segunda realización de la invención,  se elige entre el grupo que consiste en  ,  , y  , en el que  está sustituido de 0 a 3 R^1 más, que son como se han proporcionado anteriormente.

En un segundo aspecto de la segunda realización de la invención,  se elige entre el grupo que consiste en  ,



y  , en el que (A) está sustituido con 0 a 3 R^1 más, que son como se han proporcionado anteriormente. En los casos preferidos de este aspecto, (A) es  , en el que (A) está sustituido con 0 a 3 R^1 más, que son como se han proporcionado anteriormente.

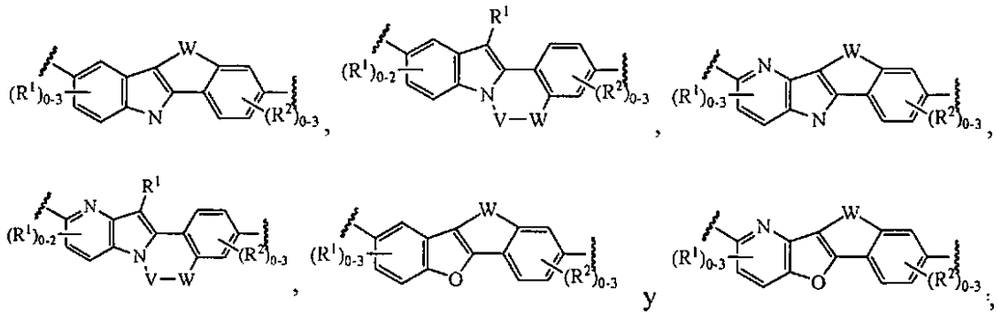
En un tercer aspecto de la segunda realización, (A) se elige entre el grupo que consiste en  ,  ,  ,  ,  y  , en el que (A) está sustituido con 0 a 3 R^1 más, que son como se han proporcionado anteriormente. En los casos preferidos de este aspecto, (A) es  , en el que (A) está sustituido con 0 a 3 R^1 más, que son como se han proporcionado anteriormente.

En aspectos adicionales de la segunda realización, cada R^1 se elige entre el grupo que consiste en hidrógeno, halógeno, -CN y alquilo C_{1-6}. En particular, cada R^1 se elige entre el grupo que consiste en hidrógeno, flúor y -CN.

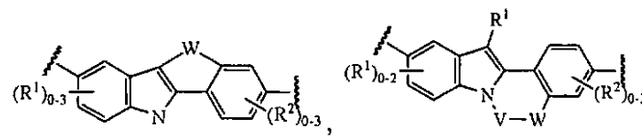
En una tercera realización de la invención, (B) se elige entre el grupo que consiste en -C≡C-, fenilo, piridinilo, pirazinilo, pirimidilo, 1,2,4-triazinilo, piridazinilo, tiazilo y sistemas de anillos bicíclicos de 9 miembros que contienen de 1 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, v es de 0 a 4, cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})$, $-N(R^{4a})_2$, $-N(R^{4a})CO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, $-N(R^{4a})SO_2R^{4a}$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4, cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8}, y cada R^{4a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y

cicloalquilo C_{3-8}. En aspectos particulares de esta realización, (B) es fenilo, v es de 0 a 2, y cada R^2 se elige independientemente entre el grupo que consiste en flúor, cloro, -OH, $-CH_3$, $-OCH_3$ y -CN. En todos los aspectos de esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior y/o en la primera o la segunda realizaciones.

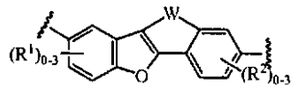
En una cuarta realización de la invención, (A) y (B), tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por un grupo elegido entre el grupo que consiste en:



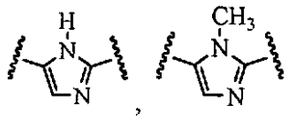
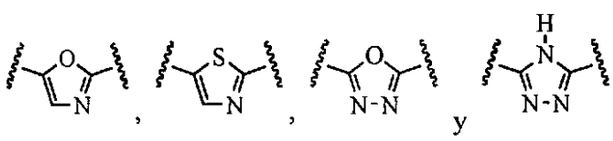
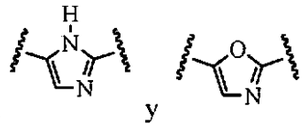
; en el que W se elige entre el grupo que consiste en $-(CH_2)_{1-3}-$, $-(CH_2)_{0-2}NH(CH_2)_{0-2}-$, $-(CH_2)_{0-2}N(\text{alquil } C_{1-6})(CH_2)_{0-2}-$, $-(CH_2)_{0-2}O(CH_2)_{0-2}-$ y $-(CH_2)_{0-2}C(O)(CH_2)_{0-2}-$, en el que W está sustituido con 0 a 4 R^w, en el que cada R^w se selecciona independientemente entre alquilo C_{1-6} y cicloalquilo C_{3-8}; y V se elige entre el grupo que consiste en -C(O)- y $-CH_2-$, y en el que V es $-CH_2-$, V está sustituido con 0 a 2 R^v, en el que cada R^v se selecciona independientemente entre el grupo que consiste en alquilo C_{1-6} y cicloalquilo C_{3-8}. En un primer aspecto de esta realización, (A) y (B), tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por un grupo elegido entre el grupo que consiste en

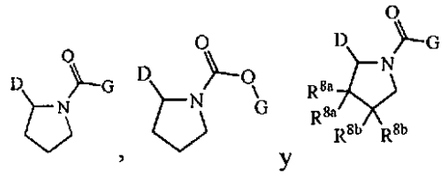
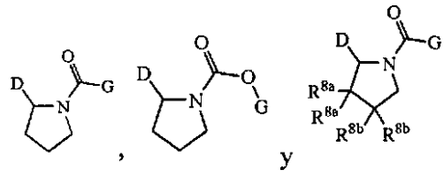


y



. En casos particulares de esta realización, y del primer aspecto de esta realización, W se elige entre el grupo que consiste en $-CH_2-$, -NH-, -N(alquil C_{1-6})-, -C(O)-, $-CH_2NH-$, $-CH_2N(\text{alquil } C_{1-6})-$, $-CH_2CH_2-$, $-C(O)CH_2-$, $-CH_2C(O)-$, $-CH_2O-$, $-CH_2CH_2CH_2-$, $-C(O)CH_2CH_2-$, $-CH_2C(O)CH_2-$, $-CH_2OCH_2-$, $-CH_2CH_2C(O)-$, $-CH_2CH_2O-$, $-CH_2CH_2NH-$, $-CH_2CH_2N(\text{alquil } C_{1-6})-$, $-CH_2NHCH_2-$, $-CH_2N(\text{alquil } C_{1-6})CH_2-$, $-NHCH_2CH_2-$ y $-N(\text{alquil } C_{1-6})CH_2CH_2-$. En todos los aspectos de esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior.

En una quinta realización de la invención, cada D se elige independientemente entre el grupo que consiste en un enlace sencillo, -C(O)N(R^5)-, -NR^5C(O)-,  ,  , y , en el que R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno -OR^6, -CN, -CO_2R^6, -C(O)N(R^6)$_2$, -N(R^6)$_2$, -N(R^6)COR^6, -SR^6, -S(O)R^6, -S(O_2)R^6, -N(R^6)SO_2R^6, -NCO_2R^6, -NC(O)N(R^6)$_2$, alquilo C_{1-6} sustituido con 0 a 3 sustituyentes R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 sustituyentes R^6, y cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8}. En aspectos particulares de esta realización, cada D se elige independientemente entre el grupo que consiste en  . En esta realización, todos los demás grupos son como se han proporcionado en la formula general anterior y/o en la primera a cuarta realizaciones.

En una sexta realización de la invención, cada E se elige independientemente entre el grupo que consiste en un enlace sencillo, -CH_2NHC(O)-, -CH_2N(CH_3)C(O)-, -C(CH_3)HNHC(O)-, -C(CH_3)HN(CH_3)C(O)-, -C(CH_3)$_2$NHC(O)-, -C(CH_3)$_2$N(CH_3)C(O)-, -CH_2NHC(O)O-, -CH_2N(CH_3)C(O)O-, -C(CH_3)HNHC(O)O-, -C(CH_3)HN(CH_3)C(O)O-, -C(CH_3)$_2$NHC(O)O-, -C(CH_3)$_2$N(CH_3)C(O)O-,  , y , en los que uno de R^{8a} y R^{8b} es -OH o flúor. En un primer aspecto de esta realización, cada E se elige independientemente entre el grupo que consiste en un enlace sencillo,  , y , en los que uno de R^{8a} y R^{8b} es -OH o flúor. En todos los aspectos de esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior y/o en la primera a cuarta realizaciones.

En algunas realizaciones, cada uno de los grupos adyacentes D y E pueden seleccionarse para que sean un enlace sencillo. En dichas realizaciones, D y E se combinan para que sean de un solo enlace, y todos los demás grupos son como se han proporcionado en la fórmula general anterior y/o en la primera, segunda, tercera y cuarta realizaciones. Es decir, cuando D es un enlace

sencillo y el E adyacente es un enlace sencillo, (A) o (B) están conectados directamente a G mediante un enlace sencillo.

En una séptima realización de la invención, cada G se elige independientemente entre el grupo que consiste en:

(a) alquilo C_{1-6} que tiene de 0 a 4 sustituyentes R^{11},

(b) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C; y

(c) sistemas de anillos arilo G' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo G' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 3 sustituyentes R^{10}. En todos los aspectos de la séptima realización, G se elige de tal forma que dé como resultado compuestos estables. En todos los aspectos de esta séptima realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior y/o en la primera a sexta realizaciones.

En una octava realización, cada G se elige independientemente entre el grupo que consiste en:

(a) hidrógeno,

(b) -CN,

(c) alquilo C_{1-5} que tiene de 1 a 3 sustituyentes R^{11},

cada R^{11} se elige independientemente entre el grupo que consiste en -OH, $-NH_2$, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, =NH, $=NCH_3$, -C(O)H, -C(O)OH, $-C(O)CH_3$, $-C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo, fenilo, piridinilo, pirimidinilo y pirrolilo, en el que

el ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo están sustituidos con 0 a 2 sustituyentes R^{12} en los átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

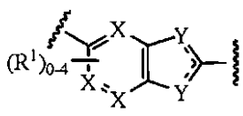
el fenilo, piridinilo, pirimidinilo y pirrolilo están sustituidos con 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} y cicloalquilo de 3 a 8 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

(d) ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C, el R^{10} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, fenilo y bencilo, y

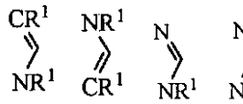
(e) sistemas de anillos arilo G' elegidos entre el grupo que consiste en: fenilo, piridinilo y sistemas de anillos bicíclicos de 9 miembros que contienen de 0 a 2 heteroátomos independientemente elegidos entre el grupo que consiste en N y O.

En un primer aspecto de la octava realización, G se elige independientemente entre el grupo que consiste en alquilo C_{1-4} que tiene de 1 a 2 sustituyentes R^{11}, en el que cada R^{11} se elige independientemente entre el grupo que consiste en -OH, -NH2, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-C(O)OCH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo, oxaciclohexilo, fenilo, piridinilo, pirimidinilo y pirrolilo. En todos los aspectos de la octava realización, G se elige de tal forma que dé como resultado compuestos estables. En todos los aspectos de esta octava realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior y/o en la primera a sexta realizaciones.

En una novena realización de la invención, se elige entre el grupo consiste en



, en la que cada X se elige independientemente entre el grupo que consiste en CR^1 y N,

 se elige entre el grupo que consiste en  y  ,

cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-6}, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes elegidos independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6},

cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

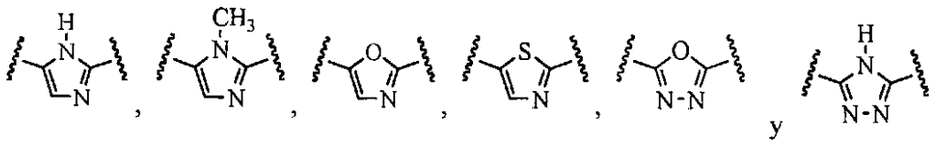
(B) se elige entre el grupo que consiste en -C≡C-, fenilo, piridinilo, pirazinilo, pirimidilo, 1,2,4-triazinilo, piridazinilo, tiazilo y sistemas de anillos bicíclicos de 9 miembros que contienen de 1 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

v es de 0 a 4,

cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{4a}, -CN, -CO_2R^{4a}, -$C(O)N(R^{4a})_2$, -$N(R^{4a})_2$, -$N(R^{4a})CO_2R^{4a}$, -SR^{4a}, -$S(O)R^{4a}$, -$S(O_2)R^{4a}$, -$N(R^{4a})SO_2R^{4a}$, -$N(R^{4a})CO_2R^{4a}$, -$N(R^{4a})C(O)N(R^{4a})$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4,

cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{4a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

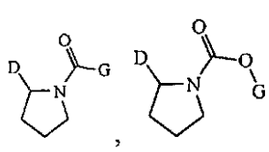
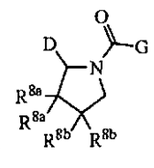
en los que cada D se elige independientemente entre el grupo que consiste en un enlace sencillo,  , en los que

R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^6, -CN, -CO_2R^6, -$C(O)N(R^6)_2$, -$N(R^6)_2$, -$N(R^6)COR^6$, -SR^6, -$S(O)R^6$, -$S(O_2)R^6$, -$N(R^6)SO_2R^6$, -NCO_2R^6, -$NC(O)N(R^6)_2$, alquilo C_{1-6} sustituido con 0 a 3 sustituyentes R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 sustituyentes R^6, y

cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

en el que cada E se elige independientemente entre el grupo que consiste en un enlace sencillo, -$CH_2NHC(O)$-, -$CH_2N(CH_3)C(O)$-, -$C(CH_3)HNHC(O)$-, -$C(CH_3)HN(CH_3)C(O)$-, -$C(CH_3)_2NHC(O)$-, -$C(CH_3)_2N(CH_3)C(O)$-, -$CH_2NHC(O)O$-, -$CH_2N(CH_3)C(O)O$-, -

$C(CH_3)HNHC(O)O$-, -$C(CH_3)HN(CH_3)C(O)O$-, -$C(CH_3)_2NHC(O)O$-, -$C(CH_3)_2N(CH_3)C(O)O$-,


, y

, en los que uno de R^{8a} y R^{8b} es -OH o flúor;

en los que cada G se elige independientemente entre el grupo que consiste en

(a) hidrógeno,

(b) -CN,

(c) alquilo C_{1-5} que tiene de 1 a 3 sustituyentes R^{11},

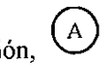
cada R^{11} se elige independientemente entre el grupo que consiste en -OH, -NH2, -NCH_3H, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, =NH, =NCH_3, -C(O)H, -C(O)OH, -$C(O)CH_3$, -$C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo, y oxaciclohexilo, fenilo, piridinilo, pirimidinilo y pirrolilo, en el que

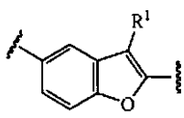
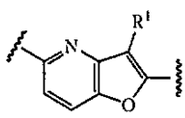
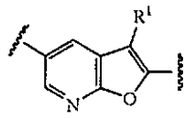
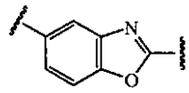
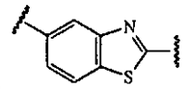
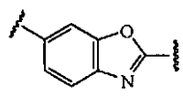
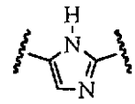
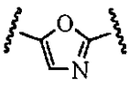
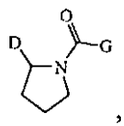
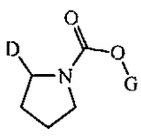
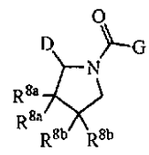
el ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo están sustituidos con 0 a 2 sustituyentes R^{12} en los átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

el fenilo, piridinilo, pirimidinilo y pirrolilo están sustituidos con 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} y cicloalquilo de 3 a 8 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

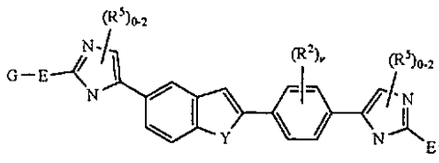
(d) ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C, el R^{10} seleccionado independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, fenilo y bencilo, y

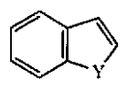
(e) sistemas de anillos arilo G' elegidos entre el grupo que consiste en: fenilo, piridinilo y sistemas de anillos bicíclicos de 9 miembros que contienen de 0 a 2 heteroátomos independientemente elegidos entre el grupo que consiste en N y O. En todos los aspectos de esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior.

En una décima realización de la invención,  se elige entre el grupo que consiste en

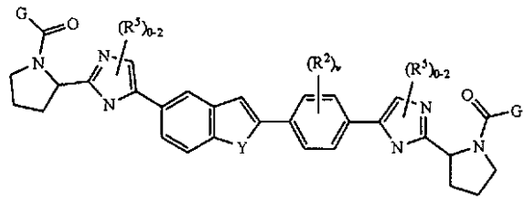

, 
, 
, 
, 
y 
; en los que (A) está sustituido con 0 a 3 R^1 más; (B) es fenilo; *v* es de 0 a 2; cada R^2 se elige independientemente entre el grupo que consiste en flúor, cloro, -OH, $-CH_3$, $-OCH_3$ y -CN; cada D se elige independientemente entre el grupo que consiste en 
y 
; cada E se elige independientemente entre el grupo que consiste en un enlace sencillo, 
, 
y 
, en el que uno de R^{8a} y R^{8b} es -OH o flúor; y cada G se elige independientemente entre el grupo que consiste en alquilo C_{1-4} que tiene de 1 a 2 sustituyentes R^{11}, en el que cada R^{11} se elige independientemente entre el grupo que consiste en -OH, -NH2, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-C(O)OCH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo, oxaciclohexilo, fenilo, piridinilo, pirimidinilo y pirrolilo. En todos los aspectos de esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior o en la octava realización.

En una undécima realización de la invención, el compuesto que tiene la fórmula estructural **(I)** es un compuesto que tiene la fórmula estructural **(Ia)**:

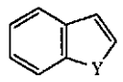
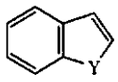
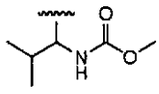

(Ia)

o una sal farmacéuticamente aceptable del mismo, en la que 
está sustituido con *u* sustituyentes R^1, e Y se selecciona entre el grupo que consiste en O y NR^1. En todos los aspectos de esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior o en una cualquiera de la primera a cuarta realizaciones.

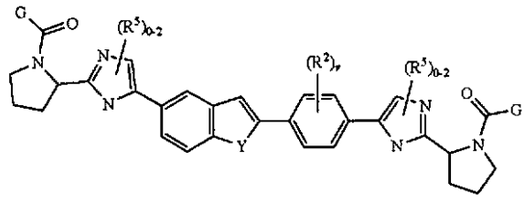
En una decimosegunda realización de la invención, el compuesto que tiene la fórmula estructural **(Ia)** es un compuesto que tiene la fórmula estructural **(Ib)**:



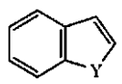
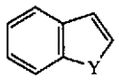
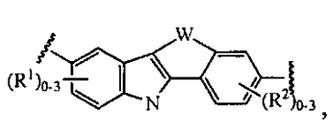
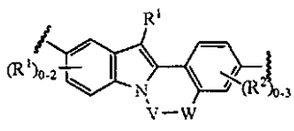
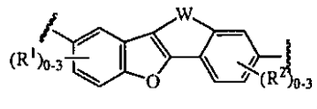
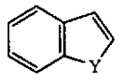
(Ib)

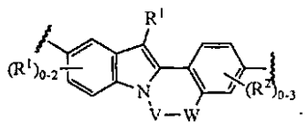
o una sal farmacéuticamente aceptable del mismo, en la que  está sustituido con ***u*** sustituyentes R^1, e Y se selecciona entre el grupo que consiste en O y NR^1. En aspectos particulares de esta realización,  está sustituido con ***u*** sustituyentes R^1, Y es O, y ambos casos de G son  . En todos los aspectos de esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior o en la undécima realización.

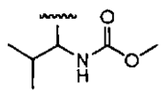
En una decimotercera realización de la invención, el compuesto que tiene la fórmula estructural **(Ia)** es un compuesto que tiene la fórmula estructural **(Ib)**:



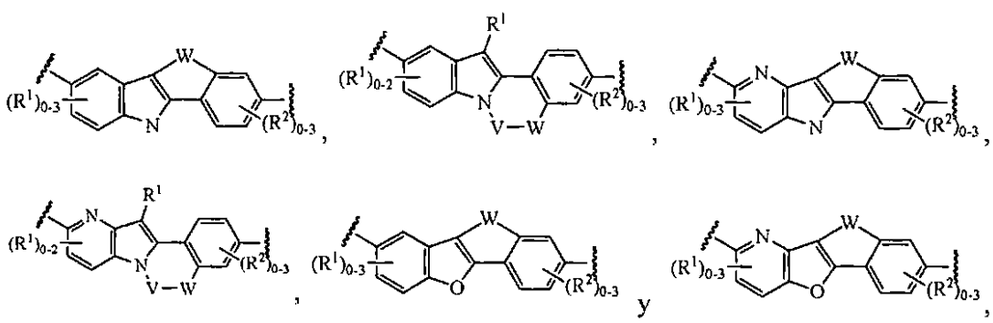
(Ib)

o una sal farmacéuticamente aceptable del mismo, en la que dicho  está sustituido con ***u*** sustituyentes R^1, y dicho  y dicho  , tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por un grupo elegido entre el grupo que consiste en  ,  y  . En aspectos particulares de esta realización,  y dicho  , tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por



, en la que V es $-CH_2-$, W es $-(CH_2)_{0-2}O(CH_2)_{0-2}-$, R^1 es flúor, y ambos casos de G son  . En todos los aspectos de esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior o en la undécima realización.

En una decimocuarta realización de la invención, (A) y (B), tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por un grupo elegido entre el grupo que consiste en:



, en las que

W se elige entre el grupo que consiste en $-(CH_2)_{1-3}-$, $-(CH_2)_{0-2}NH(CH_2)_{0-2}-$, $-(CH_2)_{0-2}N(\text{alquil } C_{1-6})(CH_2)_{0-2}-$, $-(CH_2)_{0-2}O(CH_2)_{0-2}-$ y $-(CH_2)_{0-2}C(O)(CH_2)_{0-2}-$, en el que W está sustituido con 0 a 4 R^w, en el que cada R^w se selecciona independientemente entre alquilo C_{1-6} y cicloalquilo C_{3-8}; y

V se elige entre el grupo que consiste en -C(O)- y $-CH_2-$, y en el que V es $-CH_2-$, V está sustituido con 0 a 2 R^v, en el que cada R^v se selecciona independientemente entre el grupo que consiste en alquilo C_{1-6} y cicloalquilo C_{3-8};

cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^3$, -CN, $-C(O)R^3$, $-CO_2R^3$, $-C(O)N(R^{3A})_2$, $-SR^3$, $-S(O)R^3$, $-S(O_2)R^3$, $-N(R^{3A})_2$, $-(CH_2)_{0-6}N(R^{3A})_2$, $-N(R^{3a})SO_2R^3$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})COR^3$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-6}, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3A})_2$, $-N(R^{3A})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6},

cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y

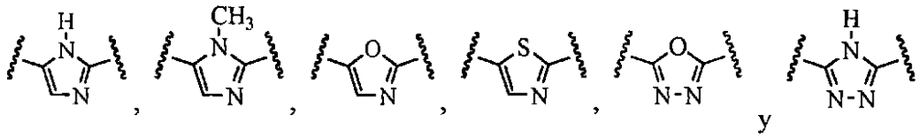
cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{4a}, -CN, -CO_2R^{4a}, -$C(O)N(R^{4A})_2$, -$N(R^{4A})_2$, -$N(R^{4a})CO_2R^{4a}$, -SR^{4a}, -$S(O)R^{4a}$, -$S(O_2)R^{4a}$, -$N(R^{4n})SO_2R^{4a}$, -$N(R^{4a})CO_2R^{4a}$, -$N(R^{4n})C(O)N(R^{4a})$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4,

cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{4n} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

en el que cada D se elige independientemente entre el grupo que consiste en un enlace sencillo, -$C(O)N(R^5)$-, -$NR^5C(O)$-,

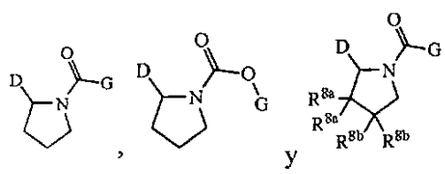


, en las que

R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno -OR^6, -CN, -CO_2R^6, -$C(O)N(R^6)_2$, -$N(R^6)_2$, -$N(R^6)COR^6$, -SR^6, -$S(O)R^6$, -$S(O_2)R^6$, -$N(R^6)SO_2R^6$, -NCO_2R^6, -$NC(O)N(R^6)_2$, alquilo C_{1-6} sustituido con 0 a 3 sustituyentes R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 sustituyentes R^6, y

cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

en el que cada E se elige independientemente entre el grupo que consiste en un enlace sencillo, -$CH_2NHC(O)$-, -$CH_2N(CH_3)C(O)$-, -$C(CH_3)HNHC(O)$-, -$C(CH_3)HN(CH_3)C(O)$-, -$C(CH_3)_2NHC(O)$-, -$C(CH_3)_2N(CH_3)C(O)$-, -$CH_2NHC(O)O$-, -$CH_2N(CH_3)C(O)O$-, -$C(CH_3)HNHC(O)O$-, -$C(CH_3)HN(CH_3)C(O)O$-, -$C(CH_3)_2NHC(O)O$-, -$C(CH_3)_2N(CH_3)C(O)O$-,



, en el que uno de R^{8a} y R^{8b} es -OH o flúor;

en el que cada G se elige independientemente entre el grupo que consiste en

(a) hidrógeno,

(b) -CN,

(c) alquilo C_{1-5} que tiene de 1 a 3 sustituyentes R^{11},

cada R^{11} se elige independientemente entre el grupo que consiste en -OH, -NH2, -NCH_3H, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, =NH, =NCH_3, -C(O)H, -C(O)OH, -$C(O)CH_3$, -$C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo,

piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo, y oxaciclohexilo, fenilo, piridinilo, pirimidinilo y pirrolilo, en el que

el ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo están sustituidos con 0 a 2 sustituyentes R^{12} en los átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

el fenilo, piridinilo, pirimidinilo y pirrolilo están sustituidos con 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} y cicloalquilo de 3 a 8 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

(d) ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C, el R^{10} seleccionado independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, fenilo y bencilo, y

(e) sistemas de anillos arilo G' elegidos entre el grupo que consiste en: fenilo, piridinilo y sistemas de anillos bicíclicos de 9 miembros que contienen de 0 a 2 heteroátomos independientemente elegidos entre el grupo que consiste en N y O. En todos los aspectos de esta realización, todos los demás grupos son como se han proporcionado en la fórmula general anterior.

En otra realización de la invención, el compuesto de la invención se selecciona entre las especies ejemplares representadas en los Ejemplos 1 a 215 mostrados a continuación, o sales farmacéuticamente aceptables de los mismos.

En otra realización de la invención, para los compuestos de fórmula (I), las variables Ⓐ, Ⓑ, D, E, G, R^1, R^2, ***u***, ***v***, R^3, R^{3a}, R^4, R^{4a}, R^5, R^6, R^7, I, J, R^{8a}, R^{8b}, R^{8c}, R^9, R^{10}, R^{10a}, R^{11}, R^{12}, R^{13}, R^{14}, W, R^w, V y R^v, se seleccionan independientemente entre sí.

Otras realizaciones de la presente invención incluyen las que se indican a continuación:

(a) Una composición farmacéutica que comprende una cantidad eficaz de un compuesto de fórmula (I) y un vehículo farmacéuticamente aceptable.

(b) La composición farmacéutica de (a), que comprende adicionalmente un segundo agente terapéutico seleccionado entre el grupo que consiste en agentes antivirales del VHC, inmunomoduladores y agentes anti-infecciosos.

(c) La composición farmacéutica de (b), en la que el agente antiviral del VHC es un antiviral seleccionado entre el grupo que consiste en inhibidores de proteasa del VHC y inhibidores de polimerasa NS5B del VHC.

(d) Una combinación farmacéutica que es (i) un compuesto de fórmula (I) y (ii) un segundo agente terapéutico seleccionado entre el grupo que consiste en agentes antivirales del

VHC, inmunomoduladores y agentes anti-infecciosos; en la que cada uno del compuesto de fórmula **(I)** y el segundo agente terapéutico se emplea en una cantidad que convierte la combinación eficaz para inhibidor la actividad NS5A del VHC, o para tratar una infección por VHC y/o reducir la probabilidad o gravedad de síntomas de una infección por VHC, o para inhibir la replicación viral del VHC y/o la producción viral del VHC en sistema basado en células.

(e) La combinación de (d), en la que el agente antiviral del VHC es un antivirus seleccionado entre el grupo que consiste en inhibidores de proteasa del VHC e inhibidores de polimerasa NS5B del VHC.

(f) Un procedimiento de inhibición de la actividad de NS5A del VHC en un sujeto que necesita el mismo, que comprende administrar al sujeto una cantidad eficaz de un compuesto de fórmula **(I)**.

(g) Un procedimiento para tratar una infección de VHC y/o reducir la probabilidad o gravedad de los síntomas de una infección por VHC en un sujeto que necesita el mismo, que comprende administrar al sujeto una cantidad eficaz de un compuesto de fórmula **(I)**.

(h) El procedimiento de (g), en el que el compuesto de fórmula **(I)** se administra junto con una cantidad eficaz de al menos un segundo agente terapéutico seleccionado entre el grupo que consiste en agentes antivirales del VHC, inmunomoduladores y agentes anti-infecciosos.

(i) El procedimiento de (h), en el que el agente antiviral del VHC es un antiviral seleccionado entre el grupo que consiste en inhibidores de proteasa del VHC e inhibidores de polimerasa NS5B del VHC.

(j) Un procedimiento para la inhibición de la replicación viral del VHC y/o la producción viral del VHC en un sistema basado en células, que comprende administrar al sujeto una cantidad eficaz de un compuesto de fórmula **(I)**.

(k) El procedimiento de (j), en el que el compuesto de fórmula **(I)** se administra junto con una cantidad eficaz de al menos un segundo agente terapéutico seleccionado entre el grupo que consiste en agentes antivirales del VHC, inmunomoduladores y agentes anti-infecciosos.

(l) El procedimiento de (k), en el que el agente antiviral del VHC es un antiviral seleccionado entre el grupo que consiste en inhibidores de proteasa del VHC e inhibidores de polimerasa NS5B del VHC.

(m) Un procedimiento para la inhibición de la actividad de NS5A del VHC en un sujeto que necesita el mismo, que comprende administrar al sujeto la composición farmacéutica de (a), (b) o (c) o la combinación de (d) o (e).

(n) Un procedimiento para tratar una infección por VHC y/o reducir la probabilidad o gravedad de los síntomas de una infección por VHC en un sujeto que necesita el mismo, que comprende administrar al sujeto la composición farmacéutica de (a), (b) o (c) o la combinación de (d) o (e).

(o) Un procedimiento para la inhibición de la replicación viral del VHC y/o la producción viral del VHC en un sistema basado en células, que comprende administrar al sujeto la composición farmacéutica de (a), (b) o (c) o la combinación de (d) o (e).

En las realizaciones de los compuestos y sales que se han proporcionado anteriormente, se entenderá que cada realización puede combinarse con una o más realizaciones diferentes, en la medida en que una combinación de este tipo proporcione un compuesto o sal estable y sea coherente con la descripción de las realizaciones. Se entenderá adicionalmente que las realizaciones de las composiciones y procedimientos que se han proporcionado como (a) a (o) anteriormente incluyen todas las realizaciones de los compuestos y/o sales, incluyendo dichas realizaciones como resultado de la combinación de las realizaciones.

La presente invención también incluye un compuesto de la presente invención para su uso (i) en, (ii) como un medicamento para, o (iii) en la preparación de un medicamento para: (a) inhibir la actividad de NS5A del VHC, o (b) tratar la infección por VHC y/o reducir la probabilidad o gravedad de los síntomas de la infección por VHC, o (c) inhibir la replicación viral de VHC y/o la producción viral del VHC en un sistema basado en células, o (d) su uso en medicina. En estos usos, los compuestos de la presente invención pueden emplearse opcionalmente junto con uno o más segundos agentes terapéuticos seleccionados entre agentes antivirales del VHC, agentes anti-infecciosos e inmunomoduladores.

Las realizaciones adicionales de la invención incluyen las composiciones farmacéuticas, combinaciones y procedimientos expuestos en (a)-(o) anteriores y los usos expuestos en el párrafo anterior, en el que el compuesto de la presente invención empleado en la misma es un compuesto de una de las realizaciones, aspectos, clases, sub-clases o características de los compuestos que se han descrito anteriormente. En todas estas realizaciones, el compuesto puede usarse opcionalmente en forma de una sal farmacéuticamente aceptable, o puede estar presente en forma de un solvato o hidrato, según sea apropiado.

Como se usa en este documento, todos los intervalos son inclusivos, y todos los sub-intervalos se incluyen dentro de dichos intervalos, aunque no se exponen necesariamente de forma explícita. Además, el término "o," como se usa en este documento, representa alternativas que pueden, cuando sea apropiado, combinarse; es decir, el término "o" incluye cada alternativa enumerada por separado, así como su combinación.

Como se usa en este documento, el término "alquilo" se refiere a cualquier grupo alquilo de cadena lineal o ramificada que tenga varios átomos de carbono en el intervalo especificado. Por lo tanto, por ejemplo, "alquilo C_{1-6}" (o "alquilo C_1-C_6") se refiere a todos los isómeros de hexil alquilo y pentil alquilo, así como a n-, *iso*-, *sec*- y terc-butilo, n- e isopropilo, etilo y metilo. Como otro ejemplo, "alquilo C_{1-4}" se refiere a n-, iso-, sec- y *terc-butilo*, n- e isopropilo, etilo y metilo. Cuando se indica, "C_0" se refiere a hidrógeno; por lo tanto, por ejemplo, "alquilo C_{0-6}" (o "alquilo C_0-C_6")

se refiere a todos los isómeros de hexil alquilo y pentil alquilo, así como n-, *iso*-, *sec*- y *terc*-butilo, n- e *iso*propilo, etilo, metilo y hidrógeno. Los grupos alquilo pueden estar sustituidos como se indique.

El término "halogenado" se refiere a un grupo o molécula en el que un átomo de hidrógeno se ha reemplazado por un halógeno. De forma análoga, el término "haloalquilo" se refiere a un grupo alquilo halogenado. El término "halógeno" (o "halo") se refiere a átomos de flúor, cloro, bromo y yodo (como alternativa se denominan flúor, cloro, bromo y yodo), preferiblemente flúor.

El término "alcoxi" se refiere a un grupo "alquil-O-", en el que el alquilo es como se ha definido anteriormente. Los grupos alcoxi pueden estar sustituidos como se indique.

El término "cicloalquilo" se refiere a cualquier anillo cíclico de un alcano o alqueno que tenga varios átomos de carbono en el intervalo especificado. Por lo tanto, por ejemplo, "cicloalquilo C_{3-8}" (o "cicloalquilo C_3-C_8") se refiere a ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo y ciclooctilo. El término "cicloalcoxi" se refiere a un grupo "cicloalquil-O-", en el que el cicloalquilo es como se ha definido anteriormente. Los grupos cicloalquilo pueden estar sustituidos según se indique.

El término "arilo" (o "sistema de anillos arilo") se refiere a sistemas de anillos aromáticos mono- y poli-carbocíclicos o heterocíclicos en el que los anillos carbocíclicos individuales en los sistemas polianillo se condensan o unen entre sí a través de un enlace sencillo. Como se usa en este documento, el término arilo incluye sistemas de anillos aromáticos mono- y poli-carbocíclicos que incluyen de 0 a 4 heteroátomos (átomos sin carbono) que se eligen independientemente entre N, O y S. Los grupos arilo adecuados incluyen fenilo, naftilo, bifenilenilo, piridinilo, pirimidinilo y pirrolilo, así como los analizados a continuación. Los grupos arilo pueden estar sustituidos como se indica. Los sistemas de anillos arilo pueden incluir, cuando sea apropiado, una indicación de la variable a la que un átomo del anillo particular está unido. A menos que se indique otra cosa, los sustituyentes de los sistemas de anillos arilo pueden estar unidos a cualquier átomo del anillo, con la condición de que dichos resultados de unión den como resultado la formación de un sistema de anillos estable.

El término "carbociclo" (y las variaciones del mismo, tal como "carbocíclico") como se usa en este documento, a menos que se indique otra cosa, se refiere a (i) un anillo saturado o insaturado monocíclico C5 a C7, o (ii) un sistema de anillos saturado o insaturado bicíclico C_8 a C_{10}. Cada anillo en (ii) es independiente de, o está condensado a, el otro anillo, y cada anillo está saturado o insaturado. Los grupos carbociclo pueden estar sustituidos como se indica. Cuando los carbociclos contienen uno o más heteroátomos independientemente elegidos entre N, O y S, los carbociclos también pueden denominarse como "heterociclos", como se define a continuación. El carbociclo puede estar unido al resto de la molécula en cualquier átomo de carbono o nitrógeno que dé como resultado un compuesto estable. Los carbociclos bicíclicos condensados son un subconjunto de los

carbociclos, es decir, la expresión "carbociclo bicíclico condensado" generalmente se refiere a un sistema de anillos bicíclico C_8 a C_{10} en el que cada anillo está saturado o insaturado y se comparten dos átomos de carbono adyacentes por cada de los anillos del sistema de anillos. Un carbociclo bicíclico condensado en el que ambos anillos están saturados es un sistema de anillos bicíclico saturado. Los anillos carbocíclicos saturados también se denominan como anillos cicloalquilo, por ejemplo, ciclopropilo, ciclobutilo, etc. Un carbociclo bicíclico condensado en el que uno o ambos anillos están insaturados es un sistema de anillos bicíclico insaturado. Los sistemas de anillos carbociclo pueden incluir, cuando sea apropiado, una indicación de la variable a la que un átomo de anillo particular está unido. A menos que se indique otra cosa, los sustituyentes para los sistemas de anillos pueden estar unidos a cualquier átomo del anillo, con la condición de que dicha unión dé como resultado la formación de un sistema de anillos estable.

A menos que se indique otra cosa, el término "heterociclo" (y variantes de los mismos, tales como "heterocíclico" o "heterociclilo") en su sentido más amplio se refiere a (i) un anillo monocíclico saturado o insaturado estable de 5 a 7 miembros, o (ii) un sistema de anillos bicíclico estable de 8 a 10 miembros, en el que cada anillo en (ii) es independiente de, o está condensado a, el otro anillo o anillos y cada anillo está saturado o insaturado, y el anillo monocíclico o el sistema de anillos bicíclico contiene uno o más heteroátomos (por ejemplo, de 1 a 6 heteroátomos, o de 1 a 4 heteroátomos) seleccionados independientemente entre N, O y S y un equilibrio de los átomos de carbono (el anillo monocíclico típicamente contiene al menos un átomo de carbono y los sistemas de anillos bicíclicos típicamente contienen al menos dos átomos de carbono); y en el que cualquiera de uno o más de los heteroátomos de nitrógeno y azufre está opcionalmente oxidado, y cualquiera de uno o más de los heteroátomos de nitrógeno esta opcionalmente cuaternizado. A menos que se especifique otra cosa, el anillo heterocíclico puede estar unido a cualquier heteroátomo o átomo de carbono, con la condición de que la unión dé como resultado la creación de una estructura estable. Los grupos heterociclo pueden estar sustituidos como se indica y, a menos que se indique otra cosa, los sustituyentes pueden estar unidos a cualquier átomo en el anillo, ya sea un heteroátomo o un átomo de carbono, con la condición de que dé como resultado una estructura química estable. Los ejemplos representativos incluyen piranilo, piperidinilo, piperazinilo, azepanilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, oxazolidinilo, isoxazolidinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, isotiazolidinilo y tetrahidrofurilo (o tetrahidrofuranoilo). A menos que se exprese otra cosa, la expresión "sistema de anillos heteroarilo" se refiere a sistemas de anillos arilo, como se ha definido anteriormente, que incluyen de 1 a 4 heteroátomos (átomos sin carbono) que se eligen independientemente entre N, O y S. En el caso de anillos heteroaromáticos sustituidos que contienen al menos un átomo de nitrógeno (por ejemplo, piridina), dichas sustituciones pueden las que den como resultado la formación de N-óxido. Los ejemplos representativos de anillos heteroaromaticos incluyen piridilo, pirrolilo, pirazinilo, pirimidinilo, piridazinilo, tienilo (o

tiofenilo), tiazolilo, furanilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, oxazolilo, isooxazolilo, oxadiazolilo, tiazolilo, isotiazolilo y tiadiazolilo. Los ejemplos representativos de heterociclos bicíclicos incluyen benzotriazolilo, indolilo, isoindolilo, indazolilo, indolinilo, isoindolinilo, quinoxalinilo, quinazolinilo, cinnolinilo, cromanilo, isocromanilo, tetrahidroquinolinilo, quinolinilo, tetrahidroisoquinolinilo, isoquinolinilo, 2,3-dihidrobenzofuranilo, 2,3-dihidrobenzo-1,4-dioxinilo y benzo-1,3-dioxolilo.

A menos que se indica específicamente otra cosa como solo "sustituido", los grupos alquilo, cicloalquilo y arilo no están sustituidos. Si están sustituidos, los sustituyentes preferidos se seleccionan entre el grupo que incluye, pero sin limitación, halo, alquilo C_1-C_{20}, -CF_3, -NH_2, -N(alquilo C_1-C_6)$_2$, -NO_2, oxo, -CN,-N_3, -OH, -O(alquilo C1-C6), cicloalquilo C_3-C_{10}, alquenilo C_2-C_6, alquinilo C_2-C_6, (alquil C_0-C_6)S(O)$_{0-2}$-, aril-S(O)$_{0-2}$-, (alquil C_0-C_6)S(O)$_{0-2}$(alquil C_0-C_6)-, (alquil C_0-C_6)C(O)NH-, HN-C(NH)-, -O(alquil C1-C6)CF_3, (alquil C_0-C_6)C(O)-, (alquil C_0-C_6)OC(O)-, (alquil C_0-C_6)0(alquil C1-C6)-, (alquil C_0-C_6)C(O)$_{1-2}$(C_0-C_6 alquil)-, (alquil C1-C6)OC(O)NH-, arilo, aralquilo, heteroarilo, heterocicloalquilo, halo-arilo, halo-aralquilo, halo-heterociclo y halo-heterocicloalquilo.

A menos que se exprese otra cosa, todos los intervalos citados en este documento son inclusivos. Por ejemplo, un anillo heteroarilo descrito como que contiene de "0 a 3 heteroátomos" se refiere a que el anillo puede contener 0, 1, 2 ó 3 heteroátomos. También se apreciará que cualquier intervalo citado en este documento incluye dentro de su alcance todos los sub-intervalos dentro de ese intervalo. Las formas oxidadas de los heteroátomos N y S también se incluyen dentro del alcance de la presente invención.

Cuando cualquier variable (por ejemplo, R^1 o R^3) aparece más de una vez en cualquier constituyente o en la fórmula **(I)** o en cualquier fórmula diferente que representa y describe los compuestos de la invención, su definición en cada caso es independiente de su definición en cada caso diferente. Además, las combinaciones de sustituyentes y/o variables únicamente se permiten si dichas combinaciones dan como resultado compuestos estables.

A menos que se indique expresamente otra cosa, la sustitución con un sustituyente nombrado se permite en cualquier átomo con la condición de que dicha sustitución se permita químicamente y dé como resultado un compuesto estable. Un compuesto "estable" es un compuesto que puede prepararse y aislarse y que tiene una estructura y propiedades que se mantienen o se pueden hacer que permanezcan inalteradas básicamente durante un periodo de tiempo suficiente para permitir el uso del compuesto para los fines descritos en este documento (por ejemplo, la administración terapéutica o profiláctica a un sujeto).

Como se usa en este documento, el término "compuesto" pretende incluir agentes químicos descritos por la fórmula genérica **(I)** en todas las formas, incluyendo hidratos y solvatos de dichos agentes químicos.

En los compuestos de fórmula genérica **(I)**, los átomos pueden mostrar sus abundancias de isótopos naturales, o uno o más de los átomos pueden estar enriquecidos de forma artificial en un isótopo particular que tiene el mismo número atómico, pero una masa atómica o número másico diferente al de la más atómica o número másico que se encuentra predominantemente en la naturaleza. La presente invención se refiere a que incluye todas las variaciones de isótopos adecuadas de los compuestos de fórmula genérica **(I)**. Por ejemplo, las formas de isótopos diferentes de hidrógeno (H) incluyen protio (^{1}H) y deuterio (^{2}H o D). El protio es el isótopo de hidrógeno predominante de origen natural. Enriquecer el deuterio puede proporcionar ciertas ventajas terapéuticas, tales como el aumento de la semivida *in vivo* o la reducción de las necesidades de dosificación, o puede proporcionar un compuesto útil como un estándar para la caracterización de muestras biológicas. Los compuestos enriquecidos con isótopos en la fórmula genérica **(I)** pueden prepararse sin demasiada experimentación mediante técnicas convencionales bien conocidas por los expertos en la técnica o mediante procesos análogos a los descritos en los Esquemas y Ejemplos en este documento usando reactivos y/o intermedios enriquecidos con isótopos apropiados.

Como resultado de la selección de sustituyentes y patrones de sustituyentes, algunos de los compuestos de la presente invención pueden tener centros asimétricos y pueden aparecer como mezclas de estereoisómeros, o como diastereómeros individuales o enantiómeros. Todas las formas isoméricas de estos compuesto, ya estén aislados o mezclados, están dentro del alcance de la presente invención.

Como se reconocerá por un experto en la técnica, algunos de los compuestos de la presente invención pueden existir en forma de tautómeros. Para los propósitos de la presente invención una referencia a un compuesto de fórmula **(I)** es una referencia al compuesto *per se,* o a cualquiera de sus tautómeros *per se,* o a mezclas de dos o más tautómeros.

Los compuestos de la presente invención pueden administrarse en forma de sales farmacéuticamente aceptables. La expresión "sal farmacéuticamente aceptable" se refiere a una sal que posee la eficacia del precursor y que no es biológicamente o de otro modo indeseable (por ejemplo, ni es óxido ni de otra manera perjudicial para el receptor del mismo). Las sales adecuadas incluyen sales de adición de ácidos que, pueden formarse mezclando una solución del compuesto de la presente invención con una solución de un ácido farmacéuticamente aceptable, tal como ácido clorhídrico, ácido sulfúrico, ácido acético, ácido trifluoroacético o ácido benzoico. Muchos de los compuestos de la invención llevan un resto ácido, en cuyo caso las sales farmacéuticamente aceptables adecuadas de los mismos pueden incluir sales de metales alcalinos (por ejemplo, sales sódicas o potásicas), sales de metales alcalinotérreos (por ejemplo, sales cálcicas o magnésicas), y sales formadas con ligandos orgánicos adecuados, tales como sales de amonio cuaternario. Además, en el caso de que esté presente un grupo ácido (-COOH) o alcohólico, los ésteres

farmacéuticamente aceptables pueden emplearse para modificar las características de solubilidad o hidrólisis del compuesto.

El término "administración" y las variantes del mismo (por ejemplo, "administrar" un compuesto) con referencia a un compuesto de la invención se refiere a proporcionar el compuesto o un profármaco del compuesto al individuo que necesita tratamiento. Cuando un compuesto de la invención o un profármaco del mismo se proporciona junto con uno o más agentes activos distintos (por ejemplo, agentes antivirales útiles para trata una infección del VHC), se entiende que "administración" y cada una de sus variantes incluye la provisión concurrente y secuencial del compuesto o sal (o hidrato) y otros agentes.

Como se usa en este documento, el término "composición" pretende incluir un producto que comprende los ingredientes especificados, así como cualquier producto que se obtenga, directamente o indirectamente, de la combinación de los ingredientes especificados.

Por "farmacéuticamente aceptable" se refiere a que los ingredientes de la composición farmacéutica han de ser compatibles entre sí y no perjudicar al receptor de la misma.

El término "sujeto" (como alternativa, denominado en este documento como "paciente") como se usa en este documento, se refiere a un animal, preferiblemente un mamífero, mucho más preferiblemente un ser humano, que ha sido objeto de tratamiento, observación o experimentación.

La expresión "cantidad eficaz", como se usa en este documento se refiere a la cantidad de compuesto activo o agente farmacéutico que provoca la respuesta biológica o medicinal en un tejido, sistema, animal o ser humano que se espera por un investigador, veterinario, médico u otro especialista. En una realización, la cantidad eficaz es una "cantidad terapéuticamente eficaz" para el alivio de uno o más síntomas de la enfermedad o afección que se está tratando. En otra realización, la cantidad eficaz es un "cantidad profilácticamente eficaz" para reducir la gravedad o probabilidad de uno o más síntomas de la enfermedad o afección. En otra realización, la cantidad eficaz es una "cantidad terapéuticamente eficaz" para la inhibición de la replicación viral del VHC y/o la producción viral del VHC. El término también incluye en este documento la cantidad de principio activo suficiente para inhibir NS5A de VHC y provocar de esta manera la respuesta que se busca (es decir, una "cantidad de inhibición eficaz"). Cuando el compuesto activo (es decir, principio activo) se administra en forma de una sal, las referencias a la cantidad de principio activo son a la forma de ácido libro o base libre del compuesto.

Se entenderá que los compuestos reivindicados causan la inhibición en la prueba de ensayo de replicón. Por lo tanto, los compuestos descritos en este documento son útiles para inhibir la replicación del VHC, específicamente la proteína NS5A. Los compuestos descritos en este documento tienen diferentes usos, incluyendo la prevención o tratamiento de uno o más de los síntomas de la infección por VHC, la inhibición de la replicación viral del VHC y/o la producción viral del VHC, y/o como ingredientes de la composición farmacéutica.

Los compuestos de esta invención son útiles en la preparación y ejecución de ensayos de exploración para compuestos antivirales. Por ejemplo, los compuestos de esta invención son útiles para identificar líneas celulares del replicón resistente a VHC que albergan mutaciones en la NS5A, que son excelentes herramientas de exploración para los compuestos antivirales más potentes. Además, los compuestos de esta invención son útiles para establecer o determinar el sitio de unión a otros antivirales a la replicasa de VHC.

Con el fin de inhibir de la proteína NS5A del VHC, tratar la infección por VHC y/o reducir la probabilidad o gravedad de síntomas de la infección por VHC e inhibir la replicación viral por VHC y/o la producción viral del VHC, los compuestos de la presente invención, opcionalmente en forma de una sal o un hidrato, pueden administrarse mediante cualquier medio que produzca el contacto del agente activo con el sitio del agente de acción. Pueden administrarse mediante uno o más medios convencionales para su uso junto con productos farmacéuticos, como agentes terapéuticos individuales o junto con agentes terapéuticos. Pueden administrarse solos, pero típicamente se administran con un vehículo farmacéutico seleccionado sobre la base de la ruta elegida de administración y la práctica farmacéutica convencional. Los compuestos de la invención, por ejemplo, pueden administrarse mediante uno o más de las siguientes vías: por vía ora, parenteral (incluyendo inyecciones subcutáneas, intravenosa, intramuscular, inyección intraesternal o técnicas de infusión), por inhalación (tal como, en forma de pulverización), o por vía recta, en forma de una dosis unitaria de una composición farmacéutica que contiene una cantidad eficaz del compuesto y transportadores, adyuvantes y vehículos farmacéuticamente aceptables no tóxicos convencionales. Las preparaciones líquidas adecuadas para la administración oral (por ejemplo, suspensiones, jarabes, elixires y similares) pueden prepararse de acuerdo con técnicas conocidas en la técnica y pueden emplear cualquiera de los medios habituales, tales como agua, glicoles, aceites, alcoholes y similares. Las preparaciones sólidas adecuadas para la administración oral (por ejemplo, polvos, píldoras, cápsulas y comprimidos) pueden prepararse de acuerdo con técnicas conocidas en la técnica y pueden emplear excipientes sólidos, tales como almidones, azúcares, caolín, lubricantes, aglutinantes, agentes disgregantes y similares. Las composiciones parenterales pueden prepararse de acuerdo con técnicas conocidas en la técnica y típicamente emplean agua estéril como transportador y opcionalmente otros ingredientes, tales como adyuvantes de solubilidad. Las soluciones inyectables pueden prepararse de acuerdo con procedimientos conocidos en la técnica, en los que el transportador comprende una solución salina, una solución de glucosa o una solución que contiene una mezcla de solución salina y glucosa. La descripción adicional de procedimientos adecuados para su uso en la preparación de composiciones farmacéuticas de la presente invención y de los ingredientes adecuados para su uso en dichas composiciones se proporciona en Remington's Pharmaceutical Sciences, 18ª edición (ed. A. R. Gennaro, Mack Publishing Co., 1990).

Los compuestos de esta invención pueden administrarse por vía oral en un intervalo de dosificación de 0,001 a 1000 mg/kg de peso corporal de un mamífero (por ejemplo, ser humano) por día en una sola dosis o en dosis divididas. Un intervalo de dosificación es de 0,01 a 500 mg/kg de peso corporal por día por vía oral en una sola dosis o en dosis divididas. Otro intervalo de dosificación es de 0,1 a 100 mg/kg de peso corporal por día por vía oral en una sola dosis o en dosis divididas. Para la administración oral, las composiciones pueden proporcionarse en forma de comprimidos o cápsulas que contienen de 1,0 a 500 mg del principio activo, particularmente 1, 5, 10, 15, 20, 25, 50, 75, 100, 150, 200, 250, 300, 400 y 500 mg del principio activo para el ajuste sintomático de la dosis al paciente que se va a tratar. El nivel de dosis específico y la frecuencia de la dosis para cualquier paciente particular puede variarse y dependerá de una diversidad de factores que incluyen la actividad del compuesto específico empleado, la estabilidad metabólica y la duración de acción de este compuesto, la edad, peso corporal, salud general, sexo, dieta, modo y tiempo de administración, velocidad de excreción, combinación de fármacos, la gravedad de la afección particular y el huésped sometido a terapia.

Como se ha indicado anteriormente, la presente invención también se refiere a un procedimiento de inhibición de la actividad del replicón del VHC, inhibición de la replicación viral del VHC y/o la producción viral del VHC, tratamiento de la infección por VHC y/o reducción de la probabilidad o gravedad de los síntomas de la infección por VHC con un compuesto de la presente invención junto con uno o más agentes terapéuticos y una composición farmacéutica que comprende un compuesto de la presente invención y uno o más agentes terapéuticos seleccionados entre el grupo que consiste en un agente antiviral del VHC, un inmunomodulador y un agente anti-infeccioso. Dichos agentes terapéuticos activos frente a VHC incluyen, pero sin limitación, ribavirina, levovirina, viramidina, timosina alfa-1, R7025 (un interferón mejorado (Roche)), interferón □, interferón □, interferón □ pegilado (peginterferón □, una combinación de interferón □ y ribavirina, una combinación de peginterferón □ y ribavirina, una combinación de interferón □ y levovirina, y una combinación de peginterferón □ y levovirina. La combinación de peginterferón □ y ribavirina representa el Estándar actual de Cuidado para el tratamiento del VHC. La combinación de uno o más compuestos de la presente invención con el Estándar de Cuidado para el tratamiento del VHC, interferón pegilado y ribaviririna se contempla específicamente incluyéndose en la presente invención. El interferón □ incluye, pero sin limitación, interferón recombinante □2a (tal como interferón ROFERON), interferón pegilado □2a (PEGASYS), interferón □2b (tal como interferón INTRON-A), interferón pegilado □2b (PEGINTRON), un interferón de consenso recombinante (tal como interferón alphacon-1), albuferon (interferón □ unido a albúmina de suero humano (Human Genome Sciences)), y un producto de interferón □ purificado. El interferón de consenso recombinante de Amgen tiene el nombre comercial INFERGEN. La levovirina es el enantiómero L de ribavirina que ha mostrado una actividad inmunomoduladora similar a la

ribavirina. La viramidina representa un análogo de ribavirina descrito en la Publicación de Solicitud de Patente Internacional WO 01/60379. De acuerdo con el procedimiento de la presente invención, los componentes individuales de la combinación pueden administrarse por separado en diferentes momentos durante el transcurso de la terapia o al mismo tiempo en formas de combinación divididas o individuales.

La ribavirina, levovirina y viramidina pueden ejercer sus efectos anti-VHC modulando las agrupaciones intracelulares de nucleótidos de guanina a través de la inhibición de la inosina monofosfato deshidrogenasa (IMPDH) de la enzima intracelular. La IMPDH es la enzima limitante de la velocidad en la ruta biosintética en la biosíntesis de nucleótidos de guanina *de novo*. La ribavirina se fosforila fácilmente de forma intracelular y el derivado de monofosfato es un inhibidor de la IMPDH. Por lo tanto, la inhibición de la IMPDH representa otro objetivo útil para el descubrimiento de inhibidores de la replicación del VHC. Por lo tanto, los compuestos de la presente invención también pueden administrarse junto con un inhibidor de la IMPDH, tal como los descritos en las Publicaciones de Solicitud de Patente Internacionales WO 97/41211, WO 01/00622 y WO 00/25780; o micofenolato mofetilo. Véase, Anthony C. Allison y Elsie M. Eugui, *Immunosuppressive and Other Anti-Rheumetic Activities of Mychofenolate Mofetil,* 44 (SUPPL.) AGENTS ACTION 165 (1993).

Para el tratamiento de la infección por VHC, los compuestos de la presente invención también pueden administrarse junto con el inhibidor de la polimerasa del agente antiviral R7128 (Roche).

Los compuestos de la presente invención también pueden combinarse para el tratamiento de una infección por HCV con ribonucleósidos antivirales de cadena 2' en Rogers E. Harry-O'Kuru *et al., A Short, Flexible Route to 2'-C-BranchedRibonucleosides,* 62 J. ORG. CHEM. 1754-59 (1997); Michael S. Wolfe y Rogers E. Harry-O'Kuru, *A Consise Synthesis of 2-C-Methylribonucleosides,* 36 TET. LETT. 7611-14 (1995); la Patente de Estados Unidos N° 3.480613; y las Publicaciones de Solicitud de Patente Internacional WO 01/90121, WO 01/92282, WO 02/32920, WO 04/002999, WO 04/003000 y WO 04/002422; el contenido de cada uno de los cuales se incorpora por referencia en su totalidad. Dichos ribonucleósidos ramificados 2'-C incluyen, pero sin limitación, 2'-C-metil-citidina, 2'-C-metil-uridina, 2'-C-metil-adenosina, 2'-C-metil-guanosina y 9-(2-C-metil-□-D-ribofuranosil)-2,6-diaminopurina, y el éster de aminoácido correspondiente de los hidroxilos de ribosa C-2', C-3' y C-5' y los ésteres de 1,3-propanodiol cíclicos opcionalmente sustituidos correspondientes de los derivados de 5'-fosfato.

Para el tratamiento de la infección por VHC, los compuestos de la presente invención también pueden administrarse junto con un agente que es un inhibidor de serina proteasa NS3 de VHC. La serina proteasa NS3 de VHC es una enzima vírica básica y se ha descrito para que sea una diana excelente para la inhibición de la replicación del VHC. Los inhibidores basados en

sustratos y sin sustratos ejemplares de los inhibidores de proteasa de NS3 del VHC se describen en las Publicaciones de Solicitud de Patente Internacionales WO 98/22496, WO 98/46630, WO 99/07733, WO 99/07734, WO 99/38888, WO 99/50230, WO 99/64442, WO 00/09543, WO 00/59929, WO 02/48116, WO 02/48172, WO 2008/057208 y WO 2008/057209, en la Patente Británica N° GB 2 337 262, y en la Patente de Estados Unidos N° 6.323.180, 7.470.664 y 7.012.066 y en Ashok Arasappan *et al., Discovery of Narlaprevir (SCH 900518): A Potent, Second Generation HCVNS3 Serine Protease Inhibitor,* ACS MED. CHEM. LETT. DOI: 10,1021/ ml9000276 (15 de febrero de 2010).

Los compuestos de la presente invención también pueden combinarse para el tratamiento de la infección por VHC con nucleósidos que tienen propiedades anti-VHC, tales como las descritas en las Publicaciones de Solicitud de Patente Internacionales WO 02/51425, WO 01/79246, WO 02/32920, WO 02/48165 y WO 2005/003147 (incluyendo R1656, (2'R)-2'-deoxi-2'-fluoro-2'-C-metilcitidina, mostrado como los compuestos 3-6 en la página 77); WO 01/68663; WO 99/43691; WO 02/18404 y WO 2006/021341, y la Publicación de Solicitud de Patente de Estados Unidos US 2005/0038240, incluyendo nucleósidos de 4'-azido, tal como R1626, 4'-azidocitidina; Publicaciones de Solicitud de Patente de Estados Unidos US 2002/0019363, US 2003/0236216, US 2004/0006007, US 2004/0063658 y US 2004/0110717; Patente de Estados Unidos N° 7.105.499, 7.125.855, 7.202.224; y las Publicaciones de Solicitud de Patente Internacional WO 02/100415, WO 03/026589, WO 03/026675, WO 03/093290, WO 04/011478, WO 04/013300 y WO 04/028481; el contenido de cada una se incorpora en este documento por referencia en su totalidad.

Para el tratamiento de la infección por VHC, los compuestos de la presente invención también pueden administrarse junto con un agente que es un inhibidor de la polimerasa NS5B del VHC. Dichos inhibidores de la polimerasa NS5B del VHC que pueden usarse como terapia de combinación incluyen, pero sin limitación, los descritos en las Publicaciones de Solicitud de Patente Internacionales WO 02/057287, WO 02/057425, WO 03/068244, WO 2004/000858, WO 04/003138 y WO 2004/007512; las Patentes de Estados Unidos N° 6.777.392, 7.105.499, 7.125.855, 7.202.224 y las Publicaciones de Solicitud de Patente de Estados Unidos US 2004/0067901 y US 2004/0110717; el contenido de cada una se incorpora en este documento por referencia en su totalidad. Otros inhibidores de la polimerasa del VHC incluyen, pero sin limitación, valopicitabina (NM-283; Idenix) y 2'-F-2'-beta-metilcitidina (véase también, el documento WO 2005/003147).

En una realización, inhibidores nucleósidos de polimerasa NS5B del VHC que se usan junto con los presentes inhibidores de VHC se seleccionan entre los siguientes compuestos: 4-amino-7-(2-C-metil-□-D-arabinofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-metilamino-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-dimetilamino-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-

d]pirimidina; 4-ciclopropilamino-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-7-(2-C-vinil-□-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(2-C-hidroximetil-□-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(2-C-fluorometil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-5-metil-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; ácido 4-amino-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina-5-carboxílico; 4-amino-5-bromo-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-5-cloro-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-5-fluoro-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 2,4-diamino-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 2-amino-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 2-amino-4-ciclopropilamino-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 2-amino-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidin-4(3H)-ona; 4-amino-7-(2-C-etil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-7-(2-C,2-O-dimetil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidin-4(3H)-ona; 2-amino-5-metil-7-(2-C,2-O-dimetil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidin-4(3H)-ona; 4-amino-7-(3-deoxi-2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-7-(3-deoxi-2-C-metil-□-D-arabinofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-2-fluoro-7-(2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-7-(3-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-d]pirimidina; 4-amino-7-(3-C-metil-□-D-xilofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-7-(2,4-di-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; 4-amino-7-(3-deoxi-3-fluoro-2-C-metil-□-D-ribofuranosil)-7H-pirrolo[2,3-*d*]pirimidina; y los 5'-trifosfatos correspondientes; o una sal farmacéuticamente aceptable de los mismos.

Los compuestos de la presente invención también pueden combinarse para el tratamiento de la infección por HCV con inhibidores no nucleósidos de polimerasa de VHC, tales como los descritos en las Publicaciones de Solicitud de Patente de Estados Unidos US 2006/0100262 y US 2009-0048239; las Publicaciones de Solicitud de Patente Internacionales WO 01/77091, WO 01/47883, WO 02/04425, WO 02/06246, WO 02/20497, WO 2005/016927 (en particular JTK003), WO 2004/041201, WO 2006/066079, WO 2006/066080, WO 2008/075103, WO 2009/010783 y WO 2009/010785; el contenido de cada una se incorpora en este documento como referencia en su totalidad.

En una realización, inhibidores no nucleósidos de polimerasa NS5B del VHC que se usan junto con los presentes inhibidores NS5A del VHC se seleccionan entre los siguientes compuestos: ácido 14-ciclohexil-6-[2-(dimetilamino)etil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-(2-morfolin-4-iletil)-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-[2-(dimetilamino)etil]-3-metoxi-5,6,7,8-tetrahidroindolo[2,1-a] [2,5]benzodiazocina-11-carboxílico;

ácido 14-ciclohexil-3-metoxi-6-metil-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ({[(14-ciclohexil-3-metoxi-6-metil-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocin-11-il)carbonil]amino}sulfonil)acetato de metilo; ácido ({[(14-ciclohexil-3-metoxi-6-metil-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocin-11-il)carbonil]amino}sulfonil)acético; 14-ciclohexil-*N*-[(dimetilamino)sulfonil]-3-metoxi-6-metil-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxamida; ácido 3-cloro-14-ciclohexil-6-[2-(dimetilamino)etil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina 11-carboxílico; bis(trifluoroacetato) de N'-(11-carboxi-14-ciclohexil-7,8-dihidro-6H-indolo[1,2-e][1,5]benzoxazocin-7-il)-N,N-dimetiletano-1,2-diaminio; ácido 14-ciclohexil-7,8-dihidro-6H-indolo[1,2-e][1,5]benzoxazocina-11-carboxílico; ácido 14-ciclohexil-6-metil-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-3-metoxi-6-metil-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-[2-(dimetilamino)etil]-3-metoxi-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-[3-(dimetilamino)propil]-7-oxo-5,6,7,8-tetrahidroindolo [2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-7-oxo-6-(2-piperidin-1-iletil)-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-(2-morfolin-4-iletil)-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-[2-(dietilamino)etil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a] [2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-(1-metilpiperidin-4-il)-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; 14-ciclohexil-N-[(dimetilamino)sulfonil]-7-oxo-6-(2-piperidin-1-iletil)-5,6,7,8-tetrahidroindolo[2,1-a] [2,5]benzodiazocina-11-carboxamida; 14-ciclohexil-6-[2-(dimetilamino)etil]-N-[(dimetilamino)sulfonil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxamida; ácido 14-ciclopentil-6-[2-(dimetilamino)etil]-7-oxo-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-5,6,7,8-tetrahidroindolo[2,1-a] [2,5]benzodiazocina-11-carboxílico; ácido 6-alil-14-ciclohexil-3-metoxi-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclopentil-6-[2-(dimetilamino)etil]-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 14-ciclohexil-6-[2-(dimetilamino)etil]-5,6,7,8-tetrahidroindolo[2,1-a][2,5]benzodiazocina-11-carboxílico; ácido 13-ciclohexil-5-metil-4,5,6,7-tetrahidrofuro[3',2':6,7][1,4]diazocin[1,8-a]indolo-10-carboxílico; ácido 15-ciclohexil-6-[2-(dimetilamino)etil]-7-oxo-6,7,8,9-tetrahidro-5H-indolo[2,1-a][2,6]benzodiazonin-12-carboxílico; ácido 15-ciclohexil-8-oxo-6,7,8,9-tetrahidro-5H-indolo[2,1-a][2,5]benzodiazonin-12-carboxílico; ácido 13-ciclohexil-6-oxo-6,7-dihidro-5H-indolo[1,2-d][1,4]benzodiazepina-10-carboxílico; y sales farmacéuticamente aceptables de los mismos.

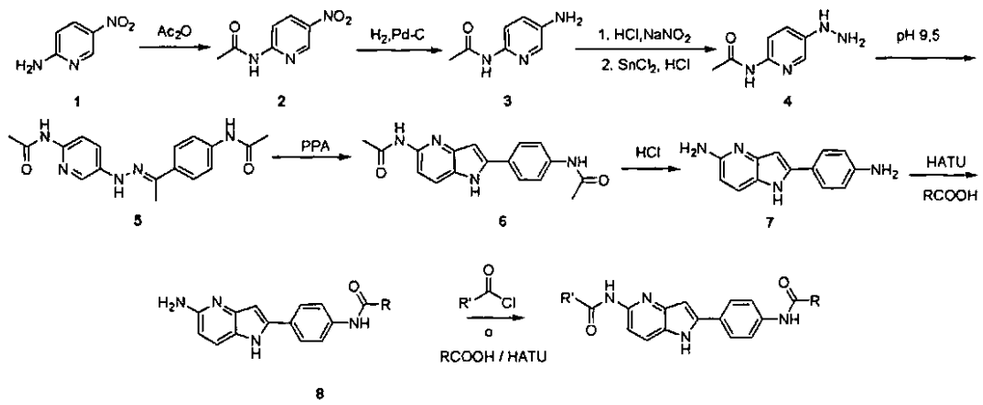
Los replicones del VHC y la actividad inhibidora de NS5A de los presentes compuestos puede ensayarse usando ensayos conocidos en la técnica. Los inhibidores de VHC, tales como los

descritos en los Ejemplos en este documento tienen actividades en los ensayos del replicón del genotipo 1b, 2a y 1a de aproximadamente 1 pM a aproximadamente 1 □M. El ensayo se realiza incubando una línea celular que alberga un replicón en presencia de un inhibidor para un periodo de tiempo determinado y la medición del efecto del inhibidor en la replicación del VHC directamente cuantificando el nivel de ARN del replicón, o indirectamente midiendo la actividad enzimática de una enzima indicadora co-codificada, tal como luciferasa o □-lactamasa. Realizando una serie de dichas mediciones a diferentes concentraciones del inhibidor se determina la concentración inhibidora eficaz del inhibidor (CE_{50} o CE_{90}). Véase, Jan M. Vrolijk *et al., A replicons-based bioassay for the measurement of interferons in patients with chronic hepatitis C,* 110 J. VIROLOGICAL METHODS 201 (2003). Dichos ensayos también pueden realizarse en un formato automatizado para un procesamiento de detección de alto rendimiento. Véase, Paul Zuck *et al., A cell-based □-lactamaase reporter gene assay for the identification of inhibitors of hepatitis C virus replication,* 334 ANALYTICAL BIOCHEMISTRY 344 (2004).

La presente invención también incluye procesos para preparar los compuestos de fórmula **(I)**. Los compuestos de la presente invención pueden prepararse fácilmente de acuerdo con los siguientes esquemas de reacción y ejemplos, o modificaciones de los mismos, usando materiales de partida, reactivos y procedimientos de síntesis convencionales que pueden obtenerse fácilmente. En estas reacciones, también es posible hacer uso de variantes que se conocen por los expertos en la técnica, pero no se mencionan en más detalle. Además, serán fácilmente evidentes otros procedimientos para preparar compuestos de la invención por un experto en la técnica a la luz de los siguientes esquemas de reacción y ejemplos. A menos que se indique otra cosa, todas las variables son como se han definido anteriormente. Los siguientes esquemas de reacción y ejemplos únicamente sirven para ilustrar la invención y su práctica.

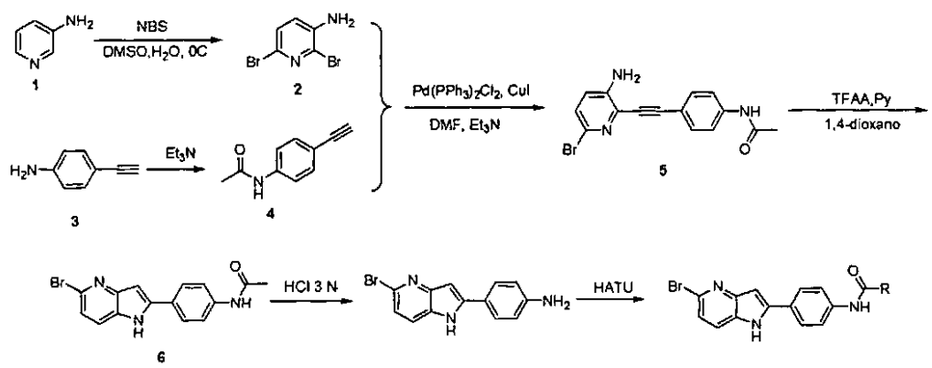
Esquemas Generales

Esquema A-1



La síntesis de análogos que contienen el núcleo 4-azaindol puede realizarse partiendo de una 2-amino-5-nitropiridina **2** protegida adecuadamente, que después puede reducirse por hidrogenación catalítica para convertir el grupo amino libre resultante en su hidrazina mediante la reacción de $NaNO_2$ y $SnCl_2$. La piridilhidrazina resultante puede condensarse con una cetona y después someterse a condiciones de ciclación de indol de Fisher para proporcionar el **6**. Puede realizarse la desprotección ácida de grupos acetilo usando un ácido fuerte para liberar la diamina, que puede acoplarse selectivamente en el nitrógeno de anilina más reactivo usando agentes de acoplamiento convencionales, tales como HATU. Después, el grupo de aminopiridina puede acilarse con un reactivo, tal como cloruro de acetilo o un ácido carboxílico, en presencia de un reactivo de formación de enlace amida.

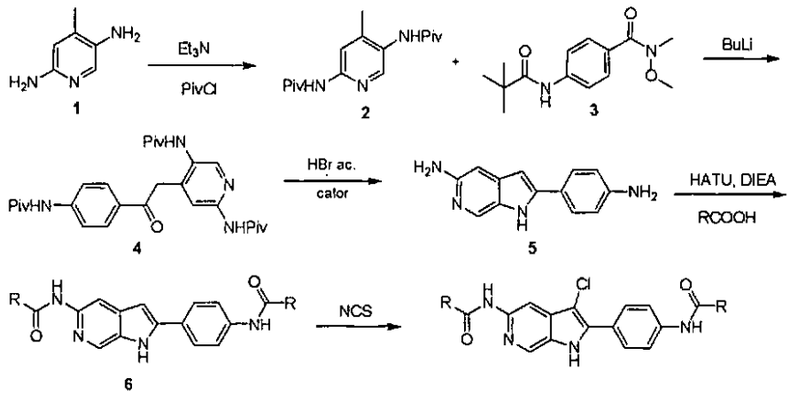
Esquema A-2



Pueden acoplarse 2-bromo-3-aminopiridinas a un alquino sustituido de forma terminal usando procedimientos de acoplamiento de Sonagashira convencionales para dar los intermedios **5**, que pueden experimentar ciclación mediada por TFAA para proporcionar los compuestos de 4-azaindol **6**. Los grupos protectores pueden retirarse con un ácido fuerte, tal como HCl acuoso, y la

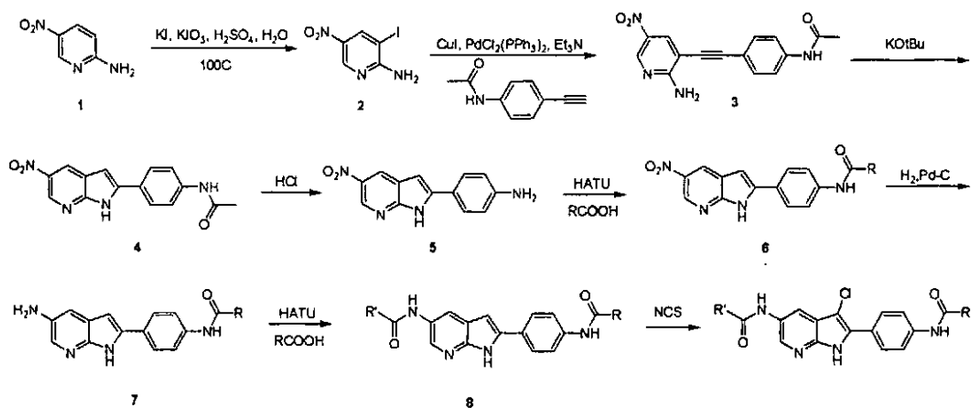
amina resultante puede acilarse usando un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU.

Esquema B



La síntesis de las estructuras B que contienen un núcleo de 6-azaindol puede realizarse mediante la metalación del análogo de 4-metilpiridina **2** con una base fuerte, tal como BuLi, e inactivando el anión resultante con el agente de acilación, tal como **3**. El intermedio **4** puede desprotegerse totalmente por la acción de un ácido fuerte, tal como HBr, para dar la estructura de diamino azaindol **5**. Ambos grupos amino pueden acilarse usando un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU. Los compuestos **6** pueden funcionalizarse adicionalmente en la posición del indol C-3 con electrófilos, tales como NCS.

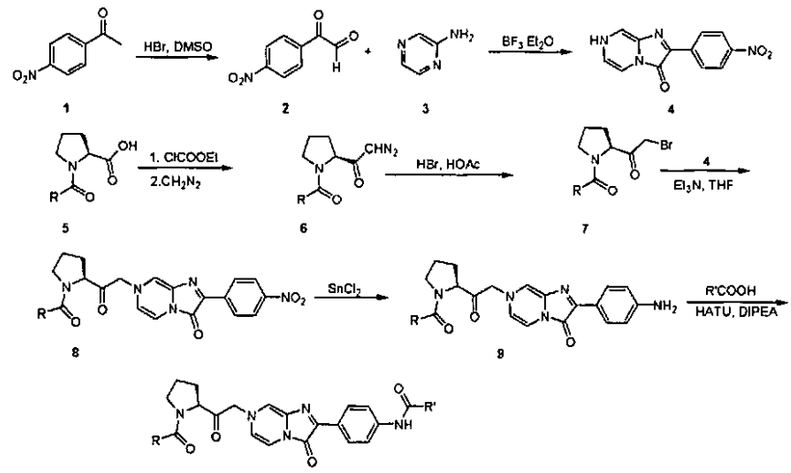
Esquema C



Las yodo aminopiridinas **2** pueden acoplarse a un alquino sustituido de forma terminal usando procedimientos de acoplamiento de Sonagashira convencionales para dar los intermedios **5**, que pueden experimentar una ciclación mediada por base usando un reactivo, tal como KOtBu, para proporcionar los compuestos de 7-azaindol **4**. Los grupos protectores pueden retirarse con un ácido fuerte, tal como HCl acuoso, y la amina resultante puede acilarse usando un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU. Después,

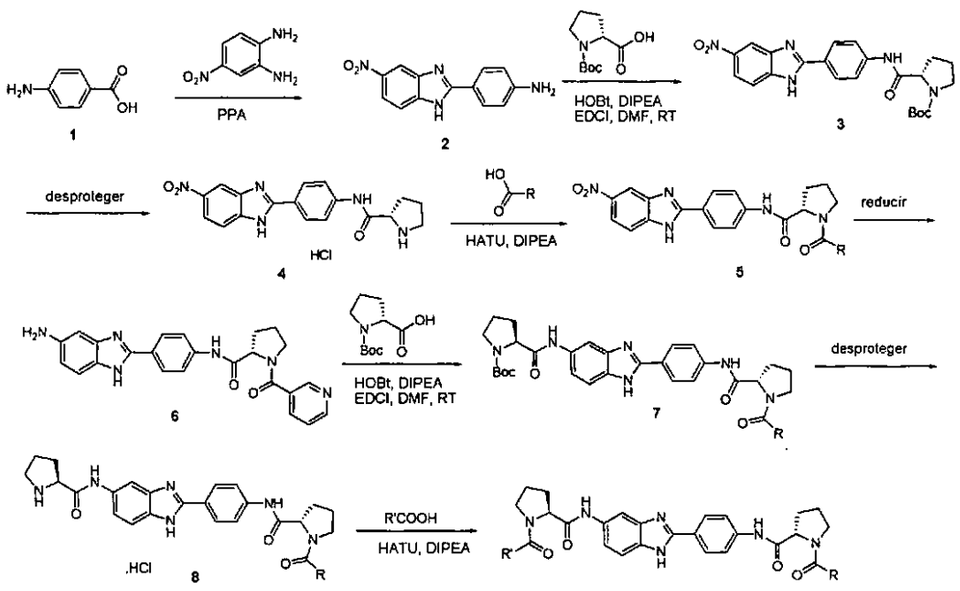
los compuestos **6** pueden reducirse usando hidrógeno y después se acopló una segunda vez un catalizador con un ácido carboxílico y HATU para proporcionar **8.** El tratamiento de **8** con un agente electrófilo, tal como NCS, proporciona los compuestos deseados.

Esquema D



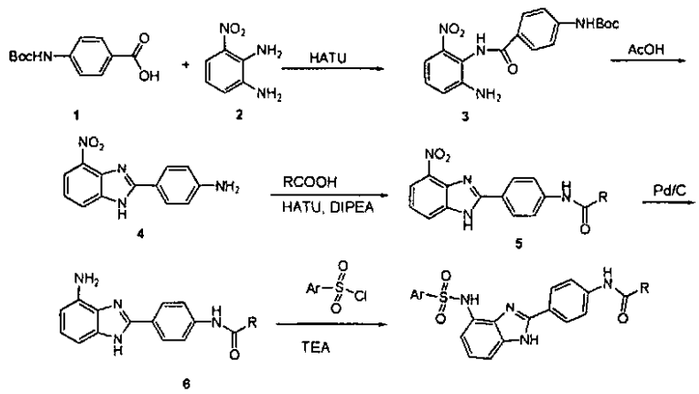
Los compuestos en la serie D pueden sintetizarse haciendo reaccionar el intermedio de dicarbonilo **2** con un derivado de 2-aminopirimidina en presencia de un ácido de Lewis, tal como eterato de trifluoruro de boro. El heterociclo resultante puede alquilarse con un análogo de bromocetona de un aminoácido, tal como prolina, en presencia de una base de amina terciaria. El grupo nitro puede reducirse, y la anilina resultante puede acilarse usando un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU, para dar los productos finales.

Esquema E-1



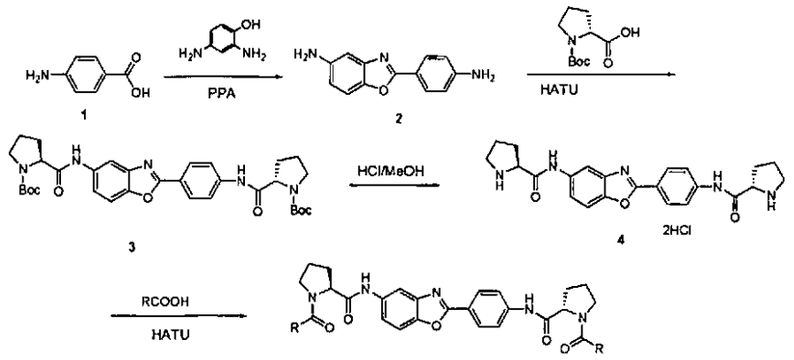
La estructura E-1 puede prepararse mediante la condensación de un derivado de ácido benzoico, tal como **1**, con un equivalente de fenilenodiamina **2** en presencia de un agente de deshidratación, tal como ácido polifosfórico. La anilina resultante puede acilarse usando un ácido carboxílico sustituido apropiadamente, tal como N-Boc-L-prolina, y un reactivo de formación de enlace amida, tal como HATU, y después se sometió a condiciones ácidas para retirar el grupo Boc. Los compuestos **4** pueden acoplarse de nuevo con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU. El grupo nitro en **5** puede reducirse en condiciones de hidrogenación catalítica, y la anilina resultante puede acoplarse adicionalmente con diversas aminas para dar los compuestos diana.

Esquema E-2



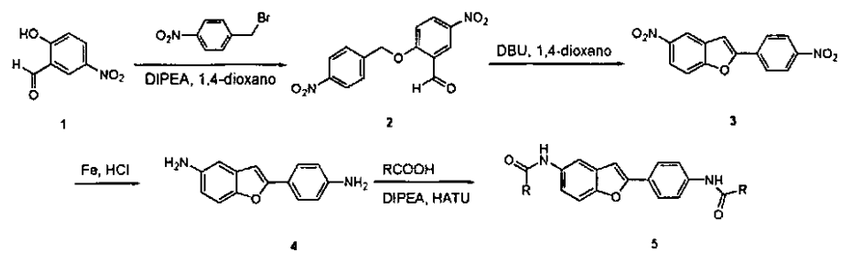
La estructura E-2 puede prepararse haciendo reaccionar con un derivado de ácido benzoico con un análogo de fenilenodiamina y un reactivo de formación de enlace amida, tal como HATU, para dar amidas **3**, que puede ciclodeshidratarse por calentamiento con un reactivo, tal como HOAc. La anilina resultante puede acilarse usando un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU, para dar los intermedios **5.** El grupo nitro puede reducirse en condiciones de hidrogenación catalítica, y la anilina resultante sulfonarse con un cloruro de sulfonilo sustituido apropiadamente y una base de amina terciaria para dar los productos diana.

Esquema F



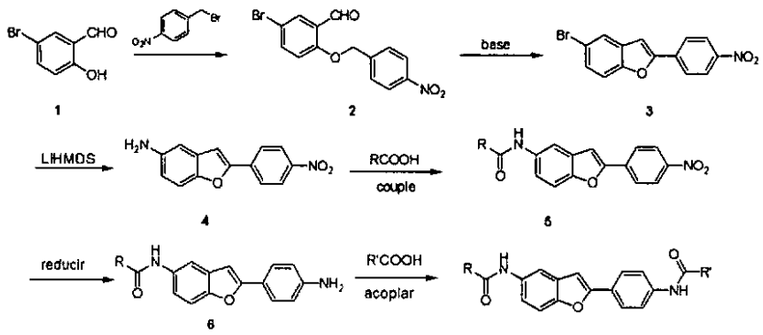
La estructura F puede prepararse por la condensación de un derivado de ácido benzoico, tal como **1**, con un equivalente de amino fenol **2** en presencia de un agente de deshidratación, tal como ácido polifosfórico. La anilina resultante puede acilarse usando un ácido carboxílico sustituido apropiadamente, tal como N-Boc-L-prolina, y un reactivo de formación de enlace amida, tal como HATU, y después puede someterse a condiciones ácidas para retirar el grupo Boc. Los compuestos **4** pueden acoplarse de nuevo con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU.

Esquema G-1



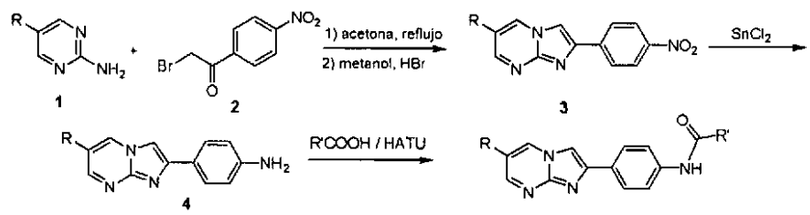
Los compuestos que tienen la estructura de benzofurano G puede prepararse haciendo reaccionar un salicilaldehído sustituido apropiadamente con un haluro de bencilo, tal como bromuro de 4-nitrobencilo, en presencia de una base de amina terciaria para dar los éteres **2.** Los éteres bencílicos pueden tratarse con una base, tal como DBU, y se calentaron a temperaturas elevadas para realizar la ciclación para dar los benzofuranos **3.** Los grupos nitro en **3** pueden reducirse en condiciones de hidrogenación catalítica, y las anilinas resultantes pueden acoplarse con diversos ácido carboxílicos para dar los compuestos diana G-1.

Esquema G-2



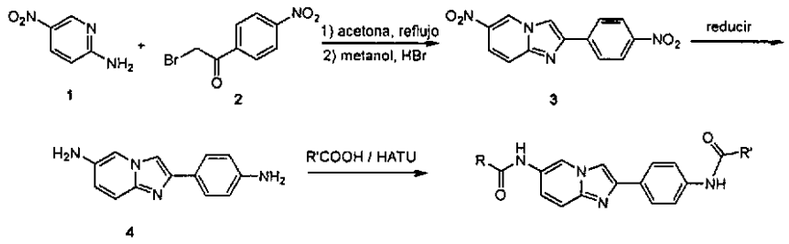
Para los compuestos sustituidos diferencialmente (R, R') que tienen la estructura de benzofurano G, la síntesis puede modificarse haciendo reaccionar un salicilaldehído de bromo sustituido apropiadamente con un haluro de bencilo, tal como bromuro de 4-nitrobencilo, en presencia de una base de amina terciaria para dar los éteres **2.** Los ésteres bencílicos pueden tratarse con una base, tal como DBU, y se calentaron a temperaturas elevadas para realizar la ciclación para dar los benzofuranos **3.** El bromuro de arilo puede convertirse en la aril amina por reacción con LHMDS y un catalizador de paladio para proporcionar **4**, que puede acoplarse a un ácido carboxílico sustituido apropiadamente para dar **5.** El grupo nitro en **5** puede reducirse en condiciones de hidrogenación catalítica, y la anilina resultante puede acoplarse con un segundo análogo de ácido carboxílico para dar los compuestos diana G-2.

Esquema H



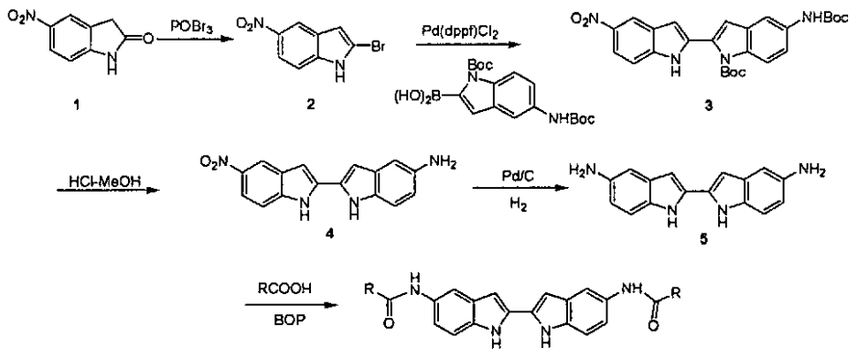
Las aminopirimidinas sustituidas apropiadamente pueden ciclodeshidratarse después de la acilación con una cetona sustituida apropiadamente, tal como 4'-nitro-2-bromobenzofenona, mediante calentamiento en un disolvente, tal como MeOH, y una fuente ácida, tal como HBr. El compuesto heterocíclico nitro resultante puede convertirse en la amina aromática mediante reducción con un reactivo, tal como $SnCl_2$. Los compuestos finales H pueden obtenerse haciendo reaccionar **4** con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU.

Esquema I



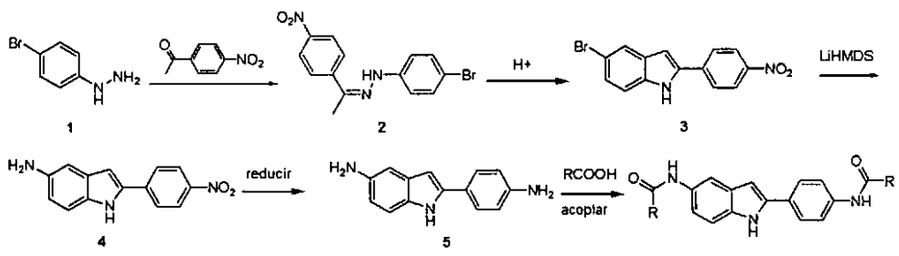
Los compuestos del esquema I pueden prepararse haciendo reaccionar la aminopiridina sustituida apropiadamente con 4'-nitro-2-bromobenzofenona mediante calentamiento en un disolvente, tal como acetona, después realizando una reacción de ciclodeshidratación usando metanol y una fuente ácida, tal como HBr. El compuesto heterocíclico nitro resultante **3** puede convertirse en la amina aromática por reducción con un reactivo, tal como $SnCl_2$. Los compuestos finales pueden obtenerse haciendo reaccionar **4** con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU.

Esquema J



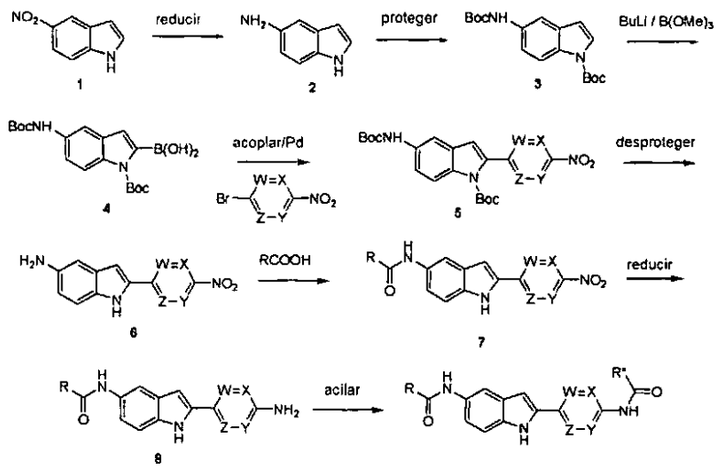
Los compuestos en el esquema J pueden prepararse acoplando ácidos indol borónicos con un 2-bromoindol sustituido apropiadamente, tal como **2,** en condiciones de Suzuki convencionales. Los grupos protectores pueden retirarse con HCl, y el grupo nitro en **4** puede reducirse en condiciones de hidrogenación catalítica. La penúltima diamina puede acoplarse con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como BOP, para dar los compuestos con la estructura central diana.

Esquema K-1



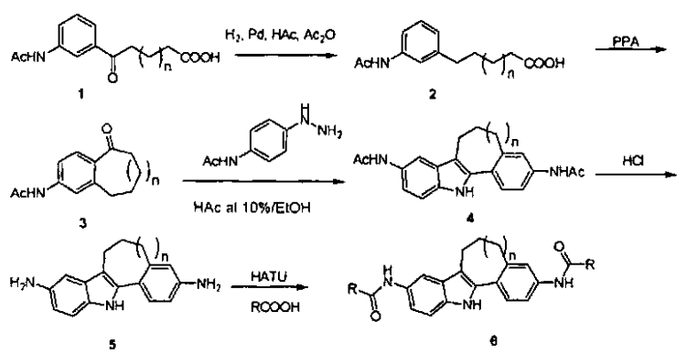
La síntesis de los compuestos con la estructura del núcleo indol K puede prepararse usando el protocolo de síntesis de indol de Fisher convencional partiendo de una aril hidrazina y una cetona, tal como **2.** La conversión del bromuro de arilo en la aril amina **4** puede realizarse mediante la reacción catalizada con Pd con LHMDS. El grupo nitro puede reducirse y la diamina puede acoplarse con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU, para dar los compuestos con la estructura diana.

Esquema K-2



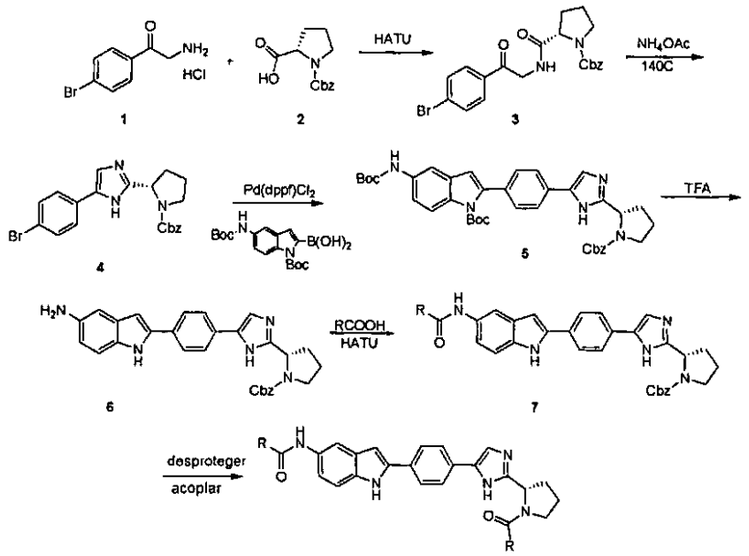
En un procedimiento alternativa, los indoles K pueden prepararse partiendo de un aminoindol protegido y sustituido adecuadamente **3**. La litiación y la inactivación con un éster boronato proporcionan el intermedio clave **4**, que puede acoplarse a un haluro de arilo o heteroarilo sustituido apropiadamente para proporcionar los compuestos diana **5.** Los grupos Boc pueden retirarse con ácido, y la anilina resultante puede acoplarse con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU. El grupo nitro en **7** puede reducirse y acoplarse en una segunda reacción de acoplamiento de amida para dar los compuestos deseados.

Esquema L



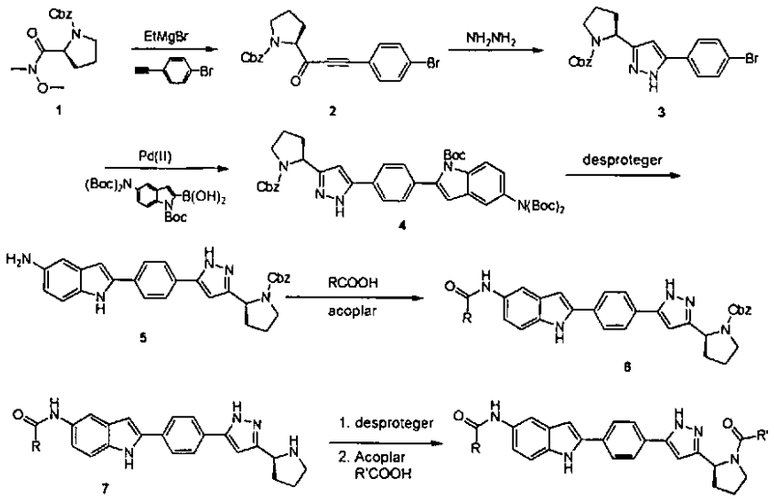
La estructura de indol tetracíclica L puede prepararse como se ha mostrado en el esquema anterior. La ciclación de un derivado de ácido carboxílico **2** con PPA puede proporcionar las cetonas **3,** que pueden participar en una reacción de indol de Fischer con una fenilhidrazina sustituida apropiadamente para dar **4.** Los grupos de acetamida pueden desprotegerse en condiciones ácidas y las aril aminas resultantes pueden acoplarse con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU, para dar los compuestos con la estructura diana.

Esquema M-1



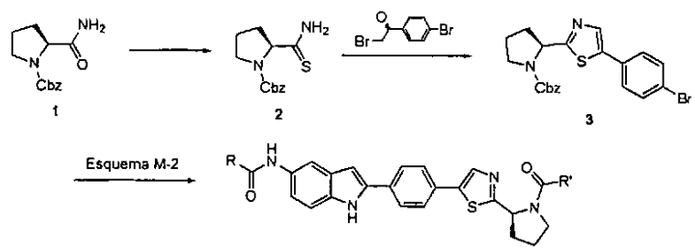
Los compuestos de estructura M-1 pueden prepararse acoplando la prolina **2** a la amino cetona **1** usando procedimientos de formación de enlace amida convencionales para proporcionar **3,** que puede ciclarse tras el calentamiento con acetato amónico a temperaturas elevadas. El intermedio **4** puede acoplarse a ácidos indol borónicos, tal como usando condiciones de tipo Suzuki convencionales. Los grupos Boc pueden retirarse con ácido, y la anilina resultante puede acoplarse con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU. El grupo protector de pirrolidina puede retirarse en condiciones de hidrogenación, y la amina resultante puede acoplarse en una segunda reacción de acoplamiento de amida para dar los compuestos deseados.

Esquema M-2



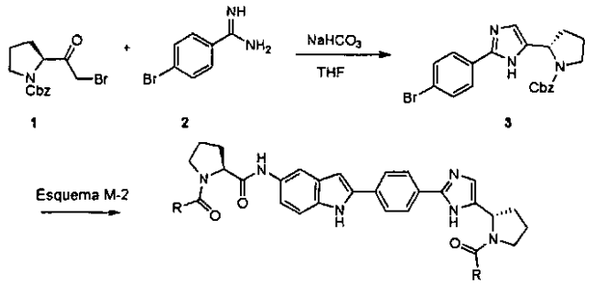
Los compuestos de estructura M-2 pueden prepararse haciendo reaccionar la prolina **1** con un anión de 4-etinilbenceno para dar el intermedio de cetona **2**, que puede ciclarse con hidrazina. El intermedio **3** puede acoplarse a ácidos indol borónicos, tal como usando condiciones de tipo Suzuki convencionales. Los grupos Boc pueden retirarse con ácido y la anilina resultante puede acoplarse con un ácido carboxílico sustituido apropiadamente, y un reactivo de formación de enlace amida, tal como HATU. El grupo protector de pirrolidina puede retirarse en condiciones de hidrogenación, y la amina resultante puede acoplarse en una segunda reacción de acoplamiento de amida para dar los compuestos deseados.

Esquema M-3



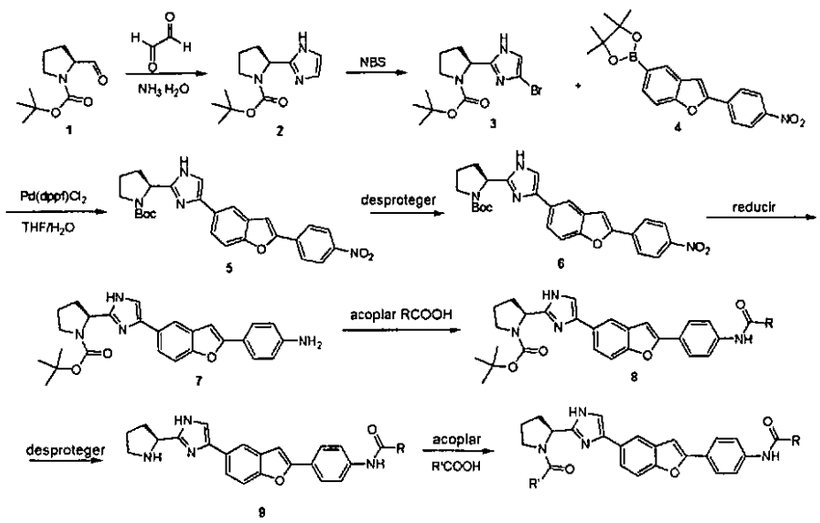
Los análogos de tiazol de la estructura M pueden prepararse a partir de la reacción de ciclocondensación de Z-prolina tioamida **2** con una alfa-bromoacetofenona. Los productos **3** pueden procesarse para dar los compuestos finales usando una metodología similar a la que se ha descrito en el esquema M-2.

Esquema M-4



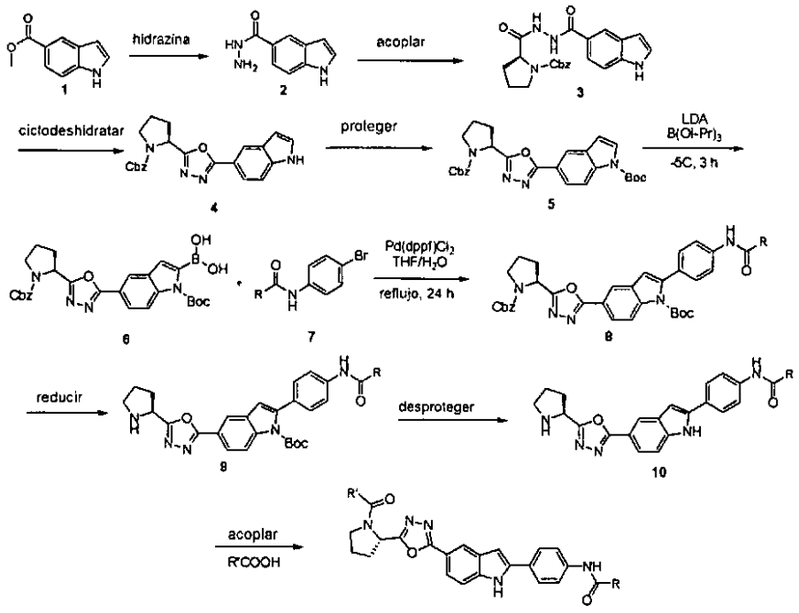
Los análogos de imidazol de la estructura M pueden prepararse a partir de la reacción de ciclocondensación de Z-prolina bromometil cetona **1** con un derivado de amidina aromática. Los productos **3** pueden procesarse para dar los compuestos finales usando una metodología similar a la que se ha descrito en el esquema M-2.

Esquema M-5



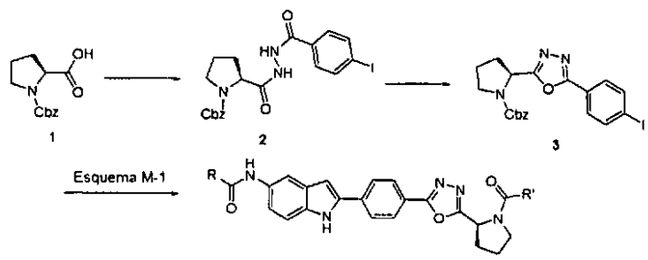
Los imidazoles isoméricos pueden prepararse partiendo de un aldehído aminoácido protegido, tal como **1,** y glioxal en presencia de amoniaco. La halogenación del imidazol **2** resultante con NBS puede seguirse de una reacción de acoplamiento cruzado catalizado por Pd con un éster boronato de indol funcionalizado, tal como **4.** La desprotección, reducción y acoplamiento con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU, pueden proporcionar los compuestos intermedios **8.** Un segundo procedimiento de desprotección/acoplamiento de amida puede proporcionar la estructura M-5 diana.

Esquema M-6



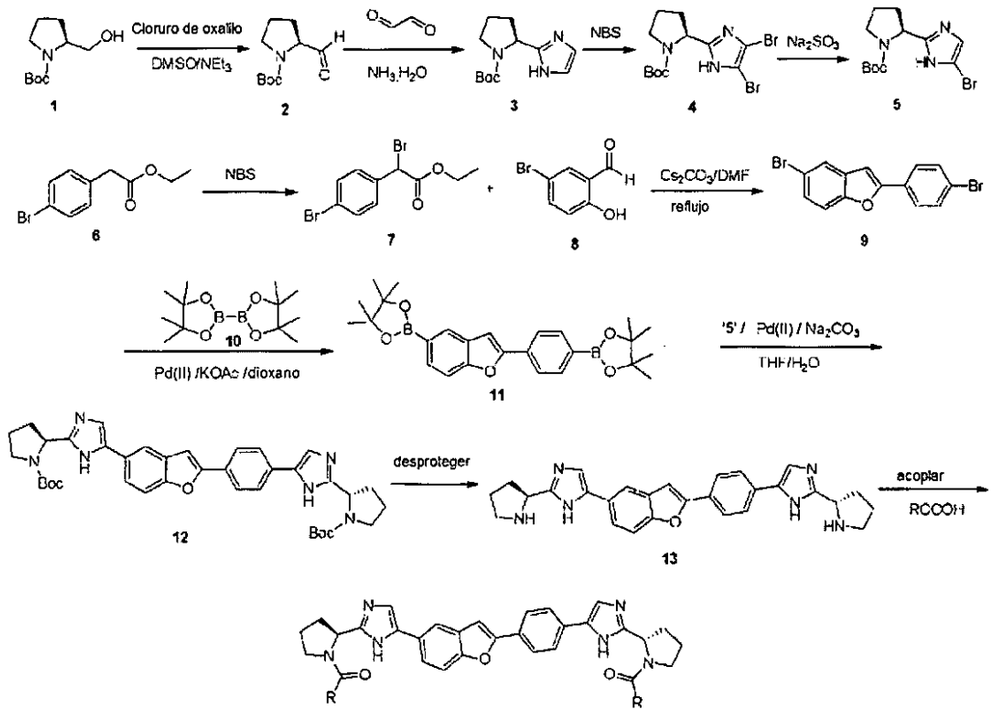
Los compuestos de oxadiazol pueden prepararse partiendo de indol hidrazida **2** y el acoplamiento a un aminoácido, tal como Z-prolina. La ciclodeshidratación del intermedio **3** puede realizarse con un reactivo, tal como TPP/yodo, para dar el oxadiazol deseado, que puede desprotegerse en el indol nitrógeno con Boc anhídrido. La introducción del grupo funcional de ácido borónico activa el compuesto **6** para el acoplamiento con un haluro de arilo sustituido **7** para dar el intermedio **8.** La retirada de los grupos cbz y Boc proporciona la penúltima estructura **10**, que puede acoplarse con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida para dar las estructuras diana M-6.

Esquema M-7



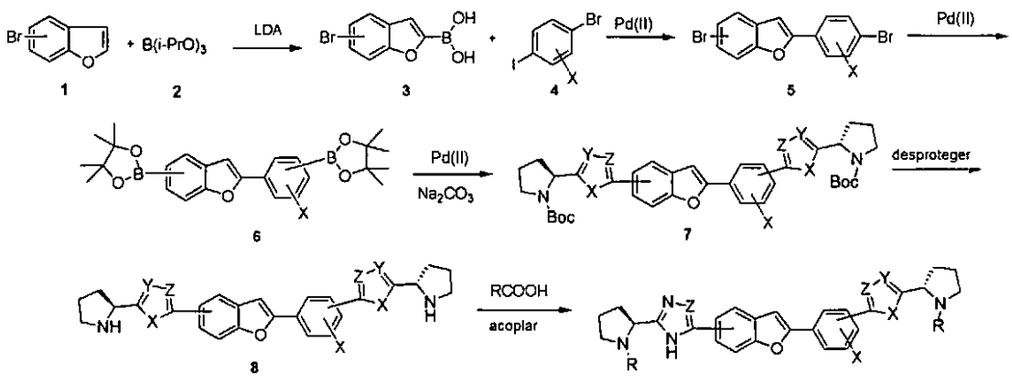
Los análogos de oxadiazol de la estructura M pueden prepararse mediante reacciones de ciclocondensación de las diacilhidrazinas **2**. El acoplamiento a ácidos borónicos heterocíclicos usando una metodología similar a la que se ha descrito en el esquema M-1 puede proporcionar los compuestos diana.

Esquema M-8



Los compuestos de benzofurano que contienen doble imidazol pueden prepararse partiendo de un aldehído de aminoácido protegido, tal como **2,** y glioxal en presencia de amoniaco. La halogenación del imidazol resultante **3** con NBS puede proporcionar por último el intermedio **5,** que puede acoplarse a un éster boronato funcionalizado, tal como **11,** para proporcionar **12.** La desprotección y el acoplamiento con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU, pueden proporcionar la estructura M-8 diana.

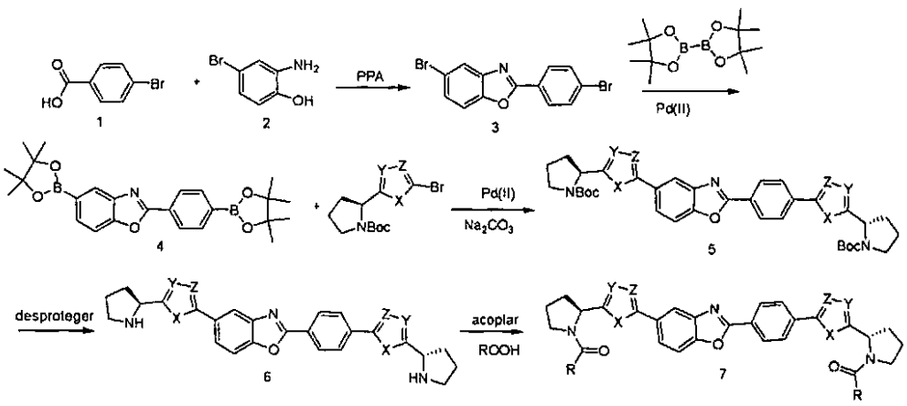
Esquema M-9



Una síntesis alternativa de benzofuranos puede realizarse partiendo del benzofurano **1,** que puede convertirse en el éster boronato **2,** que después puede acoplarse a un haluro de arilo sustituido apropiadamente para proporcionar **5.** El intermedio **5** puede convertirse posteriormente

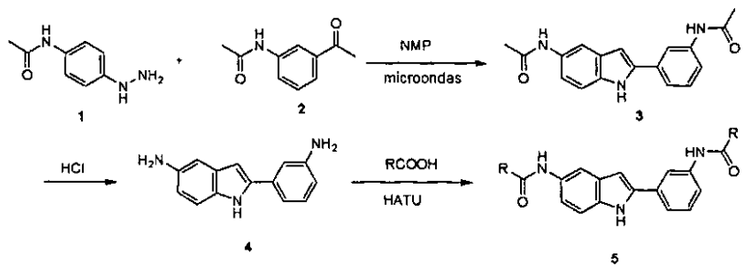
en un éster boronato funcionalizado y convertirse en los productos finales de una manera similar a la que se ha descrito en el Esquema M-8.

Esquema M-10



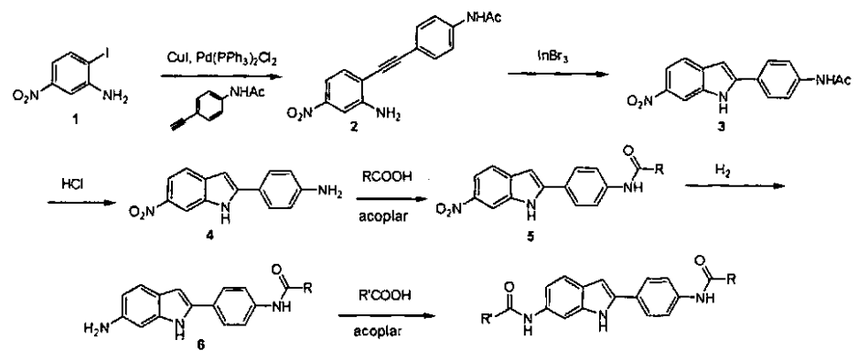
Los benzoxazoles **3** pueden prepararse partiendo de un ácido benzoico sustituido adecuadamente y un aminofenol, tal como **2**, en presencia de ácido polifosfórico. Dichos productos pueden convertirse en los ésteres boronato correspondientes usando procedimientos convencionales. Los intermedios 4 pueden acoplarse posteriormente en un haluro heterocíclico en presencia de un catalizador de Pd (II) para proporcionar los compuestos **5.** La desprotección y el acoplamiento con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU, pueden proporcionar la estructura M-10 diana.

Esquema N-1



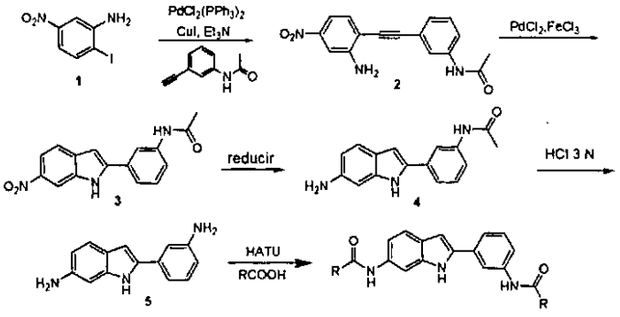
Los compuestos en el esquema N-1 pueden prepararse calentando las hidrazinas **1** con las cetonas **2** en un reactor de microondas en un disolvente aprótico polar, tal como NMP. Las indol acetamidas **3** pueden desprotegerse con ácido fuerte, tal como HCl. Las aril aminas resultantes pueden acoplarse con un ácido carboxílico sustituido apropiadamente, y un reactivo de formación de enlace amida, tal como HATU, para dar los compuestos de la estructura diana.

Esquema N-2



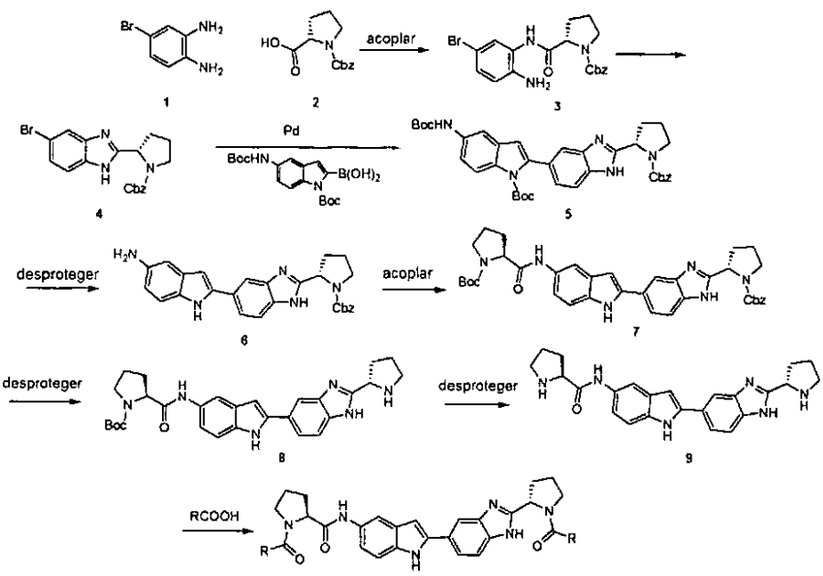
Las yodo anilinas **1** pueden acoplarse a un alquino sustituido de forma terminal usando procedimientos de acoplamiento de Sonagashira convencionales para dar los intermedios **2**, que pueden experimentar ciclación usando un reactivo, tal como bromuro de indio, para proporcionar los compuestos de indol **3**. Los grupos protectores pueden retirarse con un ácido fuerte, tal como HCl acuoso, y la amina resultante puede acilarse usando un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU. Después, los compuestos **5** pueden reducirse usando hidrógeno y un catalizador y después acoplarse una segunda vez con un ácido carboxílico y HATU para proporcionar los compuestos deseados.

Esquema N-3



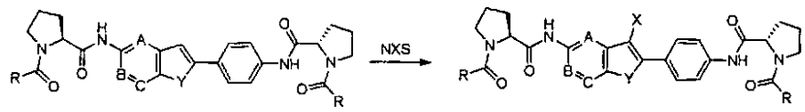
En una ligera variación del esquema N-2, las yodo anilinas **1** pueden acoplarse a un alquino sustituido de forma terminal usando procedimientos de acoplamiento de Sonagashira convencionales para dar los intermedios **2**, que pueden experimentar ciclación usando un reactivo, tal como cloruro de paladio/cloruro férrico para proporcionar los compuestos indol **3.** Después, los compuestos **3** pueden reducirse usando H_2, y el grupo protector puede retirarse con un ácido fuerte, tal como HCl acuoso, y las aminas resultantes pueden acilarse usando un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU.

Esquema O



La estructura O puede prepararse haciendo reaccionar un compuesto de prolina protegida (tal como Cbz) con un análogo de fenilenodiamina y un reactivo de formación de enlace amida, tal como HATU, para dar las amidas **3**, que pueden ciclodeshidratarse mediante calentamiento con un reactivo, tal como HOAc. El bencimidazol resultante puede acoplarse a un derivado de ácido indol borónico usando condiciones de Suzuki convencionales para proporcionar **5**. La retirada de los grupos Boc con ácido proporciona 7, que puede acilarse usando un ácido carboxílico sustituido apropiadamente, tal como Boc-L-prolina, y un reactivo de formación de enlace amida, tal como HATU, para dar los intermedios **7**. El grupo Cbz puede reducirse en condiciones de hidrogenación catalítica, y el grupo Boc puede desprotegerse con ácido para proporcionar los penúltimos compuestos **9**. La formación del enlace amida entre **9** y los ácidos carboxílico proporciona los compuestos diana.

Esquema P-1



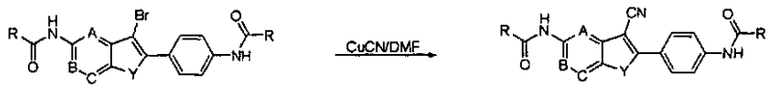
Los heterociclos pueden halogenarse en C-3 por la acción de agentes electrófilos, tales como N-halosuccinimidas, para proporcionar las diana P-1.

Esquema P-2



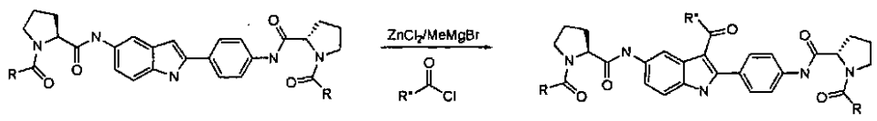
Los heterociclos pueden fluorarse en C-3 por la acción de agentes de fluoración electrófilos, tales como SELECTFLUOR, para proporcionar las dianas P-1.

Esquema P-3



Los compuestos halogenados C-3 pueden convertirse en los análogos ciano correspondientes mediante agentes de cianación, tales como CuCN.

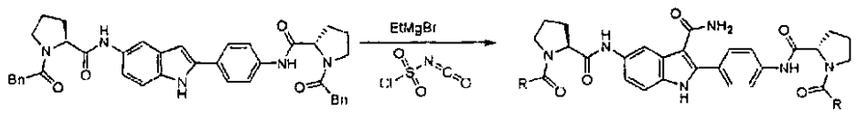
Esquema P-4



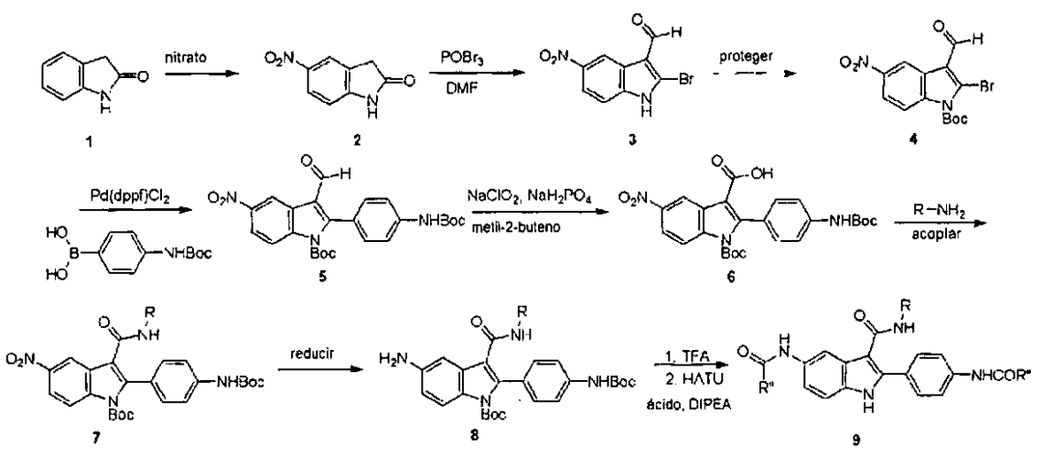
Los compuestos en el esquema P-4 pueden funcionalizarse mediante los indoles de acilación con reactivos de Grignard y cloruro de cinc.

Esquema P-5

R = H



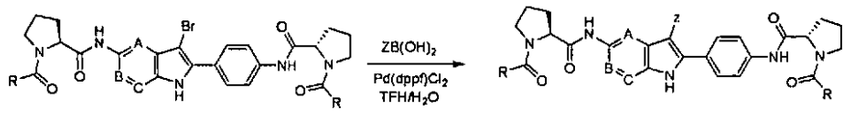
R > H



Los compuestos en el esquema P-5 pueden funcionalizarse desprotonando los indoles con una base, tal como bromuro de etilmagnesio y tratando el intermedio resultante con isocianato de clorosulfonilo. Como alternativa, los indoles **3** pueden prepararse usando condiciones de Vilsmeier-Haack, que pueden protegerse posteriormente y acoplarse en condiciones de Suzuki para dar los intermedios **5.** Los aldehídos pueden oxidarse usando la metodología convencional para la formación de ácido carboxílico. Los ácidos indol carboxílicos **6** pueden acoplarse a aminas usando un reactivo, tal como HATU, para dar **7**, que puede funcionalizarse adicionalmente por reducción

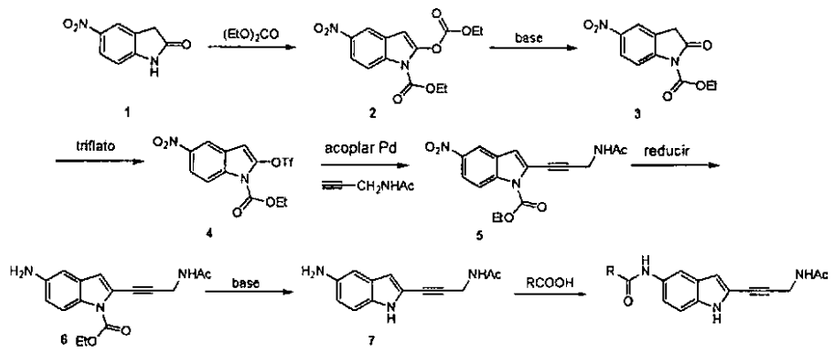
del grupo nitro, desprotección del grupo Boc y acoplamiento de las anilinas a un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU.

Esquema P-6



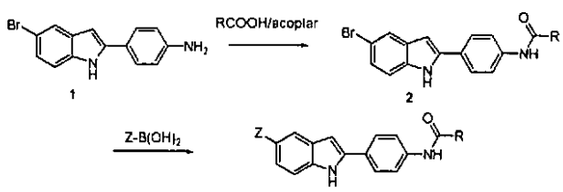
Los compuestos halogenados C-3 pueden acoplarse a una diversidad de ácidos alquil y aril borónicos usando condiciones de Suzuki convencionales.

Esquema Q



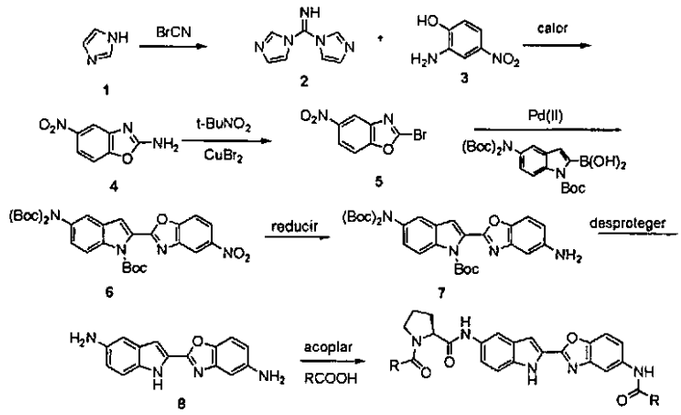
Los compuestos del esquema Q pueden prepararse partiendo de la lactama **1.** La reacción con cloroformiato de etilo y el tratamiento del producto con una base moderada, tal como carbonato de amonio, proporciona el intermedio **3**, que puede activarse para acoplarse por conversión al triflato de vinilo correspondiente **4**. El acoplamiento de Sonagashira proporciona los compuestos **5**, que pueden reducirse con hierro y cloruro de amonio para proporcionar la anilina **6.** La desprotección del indol y el acoplamiento de la anilina a un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU, proporciona las dianas deseadas.

Esquema R



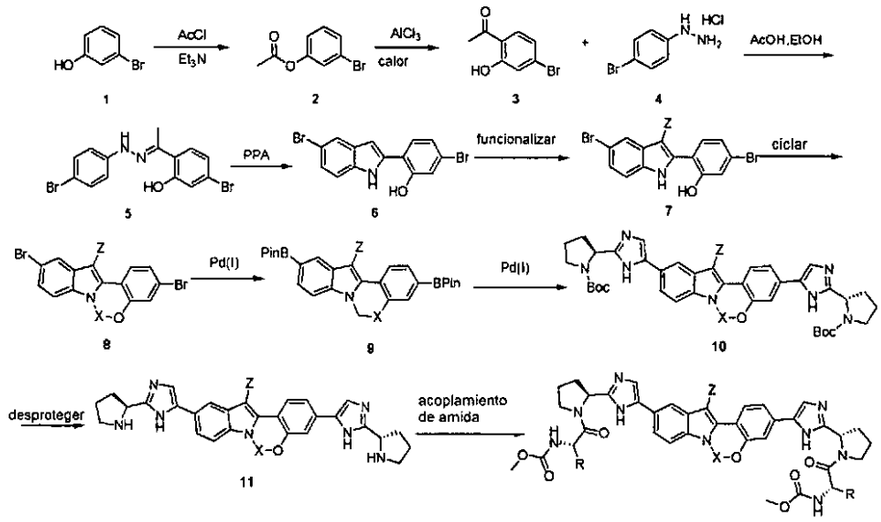
El acoplamiento de amida de la anilina del esquema K-1 con un ácido carboxílico sustituido apropiadamente y un agente de acoplamiento puede proporcionar los intermedios **2**, que después pueden someterse a reacciones de acoplamiento cruzado catalizado por Pd para proporcionar las dianas finales R.

Esquema S



Los compuestos del esquema S pueden prepararse acoplando ácidos indol borónicos con 2-bromobenzoxazoles sustituidos apropiadamente, tales como **5,** en condiciones de Suzuki convencionales. El grupo nitro en **6** puede reducirse en condiciones de hidrogenación catalítica y los grupos protectores pueden retirarse con HCl. La penúltima diamina puede acoplarse con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como BOP, reactivo para dar compuestos con la estructura central diana.

Esquema T



Los compuestos del esquema T pueden prepararse partiendo de un fenol sustituido adecuadamente **3** y un reactivo de hidrazina, tal como **4,** usando las condiciones de indol de Fisher establecidas. Después, la posición del indol 3 puede funcionalizarse o el indol NH puede ciclarse en el anillo aromático C-2 usando condiciones convencionales para dar tetraciclos **8**, que pueden convertirse posteriormente en los ésteres boronato correspondientes usando procedimientos convencionales. Después, los intermedios **9** pueden acoplarse a un haluro heterocíclico en presencia de un catalizador de Pd (II) para proporcionar los compuestos **10**. La desprotección y el

acoplamiento con un ácido carboxílico sustituido apropiadamente y un reactivo de formación de enlace amida, tal como HATU, pueden proporcionar la estructura T diana.

Los siguientes ejemplos únicamente sirven para ilustrar la invención y su práctica. Los ejemplos no se interpretan como limitaciones del alcance o espíritu de la invención.

Lista de Abreviaturas

Ac_2O	Anhídrido acético
$B(OiPr)_3$, $(iPrO)_3B$	Borato de tri*iso*propilo
$B(OMe)_3$	Borato de trimetilo
BF_3	Trifluoruro de boro
BOC, Boc, boc	*terc*-Butiloxicarbonilo
BOP	Hexafluorofosfato de benzotriazol-1-il-oxi-tris-(dimetilamino)-fosfonio
BrCN	Bromuro de cianogeno
BuLi, n-BuLi	Butil litio
CBZ, Cbz, cbz	Benciloxicarbonilo
$CDCl_3$	Deuterio-triclorometano
CH_3CN, MeCN	Acetonitrilo
Cs_2CO_3	Carbonato de cesio
$CuBr_2$	Bromuro de cobre (II)
CuCN	Cianuro de cobre (I)
CuI	Yoduro de cobre
DBU	1,8-Diazabiciclo[5.4.0]undec-7-eno
DCE	Dicloroetano
DCM, CH_2Cl_2	Diclorometano
DIPEA, DIEA	Diisopropiletilamina
DMAP	4-Dimetilamino piridina
DMF	Dimetilformamida
DMSO	Dimetilsulfóxido
DPPF, Dppf, dppf	1,1'-bis(Difenilfosfino)ferroceno
EDC, EDCI	V-(3-Dimetilaminopropil)-V'-etilcarbodiimida
Et_2O	Éter dietílico
Et_3N, TEA	Trietilamina
EtMgBr	Bromo(etil)magnesio o bromuro de etil magnesio
EtOAc	Acetato de etilo
EtOH	Etanol
$FeCl_3$	Cloruro férrico o cloruro de hierro (III)

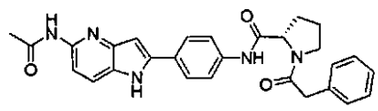
H_2	Hidrógeno o atmósfera de hidrógeno
H_2O	Agua
H_2SO_4	Ácido sulfúrico
HATU	Hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio
HBr	Ácido bromhídrico
HCl	Ácido clorhídrico
HNO_3	Ácido nítrico
HOAc, HAc	Ácido acético
HOBT, HOBt	1-Hidroxi benzotriazol
HPLC	Cromatografía líquida de alta resolución
$InBr_3$	Tribromuro de indio
iPr_2NH	Di*iso*propilamina
K_2CO_3	Carbonato potásico
KI	Yoduro potásico
KIO_3	Yodato potásico
KOAc, AcOK	Acetato potásico
KOH	Hidróxido potásico
LDA	Diisopropilamida de litio
LHMDS, LiHMDS	Hexametildisilamida de litio
MeMgBr	Bromo(metil)magnesio o bromuro de metil magnesio
MeOD	Metan(^{2}H)ol
MeOH, CH_3OH	Metanol
$MgSO_4$	Sulfato de magnesio
MOC, Moc	Metoxi carbonilo
MS	Espectroscopía de masas
N_2	Nitrógeno o atmósfera de nitrógeno
Na_2CO_3	Carbonato sódico
Na_2SO_4	Sulfato sódico (anhidro)
$NaClO_2$	Perclorato sódico
NH_2PO_4	Dihidrógeno fosfato sódico
$NaHCO_3$	hidrógeno carbonato sódico (bicarbonato sódico)
$NaNO_2$	Nitrito sódico
NaOH	Hidróxido sódico
NBS	N-bromosuccinimida
NCS	N-clorosuccinimida

NH_4OAc	Acetato de amonio
NMM	*V*-metilmorfolina
RMN, ^1H RMN	Espectroscopía de resonancia magnética nuclear de protones
NXS	N-halosuccinimida
P_2O_5, P_4O_{10}	Pentóxido de fósforo
Pd	Paladio
$Pd(dppf)Cl_2$	Dicloro(1,1'-bis(Difenilfosfino)ferroceno) paladio (II)
Pd(II)	Paladio (II)
$Pd(PPh_3)_2Cl_2$, $PdCl_2(PPh_3)_2$	Diclorobis(trifenilfosfina)paladio (II)
$Pd(PPh_3)_4$	*Tetraquis*(trifenilfosfina)paladio (0)
Pd/C, Pd-C	Paladio sobre carbono
$Pd_2(dba)_3$	Tris(dibencilideno acetona)dipaladio (0)
$PdCl_2$	Cloruro de paladio (II)
PE	Éter de petróleo
Phg	Fenilglicina
$PhCH_3$, PhMe	Tolueno
Piv	Pivaloílo
PivCl	Cloruro de pivaloílo
$POBr_3$	Oxibromuro de fósforo
PPA	Ácido polifosfórico
PPH_3, TPP	Trifenilfosfina
Pro	Prolina
Proc	Carbamato de iso-propilo
P^tBu_3	Tri-terc-butil fosfina
Py	Piridina
PyBOP	Hexafluorofosfato de (benzotriazol-1-il-oxi)-tripirrolidinofosfonio
RPLC	Cromatografía líquida de fase inversa
TA, ta, t.a.	Temperatura ambiente, aproximadamente 25 °C
SiO_2	Sílice o gel de sílice
$SnCl_2$	Cloruro estannoso o cloruro de estaño (II)
$SOCl_2$	Cloruro de tionilo
STP	Temperatura y presión convencionales
t-BuLi	*terc*-Butil litio
t-$BuNO_2$	Nitrato de *terc*-butilo
t-BuOH	*terc*-Butanol

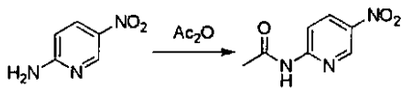
t-BuOK, KOt-Bu	*terc*-butóxido potásico
TFA	ácido trifluoroacético
TFAA	Trifluoroanhídrido acético
THF	Tetrahidrofurano
TLC	Cromatografía de capa fina
$ZnCl_2$	Cloruro de cinc

EJEMPLOS

Ejemplo 1-N-{4-[5-(acetilamino)-1H-pirrolo[3,2-b]piridin-2-il]fenil}-1-(fenilacetil)-L-prolinamida

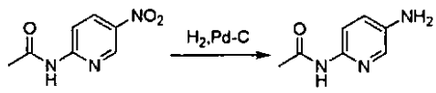


Etapa 1



A una suspensión de 2-amino-5-nitropiridina (25,0 g, 0,18 mol) y 0,5 g de DMAP en 200 ml de piridina, se le añadió gota a gota Ac_2O (37 g, 0,36 mol) a 0 °C. La mezcla se agitó a TA durante 5 horas. El producto volátil se retiró al vacío. El residuo se lavó con EtOAc para producir un sólido de color blanquecino (28 g, 86%). MS (ESI) m/e ($M+H^+$): 182.

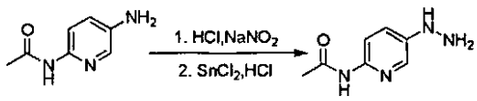
Etapa 2



Una mezcla heterogénea de 2-acetamido-5-nitropiridina (28 g, 0,15 mol) y Pd al 10%/C (2,8 g) en 300 ml de MeOH se agitó a 344,74 kPa (50 psi) de H_2 durante 6 horas. La mezcla se filtró a través de CELITE, y se concentró al vacío para producir un sólido (20,5 g).

MS (ESI) m/e ($M+H^+$): 152.

Etapa 3

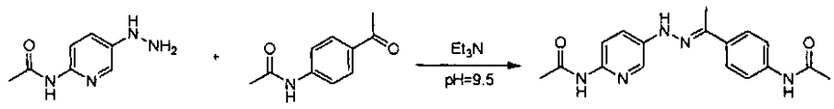


Se añadió lentamente $NaNO_2$ (5,4 g, 78,2 mmol) a una solución de 2-acetamido-5-aminopiridina (9,0 g, 60 mmol) en HCl acuoso 6 M (300 ml) a 0 °C y se agitó durante 45 minutos.

160

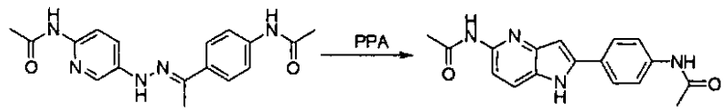
Se añadió una solución de $SnCl_2$ (40,5 g, 180 mmol) en 15 ml de HCl acuoso 6 M y la mezcla de reacción se dejó calentar a TA lentamente mientras se agitaba durante 16 horas. La mezcla de reacción se basificó con KOH acuoso al 40 por ciento, se extrajo con EtOAc (3 x), las capas orgánicas se combinaron, se secaron sobre Na_2SO_4 y se concentraron al vacío para dar el compuesto deseado (3,2 g). MS (ESI) m/e ($M+H^+$): 167.

Etapa 4



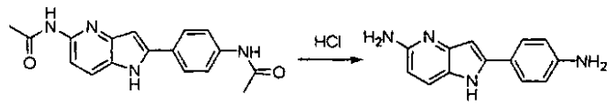
Una suspensión del producto de la etapa 3 (3,32 g, 20 mmol) y *N*-(4-acetilfenil)acetamida (3,54 g, 20 mmol) en 8 ml de EtOH se diluyó con TEA para ajustar el pH a aproximadamente 9,5. La mezcla de reacción resultante se calentó a reflujo durante 3 horas. El disolvente se retiró al vacío y el residuo resultante se trató con ácido cítrico acuoso al 5% para formar un precipitado. El precipitado se filtró, se lavó con agua y se secó al vacío (3,2 g). MS (ESI) m/e ($M+H^+$): 326.

Etapa 5



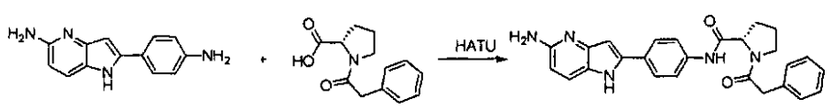
Una mezcla del producto de la etapa 4 anterior (0,6 g, 1,8 mmol) y PPA (5 ml) se calentó a 90 °C durante 75 minutos en una atmósfera de N_2. Después de enfriar a TA, la mezcla de reacción se vertió en hielo-agua, se neutralizó con NaOH sólido, mientras se mantenía la temperatura de la mezcla a o por debajo de la TA. Se añadió una solución de iso-propanol y DCM (1:3) para extraer el producto orgánico. La fase orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró al vacío. El residuo se purificó por HPLC preparativa para producir un sólido (280 mg). MS (ESI) m/e ($M+H^+$): 309.

Etapa 6



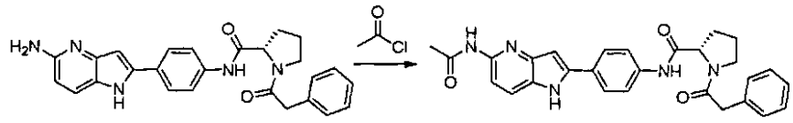
Una mezcla del 4-azaindol (280 mg, 0, 9 mmol) en 10 ml de HCl 3 N se calentó a reflujo durante 2 horas. El disolvente se retiró al vacío. El residuo se purificó por HPLC para producir un sólido (120 mg). MS (ESI) m/e ($M+H^+$): 225.

Etapa 7



A una suspensión del producto de la etapa 6 (23 mg, 0,1 mmol), ácido (23 mg, 0,1 mmol) y DIPEA (20 mg, 0,15 mmol) en 1 ml de CH_3CN se le añadió HATU (42 mg, 0,12 mmol). La mezcla resultante se agitó a TA durante una noche. Después de que la reacción se completara, la mezcla se purificó por HPLC prep. (10 mg). MS (ESI) m/e ($M+H^+$): 440.

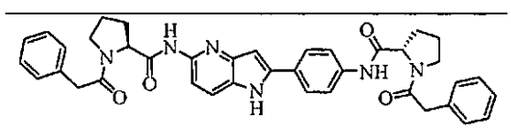
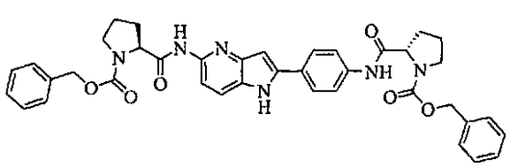
Etapa 8



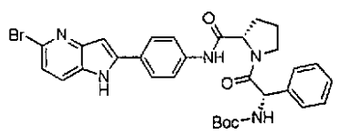
Una mezcla de producto de la etapa 7 (10 mg, 0,023 mmol) y TEA (3 g, 0,03 mmol) en CH_3CN (100 ml) se agitó a 0 °C. Se añadió gota a gota cloruro de acetilo (2 mg, 0,023 mmol) y la mezcla resultante se agitó a TA durante 0,5 horas. El disolvente se evaporó al vacío y el residuo se purificó por HPLC preparativa para proporcionar el producto deseado (5 mg). MS (ESI) m/e ($M+H^+$): 482. ^1H RMN (MeOD): □ 8,25 (d, J = 8,4 Hz, 1H), 7,74~7,89 (m, 4H), 7,26~7,32 (m, 5H), 7,00~7,02 (m, 2H), 4,63~4,64 (m, 1H), 3,72~3,84 (m, 4H), 2,18~2,33 (m, 2H), 2,07~2,10 (m, 5H).

Ejemplos 2-3

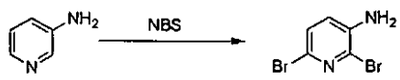
Los compuestos de los Ejemplos 2 y 3 se prepararon de una manera similar partiendo del intermedio 7 en la etapa 6.

Ejemplo	Estructura	PM	Nombre
2		654,776	(2S)-1-(fenilacetil)-*N*-{2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-pirrolo[3,2-b]piridin-5-il}pirrolidin-2-carboxamida
3		686,774	(2S)-2-[(2-{4-[({(2S)-1-[(benciloxi)carbonil]pirrolidin-2-il}carbonil)amino]fenil}-1H-pirrolo[3,2-b]piridin-5-il)carbamoil]pirrolidin-1-carboxilato de bencilo

Ejemplo 4-{(1S)-2-[(2S)-2-{[4-(5-bromo-1H-pirrolo[3,2-b]piridin-2-il)fenil]carbamoil}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

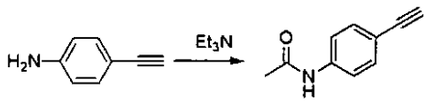


Etapa 1



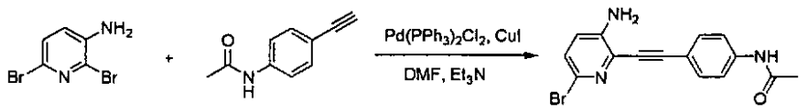
Se añadió en porciones NBS (14,9 g, 84 mmol) a una solución del compuesto 3-aminopiridina (14,9 g, 84 mmol) en DMSO (80 ml) y agua (20 ml) a 0 °C y la reacción se agitó a TA durante 3 horas. La mezcla se vertió en hielo-agua (250 ml) y se agitó durante 30 minutos. El precipitado se recogió y se secó para producir un sólido (7,0 g). MS (ESI) m/e ($M+H^+$): 250. ^1H RMN (DMSO): □ 7,28 (d, J = 7,6 Hz, 1H), 7,03 (d, J = 7,6 Hz, 1H), 5,69 (s, 2H).

Etapa 2



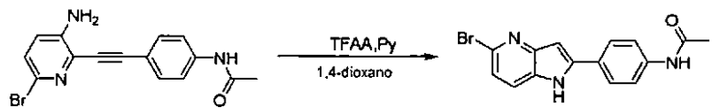
Se preparó 4-etinilacetanilida usando el procedimiento similar mostrado en el Ejemplo 1, etapa 1. MS (ESI) m/e ($M+H^+$): 160.

Etapa 3



A una solución de 3-amino-2,6-dibromopiridina (9,41 g, 37,5 mmol), 4-etinilacetanilida (4,77 g, 30 mmol) y $Pd(PPh_3)_2Cl_2$ (1,31 g, 1,9 mmol) en una mezcla de 150 ml de Et_3N y 50 ml de DMF se le añadió CuI (0,71 g, 0,4 mmol) en una atmósfera de N_2. La mezcla resultante se agitó a TA durante una noche. El disolvente se retiró y el residuo se purificó por cromatografía (8,5 g). MS (ESI) m/e ($M+H^+$): 331. ^1H RMN (DMSO): □ 7,59 (d, J = 8,8 Hz, 2H), 7,54 (d, J = 8,4 Hz, 2H), 7,21 (d, J = 8,8 Hz, 2H), 7,07 (d, J = 8,4 Hz, 2H), 2,12 (s, 3H).

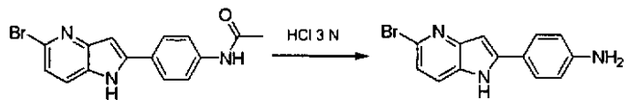
Etapa 4



A una solución a 0 °C del producto de la etapa 3 (8,5 g, 25,7 mmol) y piridina (4,0 g, 51,4 mmol) en 50 ml de 1,4-dioxano se le añadió TFAA (10,8 g, 51,4 mmol). Después, la mezcla resultante se calentó a 100 °C durante una noche. La mezcla se enfrió, se vertió en 200 ml de agua,

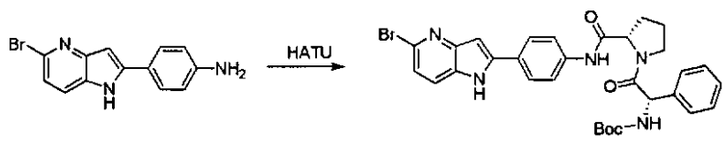
el precipitado se filtró, se lavó con agua y después se secó para dar un sólido (1,3 g). MS (ESI) m/e ($M+H^+$): 331.

Etapa 5



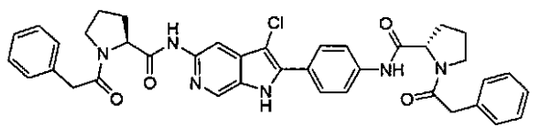
La reacción se realizó de forma similar a la que se ha descrito en el Ejemplo 1, etapa 6. MS (ESI) m/e ($M+H^+$): 288.

Etapa 6

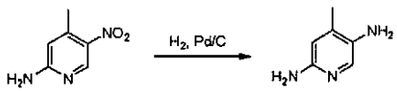


A una suspensión del producto de la etapa 5 (0,1 mmol), N-Boc-L-Phg-L-Pro-OH (0,1 mmol) y DIPEA (20 mg, 0,15 mmol) en 1 ml de CH_3CN se le añadió HATU (42 mg, 0,12 mmol). La mezcla resultante se agitó a TA durante una noche, se concentró y se purificó por RPLC para dar el compuesto deseado. MS (ESI) m/e ($M+H^+$): 619. ^1H RMN (MeOD 400) □: 7,85~7,77 (m, 5 H), 7,43~7,36 (m, 6 H), 6,89 (s, 1 H), 5,50 (s, 1H), 4,54 (d, J = 8,0 Hz 1H), 3,93(t, 1 H), 2,10~1,87 (m, 4 H) 1,41 (s, 9 H).

Ejemplo 5-(2S)-N-{3-cloro-2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-pirrolo[2,3-c]piridin-5-il}-1-(fenilacetil)pirrolidin-2-carboxamida

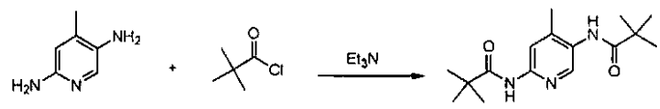


Etapa 1



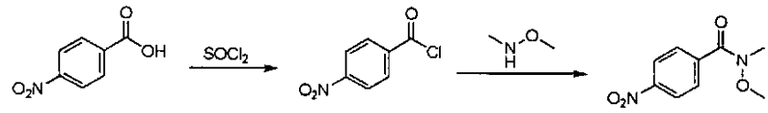
Una mezcla heterogénea de 2-amino-4-metil-5-nitropiridina (4,15 g, 27 mmol) y Pd al 10%/C (0,4 g) en 50 ml de THF se agitó en 344,74 kPa (50 psi) de H_2 durante 3 horas. La mezcla se filtró a través de CELITE y se concentró para producir un sólido de color amarillo (3,20 g). MS (ESI) m/e ($M+H^+$): 124. ^1H RMN (DMSO): □ 7,38 (s, 1 H), 6,16 (s, 1 H), 4,84 (s, 2 H), 4,06 (s, 2 H), 1,96 (s, 3 H).

Etapa 2



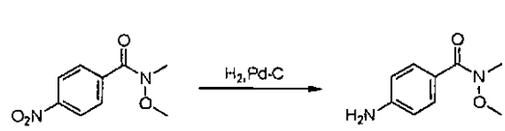
Una mezcla de diamina de la etapa 1 (3,20 g, 26 mmol), TEA (5,25 g, 52 mmol) y una cantidad catalítica de DMAP en THF (100 ml) se agitó a 5-10 °C, después se trató con cloruro de pivaloílo (3,74 g, 31 mmol). La mezcla resultante se agitó a TA durante 5 horas, se diluyó con una solución al 5% de ácido cítrico y se extrajo con EtOAc. Los extractos orgánicos combinados se lavaron secuencialmente con agua y salmuera, se secaron, se filtraron y el filtrado se concentró al vacío para producir un residuo. El residuo se purificó por cromatografía en columna sobre gel de sílice para proporcionar 7,4 g del compuesto deseado. MS (ESI) m/e ($M+H^+$): 292. ^{1}H RMN ($CDCl_3$): □ 8,77 (s, 1 H), 8,47 (s, 1 H), 8,20 (s, 1 H), 7,15 (s, 1 H), 2,24 (s, 3 H), 1,30~1,32 (m, 18 H).

Etapa 3



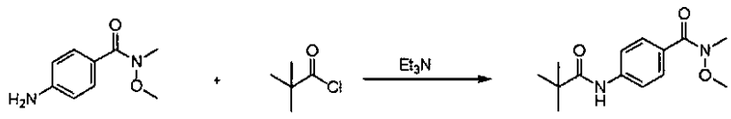
A una solución enfriada de ácido 4-nitrobenzoico (12 g, 72 mmol) en 50 ml de PhMe se le añadieron gota a gota 20 ml de $SOCl_2$. Después de la adición, la suspensión se calentó a reflujo durante 4 horas. El disolvente se retiró y el residuo se destiló azeotrópicamente con 50 ml de PhMe para proporcionar 14,5 g de cloruro de ácido en bruto. A una solución de TEA (101 g, 100 mmol), una cantidad catalítica de DMAP y *N,O*-dimetilhidroxilamina (5,3 g, 87 mmol) en 100 ml de DCM se le añadieron gota a gota 14,5 g del cloruro de ácido recién preparado en 100 ml de DCM. La mezcla resultante se agitó a TA durante 5 horas, después se diluyó con una solución del 5% de ácido cítrico y se extrajo con DCM. Los extractos orgánicos combinados se lavaron secuencialmente con agua y salmuera, se secaron, se filtraron y el filtrado se concentró para producir un residuo. El residuo se purificó por cromatografía en columna sobre gel de sílice para proporcionar 7,0 g de la amida Weinreb. MS (ESI) m/e ($M+H^+$): 211. ^{1}H RMN ($CDCl_3$): □ 8,25 (d, J = *8,8* Hz, 2 H), 7,82 (d, J = *9,6* Hz, 2 H), 3,52 (s, 3 H), 3,82 (s, 3 H).

Etapa 4



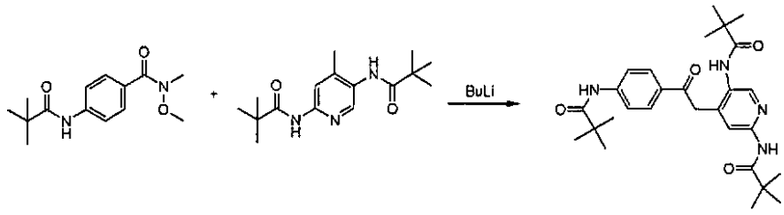
Una mezcla heterogénea del compuesto nitro anterior y Pd al 10%/C en THF se agitó a STP con un globo de H_2 durante 3 horas. La mezcla se filtró a través de CELITE y se concentró para producir un sólido de color amarillo MS (ESI) m/e ($M+H^+$): 181.

Etapa 5



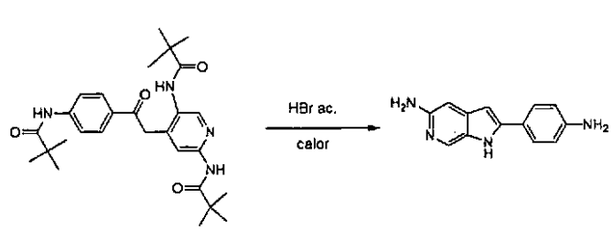
El producto de la etapa 4 se sometió a pivaloílo usando las condiciones que se han descrito en la etapa 2. MS (ESI) m/e ($M+H^+$): 265. ^1H RMN ($CDCl_3$): □ 7,66 (d, J = 8,4 Hz, 2 H), 7,56 (d, J = 8,8 Hz, 2 H), 3,51 (s, 3 H), 3,32 (s, 3 H).

Etapa 6



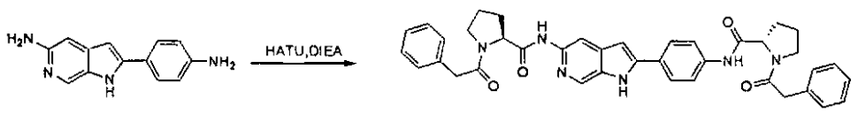
Una solución del compuesto aislado de la etapa 2 anterior (2,2 g, 7,5 mmol) en 15 ml de THF se enfrió por debajo de -40 °C. Se añadió gota a gota t-BuLi en hexano (15 ml, 2,5 M, 37,5 mmol) y la solución resultante se agitó a -40 °C durante 1 hora. Se añadió gota a gota una solución del compuesto de la etapa 5 (2,2 g, 8,25 mmol) en 10 ml de THF y la solución resultante se continuó agitando a esta temperatura durante 30 minutos antes de calentarse a TA y se agitó de nuevo durante 30 minutos. Se añadió una solución acuosa al 5% de ácido cítrico para interrumpir la reacción, que se extrajo con DCM (x 3), y las capas orgánicas combinadas se lavaron con agua y salmuera, se secaron sobre Na_2SO_4 y se concentraron al vacío. El residuo se purificó por HPLC preparativa para producir un sólido (0,4 g). MS (ESI) m/e ($M+H^+$): 495. ^1H RMN ($CDCl_3$): □ 8,85 (s, 1 H), 8,68 (s, 1 H), 8,26 (s, 1 H), 8,03~8,05 (m, 3 H), 7,21 (d, J = *8,8* Hz, 2 H), 7,53 (s, 1 H), 4,20 (s, 2 H), 1,33~1,29 (m, 27 H).

Etapa 7



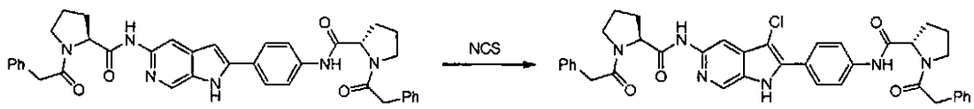
Una solución del producto de la etapa 6 (400 mg, 0,8 mmol) en HBr acuoso al 33% (15 ml) se calentó a reflujo durante una noche. Después de un periodo de refrigeración, la mezcla se concentró al vacío. El residuo se purificó por HPLC preparativa para dar un sólido (120 mg). MS (ESI) m/e ($M+H^+$): 225. ^1H RMN (MeOD): □ 8,04 (s, 1 H), 7,78 (d, 2 H), 7,04 (d, 2 H), 6,86 (s, 1 H), 6,71 (s, 1 H).

Etapa 8



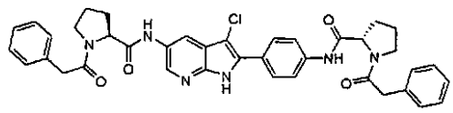
El producto de la etapa 7 se acopló a 2 equivalentes de *N*-fenilacetil-L-prolina usando 2 equivalentes de HATU y DIEA de una manera similar a la que se ha mostrado en el Ejemplo 1. MS (ESI) m/e ($M+H^+$): 687. ^{1}H RMN (MeOD): □ 8,49~8,57 (m, 1 H), 7,38~7,45 (m, 2 H), 7,72 ~7,80 (m, 2 H), 5,15~5,20 (m, 4 H), 4,42~4,50 (m, 2 H), 3,57~2,59 (m, 4 H), 2,31~2,42 (m, 4 H), 1,89~2,15 (m, 6 H).

Etapa 9

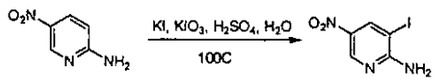


A una solución del producto de la etapa 8 (15 mg, 0,02 mmol) en 2 ml de THF seco se le añadió NCS (2 mg, 0,015 mmol). La mezcla resultante se agitó a TA durante 30 minutos. El disolvente se evaporó y el residuo se purificó por HPLC prep. para dar 5 mg del producto deseado. MS (ESI) m/e ($M+H^+$): 689. ^{1}H RMN (MeOD): □ 8,53 (s, 1 H), 7,91 (d, J = 9,2 Hz, 2 H), 7,77 (d, J = 8,8 Hz, 2 H), 7,49 (s, 1 H), 7,20~7,23 (m, 10 H), 4,53~4,59 (m, 2 H), 3,64~3,79 (m, 8 H), 1,98~2,25 (m, 8 H).

Ejemplo 6-(2S)-N-{3-cloro-2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-pirrolo[2,3-b]piridin-5-il}-1-(fenilacetil)pirrolidin-2-carboxamida



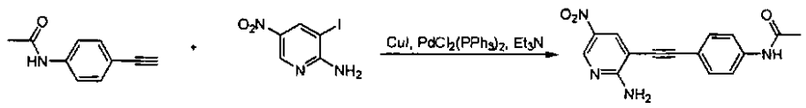
Etapa 1



Se disolvió 2-amino-5-nitropiridina (7,00 g, 50,0 mmol) en H_2SO_4 (2 M, 100 ml). Se añadió una porción de yodato potásico (4,28 g, 20 mmol) a TA con agitación. La solución se calentó a 100 °C a reflujo. Se añadió gota a gota yoduro potásico (8,00 g, 48,2 mmol) durante 1 hora en forma de una solución en agua (20 ml). Dio como resultado una solución de color pardo, con recolección de yodo sólido en el condensador de reflujo. El calentamiento a reflujo continuó durante 30 minutos y la mezcla se enfrió a TA. La mezcla se ajustó a pH 7 con la adición cuidadosa de $NaHCO_3$ sólido. La mezcla se diluyó con agua (200 ml) y se añadió CH_2Cl_2 (250 ml). Se añadió tiosulfato sódico sólido con agitación vigorosa hasta que la coloración del yodo desapareció. Una cantidad significante de sólido de color amarillento se extrajo de la solución, que se recogió por filtración, se lavó con agua y se secó para dar un sólido de color amarillo (10,5 g). La fracción de

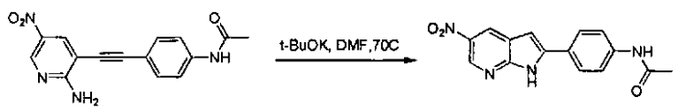
CH_2Cl_2 se filtró a través de un papel de filtro tratado con silicona y se evaporó para dar un sólido de color amarillo (2,4 g). Los sólidos se combinaron para dar la yodopiridina deseada (12,7 g). MS (ESI) m/e ($M+H^+$): 266. ^1H RMN (DMSO): □ 8,89 (s, 1 H), 8,62 (s, 1 H), 7,75 (s a, 1 H).

Etapa 2



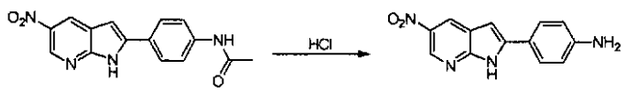
Una solución del yoduro (1,05 g, 4,8 mmol), 4-etinilacetanilida (636 mg, 4,0 mmol) y $Pd(PPh_3)_2Cl_2$ (76 mg, 0,4 mmol) en 10 ml de Et_3N y 5 ml de DMF se agitó a TA durante 17 horas en una atmósfera de N_2. El disolvente se retiró y el residuo se purificó por cromatografía en columna para dar el producto (0,9 g). MS (ESI) m/e ($M+H^+$): 297. ^1H RMN (DMSO): □ 10,11 (s, 1H), 8,80 (s, 1H), 8,22 (s, 1H), 7,59 (s, 1H), 2,01 (s, 3H).

Etapa 3



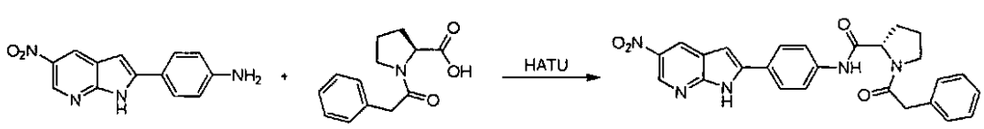
A una solución del producto de la etapa 2 (730 mg, 2,5 mmol) en 3 ml de THF y 6 ml de DMF se le añadió t-BuOK (580 mg, 5,25 mmol). La mezcla resultante se calentó a 70 °C durante 6 horas. El disolvente se retiró y se añadieron 10 ml de DCM, 5 ml de agua y el precipitado resultante se filtró para dar el producto deseado en forma de un sólido de color amarillo (680 mg). MS (ESI) m/e ($M+H^+$): 297. ^1H RMN (DMSO): □ 10,11 (s, 1 H), 8,96 (s, 1 H), 8,65 (s, 1 H), 7,88 (d, J = *8,8* Hz, 2 H), 7,63 (d, J = 8,8 Hz, 2 H), 6,98 (s, 1 H), 2,02 (s, 3 H).

Etapa 4



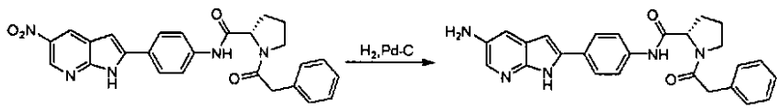
El procedimiento sintético para la retirada del grupo acetilo era el mismo que se usó en el Ejemplo 1, etapa 6. MS (ESI) m/e ($M+H^+$): 285.

Etapa 5



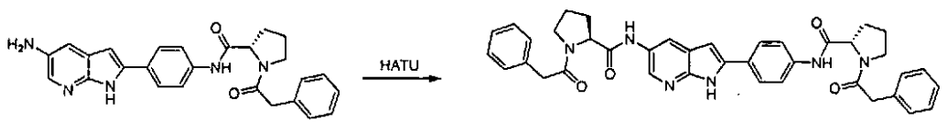
El procedimiento sintético usado para el acoplamiento del análogo de prolina a la anilina que se ha preparado en la etapa 4 era el mismo que se usó en el Ejemplo 1, etapa 7. MS (ESI) m/e ($M+H^+$): 470.

Etapa 6



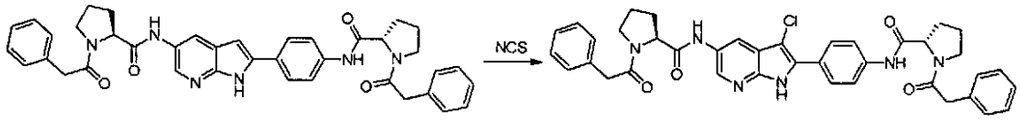
Una mezcla heterogénea del producto de la etapa 6 (20 mg, 0,04 mmol) y Pd al 10%/C en 5 ml de MeOH se agitó en 68,95 kPa (10 psi) de H_2 durante 3 horas. La mezcla se filtró a través de CELITE y se concentró al vacío para producir un sólido de color amarillo (17 g). MS (ESI) m/e $(M+H^+)$: 440.

Etapa 7



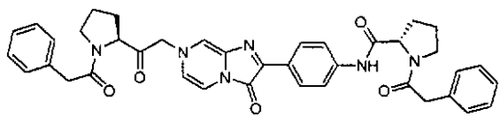
El producto de la etapa 6 se acopló a 1 equivalente de *N*-fenilacetil-L-prolina usando 1 equivalente de HATU y DIEA de una manera similar a la que se ha mostrado en el Ejemplo 1. MS (ESI) m/e $(M+H^+)$: 655. ^{1}H RMN (MeOD): □ 8,26 (s, 1 H), 8,19 (s, 1 H), 7,30~7,51 (m, 3 H), 7,18~7,27 (m, 1 H), 6,65 (s, 1 H), 4,51~4,56 (m, 2 H), 3,61~3,76 (m, 8 H), 1,95~2,15 (m, 8 H).

Etapa 8

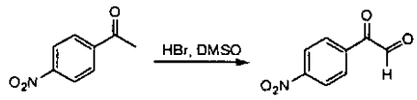


A una solución del producto de la etapa 7 (30 mg, 0,04 mmol) en 4 ml de THF seco se le añadió NCS (4 mg, 0,03 mmol). La mezcla resultante se agitó a TA durante 30 minutos. El disolvente se evaporó y el residuo se purificó por HPLC prep. para dar el producto deseado. MS (ESI) m/e $(M+H^+)$: 690. ^{1}H RMN (MeOD): □ 8,29 (s, 1 H), 8,20 (s, 1 H), 7,81~7,84 (m, 2 H), 7,66~7,69 (m, 2 H), 7,18~7,29 (m, 10 H), 4,52~4,55 (m, 2H), 3,62~3,78 (m, 8 H), 1,90~2,29 (m, 8 H).

Ejemplo 7-N-[4-(3-oxo-7-{2-oxo-2-[(2S)-1-(fenilacetil)pirrolidin-2-il]etil}-3,7-dihidroimidazo[1,2-a]pirazin-2-il)fenil]-1-(fenilacetil)-L-prolinamida



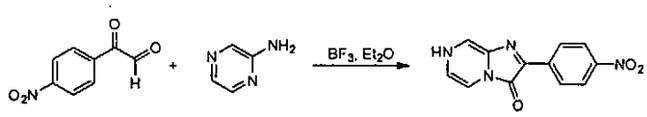
Etapa 1



A una solución agitada de 4-nitroacetofenona (20 g, 121 mmol) en 100 ml de DMSO se le añadieron lentamente 42 ml de HBr acuoso al 48% (363 mmol). La solución se agitó en un matraz

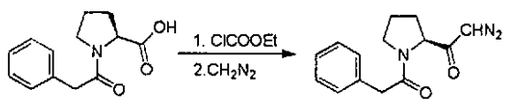
abierto a 55 °C y la reacción se siguió de TLC. Cuando el material de partida se consumió, la solución se vertió en hielo. Los productos sólidos se filtraron, se lavaron con agua y se secaron al vacío a TA sobre P_2O_5.

Etapa 2



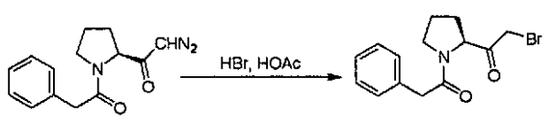
Se añadió en una porción arilglioxal hidrato (5 g, 27,8 mmol) sobre una suspensión de la amina heterocíclica (2,773 g, 29,2 mmol) en cloruro de metileno (10 ml). La suspensión resultante se trató con 1 gota de BF_3-Et_2O recién destilado y se agitó hasta que la mayor parte de la amina se consumió. Los productos de reacción se aislaron como hidratos por filtración de la mezcla de reacción espesa de un color intenso. El residuo obtenido por concentración se dejó enfriar, se filtró con succión, se lavó dos veces con éter dietílico y se secó a presión reducida para dar el producto deseado (4 g). MS (ESI) m/e ($M+H^+$): 256.

Etapa 3



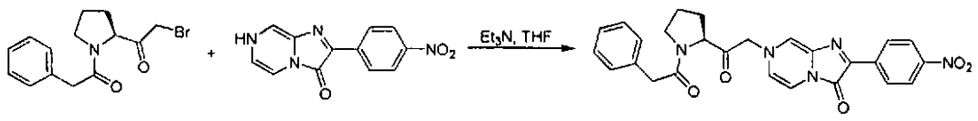
La prolina *N*-protegida (10 g, 42,8 mmol) en éter seco (60 ml) y THF (60 ml) se agitó en una atmósfera de argón a -25 °C. A esta solución se le añadieron TEA (42,8 mol, 4,08 ml) y cloroformiato de etilo (42,8 mmol, 2,6 4,14 ml). La solución se agitó durante 30 minutos más, después se dejó que la temperatura alcanzara -10 °C, y se añadió gota a gota la solución de diazometano en éter (2-3 equivalentes). La suspensión se agitó durante 3 horas más y se dejó que alcanzara la temperatura ambiente. Después, el clorhidrato de trietilamina se retiró por filtración y el filtrado se evaporó para dar la mitad de su volumen original. La solución resultante se lavó con $NaHCO_3$ acuoso saturado (50 ml) y salmuera (50 ml). La capa orgánica se secó y se evaporó para dar un producto en bruto, que se usó sin purificación adicional. MS (ESI) m/e ($M+H^+$): 258.

Etapa 4



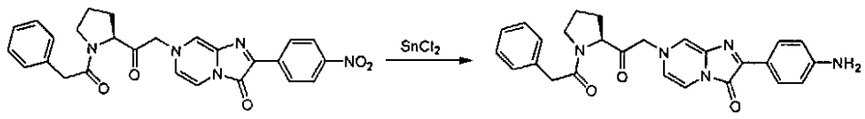
Una solución de a-diazocetona (2 g, 7,78 mmol) en HOAc glacial (25 ml) se trató gota a gota con HBr al 48% (2,8 ml) con agitación. Después de agitar durante 1 hora, la mezcla de reacción se extrajo con DCM y se lavó con agua. La evaporación del disolvente y la cristalización en éter-éter de pet. dio el producto puro. MS (ESI) m/e ($M+H^+$): 310.

Etapa 5



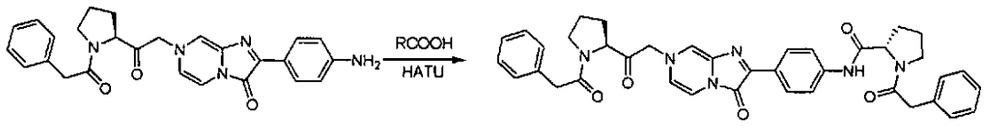
El producto de la etapa 4 (420 mg, 1,35 mmol) y el heterociclo de la etapa 2 (347 mg, 1,35 mmol) en THF (2 ml) se agitaron a TA durante una noche con Et_3N (0,3 ml). Cuando la reacción se completó, la mezcla se concentró y el residuo se purificó por RPLC para dar el producto (300 mg). MS (ESI) m/e ($M+H^+$): 486.

Etapa 6



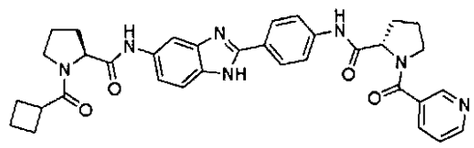
Se añadió una solución del producto de la etapa 5 (180 mg, 0,371 mmol) en EtOH absoluto (3 ml) a cloruro estannoso dihidrato (418,6 mg, 1,85 mmol) y la mezcla se agitó a 70 °C durante 2 horas. La mezcla de reacción se enfrió a TA, se vertió en hielo/agua (50 ml) y el pH se hizo alcalino fuerte mediante la adición de NaOH saturado (100 ml) antes de la extracción con EtOAc (2 x). La fase orgánica se combinó y se lavó con salmuera, se secó con $MgSO_4$, se filtró y se concentró para producir el producto en bruto (150 mg). MS (ESI) m/z: ($M+H^+$) 456.

Etapa 7

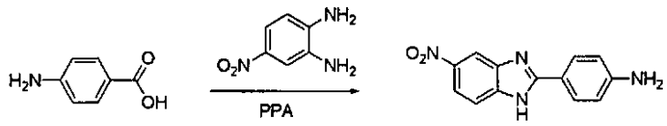


La mezcla del producto de la etapa 6 (30 mg, 0,066 mmol), *N*-fenilacetil-L-prolina (46,08 mg, 0,197 mmol), DIPEA (50,1 mg, 0,197 mmol) en CH_3CN (2 ml) se agitó a TA durante 5 minutos y después a la mezcla se le añadió HATU (74,86 mg, 0,197 mmol). La mezcla se agitó a TA durante una noche, se concentró y el residuo se purificó por RPLC para dar el compuesto deseado (20 mg). ^1H RMN (DMSO) □: 9,26 (s, 1H), 8,84-8,86 (m, 2H), 7,79-8,03 (m, 4H), 7,11-7,31(m, 12H), 4,41~4,63 (m, 2H), 3,52~3,80 (m, 12H), 2,26~2,12 (m, 2H), 1,87~1,75 (m, 6H).

Ejemplo 8-(2S)-1-(ciclobutilcarbonil)-N-{2-[4-({[(2S)-1-(piridin-3-ilcarbonil)pirrolidin-2-il]carbonillamino)fenil]-1H-bencimidazol-5-il}pirrolidin-2-carboxamida

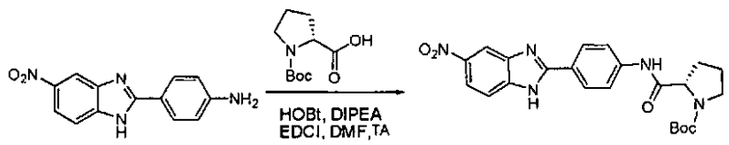


Etapa 1



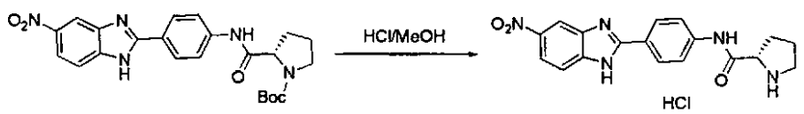
Se añadieron ácido p-aminobenzoico (0,200 g, 1,45 mmol) y nitrofenileno diamina (0,221 g, 1,45 mmol) en PPA (30 ml). La mezcla se agitó a 210 °C durante 20 minutos. Después, se vertió en hielo agua y se extrajo con DCM. La capa orgánica se lavó con salmuera, se secó ($NaSO_4$), se filtró y se concentró para proporcionar 200 mg del compuesto deseado. MS m/z: 255 (M+1).

Etapa 2



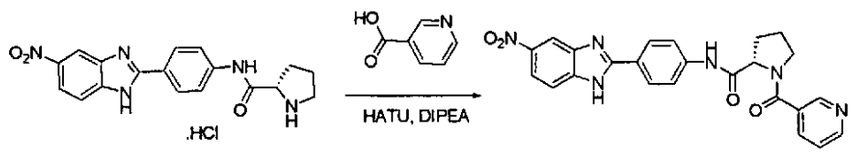
El compuesto de la etapa 1 anterior (1,2 g, 4,7 mmol), *N*-Boc-prolina (1,52 g, 7,07 mmol), EDCI (1,8 g, 9,44 mmol), HOBT (1,27 g, 9,44 mmol) y DIPEA (2,4 g, 18,8 mmol) se recogieron en DMF (30 ml) y se agitaron durante una noche a TA. La DMF se retiró a presión reducida y el residuo se extrajo con DCM/agua. La capa orgánica se lavó con salmuera, se secó ($NaSO_4$), se concentró y se purificó por columna (DCM:MeOH/100:1) para proporcionar 1,2 g del compuesto deseado. ^{1}H RMN (MeOD) ☐ 8,49 (s, 1H), 8,28-8,19 (m, 3H), 7,79-7,76 (d, J = 4,4 Hz, 2H), 7,72-7,65 (m, 1H), 4,41-4,29 (t, J = 8,8 Hz, 1H), 3,59-3,51 (m, 2H), 2,18-1,95 (m, 4H), 1,49 (s, 9H).

Etapa 3



El compuesto de la etapa 2 (0,600 g, 1,06 mmol) se agitó en MeOH/HCl (10 ml) durante 1 hora a TA, y el disolvente se retiró a presión reducida. El compuesto resultante se secó a alto vacío para proporcionar 370 mg del compuesto deseado.

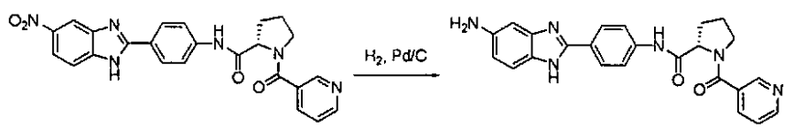
Etapa 4



El producto de la etapa 3 (0,370 g, 1,052 mmol), ácido piridina-3-carboxílico (0,157 g, 1,27 mmol), HATU (1,2 g, 3,18 mmol) y DIPEA (0,814 g, 6,36 mmol) se recogieron en DMF (10 ml) y se agitaron durante una noche a TA. La DMF se retiró a presión reducida y el residuo se extrajo con DCM/agua. La capa orgánica se lavó con salmuera, se secó ($NaSO_4$), se concentró y se purificó por columna (DCM:MeOH/100:1) para proporcionar 300 mg del compuesto deseado. ^{1}H

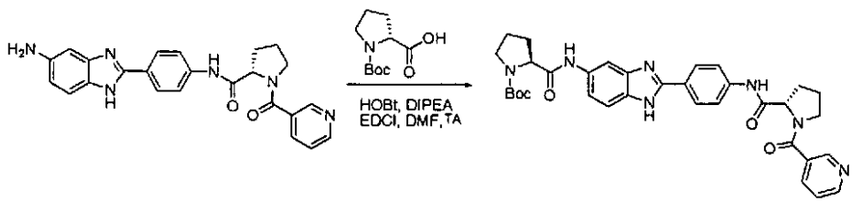
RMN (MeOD) □ ppm: 0,883 (s, 1H), 0,87-0,85 (d, *J* = 4,4 Hz, 1H), 8,49 (s, 1H), 8,21-8,18 (m, 1H), 8,17-8,10 (m, 3H), 7,98-7,95 (d, *J* = 8,8 Hz, 2H), 7,73-7,68 (m, 1H), 7,60-7,51 (m, 1H), 4,79-4,76 (t, *J* = 6 Hz, 1H), 3,77-3,73 (m, 2H), 3,27-3,19 (m, 2H), 2,19-2,12 (m, 2H).

Etapa 5



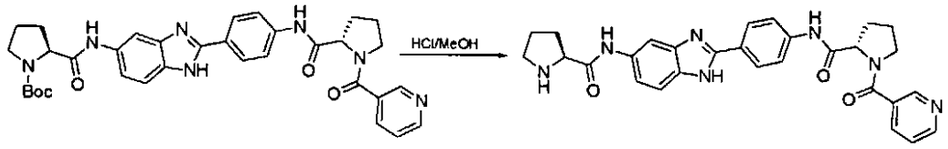
El producto de la etapa 4 (0,300 g, 0,657 mmol) se recogió en MeOH (10 ml) y Pd/C (0,07 g) se añadió en una atmósfera de N_2. La reacción se agitó durante una noche a TA en una atmósfera de H_2. El Pd/C se filtró a través de CELITE y el filtrado se concentró a presión reducida para proporcionar 234 mg del compuesto deseado.

Etapa 6



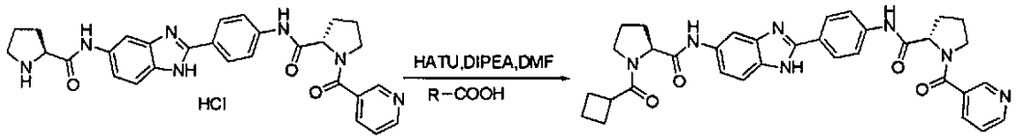
El producto de la etapa 5 (0,370 g, en bruto), *N*-Boc-prolina (0,157 g, 1,27 mmol), HATU (1,2 g, 3,18 mmol) y DIPEA (0,814 g, 6,36 mmol) se recogieron en DMF (10 ml) y se agitaron durante una noche a TA. La DMF se retiró a presión reducida y el residuo se extrajo con DCM/agua. La capa orgánica se lavó con salmuera, se secó ($NaSO_4$), se concentró y se purificó por columna (DCM:MeOH/100:1) para proporcionar 300 mg del compuesto diana.

Etapa 7



El producto de la etapa 6 (0,600 g, 1,06 mmol) se agitó en MeOH/HCl (15 ml) durante 1 hora a TA y el disolvente se retiró a presión reducida. El compuesto se secó a alto vacío para proporcionar 370 mg del compuesto deseado. ^{1}H RMN (MeOD) □: 9,39 (s, 1H), 9,18-8,82 (m, 2H), 8,39-8,38 (m, 1H), 8,32-8,22 (m, 1H), 8,21-8,10 (m, 2H), 8,09-7,98 (m, 2H), 7,86-7,72 (m, 1H), 7,71-7,65 (m, 1H), 4,87-4,84 (t, *J* = 8,8 Hz, 2H), 3,51-3,34 (m, 8H), 2,49-2,38 (m, 4H).

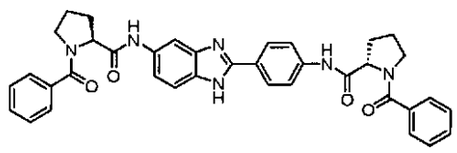
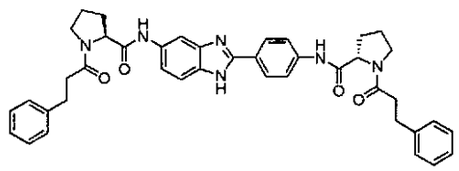
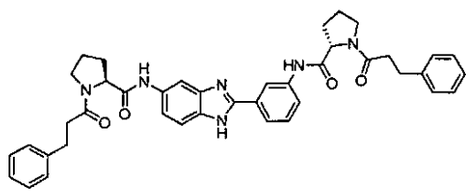
Etapa 8

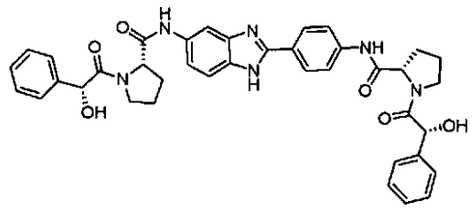
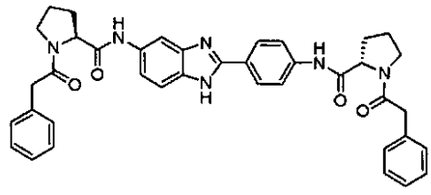
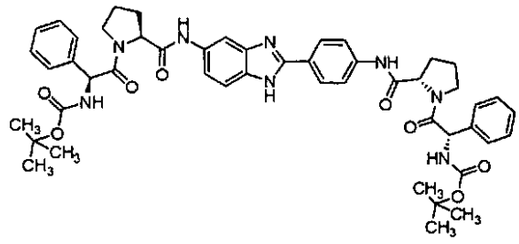
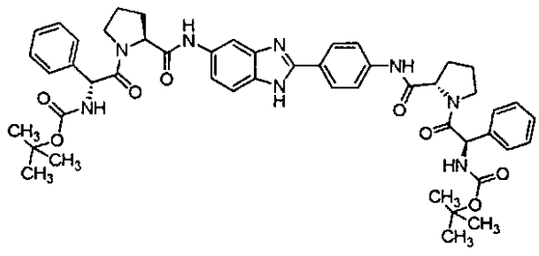


El producto de la etapa 7 (0,100 g, 0,191 mmol), ácido ciclobutanocarboxílico (0,018 mg, 0,183 mmol), HATU (0,116 g, 0,305 mmol) y DIPEA (0,059 g, 0,416 mmol) se recogieron en DMF (5 ml) y se agitaron durante una noche a TA. La DMF se retiró a presión reducida y el residuo se extrajo con DCM/agua. La capa orgánica se lavó con salmuera, se secó ($NaSO_4$) y se concentró. El residuo se purificó por HPLC para proporcionar 12 mg del producto final. ^{1}H RMN (MeOD) □: 8,91 (s, 1H), 8,75 (s, 1H), 8,41 (s, 1H), 8,25 (s,1H), 7,96-7,95 (d, *J* = 5,2 Hz, 4H), 7,73-7,67 (d, *J* = 3,2 Hz, 2H), 7,52-7,51 (d, *J* = 3,2 Hz, 1H), 4,54-4,82 (t, *J* = 3,6 Hz, 2H), 3,63-3,46 (m, 4H), 2,48-2,46 (t, *J* = 2 Hz, 1H), 2,34-2,29 (m, 6H), 2,18-2,10 (m, 4H), 2,08-2,02 (m, 4H).

Ejemplos 9-15

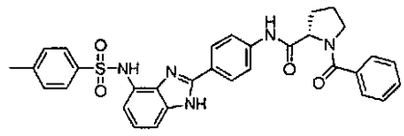
Los compuestos de los Ejemplos 9-15 se prepararon de una manera similar al Ejemplo 8.

Ejemplo	Estructura	PM	Nombre
9		626,721	(2S)-1-(fenilcarbonil)-N-{4-[5-({[(2*S*)-1-(fenilcarbonil)pirrolidin-2-il]carbonil}amino)-1H-bencimidazol-2-il]fenil}pirrolidin-2-carboxamida
10		682,83	(2S)-1-[(4Z,5Z)-4-etilidenohept-5-enoil]-N-{2-[4-({[(2*S*)-1-(3-fenilpropanoil)pirrolidin-2-il]carbonil}amino)fenil]-1H-bencimidazol-5-il}pirrolidin-2-carboxamida
11		682,83	(2S)-1-[(4Z,5Z)-4-etilidenohept-5-enoil]-N-{2-[3-({[(2*S*)-1-(3-fenilpropanoil)pirrolidin-2-il]carbonil}amino)fenil]-1H-bencimidazol-5-il}pirrolidin-2-carboxamida

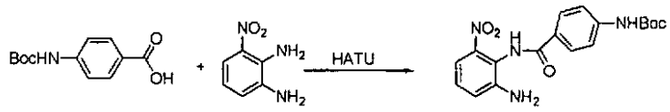
Ejemplo	Estructura	PM	Nombre
12		686,774	(2*S*)-1-[(2*R*)-2-hidroxi-2-fenilacetil]-N-(4-{5-[({(2*S*)-1-[(2*R*)-2-hidroxi-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-bencimidazol-2-il}fenil)pirrolidin-2-carboxamida
13		654,776	(2*S*)-1-(fenilacetil)-*N*-{4-[5-({[(2*S*)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-bencimidazol-2-il]fenil}pirrolidin-2-carboxamida
14		885,041	{(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2S)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-bencimidazol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
15		885,041	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-bencimidazol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-

Ejemplo	Estructura	PM	Nombre
			butilo

Ejemplo 16-(2S)-2-{[4-(4-{[(4-metilfenil)sulfonil]amino}-1H-bencimidazol-2-il)fenil]carbamoil}pirrolidin-1-carboxilato de bencilo

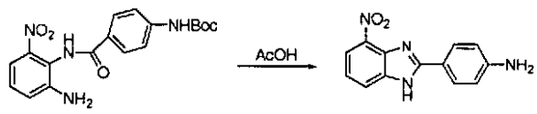


Etapa 1



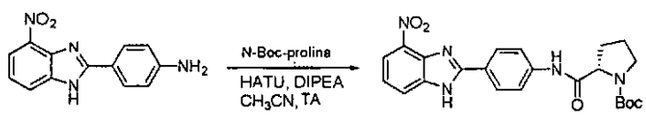
A una solución de ácido *N*-Boc-p-aminobenzoico (1,86 g, 7,84 mmol) en DMF se le añadieron 3-nitrofenilenodiamina (1,0 g, 6,536 mmol), HOBt (0,875 g, 6,536 mmol) y EDCl (2,5 g, 9,804 mmol) y la reacción se agitó durante una noche a TA. El exceso de disolvente se retiró a presión reducida y el residuo se diluyó con DCM. La capa orgánica se lavó con salmuera, se secó ($NaSO_4$), se filtró, se concentró y se purificó por columna para obtener 400 mg del compuesto. MS m/z: 273 (M+1).

Etapa 2



El compuesto de la etapa 1 anterior (0,600 g, 1,611 mmol) y KOAc (0,158 g, 1,609 mmol) se recogieron en HOAc (9,3 ml). La reacción se agitó a 120 °C durante una noche, se enfrió a TA y se vertió en hielo-agua. La capa acuosa se extrajo con DCM. La capa orgánica se lavó con salmuera, se secó ($NaSO_4$), se filtró y se concentró para obtener 120 mg del compuesto deseado. MS m/z: 255 (M+1). ^{1}H RMN (DMSO) □: 11,44 (s, 1H), 8,95-9,01 (m, 2H), 8,81-8,83 (d, *J* = 8,0 Hz, 2H), 8,22-8,27 (m, 1H), 8,22-8,27 (m, 2H), 4,97 (s, 2H).

Etapa 3



A una solución de la anilina (0,200 g, 0,787 mmol) en DMF se le añadieron N-Boc-prolina (0,186 g, 0,865 mmol), DIPEA (0,302 g, 2,361 mmol) y HATU (0,329 g, 0,865 mmol). La reacción

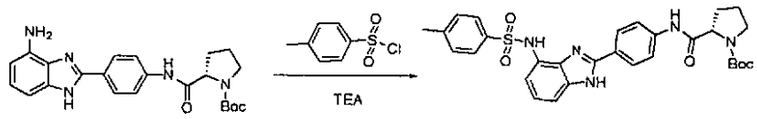
se agitó durante una noche. El exceso de disolvente se retiró a presión reducida y el residuo se diluyó con DCM. La capa orgánica se lavó con salmuera, se secó ($NaSO_4$), se filtró, se concentró y se purificó por columna para obtener 150 mg del producto deseado. MS m/z: 452 (M+1). ^{1}H RMN (MeOD) □: 8,70-8,73 (m, 2H), 8,40-8,42 (d, *J* = 8 Hz, 2H), 7,877,89 (d, *J* = 8 Hz, 1H), 7,50-7,53 (m, 2H), 6,78-6,80 (d, *J* = 8 Hz, 1H), 3,83 (s, 1H), 3,69-3,76 (m, 2H), 3,56-3,60 (m, 4H), 1,37-1,43 (m, 9H).

Etapa 4



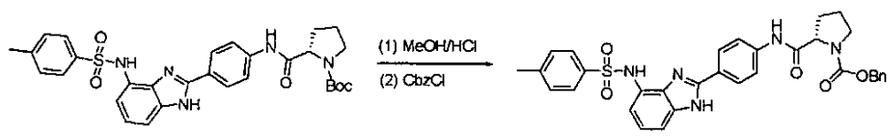
A una solución del compuesto de la etapa 3 anterior (0,200 g, 0,443 mmol) se le añadió Pd/C (10 mg) en una atmósfera de argón y la reacción se agitó durante 2 horas en H_2. El Pd/C se filtró y se lavó varias veces con MeOH. El disolvente se evaporó para obtener 180 mg del compuesto deseado. MS m/z: 422 (M+1). ^{1}H RMN (MeOD) □: 9,51 (s, 1H), 7,95-8,20 (m, 1H), 7,58-7,60 (m, 1H), 7,19-7,48 (m, 2H), 6,78-6,87 (m, 2H), 6,38 (s, 1H), 4,25-4,42 (m, 1H), 3,34-3,67 (m, 2H), 1,79-2,20 (m, 4H), 1,17-1,41 (m, 9H).

Etapa 5



A una solución del compuesto de la etapa 4 anterior (0,196 g, 0,465 mmol) en THF se le añadieron gota a gota TEA (0,070 g, 0,693 mmol) y cloruro de 4-metilbenceno-1-sulfonilo (0,088 g, 0,461 mmol) a 0 °C. La reacción se agitó durante una noche y el disolvente se retiró a presión reducida. El residuo se diluyó con DCM y se lavó con salmuera. La capa orgánica se secó ($NaSO_4$), se filtró y se concentró. El residuo se purificó por TLC preparativa para proporcionar 110 mg del compuesto deseado. MS m/z: 576 (M+1). ^{1}H RMN (MeOD) □: 7,98-8,00 (d, J = 8,0 Hz, 2H), 7,78-7,80 (d, J = 8,0 Hz, 2H), 7,66-7,68 (d, J = 8,0 Hz, 2H), 7,26-7,28 (m, 11H), 7,19-7,21 (d, J = 8,0 Hz, 2H), 7,07-7,09 (m, 2H), 4,36-4,38 (m, 1H), 3,55-3,58 (m, 2H), 2,32-2,35 (m, 4H), 1,89-2,11 (m, 3H), 1,50 (s, 9H).

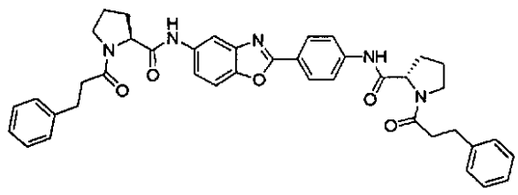
Etapa 6



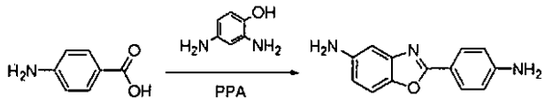
El producto de la etapa 5 anterior (0,180 g, 0,312 mmol) se agitó en MeOH/HCl (5,0 ml) durante 1 hora a TA. El disolvente se retiró a presión reducida y se secó a alto vacío. Se usó

directamente sin purificación adicional. El residuo se recogió en DMF y se añadieron ácido benzoico (0,042 g, 0,344 mmol), DIPEA (0,320 g, 2,504 mmol) y HATU (0,143 g, 0,375 mmol). La reacción se agitó durante una noche a TA. El exceso de disolvente se retiró a presión reducida y el residuo se diluyó con DCM. La capa orgánica se lavó con salmuera, se secó ($NaSO_4$), se filtró, se concentró y se purificó por columna para proporcionar 40 mg del compuesto final. MS m/z: 580 (M+1). ^{1}H RMN (MeOD) □: 7,92-7,94 (d, J = 8,8 Hz, 2H), 7,23-7,68 (m, 14H), 6,81-6,83 (d, J = 10 Hz, 1H), 5,21 (s, 2H), 4,65-4,79 (m, 1H), 3,52-3,89 (m, 2H), 2,47-2,58 (m, 1H), 2,43 (s, 3H), 1,93-2,23 (m, 3H).

Ejemplo 17-(2S)-1-(3-fenilpropanoil)-N-{4-[5-({[(2S)-1-(3-fenilpropanoil)pirrolidin-2-il]carbonil}amino)-1,3-benzoxazol-2-il]fenil}pirrolidin-2-carboxamida

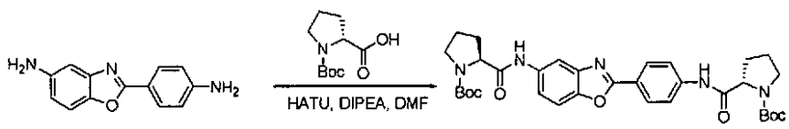


Etapa 1



Se combinaron ácido p-aminobenzoico (1,37 g, 10 mmol) y 2,4-diaminofenol (1,24 g, 10 mmol) en una atmósfera de argón y se trató con 12 ml de PPA. La solución resultante se calentó a 200 °C durante 30 minutos. La solución de color negro se vertió en hielo y el sólido de color amarillo resultante se recogió (1,12 g). ^{1}H RMN (DMSO) □: 10,2-10,5 (s, 2H), 8,10-8,20 (m, 4H), 7,10-7,80 (m, 3H). MS m/z: 226 (M+1).

Etapa 2



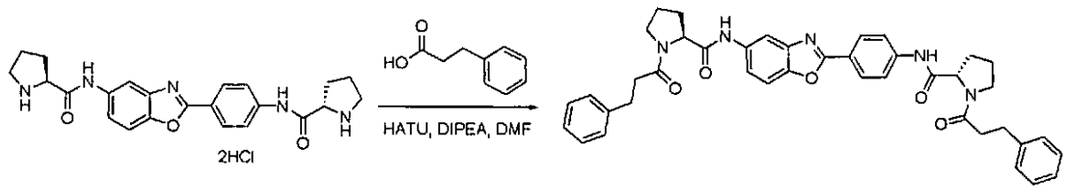
El producto de la etapa 1 anterior (0,100 g, 0,236 mmol), N-Boc-prolina (0,098 g, 0,355 mmol), HATU (0,135 g, 0,355 mmol), TEA (0,100 g, 0,944 mmol) se recogieron en DCM (10 ml) y se agitaron durante una noche a TA. La reacción se diluyó con DCM, la capa orgánica se lavó con agua y salmuera, se secó ($NaSO_4$), se concentró y se purificó por TLC preparativa para proporcionar 100 mg del compuesto deseado. MS m/z: 620 (M+1).

Etapa 3



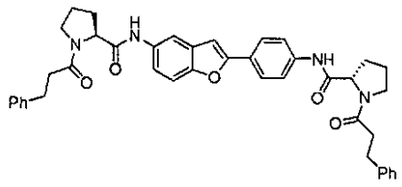
El producto de la etapa 2 anterior (0,100 g, 0,161 mmol) se agitó en MeOH/HCl (3,0 ml) durante 1 hora a TA y el disolvente se retiró a presión reducida. El compuesto se secó a alto vacío para proporcionar 80 mg del compuesto deseado. MS m/z: 420 (M+1).

Etapa 4

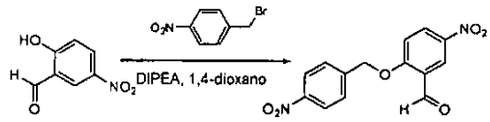


El compuesto de la etapa 3 (0,080 g, 0,191 mmol), ácido 3-fenilpropanoico (0,086 g, 0,574 mmol), HATU (0,218 g, 0,574 mmol), DIPEA (0,146 g, 1,146 mmol) se recogieron en DMF (3 ml) y se agitaron durante una noche a TA. La DMF se retiró a presión reducida y el residuo se extrajo con DCM/agua. La capa orgánica se lavó con salmuera, se secó ($NaSO_4$) y se concentró. El residuo se purificó por purificación por HPLC para proporcionar 108 mg del compuesto diana. ^1H RMN (DMSO) □: 10,2-10,5 (s, 2H), 8,10-8,20 (m, 3H), 7,10-7,80 (m, 14H), 4,37-4,55 (m, 2H), 3,32-3,58 (m, 4H), 2,67-2,85 (m, 7H), 1,80-2,4 (m, 9H).

Ejemplo 18-(2S)-1-(3-fenilpropanoil)-N-{4-[5-({[(2S)-1-(3-fenilpropanoil)pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}pirrolidin-2-carboxamida

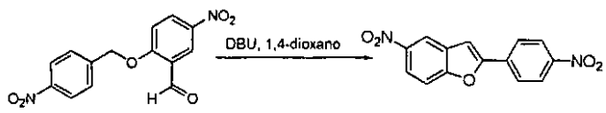


Etapa 1



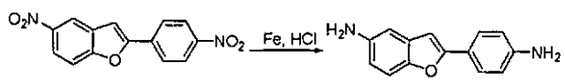
A una solución de 5-nitrosalicilaldehído (1,0 g, 5,90 mmol) en 1,4-dioxano (10 ml) se le añadieron bromuro de p-nitrobencilo (1,33 g, 6,15 mmol) y DIPEA (1,25 g, 9,70 mmol) y la reacción se calentó a reflujo a 100 °C durante 2 horas. La reacción se enfrió, los sólidos se filtraron, se lavaron con EtOH y se secaron a alto vacío para proporcionar el compuesto deseado. MS m/z: 303 (M+1).

Etapa 2



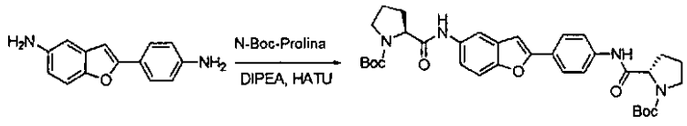
A una solución del compuesto diana de la etapa 1 (1,5 g, 4,96 mmol) en 1,4-dioxano (5 ml) se le añadió DBU (0,9 g, 6,45 mmol). La reacción se calentó a 100 °C durante 3 horas, después se enfrió a TA y el sólido resultante se retiró por filtración y se lavó lo suficiente con EtOH para proporcionar 927 mg del compuesto deseado. ^{1}H RMN (MeOD) □: 8,66 (s, 1H), 8,37-8,39 (d, J = 8,0 Hz, 2H), 8,30-8,32 (d, J = 8,0 Hz, 1H), 8,18-8,21 (d, J = 12 Hz, 2H), 7,78-7,80 (d, J = 8,0 Hz, 1H), 7,70 (s, 1H).

Etapa 3



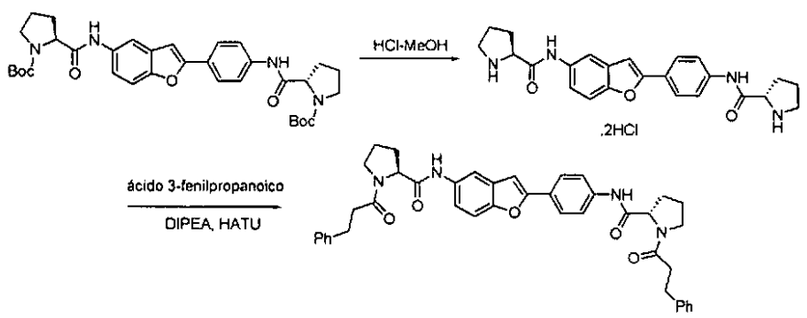
A una solución del producto de la etapa 2 anterior (0,050 g, 0,176 mmol) en 1,4-dioxano (1,8 ml) se le añadieron agua (1,8 ml), Fe (0,054 g) y HCl (1,1 □l). La reacción se calentó a 110 °C durante 3 horas. Después, el sólido se filtró y la capa orgánica se concentró para proporcionar 40 mg del compuesto deseado. ^{1}H RMN (MeOD) □: 8,01-8,05 (m, 2H), 7,90-7,96 (m, 1H), 7,79 (s, 1H), 7,46-7,51 (m, 1H), 7,34 (s, 1H), 7,17-7,21 (m, 2H). MS m/z: 225 (M+1).

Etapa 4



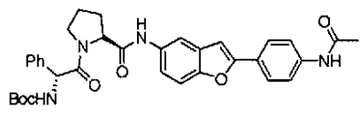
A una solución del producto de la etapa 3 anterior (0,020 g, 0,089 mmol) en DCM (10 ml) se le añadieron N-Boc-prolina (0,042 g, 0,196 mmol) y DIPEA (0,035 g, 0,267 mmol). La reacción se agitó a TA durante 5 minutos y después se añadió HATU (0,101 g, 0,267 mmol). La reacción se agitó durante una noche, se vertió en salmuera y se extrajo con EtOAc. La capa orgánica se secó (Na_2SO_4), se filtró y se concentró para proporcionar 30 mg del compuesto deseado. MS m/z: 619 (M+1).

Etapa 5

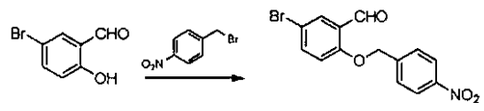


El producto de la etapa 4 (0,70 g, 1,13 mmol) se agitó en MeOH/HCl (20 ml) durante 1 hora. El disolvente se retiró a alto vacío para proporcionar el compuesto de prolina deseado, que se usó directamente a la siguiente etapa sin purificación adicional. El ácido 3-fenilpropanoico (0,428 g, 2,85 mmol) recogido en DCM (30 ml) se hizo reaccionar con el compuesto de prolina (0,500 g, 0,96 mmol) y DIPEA (0,9 g, 7,1 mmol). La reacción se agitó a TA durante 5 minutos y después se añadió HATU (1,0 g, 2,85 mmol). La reacción se agitó durante una noche, se vertió en salmuera y se extrajo con EtOAc. La capa orgánica se secó (Na_2SO_4), se concentró y se purificó por HPLC para proporcionar 30 mg del compuesto deseado. ^{1}H RMN ($CDCl_3$) □: 9,85-9,87 (d, J = 8,0 Hz, 2H), 7,86 (s, 1H), 7,42-7,44 (d, J = 8,8 Hz, 2H), 7,46-7,48 (d, J = 8,8 Hz, 2H), 7,03-7,31 (m, 9H), 6,90-6,99 (d, J = 3,6 Hz, 1H), 6,58 (s, 1H), 4,71-4,82 (m, 2H), 3,62-3,71 (m, 2H), 3,43-3,50 (m, 2H), 2,95-3,05 (m, 4H), 2,63-2,88 (m, 4H), 2,21-2,43 (m, 4H), 1,87-2,14 (m, 4H). MS m/z: 683 (M+1).

Ejemplo 19-N-{2-[4-(acetilamino)fenil]-1-benzofuran-5-il}-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}-L-prolinamida

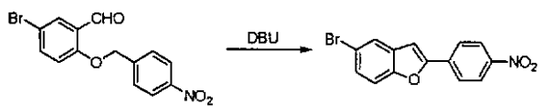


Etapa 1



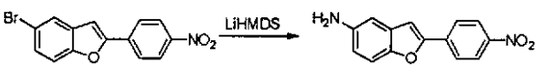
Se añadió K_2CO_3 (68 g, 0,497 mol) a una solución de bromosalicilaldehído (50 g, 0,248 mol) en DMF (300 ml). La solución resultante se agitó a TA durante 1 hora y después a ésta se le añadió el compuesto bromuro de 4-nitrobencilo (54 g, 0,25 mol). La mezcla de reacción se agitó durante 30 minutos, se filtró, el filtrado se vertió en agua y se extrajo con EtOAc (3 x). Las capas orgánicas combinadas se secaron y se concentraron. El producto se recristalizó en dioxano para proporcionar un sólido de color blanco (50 g). ^{1}H RMN ($CDCl_3$) □: 10,43 (s,1H), 8,24 (d, *J* = 4H), 7,517,58 (m, 2H), 7,37-7,42 (m, 4H), 7,31-7,36 (m, 6H), 5,52 (s, 1H), 4,57 (s, 2H), 3,90 (s, 2H), 3,34 (s, 2H), 2,06-2,15 (m, 6H), 1,86-1,88 (m, 1H), 1,41 (d, 18H).

Etapa 2



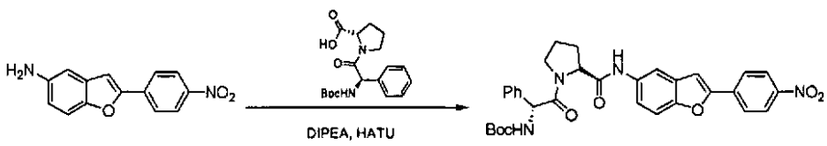
Se añadió DBU (9 ml, 61,58 mmol) a una solución del producto de la etapa 1 (10 g, 29,85 mmol) en dioxano (70 ml). La solución resultante se calentó a reflujo durante 1 hora, se enfrió y se filtró. La torta de filtro se lavó con EtOAc y se secó al aire para proporcionar un sólido de color amarillo (6,5 g).

Etapa 3



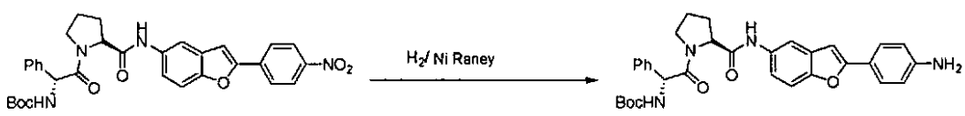
Se añadió P^tBu_3 (1,93 ml, 0,32 mmol) a una solución del producto de la etapa 2 (2 g, 6,3 mmol) y $Pd_2(dba)_3$ (0,29 g, 0,32 mmol) en THF (100 ml) en una atmósfera de N_2. Después, se añadió gota a gota una solución de LiHMDS (18,9 ml, 18,9 mmol). La solución resultante se calentó a reflujo durante 3 horas y después se enfrió a TA. La mezcla de reacción se ajustó a pH = 1 usando HCl 1 M y después se agitó durante 0,5 horas. La mezcla de reacción se basificó a pH = 8~9 usando $NaHCO_3$ ac. saturado y se extrajo con EtOAc (3 x). Las capas orgánicas combinadas se secaron y se concentraron. El residuo se recristalizó en MeOH para proporcionar el producto en forma de un sólido de color pardo.

Etapa 4



La mezcla del producto de la etapa 3 (500 mg, 2 mmol), R-Boc-Phg-L-Pro-OH (660 mg, 2,16 mmol), NMM (400 mg, 4 mmol) y DMF (30 ml) se agitó a TA durante 30 minutos y después a este se le añadió HATU (1,13 g, 3 mmol). La mezcla resultante se agitó a TA durante una noche. La mezcla de reacción se diluyó con agua y se filtró. La torta se lavó con agua y se secó; el sólido se usó en la siguiente etapa sin purificación.

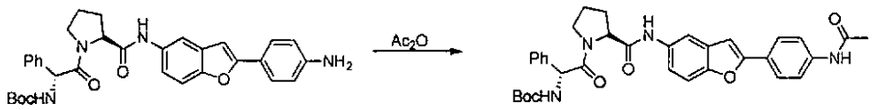
Etapa 5



El producto de la etapa 4 (0,4 g, 1,3 mmol) en THF (10 ml) se hidrogenó usando Ni Raney (0,2 mg) como el catalizador. Después de agitarse en una atmósfera de H_2 a TA durante una noche,

la suspensión de reacción se filtró a través de CELITE y el filtrado se concentró a presión reducida para proporcionar 0,33 g del compuesto deseado.

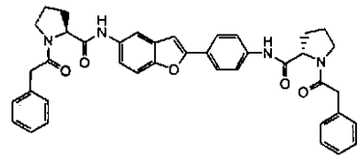
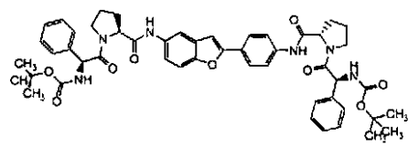
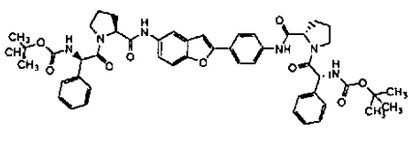
Etapa 6

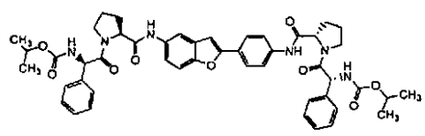
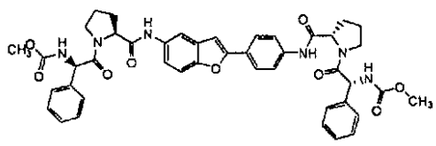
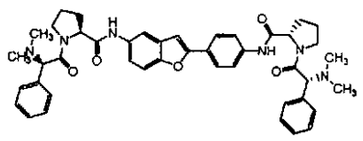
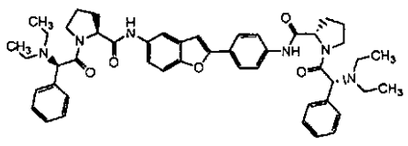
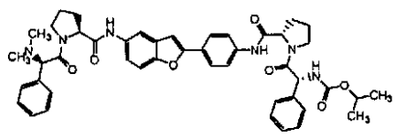


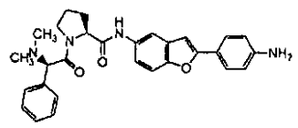
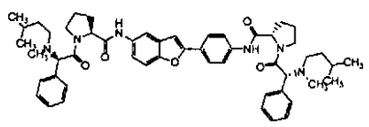
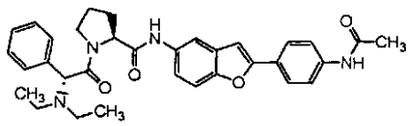
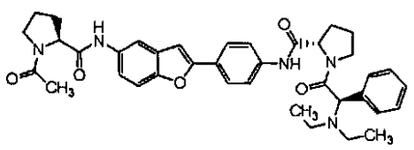
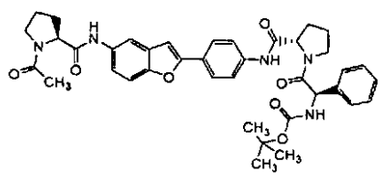
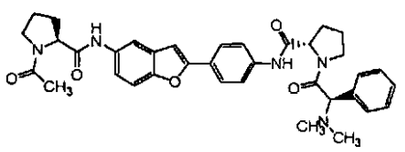
Se añadió Ac_2O (18 mg, 0,18 mmol) a una solución de la anilina de la etapa 5 (50 mg, 0,09 mmol) en THF (2 ml) a TA. La solución resultante se agitó a TA durante una noche, se concentró y el residuo se purificó por RPLC para proporcionar el producto deseado. ^1H RMN (acetona-d6) □: 7,95 (s, 1 H,NH), 7,65-7,74 (m, 7 H, ArH), 7,40 -7,43 (m, 3 H, ArH), 7,30 -7,34 (m, 2 H, ArH), 7,01 (s, 1 H, ArH), 5,64 (s, 1 H, CH), 4,56-4,59 (m, 1 H, CH), 3,93-.3,99 (m, 1 H, CH_2), 3,27-3,42 (m, 2 H, CH_2), 3,02-3,17 (m, 3 H, CH_2), 1,98 (s, 3H, CH_3), 1,98- 1,95 (m, 4 H, CH_2), 1,22 (t, J = 7,2 Hz, 6 H, CH_3).

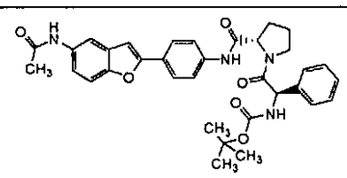
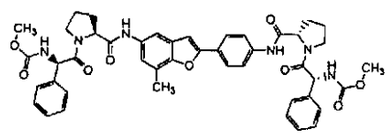
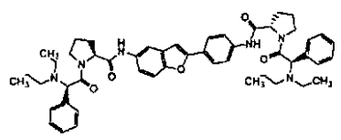
Ejemplos 20-36

Los compuestos de los Ejemplos 20-36 se prepararon de una manera similar a la que se ha descrito en el Ejemplo 18 o el Ejemplo 19.

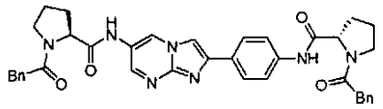
Ejemplo	Estructura	PM	Nombre
20		654,773	(2S)-1-(fenilacetil)-N-{4-[5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}pirrolidin-2-carboxamida
21		885,039	{(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2S)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
22		885,039	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

Ejemplo	Estructura	PM	Nombre
23		856,984	[(1R)-2-oxo-1-fenil-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)carbamoil]pirrolidin-1-il}etil]carbamato de propan-2-ilo
24		800,876	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo
25		740,91	(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)pirrolidin-2-carboxamida
26		797,019	(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)pirrolidin-2-carboxamida
27		798,947	[(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de propan-2-ilo

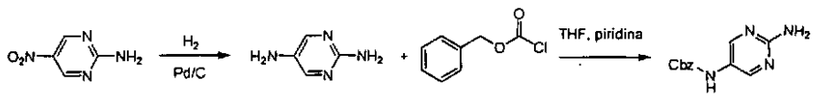
Ejemplo	Estructura	PM	Nombre
28		482,587	N-[2-(4-aminofenil)-1-benzofuran-5-il]-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolinamida
29		853,127	(2S)-1-{(2R)-2-[metil(3-metilbutil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[metil(3-metilbutil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}pirrolidin-2-carboxamida
30		552,679	N-{2-[4-(acetilamino)fenil]-1-benzofuran-5-il}-1-[(2R)-2-(dietilamino)-2-fenilacetil]-L-prolinamida
31		649,797	(2S)-1-acetil-N-(2-{4-[({(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]fenil}-1-benzofuran-5-il)pirrolidin-2-carboxamida
32		693,807	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-acetilpirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
33		621,743	(2S)-1-acetil-N-(2-{4-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]fenil}-1-benzofuran-5-il)pirrolidin-2-carboxamida

Ejemplo	Estructura	PM	Nombre
34		596,689	N-{4-[5-(acetilamino)-1-benzofuran-2-il]fenil}-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}-L-prolinamida
35		814,903	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-7-metil-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo
36		825,073	(2S)-1-{(2R)-2-[etil(propil) amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[etil(propil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}pirrolidin-2-carboxamida

Ejemplo 37-(2S)-1-(fenilacetil)-N-{4-[6-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)imidazo[1,2-a]pirimidin-2-il]fenil}pirrolidin-2-carboxamida

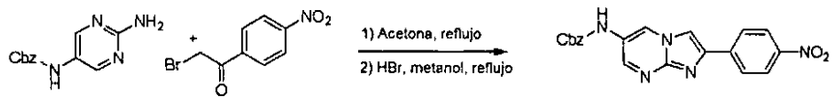


Etapa 1



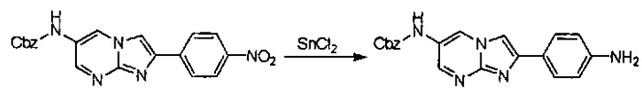
Una suspensión de pirimidina (280 mg, 2 mmol), Pd/C (15 mg, 0,1 mmol) en 40 ml de EtOH se hidrogenó en 206,84 kPa (30 psi) durante 1 hora. Después, la mezcla se filtró y después el filtrado se concentró para dar el producto (200 mg). El residuo se disolvió en 20 ml de THF y se añadieron CbzCl (375 mg, 2,19 mmol) y piridina (1 ml). La mezcla se agitó a TA durante 1 hora, después la mezcla se concentró al vacío, el residuo se extrajo con EtOAc (2 x), se lavó con H_2O (30 ml) y salmuera (30 ml), se secó sobre $NaSO_4$ anhidro y se concentró al vacío para dar el compuesto deseado en forma de un polvo de color blanco (330 mg). MS (ESI) m/e ($M+H^+$): 245.

Etapa 2



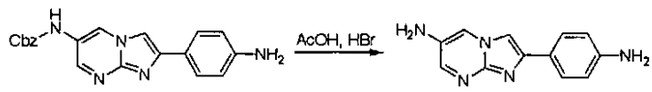
Una solución del producto de la etapa 1 anterior (244 mg, 1,00 mmol) y 2-bromo-1-(4-nitrofenil)etanona (244 mg, 1 mmol) en 40 ml de acetona se calentó a reflujo y se agitó durante 6 horas. Después, la mezcla se enfrió a TA, se filtró, después el filtrado se disolvió en 30 ml de MeOH, se añadieron 0,5 ml de HBr y la mezcla se calentó a reflujo durante 3 horas más; después de esto, la mezcla se concentró al vacío para dar el producto en forma de un polvo de color amarillo pálido (120 mg). MS (ESI) m/e ($M+H^+$): 390.

Etapa 3



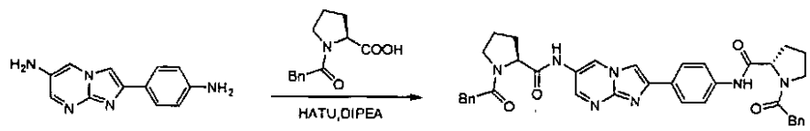
Al producto de la etapa 2 anterior (50 mg, 0,128 mmol) disuelto en 10 ml de CH_3OH se le añadió $SnCl_2$ (144 mg, 0,64 mmol). La mezcla de reacción se agitó a TA durante 30 minutos y después se calentó a reflujo durante 3 horas. El MeOH se retiró al vacío y el residuo se purificó (DCM/MeOH = 50:1) para proporcionar el compuesto deseado (35 mg). MS (ESI) m/e ($M+H^+$): 360.

Etapa 4



El compuesto de la etapa 3 (35 mg, 0,1 mmol) se disolvió en 5 ml de HOAc y después se añadió HBr (1,5 ml). La mezcla de reacción se calentó a reflujo, se agitó durante 6 horas, se enfrió y se concentró. El residuo se extrajo con EtOAc (2 x), se lavó con $NaHCO_3$ ac. y agua (30 ml) y salmuera (30 ml) y se secó sobre $NaSO_4$ anhidro. La concentración proporcionó el compuesto deseado en forma de un sólido de color pardo (16 mg). MS (ESI) m/e ($M+H^+$): 226.

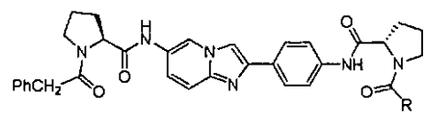
Etapa 5



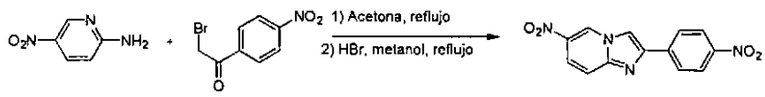
Una mezcla del producto de diamina de la etapa 4 anterior (16 mg, 0,071 mmol), N-fenilacetil-L-prolina (40 mg, 0,170 mmol), DIPEA (36,9 mg, 0,02 mmol) en CH_3CN (5 ml) se agitó a TA durante 10 minutos y después se añadió HATU (54 mg, 0,142 mmol). La mezcla se agitó a TA durante una noche, después la mezcla se concentró y el residuo se purificó para dar el compuesto (15 mg). MS (ESI) m/e ($M+H^+$): 657. ^1H RMN (MeOD) □: 9,45 (s, 1H), 8,31 (s, 1H),

8,05 (s, 1H), 7,61~7,48 (m, 4H), 7,34~7,21 (m, 10H), 4,60~4,52 (m, 2H), 3,83~3,69 (m, 8H), 2,24~1,97 (m, 8H).

Ejemplo 38-(2S)-1-(fenilacetil)-N-{4-[6-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)imidazo[1,2-a]piridin-2-il]fenil}pirrolidin-2-carboxamida

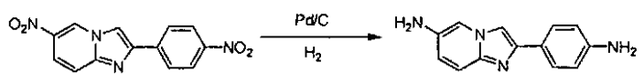


Etapa 1



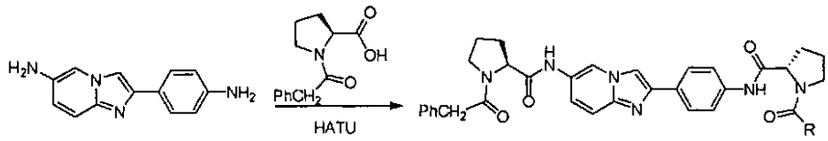
La mezcla que contenía 2-amino-5-nitropiridina (1,39 g, 10 mmol) y p-nitro-alfa-bromoacetofenona (2,42 g, 10 mmol) en 100 ml de acetona se calentó a reflujo durante 12 horas. El sólido se recogió por filtración, después se disolvió en 20 ml de MeOH y se trató con una cantidad traza de HBr. La mezcla se agitó a la temperatura de reflujo durante 1 hora, se enfrió y el sólido se recogió por filtración para dar el producto deseado (1,4 g). MS (m/z): 285 (M+H)+.

Etapa 2



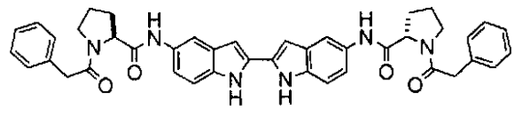
A una suspensión del producto de la etapa 1 anterior (0,7 g, 2,5 mmol) en MeOH (50 ml) se le añadieron 0,1 g de Pd/C (20%) y la suspensión se agitó a 172,37 kPa (25 psi) de H_2 a TA. Después de la filtración, el filtrado se concentró al vacío para dar el compuesto deseado. MS (m/z): 225 $(M+H)^+$.

Etapa 3

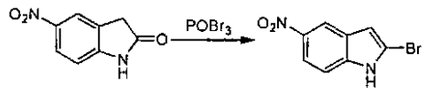


La mezcla de la diamina de la etapa 2 anterior (225 mg, 1 mmol), *N*-fenilacetilprolina (1 mmol), DIPEA (5 mmol) y HATU (380 mg, 1 mmol) en 10 ml de MeCN se agitó a TA durante 1 hora. La mezcla de reacción se concentró y el residuo se purificó por cromatografía en columna para dar el compuesto deseado. ^{1}H RMN (MeOD) □: 9,3 (s, 1H), 8,2 (s, 1H), 7,5-7,1 (m, 16H), 4,6 (m, 1H), 4,5 (m, 1H), 3,8 (m, 8H), 2,3-1,8 (m, 8H).

Ejemplo 39-(2S,2'S)-N,N'-1H,1'H-2,2'-biindolo-5,5'-diilbis[1-(fenilacetil)pirrolidin-2-carboxamida]

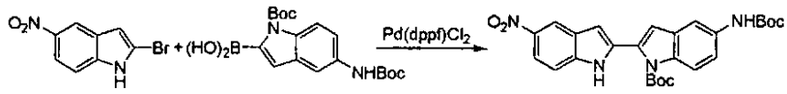


Etapa 1



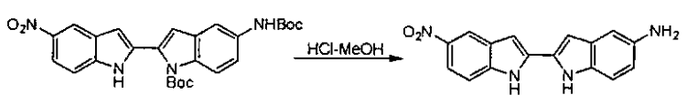
A una suspensión de la lactama (10,0 g, 56 mmol) en 200 ml de 1,2-dicloroetano se le añadió $POBr_3$ (15,3 g, 53,2 mmol) a TA. La mezcla resultante se calentó a la temperatura de reflujo en un baño de aceite a 90 °C durante 0,5 horas (la reacción formó una cantidad abundante de precipitado, y se prefirió un baño de aceite sobre un manto de calentamiento, ya que proporcionó un calentamiento suave y evitó el oscurecimiento del precipitado). La reacción se enfrió justo por debajo de la temperatura de reflujo y se añadió una porción de imidazol (4,57 g, 62 mmol). La suspensión gomosa resultante se calentó a la temperatura de reflujo en un baño de aceite durante 2 horas más. La reacción se enfrió a TA y se añadieron 100 ml de hielo-agua. A la mezcla se le añadió $NaHCO_3$ sólido (aprox. 50 g) hasta que no se desprendió más gas. La suspensión se extrajo con DCM (4 x) y los extractos de DCM combinados se lavaron con 300 ml de salmuera. Los extractos de DCM se filtraron a través de gel de sílice y se concentraron a sequedad para proporcionar un producto en bruto. El producto en bruto se recristalizó en cloroformo para dar 5,41 g del compuesto deseado en forma de un sólido de color blanco. El filtrado se concentró a sequedad y el residuo se purificó por cromatografía en columna ultrarrápida (EtOAc al 30%/Hex) para dar 2,6 g más del producto deseado. MS (ESI) m/e ($M+H^+$): 242.

Etapa 2



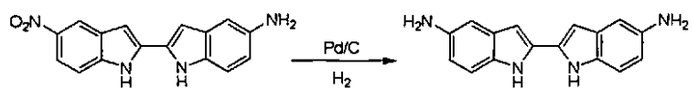
La mezcla del compuesto de la etapa 1 anterior (602,6 mg, 2,5 mmol), el ácido indol borónico (1,034 g, 2,75 mmol), $Pd(dppf)Cl_2$ (183 mg, 0,25 mmol), Na_2CO_3 (530 mg, 5,0 mmol) en 5 ml de dioxano-H_2O (5:1) se calentó a reflujo en una atmósfera de N_2 durante una noche. Cuando la reacción se completó la mezcla se vertió en agua y se extrajo con DCM. La fase orgánica se secó sobre Na_2SO_4, se concentró y el residuo se purificó para dar el compuesto del producto deseado. MS (ESI) m/e ($M+H^+$): 493.

Etapa 3



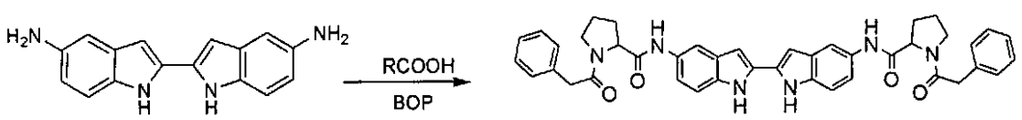
El producto de la etapa 2 (600 mg, 1,3 mmol) se añadió en HCl (30 ml, 3 M en MeOH). Después, la mezcla se agitó a TA durante 2-3 horas. Cuando la reacción se completó, la mezcla se concentró para dar el producto en bruto (400 mg). MS (ESI) m/e ($M+H^+$): 293.

Etapa 4



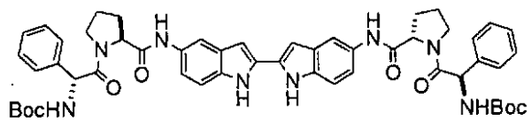
El producto de la etapa 3 (400 mg, 1,36 mmol) se disolvió en EtOAc y se trató con Pd/C (100 mg, 20%). Después, la mezcla se agitó a TA durante una noche en una atmósfera de H_2. Cuando la reacción se completó, el Pd/C se retiró por filtración y la solución resultante se concentró para dar el producto en bruto (300 mg). MS (ESI) m/e ($M+H^+$): 263.

Etapa 5



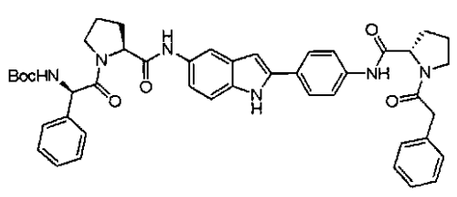
Una solución que contenía (131 mg, 0,5 mmol) del producto de la etapa 4, RCOOH (256,608 mg, 1,1 mmol), DIPEA (390 mg, 1,5 mmol) en CH_3CN (2 ml) se agitó a TA durante 5 minutos y después a la mezcla se le añadió HATU (418 mg, 1,1 mmol). La mezcla se agitó a TA durante una noche. Cuando la reacción se completó, la mezcla se concentró y el residuo se purificó para dar el producto deseado. ^1H RMN (MeOD) □: 7,15-7,75 (m, 18H), 4,51-4,59 (m, 2H), 3,56-3,80 (m, 10H), 2,37 (s, 3H), 1,97-2,30 (m, 8H). MS (ESI) m/e ($M+H^+$): 693.

Ejemplo 40-(1H,1'H-2,2'-biindolo-5,5'-diilbis{carbamoil(2S)pirrolidin-2,1-diil[(1R)-2-oxo-1-feniletano-2,1-diil]})biscarbamato de di-terc-butilo

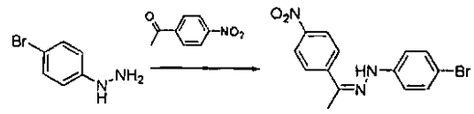


Este compuesto se preparó usando el procedimiento similar al del Ejemplo 39, etapa 5 usando N-Boc-R-Phg-L-Pro-OH. ^1H RMN (MeOD) □: 6,78-7,78 (m, 18H), 5,49 (m, 2H), 4,554,58 (m, 2H), 3,94-3,97 (m, 3H), 2,37 (s, 3H), 1,87-2,14 (m, 8H), 1,40(s, 18H). MS (ESI) m/e ($M+H^+$):924.

Ejemplo 41-{(1R)-2-oxo-1-fenil-2-[(2S)-2-({2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]etil}carbamato de terc-butilo

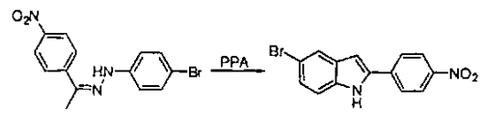


Etapa 1



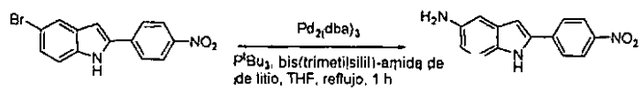
A una solución de 4-bromofenilhidrazina (2,5 g, 13,4 mmol) en ácido acético (19,5 ml) y EtOH (14,5 ml) se le añadió 4-nitroacetofenona (1,66 g, 10,0 mmol). La reacción se calentó a reflujo durante 5 horas y se añadió agua (35 ml). La mezcla resultante se agitó durante 1 hora más, el sólido resultante se filtró y lavó con agua para proporcionar 3,1 g del compuesto deseado. ^{1}H RMN (MeOD) □: 8,21-8,23 (d, *J* = 8,0 Hz, 2H), 8,01-8,03 (d, *J* = 8,0 Hz, 2H), 7,34-7,36 (d, *J* = 8,0 Hz, 2H), 7,20-7,22 (d, *J* = 8,0 Hz, 2H), 2,03 (s, 3H).

Etapa 2



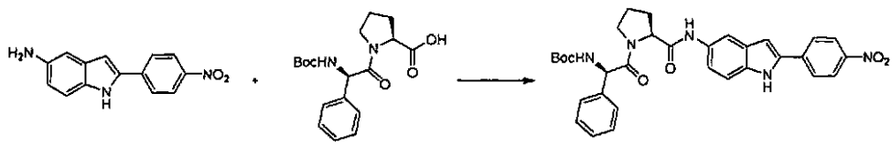
El producto de la etapa 1 anterior (2,0 g, 6,0 mmol) se añadió en PPA (20 ml), la mezcla se agitó a 80 °C durante 1 hora antes de que se enfriara en un baño de hielo, se diluyó con agua/EtOAc (60/20 ml) y se agitó durante 1 hora más. La mezcla se extrajo con EtOAc y se lavó para producir el compuesto diana. ^{1}H RMN (MeOD) □: 8,28-8,30 (d, *J* = 8,0 Hz, 2H), 7,97-7,99 (d, *J* = 8,0 Hz, 2H), 7,72 (s, 1H), 7,33-7,35 (d, *J* = 8,0 Hz, 1H), 7,24-7,26 (d, *J* = 8,0 Hz, 1H), 7,02 (s, 1H).

Etapa 3



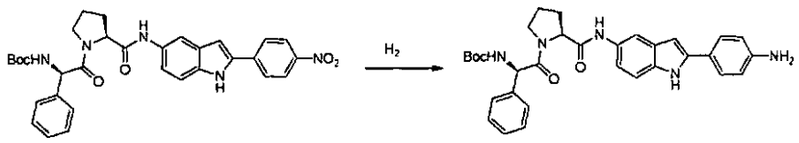
Un matraz de fondo redondo enfriado con argón y secado al horno se cargó con el indol de la etapa 2 (2,0 g, 6,31 mmol) y 0,05 equivalentes de $Pd_2(dba)_3$ en THF (100 ml). Se añadió una solución de tri-terc-butil fosfina (10% en peso) en hexano (1,93 ml, 0,63 mmol) seguido de hexametildisilazano de litio (1,0 M en THF) (18,9 ml, 18,9 mmol). La solución de color oscuro se calentó a reflujo durante una noche y después se enfrió a TA. Esta mezcla se vertió en HCl ac. 1,0 M enfriado con hielo y se agitó vigorosamente. Se añadió hexano y la agitación continuó durante 30 minutos. El precipitado se filtró, se lavó con 20 ml de agua fría y después 20 ml de una solución de THF:Hexanos (5:95). El precipitado se lavó con 200 ml de MeOH y el filtrado se concentró para dar 1,5 g del compuesto deseado. MS m/z: 254 (M+1).

Etapa 4



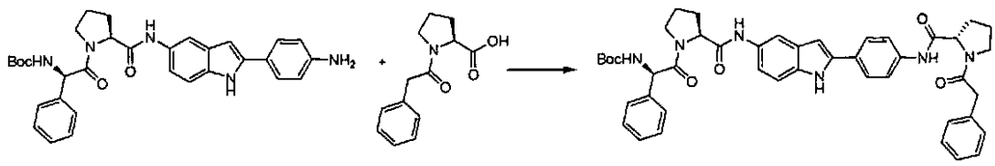
A una solución del producto de la etapa 3 anterior (1 g, 3,9 mmol) en acetonitrilo (20 ml) se le añadieron R-N-Boc-Phg-S-Pro-OH (1,4 g, 3,9 mmol), HATU (3 g, 7,8 mmol) y DIPEA (1 g, 7,8 mmol). La mezcla se agitó a TA durante una noche. El disolvente se destiló, el residuo se disolvió en EtOAc y se lavó con agua. La capa orgánica se secó, se concentró al vacío y el residuo se purificó por cromatografía en columna para dar el compuesto deseado (1,8 g). MS (ESI) m/e ($M+H^+$): 584.

Etapa 5



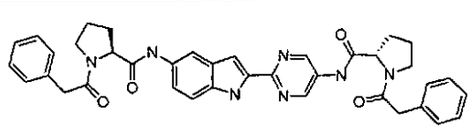
A una solución del compuesto de la etapa 4 (300 mg, 0,51 mmol) en MeOH (10 ml) se le añadió Pd/C (50 mg, 0,28 mmol). La mezcla se agitó en una atmósfera de H_2 a TA durante 1 hora. El catalizador se retiró por filtración y el filtrado se concentró al vacío para dar el compuesto deseado (230 mg) en forma de un aceite de color amarillo, que se usó directamente en la siguiente etapa. MS (ESI) m/e $(M+H)^+$: 554.

Etapa 6

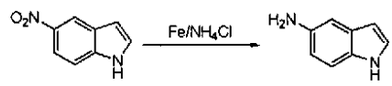


A una solución del compuesto de la etapa 5 (100 mg, 0,18 mmol) en acetonitrilo (3 ml) se le añadió el compuesto *N*-fenilacetil-L-prolina (42 mg, 0,18 mmol), HATU (140 mg, 0,36 mmol) y DIPEA (46 mg, 0,36 mmol). La mezcla se agitó a TA durante una noche, después se concentró y el residuo se purificó por RPLC para dar (60 mg). ^{1}H RMN ($CDCl_3$) □: 9,62 (s, 1H), 9,08 (s, 1H), 7,84 (s, 1H), 7,45-7,09 (m, 15H), 6,52 (s, 1H), 5,67 (s, 1H), 5,49 (m, 1H), 4,72-4,51 (m, 2H), 3,82-3,48 (m, 5H), 3,20 (m, 1H), 2,15-1,72 (m, 8H), 1,43 (s, 9H). MS (ESI) m/e ($M+H^+$): 769.

Ejemplo 42-(2S)-1-(fenilacetil)-N-{2-[5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]pirimidin-5-il}pirrolidin-2-carboxamida

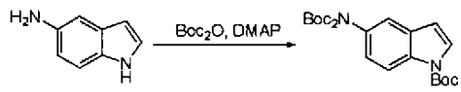


Etapa 1



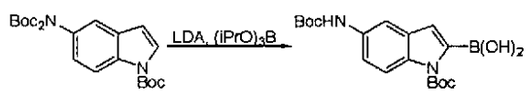
Una mezcla de 5-nitroindol (5 g, 30,9 mmol), Fe (8,6 g, 154 mmol), NH_4Cl (16,5 g, 309 mmol), EtOH (80 ml) y agua (20 ml) se calentó a reflujo en una atmósfera protectora de N_2 durante 2 horas. La mezcla se enfrió a TA y se filtró. El filtrado se concentró y se disolvió en agua. La mezcla se basificó con Na_2CO_3 y se extrajo dos veces con CH_2Cl_2. Las fases orgánicas combinadas se combinaron, se secaron sobre Na_2SO_4 y se filtraron. El filtrado se concentró para producir el producto (3,6 g). MS (ESI) m/e ($M+H^+$): 133. ^1H RMN (DMSO) □: 10,55 (s, 1H), 7,127,06 (m, 2H), 6,68 (d, J = 2,0 Hz, 1H), 6,48 (dd, J = 8,4 Hz, 2,0 Hz, 1H), 6,12 (t, J = 2,0 Hz, 1H), 4,39 (s, 2H).

Etapa 2



Una mezcla de 5-aminoindol (20 g, 76 mmol), DMAP (9,2 g, 38 mmol) THF (250 ml) y CH_3CN (100 ml) se enfrió a 0 °C y a la mezcla se le añadió lentamente Boc_2O (132 g, 304 mmol). La mezcla de reacción se dejó calentar a TA y se agitó durante el fin de semana. La mezcla se vertió en agua y extrajo tres veces con CH_2Cl_2. La fase orgánica se combinó, se secó sobre Na_2SO_4 y se filtró. El filtrado se concentró, se disolvió en CH_2Cl_2, se vertió en PE y se filtró. El sólido se purificó por cromatografía en columna (PE/AE = 20/1) para producir el producto (23 g). ^1H RMN ($CDCl_3$): □ 8,05 (d, J = 8,0 Hz, 1H), 7,56 (d, J = 3,2 Hz, 1H), 7,28 (d, J = 2,4 Hz, 1H), 7,03 (dd, J = 8,8 Hz, 1,6 Hz, 1H), 1,63 (s, 9H), 1,36 (s, 18H).

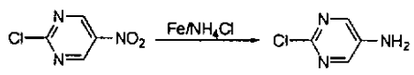
Etapa 3



Una mezcla del producto de la etapa 2 anterior (5,0 g, 11,6 mmol), $(iPrO)_3B$ (17,5 ml, 92,8 mmol) y THF seco (100 ml) se enfrió a 0 °C. A la mezcla se le añadió lentamente LDA (preparado a partir de nBuLi e iPr_2NH en THF, aproximadamente 116 mmol) a 0 °C. La mezcla se dejó calentar a TA y se agitó durante 2 horas. La mezcla se inactivó mediante la adición de HCl 1 N a pH = 3 y se extrajo tres veces con CH_2Cl_2. Las fases orgánicas combinadas se combinaron, se secaron sobre Na_2SO_4 y se filtraron. El filtrado se concentró y se purificó por cromatografía en columna (PE/CH_2Cl_2 = 1/1 a CH_2Cl_2 puro a CH_2Cl_2/acetona = 10/1 a acetona pura) para

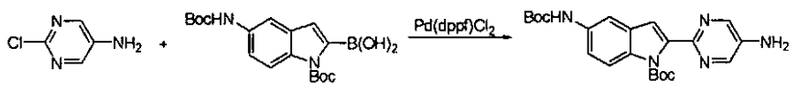
proporcionar el producto (2,8 g). ^{1}H RMN (DMSO) □: 9,22 (s, 1H), 8,10 (s, 2H), 7,84 (d, J = 9,2 Hz, 1H), 7,65 (s, 1H), 7,20 (dd, J = 9,2 Hz, 2,0 Hz, 1H), 6,48 (d, 1H), 1,51 (s, 9H), 1,41 (s, 9H).

Etapa 4



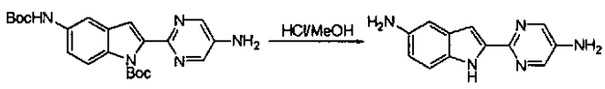
Una mezcla del compuesto de pirimidina (0,3 g, 2 mmol), polvo de Fe (560 mg, 10 mmol), NH_4Cl (1,07 g, 20 mmol), EtOH (8 ml) y agua (2 ml) se calentó a reflujo en una atmósfera de N_2 durante una noche. La mezcla se enfrió a TA y se filtró. El filtrado se concentró y se disolvió en agua. La mezcla se basificó con Na_2CO_3 y se extrajo dos veces con CH_2Cl_2. Las fases orgánicas combinadas se secaron sobre Na_2SO_4 y se filtraron. El filtrado se concentró para producir el producto (120 mg). MS (ESI) m/e ($M+H^+$): 130. ^{1}H RMN (DMSO) □: 7,99 (s, 2H), 5,73 (s, 2H).

Etapa 5



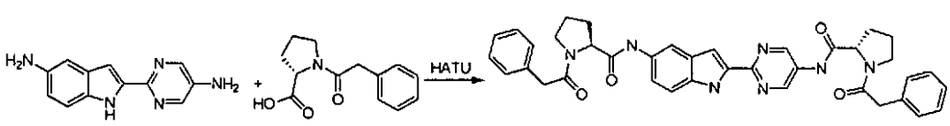
Una mezcla de la pirimidina de la etapa 4 (100 mg, 0,77 mmol), el ácido indol borónico de la etapa 3 (290 mg, 0,77 mmol), $Pd(dppf)Cl_2$ (56 mg, 0,077 mmol), Na_2CO_3 (244 mg, 2,3 mmol), THF (20 ml) y H_2O (2 ml) se calentó a reflujo en una atmósfera de N_2 durante una noche. La mezcla se vertió en agua y se extrajo con CH_2Cl_2. La fase orgánica se combinó, se secó sobre Na_2SO_4 y se filtró. El filtrado se purificó por TLC prep. (CH_2Cl_2/MeOH = 20/1) para proporcionar el producto. MS (ESI) m/e ($M+H^+$): 426.

Etapa 6



Una mezcla del compuesto de la etapa 5 anterior se añadió a una solución de HCl en MeOH (4 M) enfriada con un baño de hielo. La mezcla se dejó calentar a TA y se agitó durante una noche. La mezcla se concentró, se disolvió en agua, se lavó con CH_2Cl_2 y se concentró. El residuo se usó directamente en la siguiente etapa sin purificación adicional. MS (ESI) m/e ($M+H^+$): 226.

Etapa 7

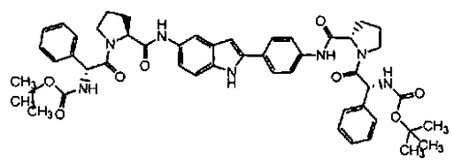
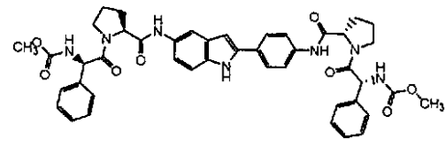
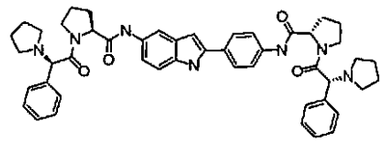
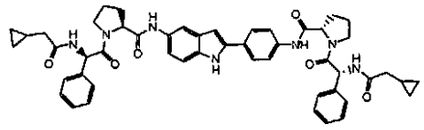


Al producto de la etapa 6 anterior (0,22 mmol), *N*-fenilacetil-L-prolina (51 mg, 0,22 mmol), DIPEA (100 mg) y DMF (3 ml) se le añadió HATU (84 mg, 0,22 mmol) y la mezcla se agitó a TA durante una noche. La mezcla se purificó por RPLC para proporcionar el producto. MS

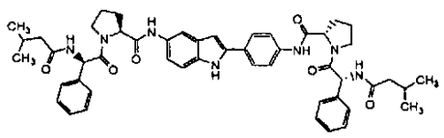
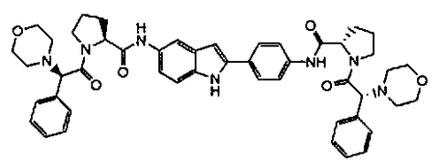
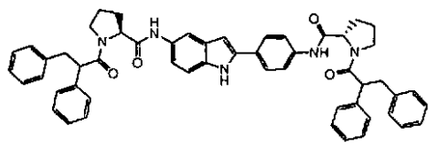
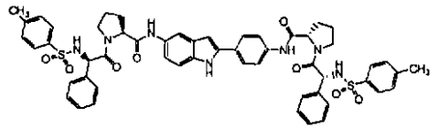
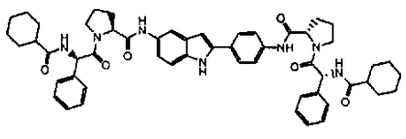
(ESI) m/e ($M+H^+$): 656. ^1H RMN ($CDCl_3$) □: 10,42 (s, 1H), 10,01 (s, 1H), 9,77 (s, 1H), 8,32 (s, 1H), 7,34-7,27 (m, 11H), 7,05-7,00 (m, 2H), 6,58 (d, J = *8,0* Hz, 1H), 4,63-4,53 (m, 2H), 3,84-3,58 (m, 8H), 2,30-1,94 (m, 8H).

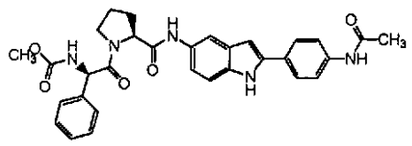
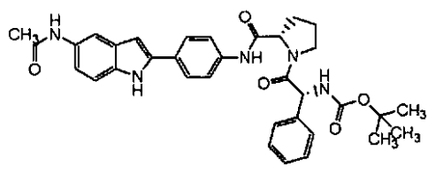
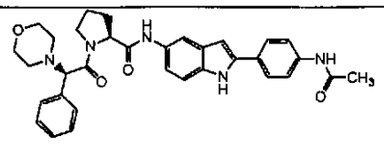
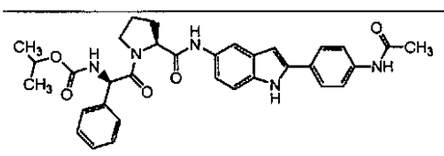
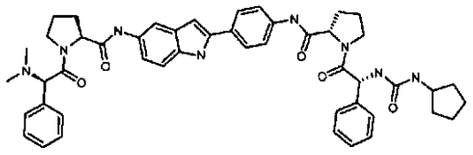
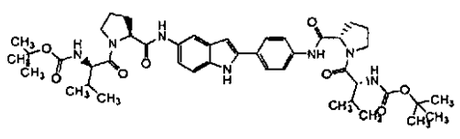
Ejemplos 43-87

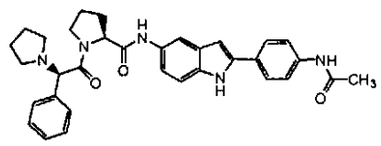
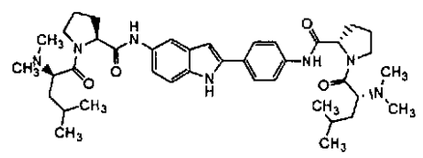
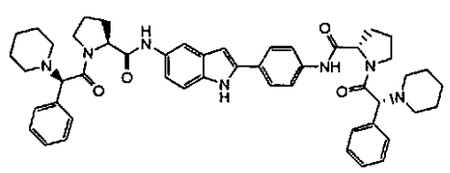
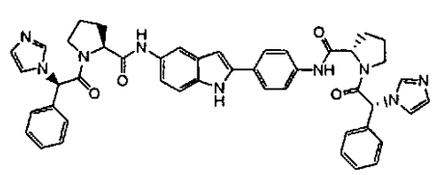
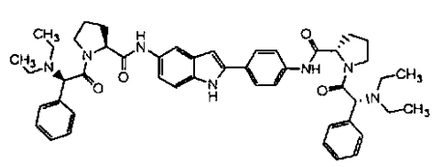
Los compuestos de los Ejemplos 43-87 se prepararon de una manera similar a la que se ha descrito en el Ejemplo 41 o el Ejemplo 42.

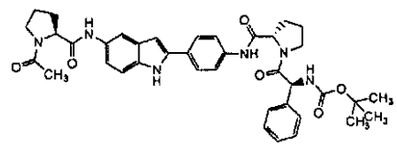
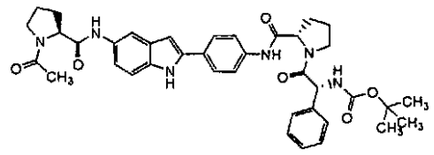
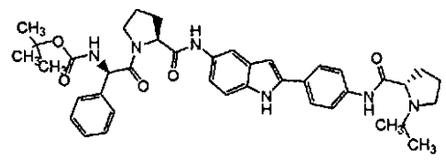
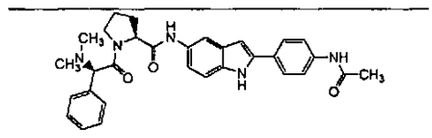
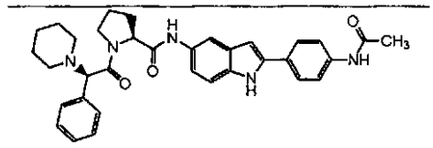
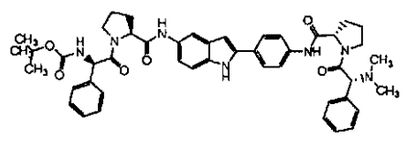
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44		799,891	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo
45		792,002	(2S)-1-{(2R)-2-fenil-2-(pirrolidin-1-il)acetil]-N-(4-{5-[({(2S)-1-[(2^)-2-fenil-2-(pirrolidin-1-il)acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida
46		848,023	(2S)-1-[(2R)-2-[(ciclopropilacetil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[(ciclopropilacetil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil} pirrolidin-2-carboxamida

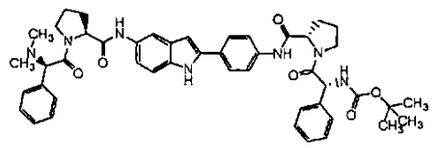
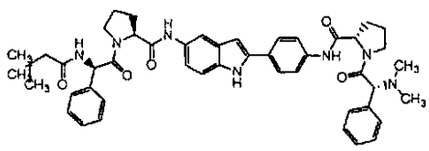
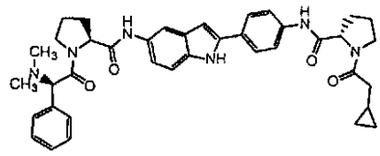
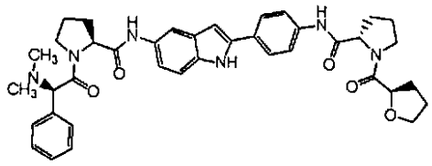
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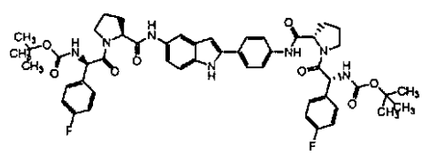
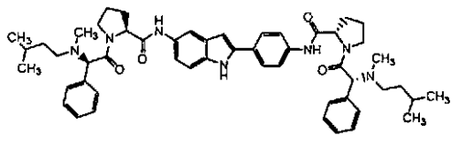
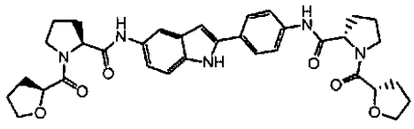
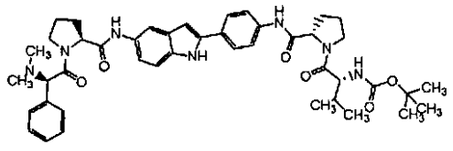
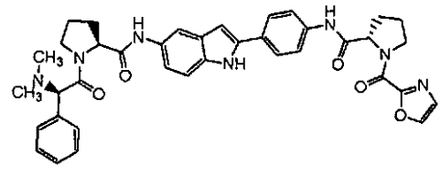
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48		824,001	(2S)-1-[(2R)-2-(morfolin-4-il)-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-(morfolin-4-il)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida
49		834,04	(2S)-1-(2,3-difenilpropanoil)-N-{4-[5-({[(2S)-1-(2,3-difenilpropanoil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida
50		992,195	(2S)-1-[(2R)-2-{[(4-metilfenil)sulfonil]amino}-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-{[(4-metilfenil)sulfonil]amino}-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida
51		904,132	(2S)-1-{(2R)-2-[(ciclohexilcarbonil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[(ciclohexilcarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida

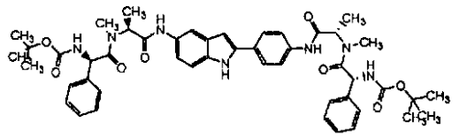
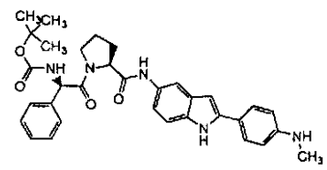
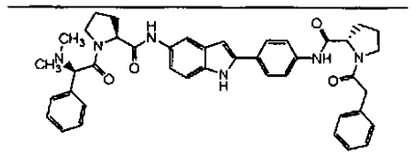
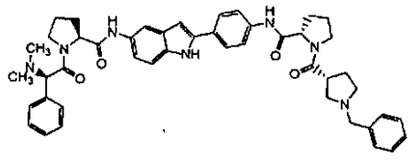
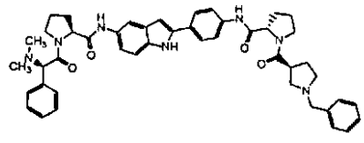
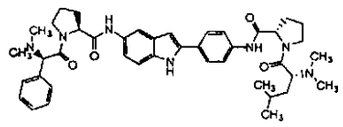
Ejemplo	Estructura	PM	Nombre
52		553,623	{(1R)-2-[(2,S)-2-({2-[4-(acetilamino)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo
53		595,704	{(1R)-2-[(2,S)-2-({4-[5-(acetilamino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
54		565,678	N-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1-{(2R)-2-(morfolin-4-il)-2-fenilacetil]-L-prolinamida
55		581,677	{(1R)-2-[(2,S)-2-({2-[4-(acetilamino)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo
56		817,953	(2S)-1-{(2R)-2-[(ciclopentilcarbamoil)amino]-2-fenilacetil}-N-(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida
57		816,019	{(2R)-1-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de terc-butilo

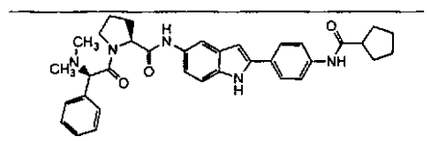
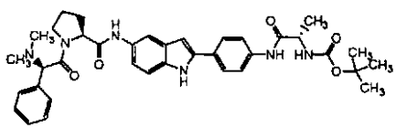
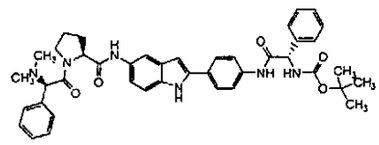
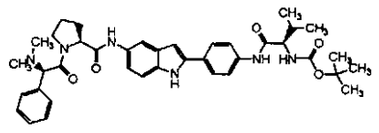
Ejemplo	Estructura	PM	Nombre
58		549,679	N-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1-[(2R)-2-fenil-2-(pirrolidin-1-il)acetil]-L-prolinamida
59		699,945	(2S)-1-[(2R)-2-(dimetilamino)-4-metilpentanoil]-N-(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-4-metilpentanoil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida (nombre no preferido)
60		820,056	(2S)-1-[(2R)-2-fenil-2-(piperidin-1-il)acetil]-N-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-(piperidin-1-il)acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida
61		785,914	(2S)-1-[(2R)-2-(1H-imidazol-1-il)-2-fenilacetil]-N-[4-{5-[({(2S)-1-[(2R)-2-(1H-imidazol-1-il)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida
62		796,034	(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]-N-[4-{5-[({(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida

Ejemplo	Estructura	PM	Nombre
63		692,822	{(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-acetilpirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
64		692,822	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-acetilpirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
65		692,866	{(1R)-2-oxo-1-fenil-2-[(2S)-2-({2-[4-({[(2S)-1-(propan-2-il)pirrolidin-2-il]carbonil}amino)fenil]indol-5-il}carbamoil)pirrolidin-1-il]etil}carbamato de terc-butilo
66		523,64	*N*-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolinamida
67		563,706	*N*-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1-[(2R)-2-fenil-2-(piperidin-1-il)acetil]-L-prolinamida
68		811,99	[(1R)-2-{(2,S)-2-[(2-{4-[({(2S)-1-{(2R)-2-(dimetilammo)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]fenil}-1H-indol-5-il)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de terc-butilo

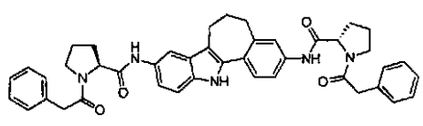
Ejemplo	Estructura	PM	Nombre
69		811,99	[(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de terc-butilo
70		810,017	(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-{4-[5-({[(2S)-1-{(2R)-2-[(3,3-dimetilbutanoil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida
71		660,823	(2S)-1-(ciclopropilacetil)-N-[4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida
72		676,823	(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-(2-{4-[({(2S)-1-[(2R)-tetrahidrofurano-2-ilcarbonil]pirrolidin-2-il}carbonil)amino]fenil}-1H-indol-5-il)pirrolidin-2-carboxamida

Ejemplo	Estructura	PM	Nombre
73		920,035	[(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-(4-fluorofenil)acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)carbamoil]pirrolidin-1-il}-1-(4-fluorofenil)-2-oxoetil]carbamato de terc-butilo
74		852,142	(2S)-1-{(2R)-2-[metil(3-metilbutil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[metil(3-metilbutil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida
75		613,72	(2S)-1-[(2S)-tetrahidrofurano-2-ilcarbonil]-N-(4-{5-[({(2S)-1-[(2S)-tetrahidrofurano-2-ilcarbonil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida
76		777,972	N-(terc-butoxicarbonil)-D-valil-N-{4-[5-({1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolil}amino)-1H-indol-2-il]fenil}-L-prolinamida
77		673,778	(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-{2-[4-({[(2S)-1-(1,3-oxazol-2-ilcarbonil)pirrolidin-2-il]carbonil}amino)fenil]indol-5-il}pirrolidin-2-carboxamida

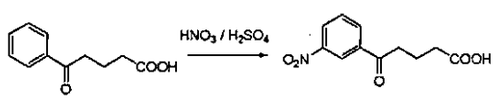
Ejemplo	Estructura	PM	Nombre
78		860,032	[(1R)-2-{[(2S)-1-({4-[5-({(2S)-2-[{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}(metil)amino]propanoil}amino)-1H-indol-2-il]fenil}amino)-1-oxopropan-2-il](metil)amino}-2-oxo-1-feniletil]carbamato de terc-butilo
79		567,694	{(1R)-2-[(2S)-2-({2-[4-(metilamino)fenil] -1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
80		696,857	(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-{2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]indol-5-il}pirrolidin-2-carboxamida
81		765,964	(2S)-1-{[(3R)-1-bencilpirrolidin-3-il]carbonil}-N-(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida
82		765,964	(2S)-1-{[(3S)-1-bencilpirrolidin-3-il]carbonil}-N-(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida
83		719,935	N,N-dimetil-D-leucil-N-{4-[5-({1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolil}amino)-1H-indol-2-il]fenil}-L-prolinamida

Ejemplo	Estructura	PM	Nombre
84		577,733	N-(2-{4-[(ciclopentilcarbonil)amino]fenil}-1H-indol-5-il)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolinamida
85		652,8	[(2S)-1-({4-[5-({1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolil}amino)-1H-indol-2-il]fenil}amino)-1-oxopropan-2-il]carbamato de terc-butilo
86		714,872	[(1S)-2-({4-[5-({1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolil}amino)-1H-indol-2-il]fenil}amino)-2-oxo-1-feniletil]carbamato de terc-butilo
87		680,855	[(2R)-1-({4-[5-({1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolil}amino)-1H-indol-2-il]fenil}amino)-3-metil-1-oxobutan-2-il]carbamato de terc-butilo

Ejemplo 88-(2S,2'S)-N,N'-5,6,7,12-tetrahidrobenzo[6,7]ciclohepta[1,2-b]indolo-3,9-diilbis[1-(fenilacetil)pirrolidin-2-carboxamida]

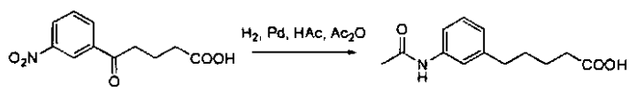


Etapa *1*



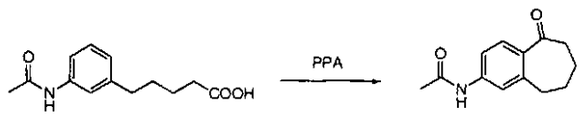
A una mezcla de HNO_3 (4 ml) y H_2SO_4 (2 ml) a 0 °C se le añadió lentamente el ácido carboxílico anterior (2 g, 10,4 mmol). La mezcla se agitó a 0 °C durante 30 minutos. La solución resultante se vertió en 20 ml de H_2O a 0 °C y el precipitado se filtró para dar el compuesto (2 g) en forma de un sólido de color amarillo. MS (ESI) m/e ($M+H^+$): 238.

Etapa 2



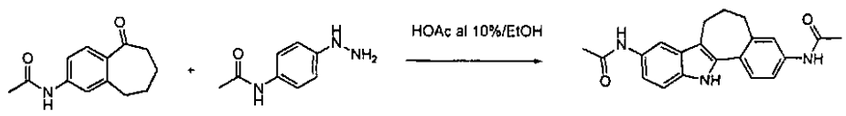
A una mezcla de HOAc (10 ml) y Ac_2O (3 ml) se le añadió el compuesto nitro de la etapa 1 (1 g, 4,3 mmol) y Pd/C (100 mg, 0,6 mmol). La mezcla se agitó en una atmósfera de H_2 durante 6 horas. El catalizador se filtró y el filtrado se concentró al vacío para dar el compuesto deseado (1 g) en forma de un sólido de color pardo. MS (ESI) m/e ($M+H^+$): 236.

Etapa 3



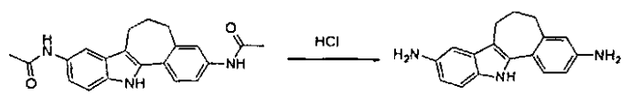
El compuesto de la etapa 2 anterior (150 mg, 0,64 mmol) se añadió lentamente a PPA (6 ml) a 100 °C. La mezcla se agitó durante 3 horas. Después de un periodo de refrigeración, la solución resultante se vertió en 40 ml mezcla de agua y hielo y se extrajo con DCM. La capa orgánica se concentró para dar el producto cíclico (70 mg) en forma de un sólido de color pardo. MS (ESI) m/e ($M+H^+$): 218.

Etapa 4



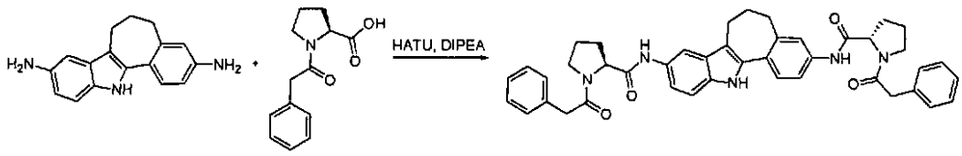
A una solución de la cetona de la etapa 3 (140 mg, 0,65 mmol) en HOAc al 10%/EtOH (10 ml) se le añadió 4-acetamidofenilhidrazina (144 mg, 0,72 mmol). La mezcla se agitó a la temperatura de reflujo durante 4 horas. Después de un periodo de refrigeración, la solución resultante se concentró al vacío, se lavó con agua y se extrajo con EtOAc. La capa orgánica se concentró al vacío para dar el compuesto deseado (200 mg) en forma de un sólido de color pardo. MS (ESI) m/e ($M+H^+$): 348.

Etapa 5



A una solución del producto de la etapa 4 anterior (200 mg, 0,57 mmol) en EtOH (10 ml) se le añadió HCl 6 N (2 ml, 12 mmol). La mezcla se agitó a la temperatura de reflujo durante una noche, se enfrió, la solución resultante se concentró después se purificó por cromatografía ultrarrápida sobre gel de sílice (éter de petróleo/acetato de etilo = 5:1) para dar el compuesto deseado (150 mg) en forma de un sólido de color pardo. MS (ESI) m/e ($M+H^+$): 264.

Etapa 6

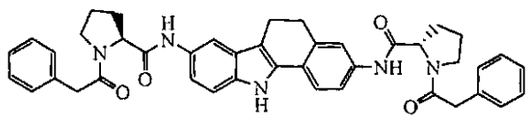
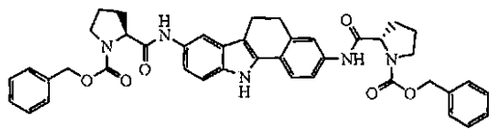
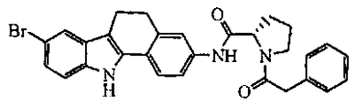
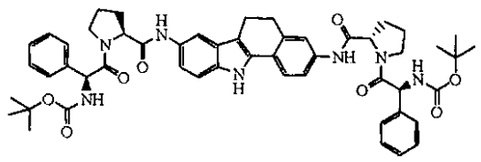
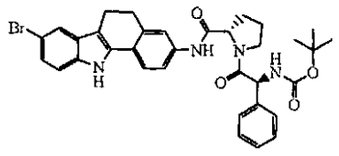
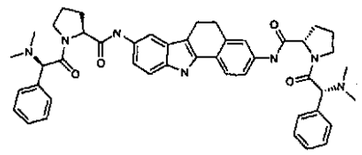


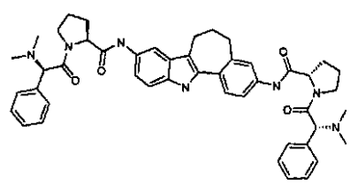
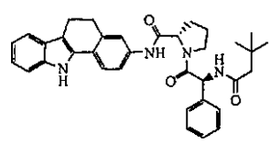
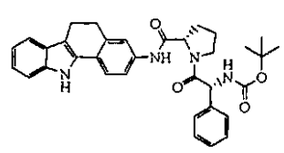
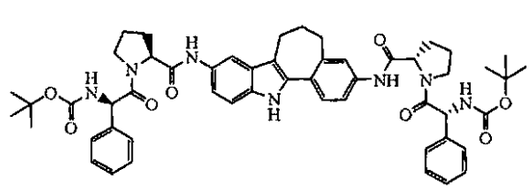
A una solución de la anilina de la etapa 5 (40 mg, 0,15 mmol) en MeCN (5 ml) se le añadieron el análogo de prolina (70 mg, 0,3 mol), HATU (250 mg, 0,6 mmol) y DIPEA (80 mg, 0,6 mmol). La mezcla se agitó durante una noche. La solución resultante se purificó por HPLC prep. para dar el compuesto deseado (10 mg) en forma de un sólido de color pardo. ^{1}H RMN □: 7,62-7,20 (m, 16H), 4,58-4,54 (m, 2H), 3,79-3,60 (m, 6H), 2,95 (m, 2H), 2,80 (m, 2H), 2,26-1,94 (m, 8H). MS (ESI) m/e ($M+H^+$): 694.

Ejemplos 89-98

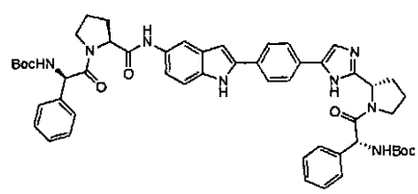
Los compuestos de los Ejemplos 89-98 se prepararon de una manera similar a la que se ha descrito en el Ejemplo 88.

183

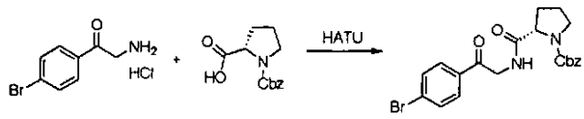
Ejemplo	Estructura	PM	Nombre
89		679,826	(2S,2'S)-N,N'-6,11-dihidro-5H-benzo[a]carbazol-3,8-diilbis[1-(fenilacetil)pirrolidin-2-carboxamida]
90		711,825	(2S,2'S)-2,2'-(6,11-dihidro-5H-benzo[a]carbazol-3,8-diildicarbamoil)dipirrolidin-1-carboxilato de dibencilo
91		528,453	N-(8-bromo-6,11-dihidro-5H-benzo[a]carbazol-3-il)-1-(fenilacetil)-L-prolinamida
92		910,092	(6,11-dihidro-5H-benzo[a]carbazol-3,8-diilbis{carbamoil(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-feniletano-2,1-diil]})biscarbamato de di-terc-butilo
93		643,586	[(1S)-2-{(2S)-2-[(8-bromo-6,11-dihidro-5H-benzo[a]carbazol-3-il)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de terc-butilo
94		765,942	(2S,2'S)-N,N'-6,11-dihidro-5H-benzo[a]carbazol-3,8-diilbis{1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-carboxamida}

Ejemplo	Estructura	PM	Nombre
95		779,968	(2S,2'S)-N,N'-5,6,7,12-tetrahidrobenzo[6,7]ciclohepta[1,2-b]indolo-3,9-diilbis{1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-carboxamida}
96		562,718	N-(6,11-dihidro-5H-benzo[a]carbazol-3-il)-1-{(2S)-2-[(3,3-dimetilbutanoil)amino]-2-fenilacetil}-L-prolinamida
97		564,69	{(1R)-2-[(2S)-2-(6,11-dihidro-5H-benzo[a]carbazol-3-ilcarbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
98		924,119	(5,6,7,12-tetrahidrobenzo[6,7]ciclohepta[1,2-b]indolo-3,9-diilbis{carbamoil(2S)pirrolidin-2,1-diil[(1R)-2-oxo-1-feniletano-2,1-diil]})biscarbamato de di-terc-butilo

Ejemplo 99-{(1R)-2-[(2S)-2-(5-{4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

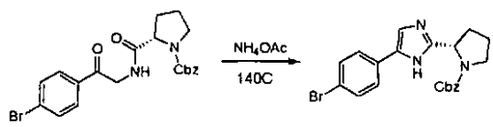


Etapa 1



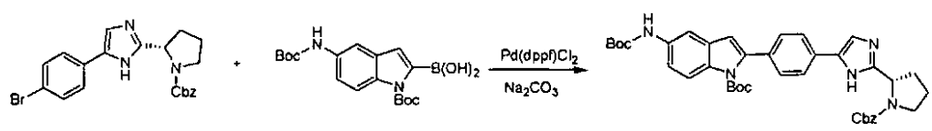
Se añadió HATU (20 g, 52,3 mmol) a una mezcla heterogénea de la amino cetona (12 g, 48,5 mmol) y L-Cbz-Pro (12,4 g, 50 mmol) en MeCN (156 ml). La mezcla se enfrió en un baño de hielo-agua e inmediatamente después se añadió gota a gota DIPEA (27 ml, 155 mmol). Después de la adición de la base, el baño de refrigeración se retiró y la mezcla de reacción se agitó durante 50 minutos más. El componente volátil se retiró, al sólido en bruto resultante se le añadió agua (125 ml) y se agitó durante aproximadamente 1 hora. El sólido de color blanquecino se filtró, se lavó con abundante agua y se secó al vacío para proporcionar el compuesto deseado en forma de un sólido de color blanco (20,68 g). MS (ESI) m/e ($M+H^+$): 446.

Etapa 2



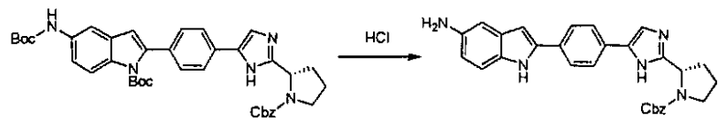
Una mezcla del producto de la etapa 1 anterior (12,8 g, 31,12 mmol) y NH_4OAc (12,0 g, 155,7 mmol) en xilenos (155 ml) se calentó en un tubo cerrado herméticamente a 160 °C durante 2 horas. El componente volátil se retiró al vacío, el residuo se repartió cuidadosamente entre EtOAc y agua, donde se añadió una solución saturada de $NaHCO_3$ suficiente para hacer el pH de la fase acuosa ligeramente básico después de la agitación del sistema bifásico. Las capas se separaron y la capa acuosa se extrajo con más cantidad de EtOAc. La fase orgánica combinada se lavó con salmuera, se secó, se filtro y se concentró al vacío para producir un sólido de color amarillo. MS (ESI) m/e ($M+H^+$): 426. ^1H RMN ($CDCl_3$) □: 7,31-7,52 (m, 9H), 7,17 (s, 1H), 5,12~5,20 (m, 2H), 5,00~5,01 (m, 1H), 3,50~3,52 (m, 2H), 2,96~2,97 (m, 1H), 1,97~2,17 (m, 3H).

Etapa 3



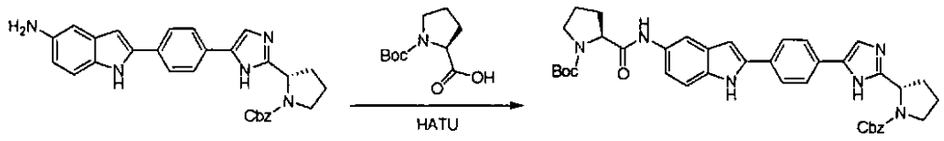
Una mezcla del producto de la etapa 2 anterior (327 mg, 0,77 mmol), el ácido indol borónico del Ejemplo 42 (290 mg, 0,77 mmol), $Pd(dppf)Cl_2$ (56 mg, 0,077 mmol), Na_2CO_3 (244 mg, 2,3 mmol), THF (20 ml) y H_2O (2 ml) se calentó a reflujo en una atmósfera de N_2 durante una noche. La mezcla se vertió en agua y se extrajo con CH_2Cl_2. La fase orgánica se combinó, se secó sobre Na_2SO_4 y se filtró para dar el compuesto deseado, que se usó directamente en la siguiente etapa. MS (ESI) m/e ($M+H^+$): 678.

Etapa 4



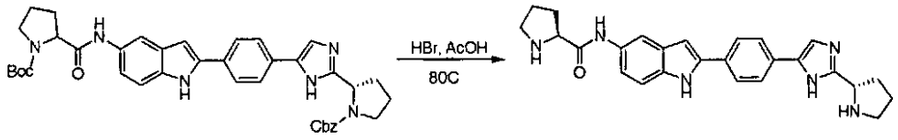
Una solución del producto de la etapa 3 en HCl/CH_3OH (5 N) se agitó durante 3 horas. La concentración al vacío proporcionó el producto en bruto. MS (ESI) m/e ($M+H^+$): 478.

Etapa 5



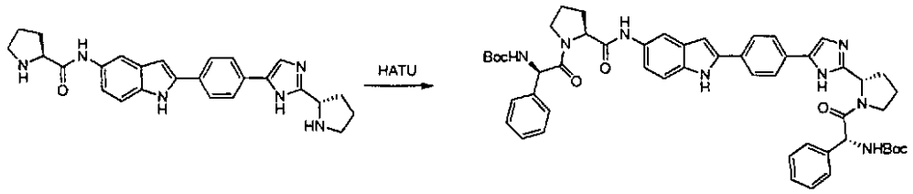
Esta reacción se realizó usando el procedimiento de acoplamiento mediado por HATU que se ha descrito en la etapa 1 entre Boc-L-Pro-OH y el producto de la etapa 4 anterior. MS (ESI) m/e ($M+H^+$): 808. ^1H RMN (MeOD) □: 8,95 (s a, 1H), 6,82~7,56 (m, 17H), 6,50~6,62 (m, 1H), 5,74 (s a, 1H), 5,38~5,39 (m, 1H), 4,91~5,08 (m, 2H), 4,66 (s a, 1H), 3,79 (s a, 1H), 3,40~3,54 (m, 2H), 3,19 (s a, 1H), 1,93~2,25 (m, 4H), 1,75~1,88 (m, 4H), 1,35~1,32 (m, 9H).

Etapa 6



A una solución del producto de la etapa 5 (220 mg, 0,3 mmol) en 20 ml de AcOH se le añadieron 3 ml de HBr al 48%. La solución se calentó a 80 °C durante 6 horas. Los volátiles se retiraron al vacío, el residuo se disolvió en DCM/i-PrOH (3:1), se lavó con Na_2CO_3 saturado y salmuera, se secó y se concentró al vacío para dar un sólido, que se usó en la siguiente etapa directamente. MS (ESI) m/e ($M+H^+$): 441.

Etapa 7

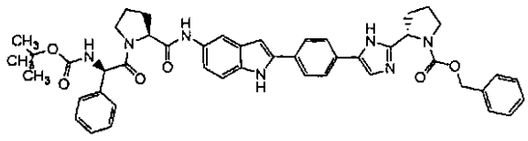
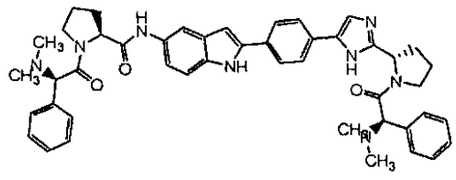
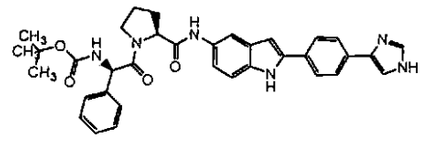
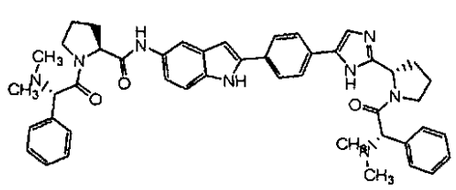


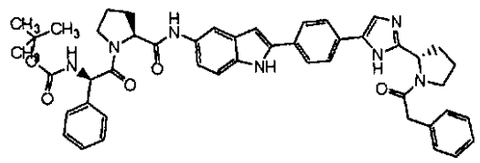
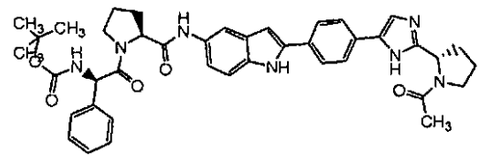
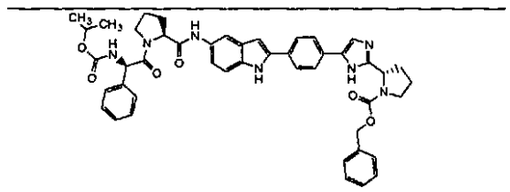
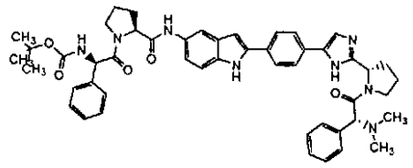
Se añadió gota a gota una solución enfriada que contenía HATU (0,6 mmol), la diamina de la etapa 6 anterior (132 mg, 0,3 mmol) y R-Boc-Pro (129 mg, 0,6 mmol) en MeCN (3 ml), se trató con DIPEA (2,4 mmol) durante 13 minutos. Después de que la adición de la base se completara, el baño de refrigeración se retiró y la mezcla de reacción se agitó durante 30 minutos más. El componente volátil se retiró al vacío; al sólido en bruto resultante se le añadió agua y se agitó

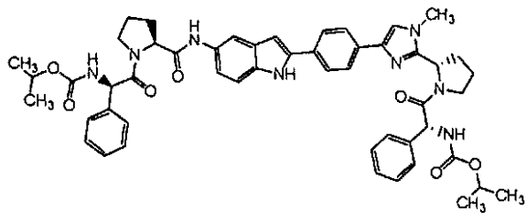
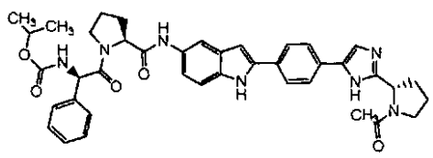
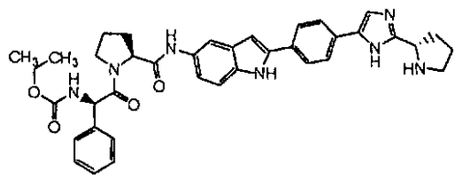
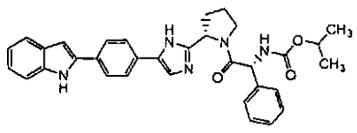
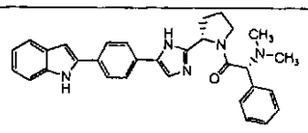
durante aproximadamente 1 hora. El sólido de color blanquecino se filtró, se lavó con agua y se secó al vacío para proporcionar el compuesto deseado en forma de un sólido de color blanco. MS (ESI) m/e ($M+H^+$): 908. ^1H RMN (MeOD) 5: 7,66~7,84 (m, 6 H), 7,28~7,40 (m, 12H), 6,80 (s, 1H), 5,40~5,45 (m, 2H), 5,18~5,20 (m, 1H), 3,70~4,02 (m, 4 H), 1,80~2,12 (m, 8 H), 1,35~1,37 (m, 18 H).

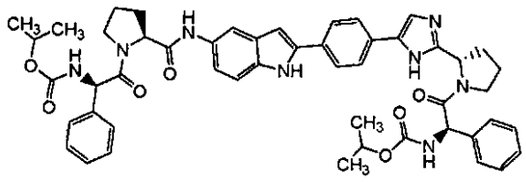
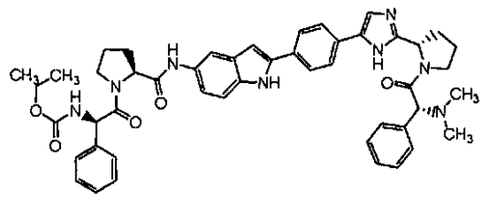
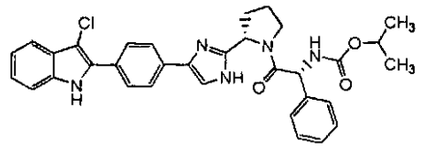
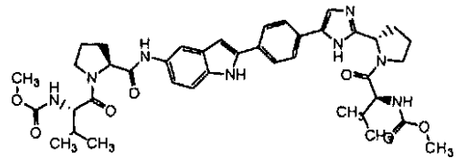
Ejemplos 100-116

Los compuestos de los Ejemplos 100-116 se prepararon de una manera similar a la que se ha descrito en el Ejemplo 99.

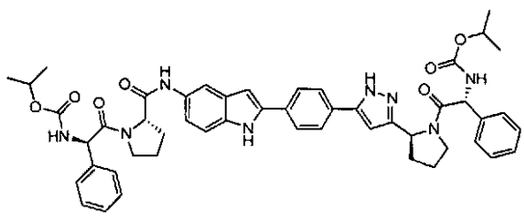
Ejemplo	Estructura	PM	Nombre
100		807,958	(2S)-2-[5-(4-{5-[(1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}-L-prolil)amino]-1H-indol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-carboxilato de bencilo
101		762,963	1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-{2-[4-(2-{(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-*1H*-indol-5-il}-L-prolinamida
102		604,715	{(1R)-2-[(2S)-2-({2-[4-(1H-imidazol-4-il)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
103		762,963	1-[(2S)-2-(dimetilamino)-2-fenilacetil]-N-{2-[4-(2-{(2S)-1-[(2S)-2-(dimetilamino)-2-fenilaceril]pirrolidin-2-il}-1H-imidazol-5-il)fenil]indol-5-il}-L-prolinamida

Ejemplo	Estructura	PM	Nombre
104		791,958	{(1R)-2-oxo-1-fenil-2-[(2S)-2-{[2-(4-{2-[(2S)-1-(fenilacetil)pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-indol-5-il]carbamoil}pirrolidin-1-il]etil}carbamato de terc-butilo
105		715,86	{(1R)-2-[(2S)-2-{[2-(4-{2-[(2S)-1-acetilpirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-indol-5-il]carbamoil}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
106		793,931	(2S)-2-(5-{4-[5-({1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]-L-prolil}amino)-1H-indol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-carboxilato de bencilo
107		835,027	{(1R)-2-[(2S)-2-({2-[4-(2-{(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

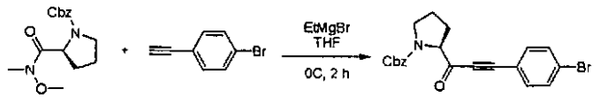
Ejemplo	Estructura	PM	Nombre
108		893,064	[(1R)-2-{(2S)-2-[1-metil-4-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de propan-2-ilo
109		701,833	{(1R)-2-[(2S)-2-{[2-(4-{2-[(2S)-1-acetilpirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-indol-5-il]carbamoil}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo
110		659,795	{(1R)-2-oxo-1-fenil-2-[(2S)-2-{[2-(4-{2-[(2S)-pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-indol-5-il]carbamoil}pirrolidin-1-il]etil}carbamato de propan-2-ilo
111		547,663	{(1R)-2-[(2S)-2-{5-[4-(1H-indol-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo
112		489,626	(2R)-2-(dimetilamino)-1-[(2S)-2-{5-[4-(1H-indol-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-feniletanona

Ejemplo	Estructura	PM	Nombre
113		879,037	[(1R)-2-oxo-1-fenil-2-{(2S)-2-[5-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}etil]carbamato de propan-2-ilo
114		821	{(1R)-2-[(2S)-2-({2-[4-(2-{(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo
115		582,108	{(1R)-2-[(2S)-2-{4-[4-(3-cloro-1H-indol-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo
116		754,894	N-(metoxicarbonil)-L-valil-N-{2-[4-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1H-indol-5-il}-L-prolinamida

Ejemplo 117-[(1R)-2-oxo-1-fenil-2-{(2S)-2-[3-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1H-pirazol-5-il]pirrolidin-1-il}etil]carbamato de propan-2-ilo

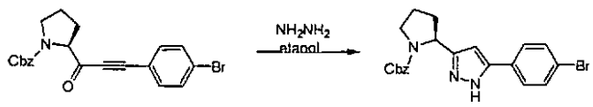


Etapa 1



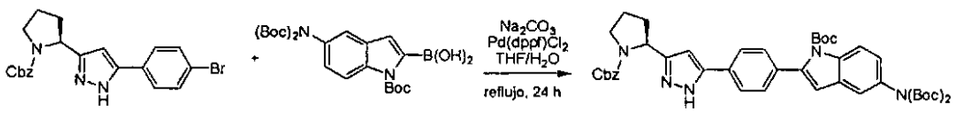
Una solución de 4-bromofenilacetileno (5,0 g, 27,6 mmol) en THF (100 ml) a 0 °C se trató una solución de EtMgBr (3 M en THF, 9,84 ml, 29,5 mmol). Después de 10 minutos, el baño de refrigeración se retiró y la mezcla se dejó en agitación a TA durante 3 horas. Después, la mezcla de reacción se enfrió a 0 °C y se añadió a la amida de Weinreb de Z-prolina (6,10 g, 20,9 mmol) en THF (50 ml). La mezcla de reacción se calentó a TA durante 48 horas. La mezcla de reacción se inactivó con NH_4Cl saturado y se diluyó con EtOAc/H_2O. La fase acuosa se extrajo de nuevo con EtOAc (2 x), las capas orgánicas combinadas se lavaron (H_2O y salmuera), se secaron (Na_2SO_4) y se filtraron. El disolvente se retiró y el residuo se purificó por gel de sílice (PE:AE = 10:1-4:1) para dar el producto (7,0 g) en forma de un sólido de color crema. ^1H RMN ($CDCl_3$) □: 7,37~7,47 (m, 2 H), 7,10~7,30 (m, 7 H), 4,98~5,32 (m, 2 H), 4,32~4,47 (m, 1 H), 3,45~3,61 (m, 2 H), 2,15~2,27 (m, 1 H), 2,03~2,12 (m, 1 H), 1,76~193 (m, 2 H). MS (ESI) m/e ($M+H^+$): 413.

Etapa 2



Una mezcla del producto de la etapa 1 (7,0 g, 17 mmol) e hidrazina hidrato (85%, 1,6 ml) en EtOH (50 ml) se calentó a 80 °C durante 16 horas. La mezcla de reacción se enfrió y se concentró para proporcionar el producto deseado (6,7 g). MS (ESI) m/e ($M+H^+$): 426.

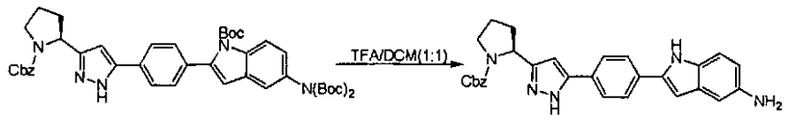
Etapa 3



Una mezcla del producto de la etapa 2 anterior (0,77 mmol), el ácido indol borónico del Ejemplo 42 (290 mg, 0,77 mmol), $Pd(dppf)Cl_2$ (56 mg, 0,077 mmol), Na_2CO_3 (244 mg, 2,3 mmol), THF (20 ml) y H_2O (2 ml) se calentó a reflujo en una atmósfera de N_2 durante una noche. La

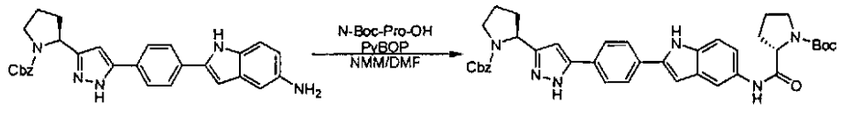
mezcla se vertió en agua, se extrajo con CH_2Cl_2, se secó sobre Na_2SO_4 y se filtró para dar el compuesto deseado, que se usó directamente en la siguiente etapa. MS (ESI) m/e ($M+H^+$): 678.

Etapa 4



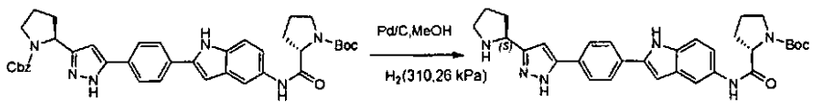
Una solución del producto de la etapa 3 anterior (339 mg, 0,5 mmol) se disolvió en 3 ml de DCM y se enfrió a 0 °C. Después de la adición de 3 ml de TFA, la mezcla de reacción se calentó a TA y se agitó durante 3 horas. La retirada del disolvente dejó el producto deseado en forma de un aceite, que se usó directamente en la siguiente reacción. MS (ESI) m/e ($M+H^+$): 378.

Etapa 5



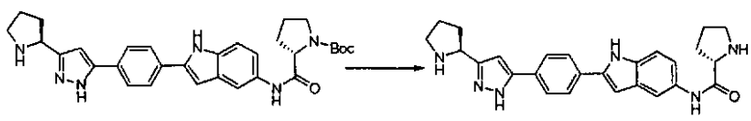
Una solución que contenía PyBOP (0,3 mmol), la amina de la etapa 4 anterior (132 mg, 0,3 mmol) y N-Boc-L-Pro-OH (62 mg, 0,3 mmol) en DMF (2 ml) se trató con N-metilmorfolina (1,2 mmol). La mezcla de reacción se agitó durante 3 horas, se diluyó con EtOAc y se lavó con agua (5 x). La fase orgánica se secó, se concentró y después se sometió a cromatografía por RPLC para proporcionar el compuesto deseado. MS (ESI) m/e ($M+H^+$): 675.

Etapa 6



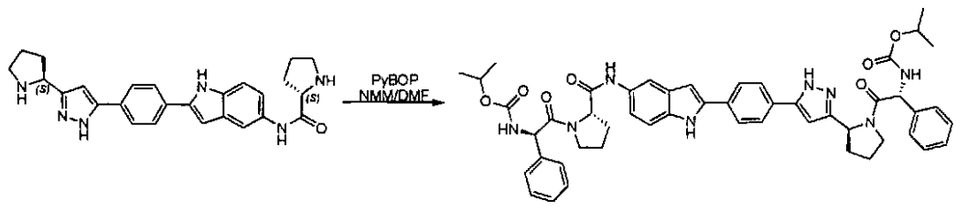
El producto de la etapa 5 (100 mg, 0,15 mmol) se disolvió en MeOH y se trató con 20 mg de % $Pd(OH)_2$ al 20% y después se hidrogenó a 310,26 kPa (45 psi) durante 4 horas. El catalizador se retiró por filtración a través de CELITE y el filtrado se evaporó para dejar el producto deseado. MS (ESI) m/e ($M+H^+$): 541.

Etapa 7



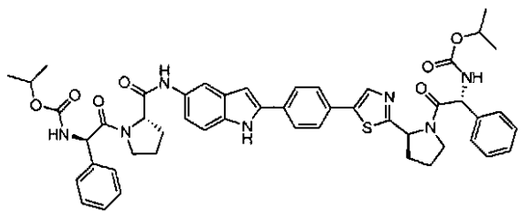
Una solución del producto de la etapa 6 anterior se disolvió en 2 ml de DCM y 2 ml de TFA. La mezcla de reacción se agitó durante 3 horas antes de que el disolvente se evaporara para dar el producto deseado en forma de un aceite, que se usó directamente en la siguiente reacción. MS (ESI) m/e ($M+H^+$): 441.

Etapa 8

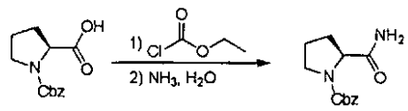


Una solución que contenía PyBOP (0,6 mmol), la diamina de la etapa 7 anterior (132 mg, 0,3 mmol) y R-i-Proc-Phg-OH (125 mg, 0,6 mmol) en DMF (5 ml) se trató con N-metilmorfolina (2,4 mmol). La mezcla de reacción se agitó durante 3 horas, se diluyó con 20 ml de EtOAc y se lavó con agua (5 x). La fase orgánica se secó, se concentró y después se sometió a cromatografía por RPLC para proporcionar el compuesto deseado. ^{1}H RMN (MeOD) □: 7,70~7,80 (m, 4H), 7,05~7,55 (m, 14H), 6,80~7,00 (m, 1H), 5,10~5,50 (m, 3H), 4,40~4,65 (m, 2H), 3,25~4,00 (m, 4H), 1,70~2,40 (m, 9H), 1,05~1,20 (m, 12H). MS (ESI) m/e ($M+H^+$): 880.

Ejemplo 118-[(1R)-2-oxo-1-fenil-2-{(2S)-2-[5-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1,3-tiazol-2-il]pirrolidin-1-il}etil]carbamato de propan-2-ilo

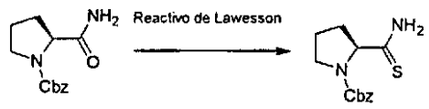


Etapa 1



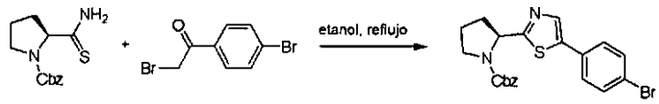
Se añadió gota a gota cloroformiato de etilo (12 ml, 125 mmol) en 180 ml de THF a una solución enfriada (-5 °C) del compuesto Z-Pro-OH (13,8 g, 55,5 mmol), TEA (7,71 ml, 55,5 mmol). La suspensión resultante se agitó durante 20 minutos a -5 °C antes de añadir el NH_4OH saturado (15 ml). La solución se agitó a TA durante 18 horas, los volátiles se retiraron y el residuo se recogió en EtOAc (180 ml). El precipitado de color blanco sin disolver se retiró por filtración y se aclaró con EtOAc (100 ml). Las capas orgánicas se secaron sobre Na_2SO_4 y se concentró al vacío para dar el producto deseado (13,5 g) en forma de un sólido amorfo de color blanquecino. MS (ESI) m/e ($M+H^+$): 249.

Etapa 2



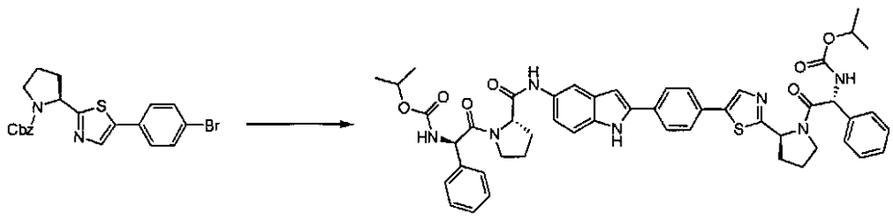
Se añadió reactivo de Lawesson (16,1 g, 39,9 mmol) a una suspensión agitada de la amida (18 g, 72,6 mmol) en PhMe (200 ml) a TA. La mezcla de reacción se calentó a 100 °C durante 3 horas antes de retirar el disolvente. El residuo se purificó por cromatografía ultrarrápida de SiO_2 (DCM/MeOH = 1:0-20:1) para proporcionar el producto (18 g). MS (ESI) m/e ($M+H^+$): 265.

Etapa 3



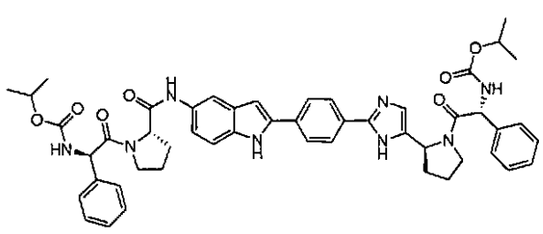
Una mezcla de la tioamida de la etapa 2 (10,0 g, 37,8 mmol) y la bromoacetofenona (10,0 g, 35,9 mmol) en EtOH (100 ml) se calentó a 90 °C durante 150 minutos. La mezcla de reacción se enfrió, se concentró y el residuo se purificó por cromatografía sobre SiO_2 para proporcionar el producto (11 g). MS (ESI) m/e ($M+H^+$): 444.

Etapa 4

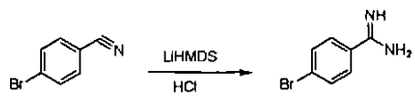


El producto de la etapa 3 anterior puede convertirse en los compuestos finales usando el mismo procedimiento que se ha descrito en el Ejemplo 117, etapas 4-8. ^1H RMN (MeOD) □: 7,00~8,10 (m, 19H), 5,40~5,60 (m, 3H), 4,50~4,70 (m, 1H), 3,45~4,10 (m, 4H), 3,35~3,40 (m, 1H), 1,80~2,6 (m, 9H), 1,05~1,30 (m, 12H). MS (ESI) m/e ($M+H^+$): 897.

Ejemplo 119-[(1R)-2-oxo-1-fenil-2-{(2S)-2-[2-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]aminoacetil}pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1H-imidazol-5-il]pirrolidin-1-il}etil]carbamato de propan-2-ilo

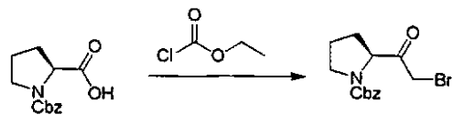


Etapa 1



A una solución de 4-bromobenzonitrilo (1,82 g, 10 mmol) en THF anhidro (50 ml) se le añadió LiHMDS (2 N, 15 mmol) en una atmósfera de N_2 a TA y la mezcla se agitó durante 1 hora. Después de inactivar con HCl 1 N, la mezcla de reacción se calentó a reflujo durante 5 minutos. El precipitado se recogió por filtración y después se secó al vacío para dar el compuesto deseado (1,9 g). ^{1}H RMN (DMSO) □: 7,74 (d, 2H, J = 8,2 Hz), 7,62 (d, 2H, J = 8,2 Hz) 6,43 (a, 3H).

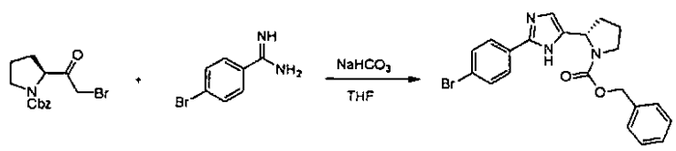
Etapa 2



A una solución de Cbz-Pro-OH (2,9986 g, 12,0 mmol) en THF (100 ml) se le añadió TEA (1,7 ml, 12,2 mmol). La solución se enfrió a -25 °C y se añadió cloroformiato de etilo (1,6 ml, 12,3 mmol). La solución resultante se agitó a TA durante 1 hora. El precipitado se retiró por filtración y el filtrado se usó en la siguiente etapa sin purificación. A la mezcla de reacción anterior se le añadió una solución de diazometano 0,5 M. La muestra se agitó a -10 °C durante 1 hora. La mezcla de reacción se concentró para dar un medio de su volumen original y se lavó una vez con $NaHCO_3$ saturado (50 ml). La capa orgánica se secó sobre $MgSO_4$ y se filtró. El material en bruto se absorbió sobre gel de sílice y se purificó por cromatografía ultrarrápida (40 g de SiO_2, acetato de etilo al 0-50% en hexanos) para dar la diazocetona (2,29 g). ^{1}H RMN ($CDCl_3$) □: 7,32 (m, 5H) 5,13 (m, 2H), 4,61 (m, 1H), 3,81, 4,03, 4,17 (s, cuadruplete AB, 2H, J = 4,0 Hz), 3,58 (m, 2H), 1,88-2,09, 2,17-2,38 (2, m a, 4H).

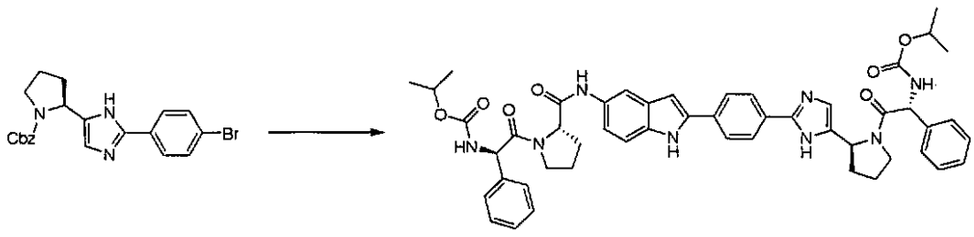
A una solución de la *N*-carbobenciloxi-L-prolina diazocetona (1,0 g, 3,6 mmol) en éter dietílico anhidro (10 ml) se le añadió una solución saturada de HBr en éter dietílico hasta que el desprendimiento de N_2 cesó. La solución se agitó durante aproximadamente 1 hora a aproximadamente 25 °C y después se lavó con $NaHCO_3$ saturado, agua y salmuera. El material en bruto se purificó por cromatografía en columna sobre gel de sílice y se eluyó con acetato de etilo al 40% en pentano para obtener la bromocetona (0,49 g) en forma de un aceite transparente. ^{1}H RMN ($CDCl_3$; mezcla de rotámeros de amida *cis-trans*) □: 7,35 (m, 5H), 5,28 (t, 1H), 5,17 (m, 2H), 4,32 (m, 1H), 3,58 (m, 2H), 1,84-2,30 (m a, 4H).

Etapa 3



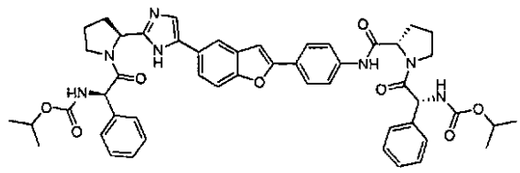
A una mezcla de bromocetona (3,25 g, 10 mmol) y la amidina (1,97 g, 10 mol) en THF (100 ml) se le añadió $NaHCO_3$ (1,7 g, 20 mmol) y la suspensión se agitó a la temperatura de reflujo durante 12 horas. La reacción se enfrió, se concentró y se sometió a cromatografía para dar el compuesto 7 (0,425 g). MS (ESI) m/e ($M+H^+$): 426, 428.

Etapa 4



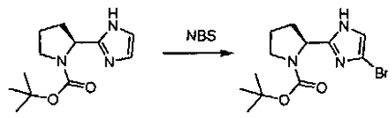
El producto de la etapa 3 anterior puede convertirse en los compuestos finales usando el mismo procedimiento que se ha descrito en el Ejemplo 117, etapas 4-8. ^1H RMN (MeOD) □: 7,7-8,0 (m, 5H), 7,3-7,5 (m, 10H), 6,9-7,1 (m, 3H), 6,8 (d, J = 4,8 Hz, 10H), 5,4-5,6 (m, 2H), 5,2-5,3 (m, 1H), 4,8 (s, 2H), 4,5-4,7 (m, 10H), 4,0 (d, J = 2,4 Hz, 1H), 3,7 (d, J = 4,84 Hz, 1H), 3,1-3,3 (m, 1H), 2,3-2,5 (m, 1H), 1,8-2,2 (m, 1H), 1,1-1,4 (m, 12H). MS (ESI) m/e ($M+H^+$): 880.

Ejemplo 120-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]-N-{4-[5-(2-{(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]aminoacetil]pirrolidin-2-il}-1H-imidazol-5-il)-1-benzofuran-2-il]fenil}-L-prolinamida



Se añadió gota a gota glioxal (2,0 ml del 40% en agua) a una solución en MeOH de NH_4OH (32 ml) y *(S)*-Boc-prolinal (8,564 g, 42,98 mmol) y después el conjunto se agitó a temperatura ambiente durante 19 horas. El componente volátil se retiró al vacío y el residuo se purificó por una cromatografía ultrarrápida (gel de sílice, acetato de etilo) seguido de una recristalización (acetato de etilo) para proporcionar el compuesto en forma de un sólido esponjoso de color blanco (4,43 g). ^1H RMN (DMSO) □: 11,68/11,59 (s a, 1H), 6,94 (s, 1H), 6,76 (s, 1H), 4,76 (m, 1H), 3,48 (m, 1H), 3,35-3,29 (m, 1H), 2,23-1,73 (m, 4H), 1,39/1,15 (s, 9H).

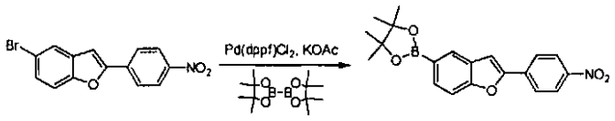
Etapa 2



Se añadió en lotes NBS (838,4 mg, 4,71 mmol) durante 15 minutos a una solución enfriada (hielo/agua) en CH_2Cl_2 (20 ml) de imidazol (1,06 g, 4,50 mmol). La mezcla de reacción se agitó

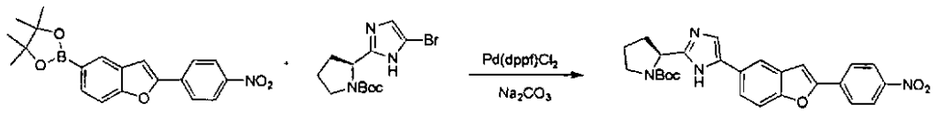
durante 75 minutos y se concentró. El material en bruto se purificó por RPLC para separar el bromuro de bromo de su análogo de dibromo y el material de partida. El eluato de HPLC se neutralizó con exceso de NH_3/MeOH y el componente volátil se retiró al vacío. El residuo se repartió entre CH_2Cl_2 y agua y la capa acuosa se extrajo con agua. La fase orgánica combinada se secó ($MgSO_4$), se filtró y se concentró para proporcionar un compuesto en forma de un sólido de color blanco (374 mg). ^{1}H RMN (DMSO) □: 12,12 (s a, 1H), 7,10 (m, 1H), 4,70 (m, 1H), 3,31 (m, 1H; solapado con una señal de agua), 2,25-1,73 (m, 4H), 1,39/1,17 (s, 3,8H + 5,2H).

Etapa 3



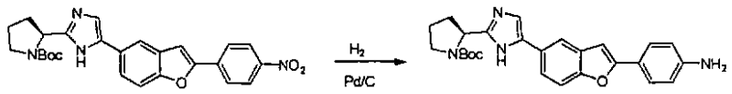
A una mezcla del benzofurano del Ejemplo 19, etapa 1 (15 g, 0,05 mol), bis(pinacolato)diboro (25,4 g, 0,1 mol), $Pd(dppf)Cl_2$ (1 g), KOAc (0,1 mol) en dioxano (500 ml) se agitó a la temperatura de reflujo en una atmósfera de N_2 durante 2 horas. La concentración de la mezcla de reacción dejó un residuo que se sometió a cromatografía para dar el compuesto deseado (12 g). ^{1}H RMN (DMSO) □: 8,28 (d, J = 8,8 Hz, 2H), 8,10 (s, 1H), 7,95 (d, J = 8,8 Hz, 2H), 7,72 (d, J = 8,8 Hz, 1H), 7,43 (d, J = 8,8 Hz, 1H), 7,05 (s, 1H).

Etapa 4



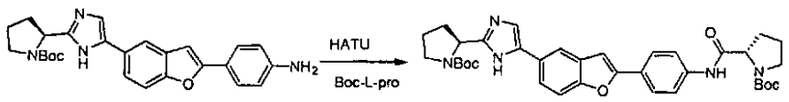
Esta reacción se realizó de una manera similar a la que se ha descrito en el Ejemplo 117. MS (ESI) m/e ($M+H^+$): 475.

Etapa 5



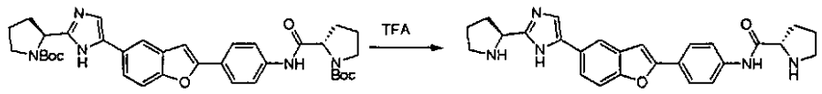
El producto de la etapa 4 (475 mg, 1,0 mmol) se disolvió en EtOH y se trató con 20 mg de Pd al 10%/C y después se hidrogenó durante 5 horas. El catalizador se retiró por filtración a través de CELITE y el filtrado se evaporó para dejar el producto deseado. MS (ESI) m/e ($M+H^+$): 445.

Etapa 6



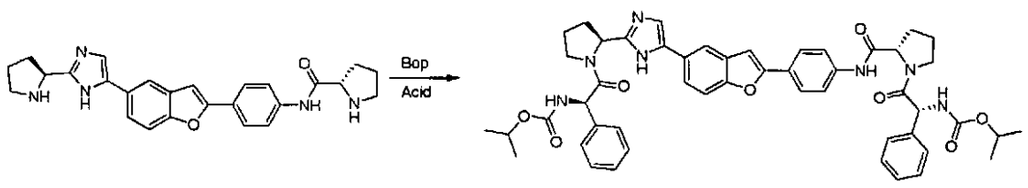
Una solución que contenía HATU (1,0 mmol), la amina de la etapa 5 anterior (445 mg, 1,0 mmol) y N-Boc-L-Pro-OH (215 mg, 1,0 mmol) en MeCN (10 ml) se trató con DIPEA (1,2 mmol). La mezcla de reacción se agitó durante 3 horas, se diluyó con EtOAc y se lavó con agua (5 x). La fase orgánica se secó, se concentró y después se sometió a cromatografía sobre gel de sílice (EtOAc) para proporcionar el compuesto deseado. MS (ESI) m/e ($M+H^+$): 642.

Etapa 7



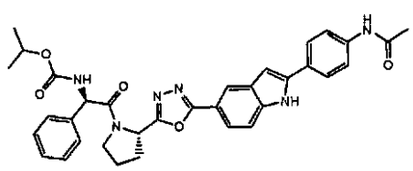
Una solución del producto de la etapa 6 anterior se disolvió en 2 ml de DCM y 2 ml de TFA. La mezcla de reacción se agitó durante 3 horas antes de que el disolvente se evaporara para dar el producto deseado en forma de un aceite, que se usó directamente en la siguiente reacción. MS (ESI) m/e ($M+H^+$): 442.

Etapa 8

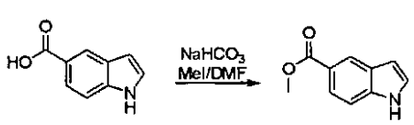


Una solución que contenía el reactivo BOP (222 mg, 0,5 mmol), la diamina de la etapa 7 anterior (112 mg, 0,25 mmol) y R-i-Proc-Phg-OH (125 mg, 0,6 mmol) en DMF (5 ml) se trató con N-metilmorfolina (2,4 mmol). La mezcla de reacción se agitó durante 3 horas, se diluyó con 20 ml de EtOAc y se lavó con agua (5 x). La fase orgánica se secó, se concentró y después se sometió a cromatografía por RPLC para proporcionar el compuesto deseado. ^1H RMN (MeOD) □: 6,8-7,9 (m, 19H), 5,1-5,5 (m, 3H), 4,5 (m, 1H), 3,5-4,04 (m, 2H), 1,6-2,5 (m, 9H), 0,9-1,3(m, 12H). MS (ESI) m/e ($M+H^+$): 880.

Ejemplo 121-{(1R)-2-[(2S)-2-(5-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1,3,4-oxadiazol-2-il)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo

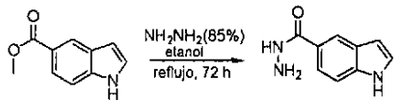


Etapa 1



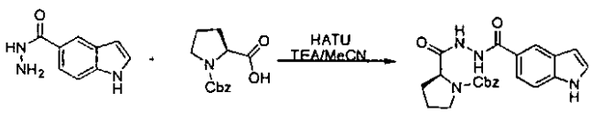
Una mezcla de 5-carboxiindol (32,2 g, 0,2 mol), $NaHCO_3$ (53,36 g, 0,64 mol), yoduro de metilo (122,22 g, 0,86 mol) en 60 ml de DMF se agitaron a TA durante 2 días. Se añadieron agua y EtOAc, la capa orgánica se lavó con una solución de bicarbonato, se secó y se concentró para obtener 5-(metoxicarbonil)indol. ^{1}H RMN (DMSO) □: 11,44 (s, 1H), 8,22 (s, 1H), 7,68(d, J = 8,4 Hz, 1H), 7,37~7,47 (m, 2 H), 6,56(d, J = 2,0 Hz, 1H), 3,80 (s, 3H). MS (ESI) m/e ($M+H^+$): 176.

Etapa 2



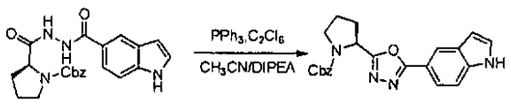
Una mezcla del éster (28 g, 0,16 mmol) y NH_2NH_2 (85%, 50 ml) en etanol (200 ml) se calentó a reflujo durante 48 horas. La mezcla de reacción se concentró y el residuo se purificó por cromatografía en columna (MeOH al 5%/DCM) para dar el compuesto (25 g). ^{1}H RMN (DMSO) □: 11,27 (s, 1H), 9,54 (s, 1H), 8,06 (s, 1H), 7,57 (d, J = 8,8 Hz, 1H), 7,37 (d, J = 8,8 Hz, 2H), 4,42 (s, 1H), 6,48 (s, 2H), 3,32 (s, 1H). MS (ESI) m/e ($M+H^+$): 176.

Etapa 3



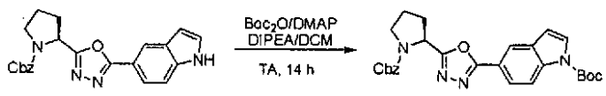
El producto de la etapa 3 anterior se acopló usando un procedimiento de formación de enlace amida HATU convencional. MS (ESI) m/e ($M+H^+$): 407.

Etapa 4



A una suspensión del producto de la etapa 3 anterior (100 g, 0,25 mol), PPh_3 (98,4 g, 0,375 mol) y DIPEA (96,7 g, 0,75 mol) en CH_3CN (500 ml) a TA se le añadió C_2Cl_6 (82,8 g, 0,35 mol). La reacción se agitó a TA durante 1,5 horas, el disolvente se retiró y el residuo se repartió en porciones con EtOAc/H_2O. Las capas se separaron, la fase acuosa se extrajo de nuevo con EtOAc (2 x), las capas orgánicas combinadas se retiraron al vacío y el residuo se purificó por columna cromatografía (MeOH al 5%/DCM) para dar el compuesto 4 (55 g). MS (ESI) m/e ($M+H^+$): 389

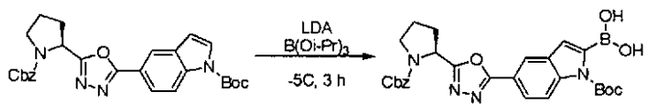
Etapa 5



Se añadió gota a gota dicarbonato de di-terc-butilo (30,7 g, 142 mmol) a una solución de indol (55,0 g, 142 mmol), DMAP (2,0 g) y DIPEA (18,3 g, 142 mmol) en 50 ml de DCM a 0 °C.

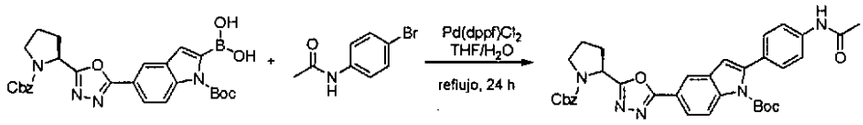
La reacción se dejó en agitación a TA durante una noche antes de que se concentrara y el residuo se purificó por TLC prep. (PE/AE = 2:1). MS (ESI) m/e ($M+H^+$): 489.

Etapa 6



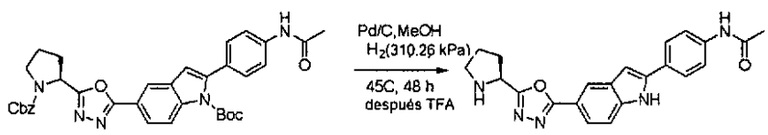
Una mezcla del compuesto indol de la etapa 5 (977 mg, 2 mmol), (iPrO)$_3$B (3,0 g, 16 mmol) y THF seco (100 ml) se enfrió a 0 °C. Se añadió lentamente LDA (preparado a partir de n-BuLi e iPr$_2$NH en THF, aproximadamente 8 mmol) y la mezcla se dejó calentar a TA durante 2 horas. La mezcla se inactivó por HCl 1 N a pH = 3 y se extrajo tres veces con CH_2Cl_2. Las fases orgánicas combinadas se combinaron, se secaron sobre Na_2SO_4 y se filtraron. El filtrado se concentró y se purificó por cromatografía en columna (PE/DCM = 1/1 a CH_2Cl_2 puro a CH_2Cl_2/acetona = 10/1 a acetona pura) para proporcionar el producto 8 (0,5 g).

Etapa 7



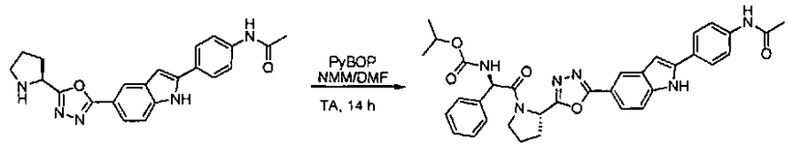
Una mezcla del producto de la etapa 6 (0,38 mmol), ácido indol borónico del Ejemplo 42 (145 mg, 0,38 mmol), Pd(dppf)Cl_2 (28 mg, 0,038 mmol), Na_2CO_3 (122 mg, 1,15 mmol), THF (10 ml) y H_2O (1 ml) se calentó a reflujo en una atmósfera de N_2 durante una noche. La mezcla se vertió en agua y se extrajo con CH_2Cl_2. La fase orgánica se combinó, se secó sobre Na_2SO_4 y se filtró para dar el compuesto deseado, que se usó directamente en la siguiente etapa. MS (ESI) m/e ($M+H^+$): 622.

Etapa 8



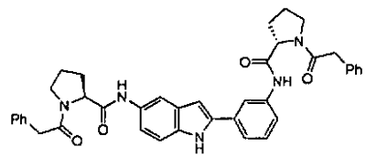
El producto de la etapa 7 (0,15 mmol) se disolvió en MeOH, se trató con 20 mg de Pd(OH)$_2$ al 20% y después se hidrogenó a 310,26 kPa (45 psi) durante 4 horas. El catalizador se retiró por filtración a través de CELITE, el filtrado se evaporó, después se disolvió en 1 ml de DCM y después se trató con 1 ml de TFA. Después de agitar durante 2 horas, la mezcla se evaporó y el residuo se usó directamente en la siguiente reacción sin purificación adicional. MS (ESI) m/e ($M+H^+$): 488.

Etapa 9

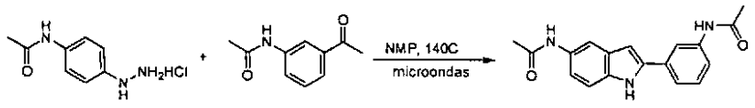


Una solución que contenía PyBOP (44 mg, 0,1 mmol), la amina de la etapa 8 anterior (49 mg, 0,1 mmol) y R-i-Proc-Phg-OH (21 mg, 0,1 mmol) en DMF (1 ml) se trató con N-metilmorfolina (0,6 mmol). La mezcla de reacción se agitó durante 3 horas, se diluyó con EtOAc y se lavó (cinco veces) con agua. La fase orgánica se secó, se concentró y después se sometió a cromatografía por RPLC para proporcionar el compuesto deseado. ^{1}H RMN (MeOD): 57,90~8,35(m, 1H), 7,70~7,85(m, 2H), 7,60~7,70(m, 2H), 7,20~7,52(m, 7H), 6,55~7,20(m, 1H), 5,50~5,60(m, 1H), 5,30~5,50(m, 1H), 4,75~4,85(m, 1H), 3,70~4,10(m, 1H), 3,35~3,50(m, 1H), 1,95~2,50(m, 7H), 1,10~1,30(m, 6H). MS (ESI) m/e (M+H$^+$): 607.

Ejemplo 122-(2S)-1-(fenilacetil)-N-{3-[5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il][fenil}pirrolidin-2-carboxamida

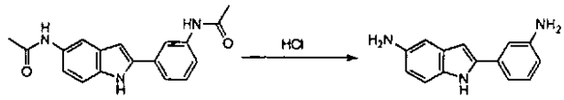


Etapa 1



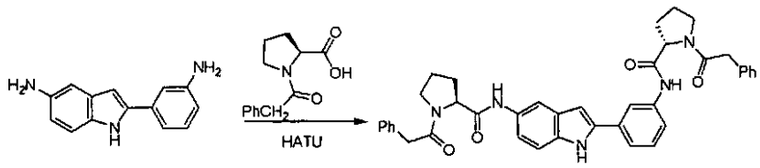
Una solución de la hidrazina (1 g, 5 mmol) y 3-acetilacetanilida (0,88 g, 5 mmol) en NMP (5 ml) se calentó a 150 °C en microondas durante 10 minutos. La solución se vertió en agua y se extrajo tres veces con EtOAc. La capa orgánica se lavó con agua, se secó sobre sulfato sódico y después se concentró al vacío. El residuo se purificó por RPLC para dar el compuesto deseado. MS (m/z): 308 (M+H)$^+$.

Etapa 2



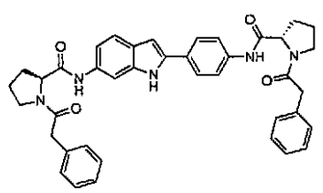
A HCl acuoso (4 N, 5 ml) se le añadió el producto de la etapa 1 anterior (300 mg, 1 mmol) y la mezcla se calentó a reflujo durante 1 hora. La mezcla de reacción se enfrió, se concentró y el residuo se purificó por RPLC para dar el compuesto (200 mg). MS (m/z): 224 (M+H)$^+$.

Etapa 3

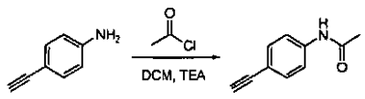


A una solución del compuesto de la etapa 2 anterior (35 mg, 0,148 mmol) en MeCN (5 ml) se le añadieron *N*-fenilacetil-L-prolina (15 mg, 0,0673 mmol), DIPEA (26 mg, 0,202 mmol) y HATU (56 mg, 0,148 mmol). La reacción se agitó durante una noche, se concentró y el residuo se purificó por RPLC para dar el producto deseado (15 mg). MS (ESI) m/e ($M+H^+$): 654. ^1H RMN (MeOD) □: 8,0 (m, 1H), 7,7(m, 1H), 7,6-7,1 (m, 14H), 6,7 (m, 1H), 4,6 (m, 2H), 3,9-3,5 (m, 9H), 2,4-1,7 (m, 8H).

Ejemplo 123-(2S)-1-(fenilacetil)-N-[4-[6-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida

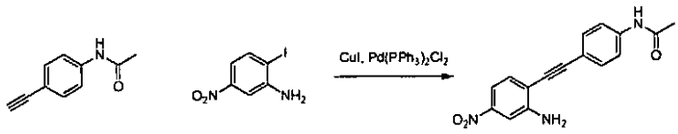


Etapa 1



A una solución agitada de 4-etinilanilina (1 g, 8,5 mmol) en DCM (60 ml) se le añadieron cloruro de acetilo (0,8 g, 10 mmol) y TEA (1,7 g, 17 mmol). La mezcla se agitó durante 3 horas. La solución resultante se lavó con agua, HCl 1 N y salmuera. La capa orgánica se concentró al vacío para dar el producto deseado (900 mg), que se usó en la siguiente etapa sin purificación. MS (ESI) m/e ($M+H^+$): 160.

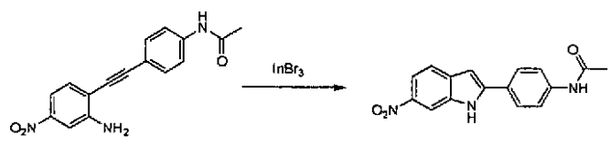
Etapa 2



A una solución agitada de 4-etinilacetanilida (800 mg, 3,1 mmol) en THF anhidro (6 ml) se le añadieron el compuesto 2 (0,5 g, 3,1 mmol), $PdCl_2(PPh)_3$ (33 mg, 0,05 mmol), CuI (10 mg, 0,05 mmol) y TEA (2 ml). La mezcla se protegió de la luz y se agitó a TA durante una noche. La solución resultante se concentró al vacío y el residuo se lavó con DCM para dar el compuesto deseado (300 mg) en forma de un sólido de color amarillo. MS (ESI) m/e ($M+H^+$): 296.

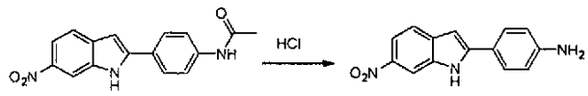
193

Etapa 3



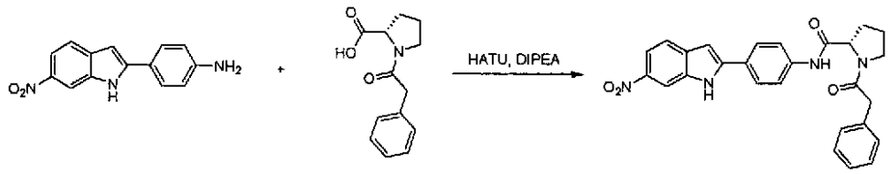
A una solución agitada del compuesto de la etapa 2 anterior (200 mg, 0,68 mmol) en tolueno (2 ml) se le añadió $InBr_3$ (2 mg, 0,004 mmol). La mezcla se agitó a la temperatura de reflujo durante 3 horas. La solución resultante se lavó con agua y se extrajo con EtOAc. Las capas orgánicas combinadas se secaron sobre sulfato sódico y se concentraron al vacío para dar el indol deseado (170 mg) en forma de un sólido de color pardo. MS (ESI) m/e ($M+H^+$): 296.

Etapa 4



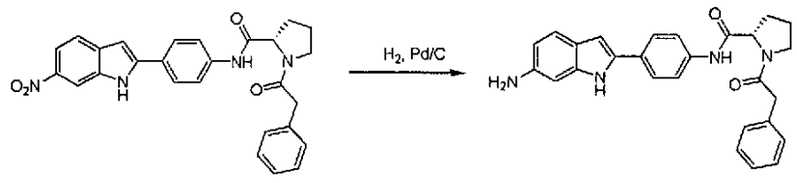
A una solución agitada del producto de la etapa 3 anterior (100 mg, 0,34 mmol) en EtOH (5 ml) se le añadió HCl 3 N (1 mg). La mezcla se agitó a la temperatura de reflujo durante una noche. La solución resultante se concentró al vacío para dar la anilina deseada (80 mg) en forma de un sólido de color pardo. MS (ESI) m/e ($M+H^+$): 254.

Etapa 5



A una solución de la anilina de la etapa 4 (50 mg, 0,2 mmol) en acetonitrilo (5 ml) se añadió *N*-fenilacetil-L-prolina (56 mg, 0,2 mol), HATU (167 mg, 0,4 mmol) y DIPEA (100 mg, 0,8 mmol). La mezcla se agitó durante una noche. La solución resultante se purificó por RPLC para dar el compuesto deseado (40 mg) en forma de un sólido de color pardo. MS (ESI) m/e ($M+H^+$): 469.

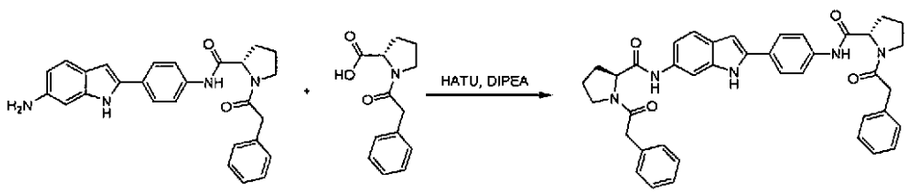
Etapa 6



A una solución del compuesto nitro (40 mg, 0,08 mmol) en THF (2 ml) se le añadió Pd/C (20 mg, 0,1 mmol). La mezcla se agitó en una atmósfera de H_2 durante 1 hora. Después del

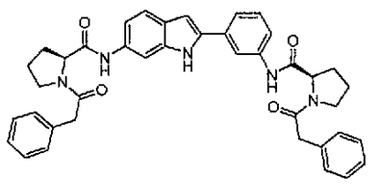
reemplazo de H_2 con N_2, el Pd/C se retiró por filtración y el filtrado se evaporó al vacío para dar el aminoindol deseado (40 mg) en forma de un sólido de color pardo. MS (ESI) m/e ($M+H^+$): 439.

Etapa 7

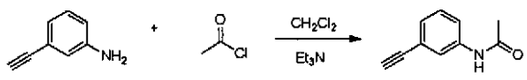


A una solución del producto de la etapa 6 anterior (40 mg, 0,1 mmol) en acetonitrilo (5 ml) se añadió *N*-fenilacetil-L-prolina (23 mg, 0,1 mmol), HATU (70 mg, 0,2 mmol) y DIPEA (25 mg, 0,2 mmol). La mezcla se agitó durante una noche. La solución resultante se purificó por RPLC para dar el compuesto deseado (15 mg) en forma de un sólido de color pardo. ^{1}H RMN (MeOD) □: 7,81 (m, 1H), 7,70 (d, J = 8,6 Hz, 2H), 7,60 (d, J = 8,4 Hz, 2H), 7,39 (m, 1H), 7,30-7,28 (m, 10H), 6,96 (m, 1H), 6,69 (s, 1H), 4,63-4,50 (m, 2H), 3,78-3,60 (m, 8H), 2,23-1,92 (m, 8H). MS (ESI) m/e ($M+H^+$): 654.

Ejemplo 124-(2S)-1-(fenilacetil)-N-{3-[6-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida

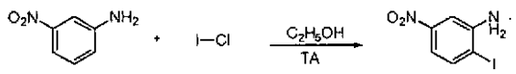


Etapa 1



A una solución de 3-etinilanilina (1,17 g, 10 mmol) y 1,5 ml de Et_3N en 40 ml de DCM se le añadió gota a gota cloruro de acetilo (1 g, 13 mmol). La mezcla de reacción se agitó a TA durante 1 hora. Después de esto, los disolventes se evaporaron, el residuo se extrajo con EtOAc (100 ml), se lavó con agua (50 ml) y salmuera (50 ml), se secó sobre $NaSO_4$ anhidro y se concentraron al vacío para proporcionar 3-etinilacetanilida (1,5 g). MS (ESI) m/e ($M+H^+$): 160.

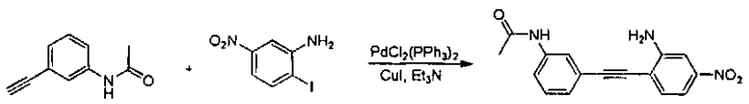
Etapa 2



Se disolvió 3-nitroanilina (6,9 g, 0,05 mmol) en 150 ml de etanol y se añadió gota a gota cloruro de yodo (8,1 g, 0,05 mmol). La mezcla de reacción se agitó a TA durante 4 horas. Después

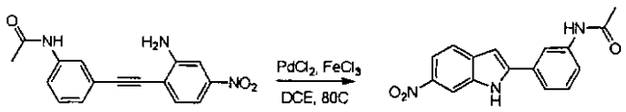
de esto, los disolventes se evaporaron, el residuo se extrajo con EtOAc (100 ml), se lavó con agua (50 ml) y salmuera (50 ml) y se secó sobre $NaSO_4$ anhidro. Después de que se concentrara al vacío, el residuo se purificó por cromatografía en columna (PE/EtOAc = 40:1 □ 20:1) para proporcionar el producto deseado (8,9 g). MS (ESI) m/e ($M+H^+$): 265.

Etapa 3



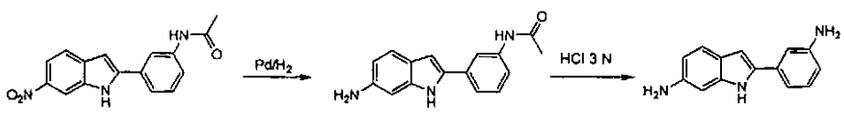
Se disolvieron 3-etinilacetanilida (480 mg, 3 mmol) y 2-yodo-5-introanilina (800 mg, 3 mmol) en THF anhidro (30 ml), $PdCl_2(PPh_3)_2$ (105 mg,0,15 mmol) y se añadieron secuencialmente CuI (28,5 mg,0,15 mmol) Et_3N (1 ml). La mezcla de reacción se protegió con N_2 y se agitó a TA durante una noche. Después de esto, los disolventes se evaporaron, el residuo se extrajo con EtOAc (50 x 2 ml), se lavó con agua (40 ml) y salmuera (30 ml), se secó sobre $NaSO_4$ anhidro. Después de que se concentrara al vacío, el residuo se purificó por cromatografía en columna (DCM/MeOH = 50:1 □ 20:1) para proporcionar el producto deseado (620 mg). MS (ESI) m/e ($M+H^+$): 296.

Etapa 4



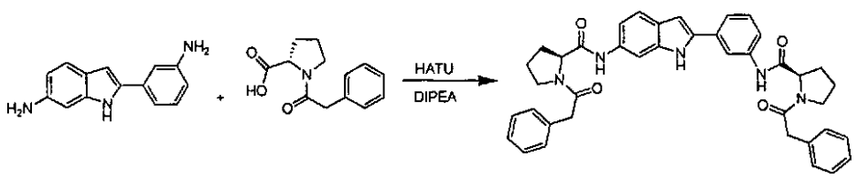
A una solución del producto de la etapa 3 (295 mg, 1,0 mol) en DCE (15 ml) se le añadieron $PdCl_2$ (9 mg, 0,05 mmol) y $FeCl_3$ (8 mg, 0,05 mmol). La mezcla de reacción se calentó a 80 °C durante 2 horas. La reacción se enfrió, los disolventes se evaporaron, el residuo se extrajo con EtOAc (2 x), se lavó con agua (30 ml) y salmuera (30 ml) y se secó sobre Na_2SO_4 anhidro. Después de que se concentrara al vacío, el residuo se purificó por TLC prep. (DCM/MeOH = 50:1) para proporcionar el producto deseado (240 mg). MS (ESI) m/e ($M+H^+$): 296. ^1H RMN (DMSO) □: 0,12 (s, 1 H), 8,25 (d, J = 8,0 Hz, 2 H), 7,45~7,94 (m, 6 H), 7,03 (s, 1 H), 2,10 (s, 3 H).

Etapa 5



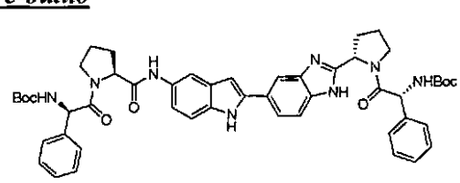
Una suspensión del producto de la etapa 4 (200 mg, 0,67 mmol), Pd/C (10 mg, 0,034 mmol) en 40 ml de EtOH estaba en una atmósfera protectora de H_2 y se agitó durante 1 hora. Después, la mezcla se filtró y después el filtrado se concentró para dar el producto (160 mg). El residuo se disolvió en 20 ml de HCl 3 N, la mezcla se agitó a 80 °C durante 1 hora. Se enfrió a TA, se concentró al vacío y el residuo se purificó para dar el compuesto deseado (120 mg) en forma de un sólido de color pardo. MS (m/z) ($M+H^+$): 224.

Etapa 6

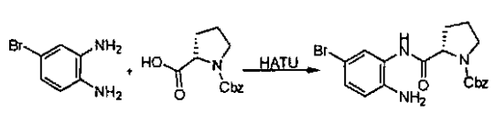


La mezcla del compuesto 10 (50 mg, 0,224 mmol), *N*-fenilacetil-L-prolina (110 mg, 0,45 mmol), DIPEA (88 mg, 0,7 mmol) en CH_3CN (5 ml) se agitó a TA durante 5 minutos y a esta se le añadió HATU (82 mg, 0,54 mmol). La mezcla se agitó a TA durante una noche. Cuando la reacción se completó, la mezcla se concentró al vacío, el residuo se purificó por cromatografía sobre gel de sílice para dar el compuesto diana deseado (70 mg). MS (ESI) m/e ($M+H^+$): 654 ^1H RMN (MeOD): □ 7,95 (d, J = 8,0 Hz, 2 H), 7,86~7,21 (m, 13 H), 6,98 (d, J = 8,0 Hz, 1 H), 6,72 (s, 1 H), 4,57(m, 2H), 3,53 (m, 3 H), 2,02~2,31 (m, 8 H).

Ejemplo 125-[(1R)-2-((2S)-2-[(2-(2-[(2S)-1-((2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1H-indol-5-il)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de terc-butilo

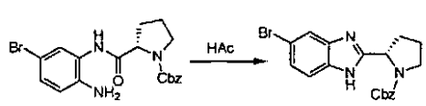


Etapa 1



La mezcla de 4-bromo-1,2-fenilenodiamina (3,1 g, 16 mmol), L-prolina (4,3 g, 16 mmol), DIPEA (3 ml) en MeCN (100 ml) se agitó a TA durante 5 minutos y después se añadió HATU (6 g, 17 mmol). La mezcla se agitó a TA durante una noche. Cuando la reacción se completó, la mezcla se concentró, el residuo se lavó con agua (100 ml) y se extrajo con EtOAc (tres veces), se lavó con salmuera (50 ml) y se secó sobre Na_2SO_4 anhidro. El residuo se purificó por cromatografía en columna (DCM/MeOH = 100:1 □ 50:1) para proporcionar el compuesto deseado (5,0 g). MS (ESI) m/e ($M+H^+$): (418,420).

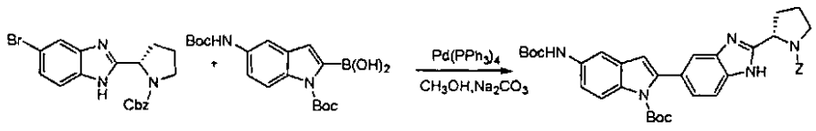
Etapa 2



El producto de la etapa 1 (5 g, 7,2 mmol) se disolvió en 50 ml de ácido acético. La mezcla de reacción se agitó a 100 °C durante 4 horas. La mezcla se enfrió y el ácido acético se retiró al

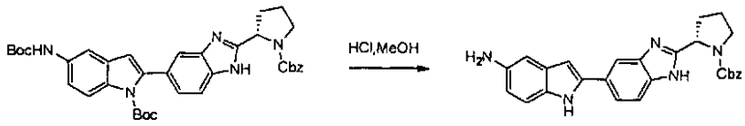
vacío. El residuo se purificó por cromatografía en columna (DCM/MeOH = 150:1 □ 100:1) para proporcionar el compuesto deseado (3,8 g). MS (ESI) m/e ($M+H^+$): (400, 402).

Etapa 3



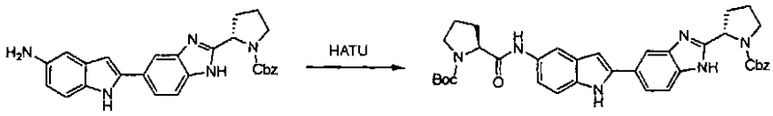
Una suspensión del producto de la etapa 3 (1,2 g, 3 mmol), ácido 1,5-bis-Boc-5-aminoindolo-2-borónico (1,2 g, 3 mmol), $Pd(PPh_3)_4$ (240 mg), Na_2CO_3 (1 g, 9 mmol) y H_2O (3 ml) en 30 ml de THF en una atmósfera protectora de N_2 se hizo reaccionar con reflujo a 75 °C durante una noche. La mezcla se filtró, el filtrado se lavó con 50 ml de agua y se extrajo con 100 ml de EtOAc y se secó sobre Na_2SO_4 anhidro. La retirada del disolvente y la cromatografía en columna (CH_2Cl_2/MeOH = 250:1 □ 200:1) proporcionaron el compuesto deseado (500 mg). MS (ESI) m/e ($M+H^+$): 652.

Etapa 4



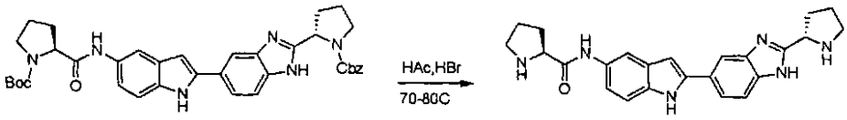
El producto de la etapa 3 (500 mg, 0,9 mmol) se agitó en MeOH/HCl (20 ml) durante 16 horas. El disolvente se retiró a presión reducida y el residuo se secó a alto vacío. MS (ESI) m/e ($M+H^+$): 452.

Etapa 5



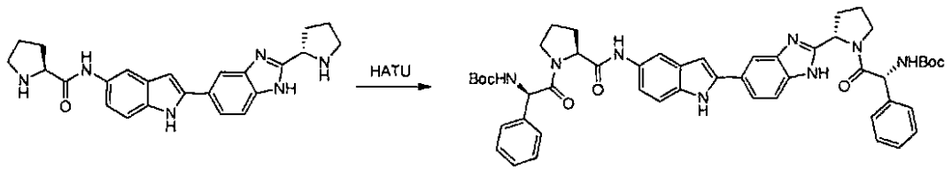
La mezcla de anilina de la etapa 4 (450 mg, 1 mmol), *(S)-N*-Boc prolina (215 mg 1 mmol), DIPEA (0,4 ml) en CH_3CN (10 ml) se agitó a TA durante 10 minutos y después se añadió HATU (400 mg, 1,1 mmol). La mezcla se agitó a TA durante una noche, se concentró y el residuo se purificó por cromatografía en columna (CH_2Cl_2/MeOH = 250:1 □ 200:1). MS (ESI) m/e ($M+H^+$): 649.

Etapa 6



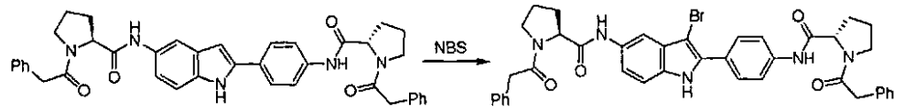
El producto de la etapa 5 (290 mg, 0,45 mmol) se disolvió en 5 ml de ácido acético y se añadió HBr (1 ml). La mezcla de reacción se calentó a 70-80 °C y se agitó durante 4 horas. La mezcla se enfrió a TA y se concentró al vacío. El residuo se extrajo con EtOAc (2 x), se lavó con $NaHCO_3$ ac. y agua (30 ml) y salmuera (30 ml) y se secó sobre sulfato sódico anhidro. La evaporación del disolvente proporcionó el compuesto deseado en forma de un sólido de color pardo (160 mg). MS (ESI) m/e ($M+H^+$): 415.

Etapa 7



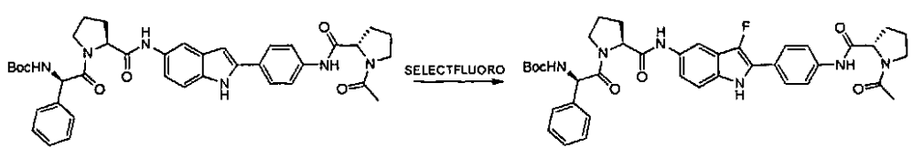
Una mezcla del producto de la etapa 6 (100 mg, 0,24 mmol), *(R)-N*-Boc-Phg (120 mg, 0,48 mmol), DIPEA (0,4 ml) en CH_3CN (10 ml) se agitó a TA durante 10 minutos y se añadió HATU (200 mg, 0,5 mmol). La mezcla se agitó a TA durante una noche, después se concentró y el residuo se purificó por RPLC para proporcionar el compuesto deseado (54 mg). MS (ESI) m/e ($M+H^+$): 882. ^{1}H RMN (MeOD) □: 7,96~7,69(m, 4H), 7,49~6,84(m, 13H), 5,50~5,40(m, 2H), 4,06~3,94 (m, 2H), 2,27~1,88 (m, 8H), 1,37 (s, 18H).

Ejemplo 126-(2S)-N-{4-[3-bromo-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonillamino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida



A una solución del indol (1 equiv.) en 5 ml de THF se le añadió NBS (278 mg, 1 mmol) a TA y la mezcla se agitó durante 1 hora. La concentración del disolvente y la purificación del residuo por RPLC proporcionaron los compuestos halogenados diana. ^{1}H RMN (MeOD) □: 7,9-7,5 (m, 5H), 7,4-7,0 (m, 12H), 5,2-4,9 (m, 2H), 4,4 (m, 2H), 3,8-3,5 (m, 6H), 2,5-1,8 (m, 8H).

Ejemplo 127-{(1S)-2-[(2S)-2-({2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

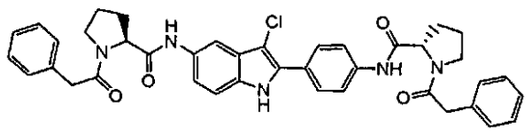
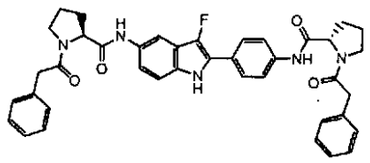
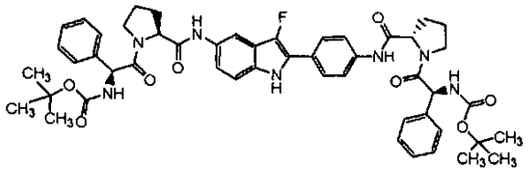
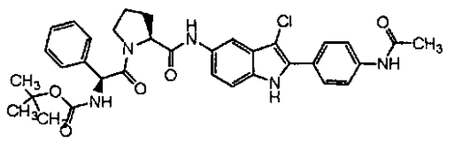
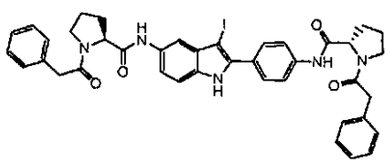


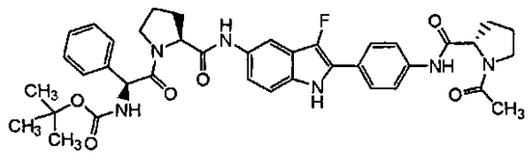
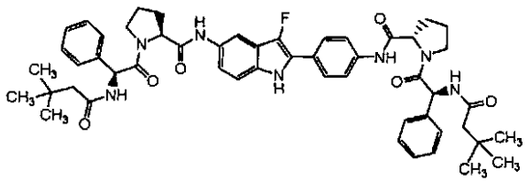
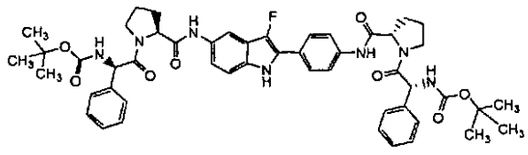
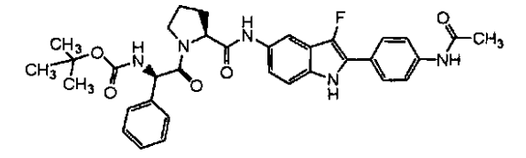
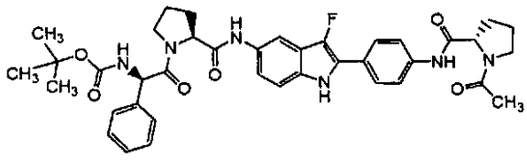
A una solución del indol (1 equiv.) en acetonitrilo/DMSO (5 ml, 1:1) se le añadió SELECTFLUORO (1 equiv.) a 0 °C. La mezcla se agitó a TA durante 3 horas antes de que se concentrara y el residuo se purificó por RPLC. ^{1}H RMN (MeOD) □: 7,9-7,c8 (m, 3H), 7,8-7,7 (m, 2H), 7,5-7,3 (m, 6H), 7,3 (m, 1H), 5,5 (s, 1H), 4,6-4,5 (m, 2H), 4,0-3,9 (m, 1H), 3,8 (m, 1H), 3,7

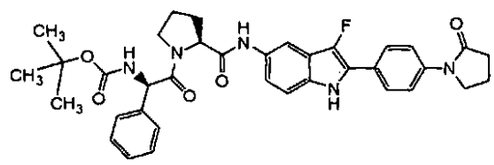
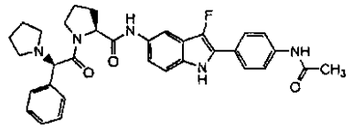
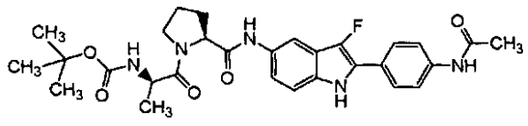
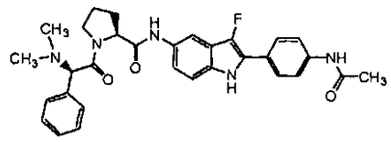
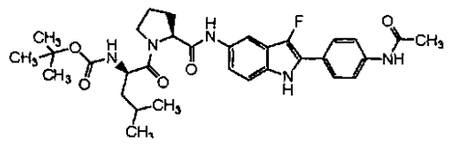
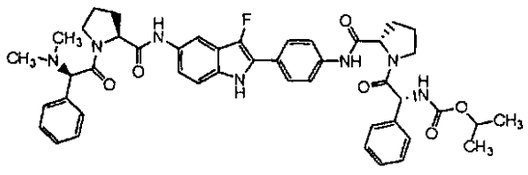
(m, 1H), 2,4-2,3 (m, 1H), 2,2-2,1 (m, 7H), 2,1-2,0 (m, 3H), 2,0-1,9 (m, 1H), 1,4 (m, 9H). MS (m/z): 711 $(M+H)^+$.

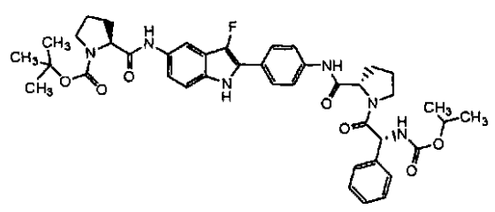
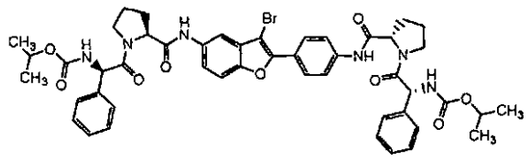
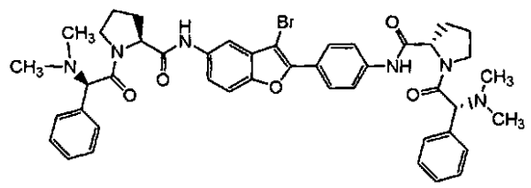
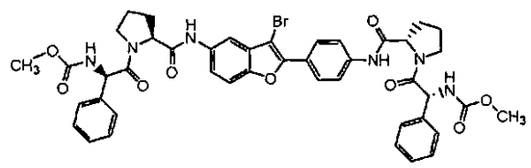
Ejemplos 128-154

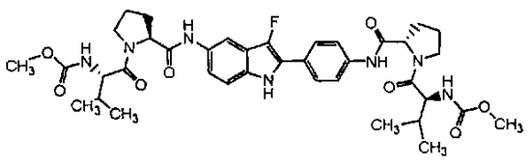
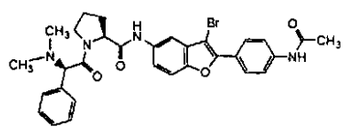
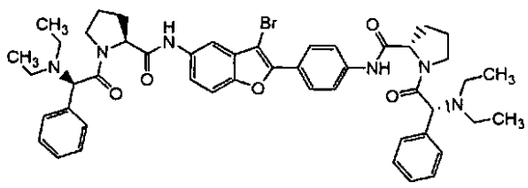
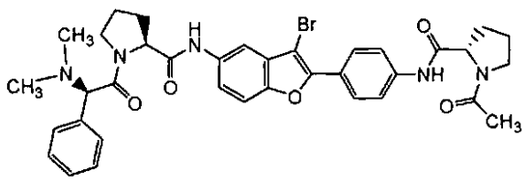
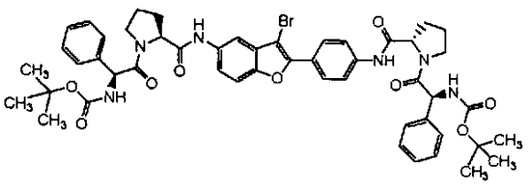
Los compuestos de los Ejemplos 128-154 pueden prepararse por halogenación directa de los compuestos indol o benzofurano de una manera similar a la que se ha descrito en el Ejemplo 126 o el Ejemplo 127.

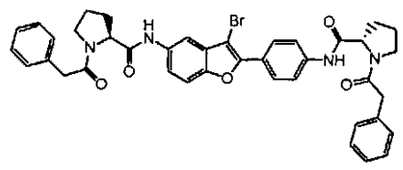
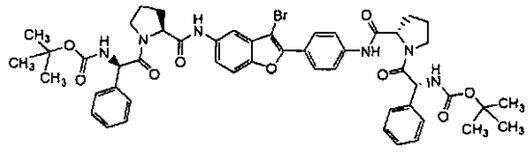
Ejemplo	Estructura	PM	Nombre
128		688,233	(2S)-N-{4-[3-cloro-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida
129		671,778	(2S)-N-{4-[3-fluoro-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida
130		902,044	{(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2S)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-fluoro-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
131		630,15	{(1S)-2-[(2S)-2-({2-[4-(acetilamino)fenil]-3-cloro-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
132		779,684	(2S)-N-{4-[3-yodo-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida

Ejemplo	Estructura	PM	Nombre
133		710,813	{(1S)-2-[(2S)-2-({2-[4-({[(2S)-1-acetilpirrolidin-2-il]carbonil}amino)fenil]-3-fluoro-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
134		898,1	(2S)-1-{(2S)-2-[(3,3-dimetilbutanoil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2S)-2-[(3,3-dimetilbutanoil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-fluoro-1H-indol-2-il]fenil}pirrolidin-2-carboxamida
135		902,044	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-fluoro-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
136		613,695	{(1R)-2-[(2S)-2-({2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
137		710,813	{(1R)-2-[(2S)-2-({2-[4-({[(2S)-1-acetilpirrolidin-2-il]carbonil}amino)fenil]-3-fluoro-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

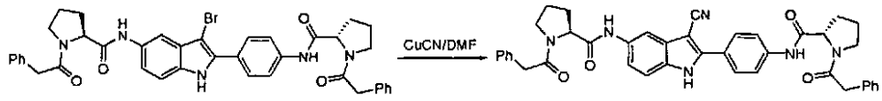
Ejemplo	Estructura	PM	Nombre
138		639,733	{(1R)-2-[(2S)-2-({3-fluoro-2-[4-(2-oxopirrolidin-1-il)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
139		567,669	*N*-{2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-1H-[(2R)-2-fenil-2-(pirrolidin-1-il)acetil]-L-prolinamida
140		551,623	*N*-(terc-butoxicarbonil)-D-alanil-*N*-{2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-il}-L-prolinamida
141		541,631	*N*-{2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-il}-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolinamida
142		593,705	N-(terc--butoxicarbonil)-D-leucil-N-{2-[4-(acetilammo)fenil]-3-fluoro-1H-indol-5-il}-L-prolinamida
143		815,953	[(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-3-fluoro-1H-indol-2-il}fenil)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de propan-2-ilo)

Ejemplo	Estructura	PM	Nombre
144		754,866	(2S)-2-[(3-fluoro-2-{4-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]fenil}-1H-indol-5-il)carbamoil]pirrolidin-1-carboxilato de terc-butilo
145		935,88	[(1R)-2-{(2S)-2-[(4-{3-bromo-5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de propan-2-ilo
146		819,806	(2S)-*N*-(4-{3-bromo-5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-carboxamida
147		879,772	{(1R)-2-[(2S)-2-({4-[3-bromo-5-({[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo

Ejemplo	Estructura	PM	Nombre
148		749,847	{(2S)-1-[(2S)-2-({4-[3-fluoro-5-({[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo
149		603,521	*N*-{2-[4-(acetilamino)fenil]-3-bromo-1-benzofuran-5-il}-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolinamida
150		875,915	(2S)-*N*-{3-bromo-5-[({(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-carboxamida
151		700,639	(2S)-1-acetil-*N*-{3-bromo-5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)pirrolidin-2-carboxamida
152		963,935	{(1S)-2-[(2S)-2-({4-[3-bromo-5-({[(2S)-1-{(2S)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

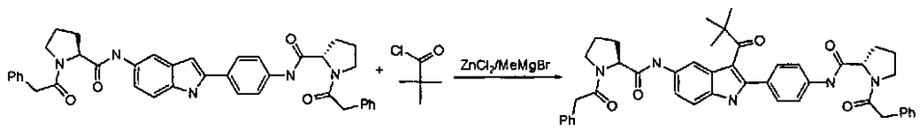
Ejemplo	Estructura	PM	Nombre
153		733,669	(2S)-N-{4-[3-bromo-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida
154		963,935	{(1R)-2-[(2S)-2-({4-[3-bromo-5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

Ejemplo 155-(2S)-N-{4-[3-ciano-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida



Una mezcla del compuesto de bromo del Ejemplo 126 (150 mg, 0,2 mmol), CuCN (50 mg, 0,6 mmol) y DMF (3 ml) se calentó a reflujo en una atmósfera protectora de N_2 durante una noche. La mezcla se purificó por RPLC para proporcionar el producto. MS (ESI) m/e ($M+H^+$): 679. ^1H RMN ($CDCl_3$) □: 7,73-7,70 (m, 4H), 7,38-7,29 (m, 4H), 7,21-7,04 (m, 6H), 4,63-4,60 (m, 1H), 4,494,47 (m, 1H), 3,81-3,59 (m, 4H), 2,48-1,97 (m, 8H).

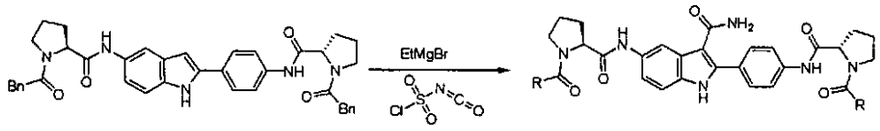
Ejemplo 156-(2S)-N-{4-[3-(2,2-dimetilpropanoil)-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida



A una solución agitada del indol (50 mg, 0,076 mmol) en CH_2Cl_2 (5 ml) se le añadió $ZnCl_2$ anhidro (54 mg, 0,4 mmol) y después MeMgBr (3,0 M en Et_2O, 0,4 ml, 0,4 mmol). La suspensión resultante se agitó durante 10 minutos a TA y después se enfrió a 0 °C en un baño de hielo. A la mezcla se le añadió una solución de cloruro de pivaloílo (14 mg) en CH_2Cl_2 (0,2 ml). La mezcla de reacción se dejó calentar a TA y se agitó durante una noche. La mezcla de reacción se inactivó por NH_4Cl acuoso saturado y se extrajo 3 veces con CH_2Cl_2. Las capas orgánicas se combinaron, se

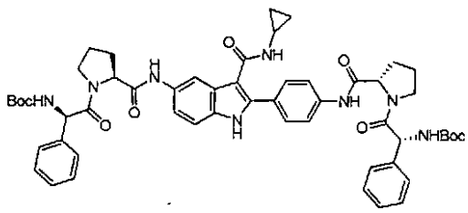
secaron sobre Na_2SO_4 anhidro y se filtraron. El filtrado se concentró y se purificó por RPLC para producir el producto. MS (ESI) m/e ($M+H^+$): 738. ^1H RMN (MeOD) □: 7,69-7,63 (m, 3H), 7,44-7,41 (m, 2H), 7,31-7,21 (m, 12H), 4,55-4,52 (m, 2H), 3,76-3,59 (m, 8H), 2,26-1,94 (m, 8H).

Ejemplo 157-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-indolo-3-carboxamida

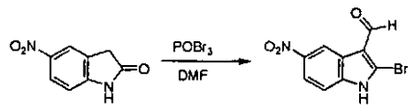


A una solución del indol (653 mg, 1 mmol) en THF 10 (ml) se le añadió EtMgBr (2 ml, 6 mmol) y la mezcla se agitó a TA durante 30 minutos. A la misma se le añadió isocianato de clorosulfonilo (140 mg, 1 mmol) y la mezcla se agitó a TA durante 20 minutos. Después, a la mezcla anterior se le añadió DMF (146 mg, 2 mmol) y la agitación continuó durante 20 minutos. Después de añadir el NaOH acuoso (2 N, 1 ml), la solución resultante se calentó a reflujo durante 5 minutos. La concentración al vacío, el residuo se purificó con RPLC para dar (67 mg). ^1H RMN (MeOD) □: 8,0 (s, 1H), 7,6 (m, 4H), 7,1-7,4 (m, 12H), 4,5 (m, 4H), 3,5-3,7 (m, 8H), 2,5-2,0 (m, 6H).

Ejemplo 158-{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-(ciclopropilcarbamoil)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

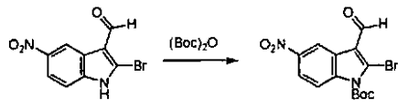


Etapa 1



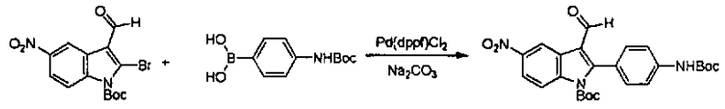
A una solución de $POBr_3$ (113,2 g, 0,4 mol) en DCE (1 l) se le añadió gota a gota DMF (14,6 g, 0,2 mol) en un baño de hielo y la mezcla se agitó a TA durante 30 minutos. A la misma se le añadió el compuesto nitro (17,8 g, 0,1 mol) y la mezcla se agitó a la temperatura de reflujo durante 4 horas. El precipitado se recogió por filtración y después se lavó con agua y MeOH. El sólido se secó al vacío para dar el compuesto deseado (13,5 g). ^1H RMN (DMSO) □: 13,6 (s, 1H), 9,8 (s, 1H), 8,8 (s, 1H), 8,1 (d, J = 9,2 Hz, 1H), 7,6 (d, J = 9,2 Hz, 1H).

Etapa 2



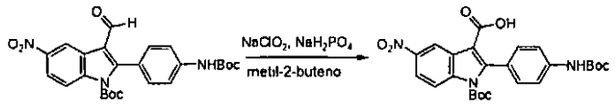
A una solución del aldehído de la etapa 1 (13,5 g, 0,05 mol) en DCM (100 ml) se le añadieron DMAP (0,6 g, 0,005 mol), TEA (10,1 g, 0,1 mol) y $(Boc)_2O$ (21,8 g, 0,1 mol) y la mezcla se agitó a TA durante una noche. La mezcla se concentró y el residuo se purificó por cromatografía en columna para dar el compuesto deseado (14,7 g). ^1H RMN ($CDCl_3$) □: 9,8 (s, 1H), 8,8 (s, 1H), 8,1 (d, J = 9,2 Hz, 1H), 7,6 (d, J = 9,2 Hz, 1H), 1,4 (s, 9H).

Etapa 3



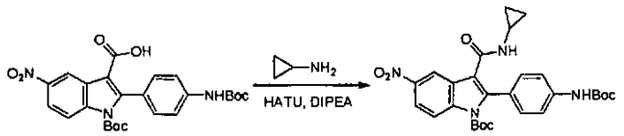
El procedimiento de acoplamiento de Suzuki era el mismo que el que se ha descrito en el Ejemplo 117, etapa 3. MS (m/z): 482 $(M+H)^+$.

Etapa 4



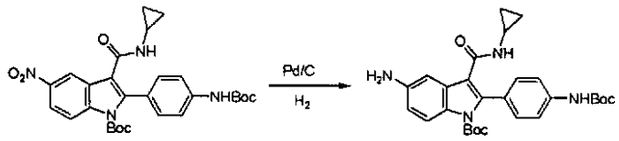
A una solución del compuesto de la etapa 3 (2,4 g, 5 mmol) en pH 3,5, tampón fosfato (24 ml) y t-BuOH (30 ml) se le añadieron 2-metil-2-buteno (10 ml) y clorato sódico (0,89 g, 10 mmol). La reacción se agitó a TA durante 16 horas y después se extrajo con DCM (3 x). Los extractos orgánicos combinados se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro y se concentraron al vacío para dar el ácido carboxílico deseado (2,3 g). MS (m/z): 498 (M+H)+.

Etapa 5



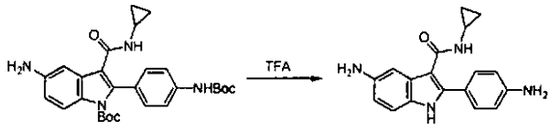
La mezcla del compuesto de la etapa 4 (1 mmol), ciclopropil amina (1 mmol), HATU (1 mmol) y DIPEA (5 mmol) en DCM se agitó a TA durante una noche. La concentración y la purificación del residuo por RPLC dieron el compuesto deseado (0,8 mmol). MS (m/z): 538 (M+H)+.

Etapa 6



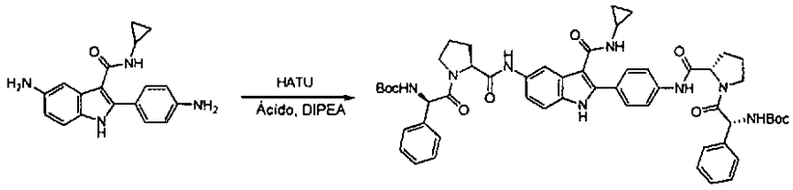
A una solución de la amida de la etapa 5 (0,8 mmol) en MeOH (10 ml) se le añadió Pd/C (100 mg) y la mezcla se agitó en una atmósfera de H_2 a TA durante 1 hora. El Pd/C se retiró por filtración y el filtrado se concentró para dar el compuesto deseado (0,7 mmol). MS (m/z): 507 $(M+H)^+$.

Etapa 7



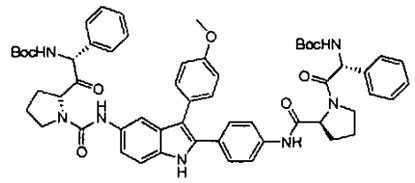
A una solución del compuesto de la etapa 6 (0,7 mmol) en DCM (5 ml) se le añadió TFA (2 ml) y la mezcla se agitó a TA durante una noche. La solución se concentró y el residuo se usó en la siguiente etapa sin purificación. MS (m/z): 307 $(M+H)^+$.

Etapa 8

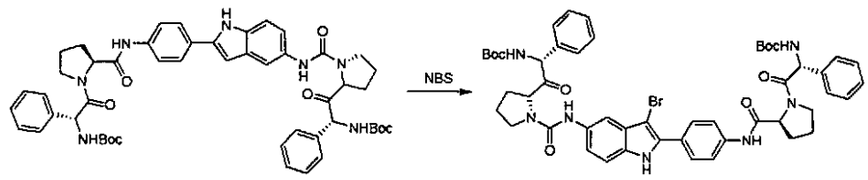


El procedimiento de acoplamiento era el mismo que se ha usado en el Ejemplo 72, etapa 7. ^{1}H RMN (MeOD) □: 6,9-7,9 (m, 17H), 5,2-5,5 (m, 2H), 4,4-4,5 (m, 2H), 3,5-3,9 (m, 3H), 2,7-2,8 (m, 1H), 1,7-2,2 (m, 8H), 1,4 (s, 18H), 1,2 (m, 1H), 0,4-0,8 (m, 4H). MS (m/z): 967 (M+H)+.

Ejemplo 159-{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxi-carbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-(4-metoxifenil)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo



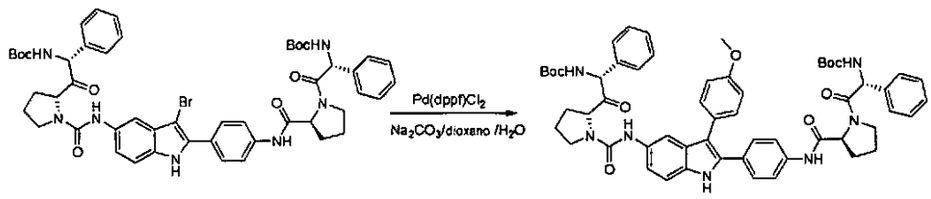
Etapa 1



Se añadió en porciones NBS (103 mg, 0,5769 mmol) a la solución del indol (510 mg, 0,5769 mmol) en 20 ml de THF, la mezcla se agitó a TA durante 1 hora y después se concentró. El residuo se purificó por HPLC prep. para proporcionar el compuesto deseado (500 mg).

MS (ESI) m/e ($M+H^+$): 962.

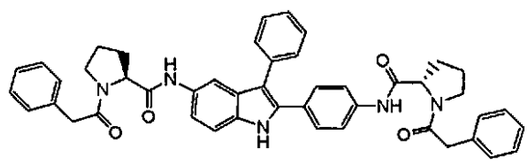
Etapa 2

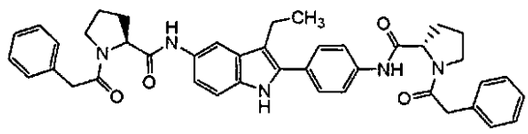
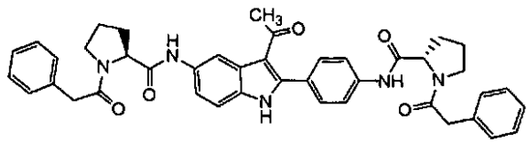
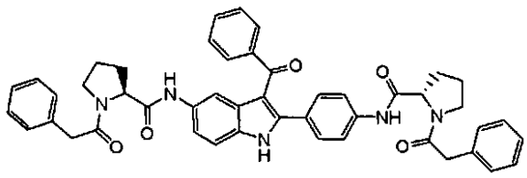
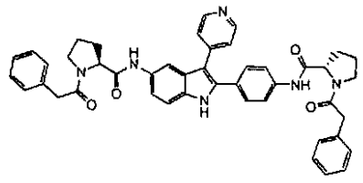
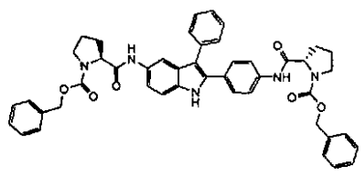


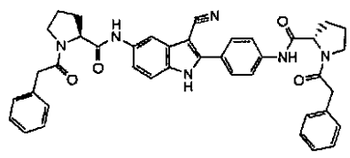
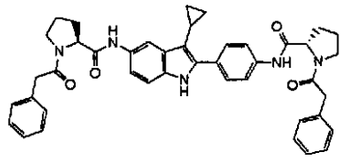
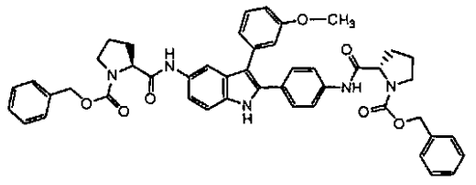
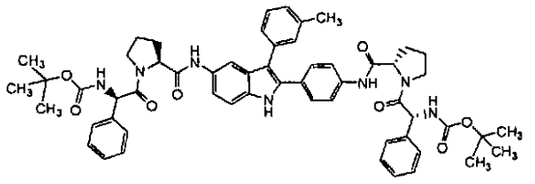
La mezcla del producto de la etapa 1 anterior (100 mg, 0,104 mmol), ácido 4-metoxi-fenilborónico (24 mg, 0,1558 mmol), $Pd(dppf)Cl_2$ (7,6 mg, 0,0104 mmol), Na_2CO_3 (3,3 mg, 0,0312 mmol) en 10 ml de dioxano y 2 ml de agua se calentó a reflujo en una atmósfera de N_2 durante una noche. La mezcla se enfrió, se concentró y después el residuo se purificó por RPLC para dar el producto deseado (30 mg). ^1H RMN (MeOD) □: 7,71~7,54 (m, 3H), 7,42~7,26 (m, 16H), 6,96~6,92 (m, 3H), 5,45 (s, 2H), 4,53~4,50 (m, 2H), 3,92~3,81 (m, 5H), 2,08~1,84 (m, 8H), 1,42~1,32 (m, 18H). MS (ESI) m/e ($M+H^+$): 991.

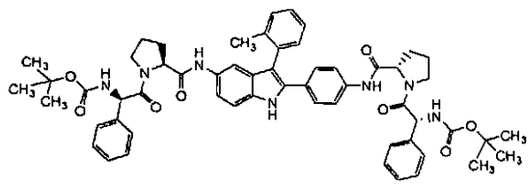
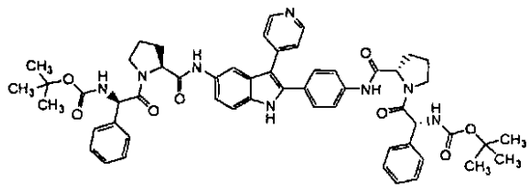
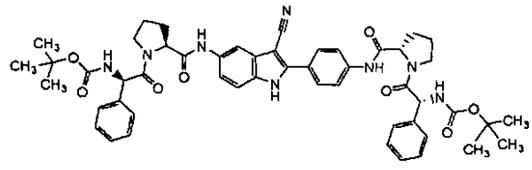
Ejemplos 160-177

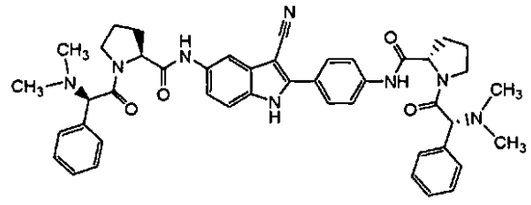
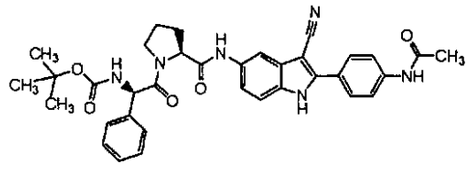
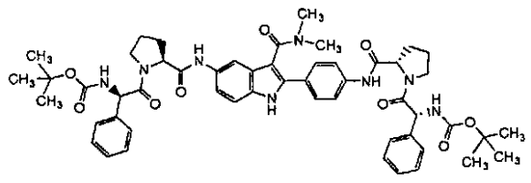
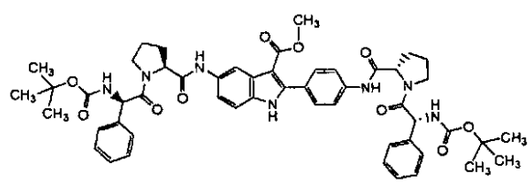
Los compuestos de los Ejemplos 160-177 se prepararon de una manera similar a la que se ha descrito en los Ejemplos 155-159.

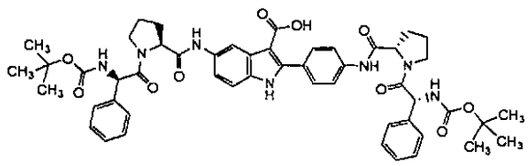
Ejemplo	Estructura	PM	Nombre
160		729,887	(2S)-1-(fenilacetil)-N-{4-[3-fenil-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida

Ejemplo	Estructura	PM	Nombre
161		681,842	(2S)-N-{4-[3-etil-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida
162		695,826	(2S)-N-{4-[3-acetil-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida
163		757,897	(2S)-1-(fenilacetil)-N-{4-[5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-3-(fenilcarbonil)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida
164		730,874	(2S)-1-(fenilacetil)-N-{2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-3-(piridin-4-il)-1H-indol-5-il}pirrolidin-2-carboxamida
165		761,886	(2S)-2-[(4-{5-[({(2S)-1-[(benciloxi)carbonil]pirrolidin-2-il}carbonil)amino]-3-fenil-1H-indol-2-il}fenil)carbamoil]pirrolidin-1-carboxilato de bencilo

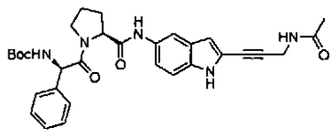
Ejemplo	Estructura	PM	Nombre
166		678,798	(2S)-N-{4-[3-ciano-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida
167		693,853	(2S)-N-{4-[3-ciclopropil-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida
168		791,912	(2S)-2-[(4-{5-[({(2S)-1-[(benciloxi)carbonil]pirrolidin-2-il}carbonil)amino]-3-(3-metoxifenil)-1H-indol-2-il}fenil)carbamoil]pirrolidina-1-carboxilato de bencilo
169		974,18	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-(3-metilfenil)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

Ejemplo	Estructura	PM	Nombre
170		974,18	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-(2-metilfenil)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
171		961,14	{(1R)-2-[(2S)-2-({2-[4-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)fenil]-3-(piridin-4-il)-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
172		909,064	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-ciano-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

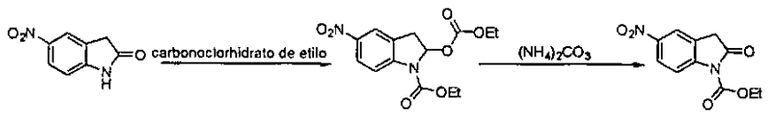
Ejemplo	Estructura	PM	Nombre
173		764,936	(2S)-N-(4-{3-ciano-5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-carboxamida
174		620,714	{(1R)-2-[(2S)-2-({2-[4-(acetilamino)fenil]-3-ciano-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
175		955,133	{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-(dimetilcarbamoil)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
176		942,091	5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-2-[4-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)fenil]-1H-indolo-3-carboxilato de metilo

Ejemplo	Estructura	PM	Nombre
177		928,064	ácido 5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-2-[4-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)fenil]-1H-indolo-3-carboxílico

Ejemplo 178-{(1R)-2-[(2S)-2-({2-[3-(acetilamino)prop-1-in-1-il]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo

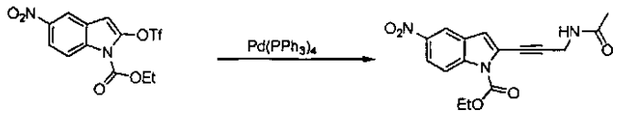


Etapa 1



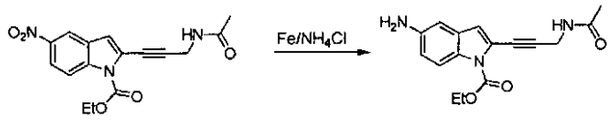
Se añadió carbonocloridato de etilo (3 ml) a la nitro lactama (2,0 g, 11,2 mmol) y la mezcla se agitó durante 3 horas antes de concentrarse para dar el producto en bruto. MS (ESI) m/e ($M+H^+$): 325. El producto en bruto se disolvió en DMF (25 ml), después se añadió $(NH_4)_2CO_3$ (1,5 g) y la mezcla se agitó durante una noche. La mezcla se evaporó y el residuo se vertió en hielo-agua, se extrajo con DCM y los productos orgánicos se secaron. El disolvente se retiró y el residuo se purificó por cromatografía sobre gel de sílice para dar el compuesto deseado en forma de un sólido de color blanco. MS (ESI) m/e ($M+H^+$): 251.

Etapa 2



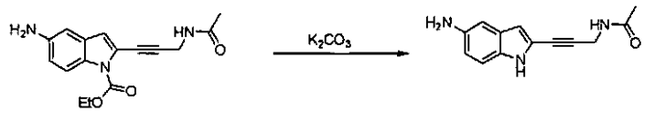
La mezcla del triflato (382 mg, 1,0 mmol), N-(prop-2-inil)acetamida (97 mg, 1,0 mmol), Et_3N (3 ml) en CH_3CN(3 ml) se agitó a TA durante 3 horas. La mezcla se concentró y el residuo se purificó por cromatografía sobre gel de sílice para dar el compuesto diana (254 mg). MS (ESI) m/e ($M+H^+$): 330.

Etapa 3



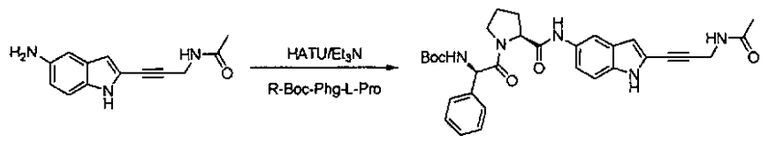
A una solución del compuesto nitro de la etapa 2 anterior (165 mg, 0,50 mmol) en EtOH absoluto (3 ml) se le añadieron polvo de Fe (280 mg, 2,5 mmol) y NH_4Cl (535 mg, 5,0 mmol). La mezcla se agitó a 70 °C durante 2 horas, se enfrió y se vertió en hielo/agua (50 ml). La mezcla se extrajo con EtOAc (200 ml), la fase orgánica se combinó, se lavó con salmuera, se secó y se concentró para producir el producto en bruto (150 mg). MS (ESI) m/z :(M+H) 300.

Etapa 4

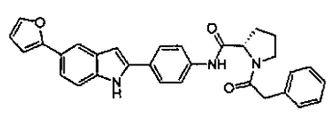


A una solución de la anilina de la etapa 3 (150 mg, 0,50 mmol) en EtOH absoluto (3 ml) se le añadió K_2CO_3 (138 mg, 1,0 mmol) y la mezcla se agitó a TA durante 12 horas. La mezcla de reacción se vertió en agua (10 ml), se extrajo con EtOAc (20 ml), las fases orgánicas se combinaron, se lavaron con salmuera, se secaron sobre $MgSO_4$ y se concentraron para producir el producto en bruto (113 mg). MS (ESI) m/z :$(M+H^+)$ 228.

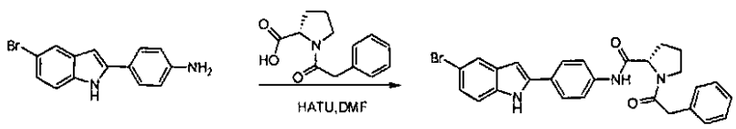
Etapa 5



La mezcla del indol (113 mg, 0,5 mmol), R-Boc-Phg-L-Pro-OH (175 mg, 0,5 mmol), DIPEA (115 mg, 1,0 mmol) en MeCN (2 ml) se agitó a TA durante 5 minutos y después a la mezcla se le añadió HATU (190 mg, 0,5 mmol). La mezcla se agitó a TA durante una noche y después se concentró. El residuo se purificó por RPLC para dar el compuesto deseado (110 mg). ^1H RMN (MeOD) □: 1,37 (s, 9H), 1,96~2,14 (m, 7H), 3,92~3,94 (m, 2H), 4,51~4,54 (m, 1H), 5,41 (s, 1H), 6,56 (s, 1H), 7,20~7,43 (m, 7H), 7,72 (s, 1H). MS (ESI) m/z :$(M+H^+)$ 576, ***Ejemplo 179-N-{4-[5-(furan-3-il)-1H-indol-2-il]fenil}-1-(fenilacetil)-L-prolinamida***

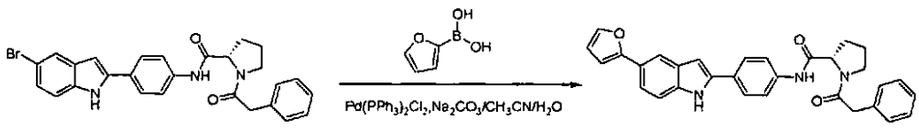


Etapa 1



La mezcla del indol del Ejemplo 41 (1,6 mg, 5,575 mmol), ácido 1-fenilacetil pirrolidin-2-carboxílico (1,3 g, 5,575 mmol), DIPEA (1,45 g, 11,15 mmol) en DMF (50 ml) se agitó a TA durante 30 minutos y después se añadió HATU (2,54 g, 6,689 mmol). La mezcla se agitó a TA durante una noche, se concentró al vacío y el residuo se purificó por cromatografía sobre gel de sílice para dar el producto deseado (2,3 g). MS (ESI) m/e ($M+H^+$): 504.

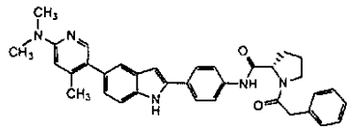
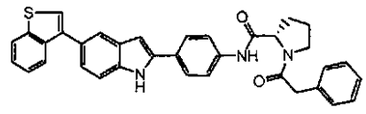
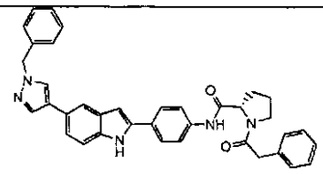
Etapa 2

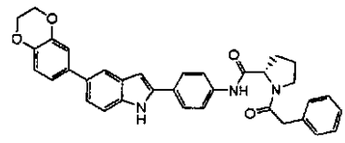
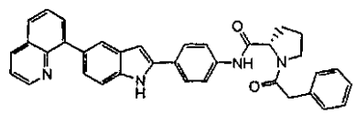
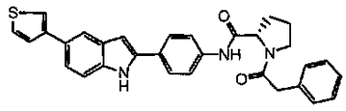
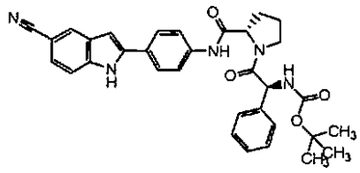
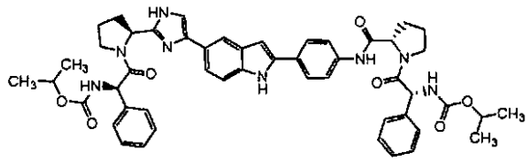
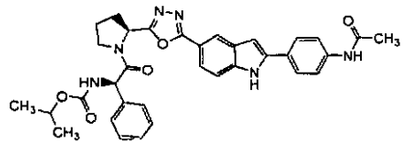


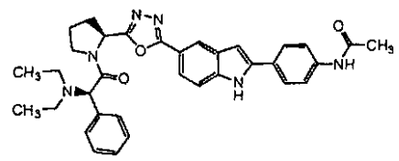
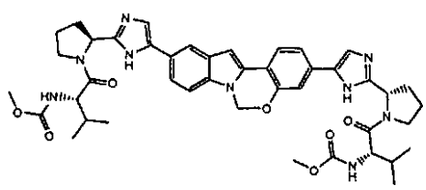
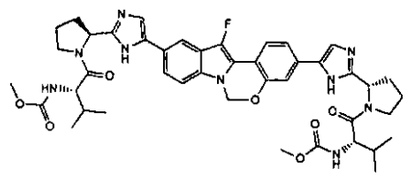
Una suspensión del producto de la etapa 1 anterior (18 mg, 0,03583 mmol), ácido furan-2-borónico (6 mg, 0,05374 mmol), $Pd(PPh_3)_2Cl_2$ (1,4 mg), Na_2CO_3 (7,6 mg, 0,07166 mmol) y H_2O (0,15 ml) en 0,5 ml de acetonitrilo en una atmósfera protectora de N_2 se calentó a 150 °C durante 10 minutos en un reactor de microondas. La mezcla se enfrió, se filtró y se lavó con 10 ml de DCM. Los disolventes se retiraron, y el residuo se purificó por HPLC para dar el producto deseado. ^1H RMN (MeOD) □: 7,79~7,74 (m, 3H), 7,67~7,62 (m, 3H), 7,50 (s, 1H), 7,37~7,22 (m, 6H), 6,78~6,75 (m, 2H), 4,57~4,55 (m, 1H), 3,78~3,61 (m, 4H), 2,24~1,99 (m, 4H).

Ejemplos 180-189b

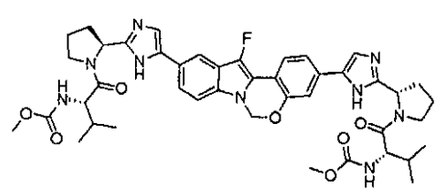
Los compuestos de los Ejemplos 180-189b se prepararon de una manera similar a la que se ha descrito en el Ejemplo 179.

Ejemplo	Estructura	PM	Nombre
180		557,701	N-(4-{5-[6-(dimetilamino)-4-metilpiridin-3-il]-1H-indol-2-il}fenil)-1-(fenilacetil)-L-prolinamida
181		555,704	N-{4-[5-(1-benzotiofen-3-il)-1H-indol-2-il]fenil}-1-(fenilacetil)-L-prolinamida
182		579,708	N-{4-[5-(1-bencil-1H-pirazol-4-il)-1H-indol-2-il]fenil}-1-(fenilacetil)-L-prolinamida

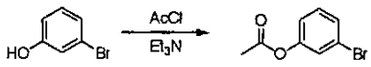
Ejemplo	Estructura	PM	Nombre
183		557,655	N-{4-[5-(2,3-dihidro-1,4-benzodioxin-6-il)-1H-indol-2-il]fenil}-1-(fenilacetil)-L-prolinamida
184		550,666	1-(fenilacetil)-N-{4-[5-(quinolin-8-il)-1H-indol-2-il]fenil}-L-prolinamida
185		505,644	1-(fenilacetil)-N-{4-[5-(tiofen-3-il)-1H-indol-2-il]fenil}-L-prolinamida
186		563,662	{(1S)-2-[(2S)-2-{[4-(5-ciano-1H-indol-2-il)fenil]carbamoil}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo
187		879,037	[(1R)-2-oxo-1-fenil-2-{(2S)-2-[4-(2-{4-[({(2S)-1-{(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]fenil}-1H-indol-5-il)-1H-imidazol-2-il]pirrolidin-1-il}etil]carbamato de propan-2-ilo
188		606,687	{(1R)-2-[(2S)-2-(5-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1,3,4-oxadiazol-2-il)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo

Ejemplo	Estructura	PM	Nombre
189		576,704	N-{4-[5-(5-{(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}-1,3,4-oxadiazol-2-il)-1H-indol-2-il]fenil}acetamida
189a		806,9	[(2S)-1-{(2S)-2-[5-(10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo
189b		824,9	[(2S)-1-{(2S)-2-[5-(12-fluoro-10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 189b (Procedimiento Alternativo: [(2S)-1{(2S)-2-[5-(12-fluoro-10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

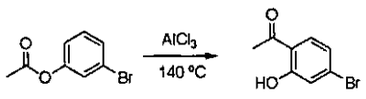


Etapa 1



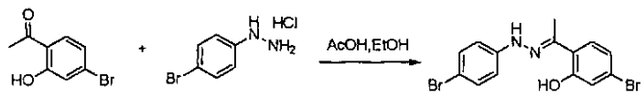
A una solución del compuesto 3-bromofenol (51 g, 0,3 mol) y Et_3N (36 g, 0,36 mol) en 500 ml de DCM se le añadió gota a gota cloruro de acetilo (26 g, 0,33 mol) en un baño de hielo-agua. La mezcla se agitó a TA durante 30 minutos. La mezcla se lavó con HCl 1 N, Na_2CO_3 saturado y salmuera, se secó sobre Na_2SO_4 y se concentró al vacío para dar un aceite (62 g).

Etapa 2



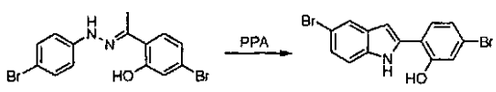
Se añadió lentamente $AlCl_3$ (40 g, 0,3 mol) al producto de la etapa 1 (21,5 g, 0,1 mol) en un baño de hielo-agua. La mezcla se agitó a 140 °C durante 2 horas. Después de enfriar a 60-70 °C, la mezcla se vertió lentamente en hielo-agua. La solución resultante se extrajo con DCM. Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron al vacío. El residuo se purificó por cromatografía en columna para dar el compuesto deseado (14 g). MS (ESI) m/e ($M+H^+$): 214.

Etapa 3



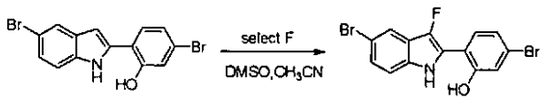
Una mezcla de la cetona obtenida en la etapa 2 (4,2 g, 20 mmol) y clorhidrato de 4-bromofenilo hidrazina (4,4 g, 20 mmol) en AcOH y EtOH (1:10, 100 ml) se calentó a reflujo durante 6 horas. El disolvente se retiró al vacío para dar un sólido, que se usó en la siguiente etapa sin purificación adicional (9,2 g en bruto). MS (ESI) m/e ($M+H^+$): 383.

Etapa 4



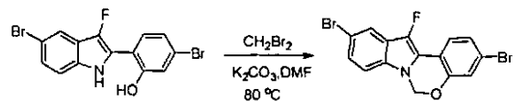
Una mezcla de producto de la etapa 3 (9,2 g) en PPA se calentó a 80 °C durante 2 horas. Después de enfriar a TA, la mezcla se vertió en hielo agua. La solución resultante se extrajo con DCM. Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron al vacío. El residuo se purificó por cromatografía en columna para dar el indol deseado (4,8 g). MS (ESI) m/e ($M+H^+$): 368.

Etapa 5



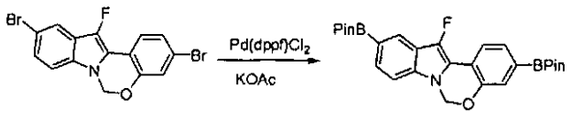
A una mezcla del indol de la etapa 4 (6 g, 16,3 mmol) en DMSO/CH_3CN (1:1, 24 ml) se le añadió en porciones SELECTFLUOR® (5,8 g, 16,3 mmol) a TA. La mezcla se agitó durante 1 hora más a TA y la mezcla se purificó por HPLC para dar un sólido (1,0 g). MS (ESI) m/e ($M+H^+$): 386.

Etapa 6



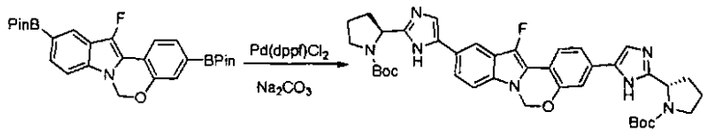
Una mezcla del compuesto de la etapa 5 (650 mg, 1,63 mmol), CH_2Br_2 (1,5 g, 8,62 mmol) y K_2CO_3 (1,2 g, 8,7 mmol) en DMF (32,5 ml) se agitó durante 5 horas a 80 °C. Después, la mezcla se evaporó al vacío. El residuo se diluyó con AE y agua. La capa orgánica se separó, se secó sobre Na_2SO_4 y se concentró al vacío para dar un sólido, que se usó directamente en la siguiente etapa sin purificación adicional (610 mg). MS (ESI) m/e ($M+H^+$): 396.

Etapa 7



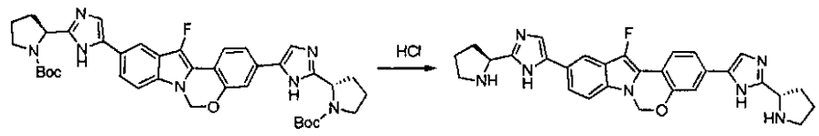
A una solución del producto de la etapa 6 (1 mmol) en 1,4-dioxano se le añadieron bis pinacol borato (1,1 mmol) y $Pd(dppf)Cl_2$ (0,02 mmol) y KOAc (2 mmol). La mezcla de reacción se agitó en una atmósfera de N_2 y se calentó a 110 °C durante 3 horas. Después de esto, el disolvente se retiró al vacío y el residuo se purificó por cromatografía en columna para proporcionar el producto. MS (ESI) m/e ($M+H^+$): 492.

Etapa 8



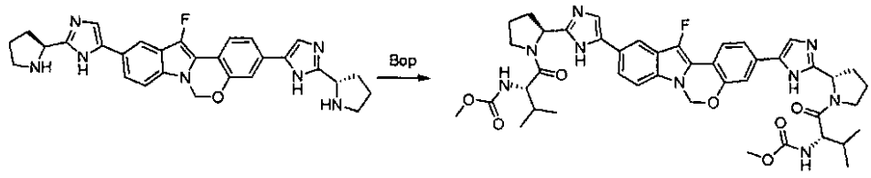
Una suspensión del boronato anterior (2 mmol), 2-(2-bromo-1*H*-imidazol-5-il)pirrolidin-1-carboxilato de terc-butilo (2,4 mmol), $Pd(dppf)Cl_2$ (200 mg), Na_2CO_3 (3 mmol) y en THF/H_2O (10:1, 33 ml) se calentó a reflujo a 75 °C durante una noche en una atmósfera protectora de N_2. La mezcla se enfrió, se filtró, el filtrado se lavó con agua (50 ml), se extrajo con EtOAc (100 ml), se lavó con salmuera y se secó sobre sulfato sódico anhidro. Después de la concentración al vacío, el residuo se purificó por cromatografía en columna para proporcionar el compuesto deseado. MS (ESI) m/e ($M+H^+$): 710.

Etapa 9



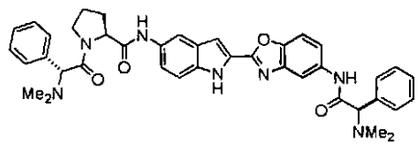
La prolina protegida anterior (1,3 mmol) se añadió a HCl/CH_3OH (10 ml, 3 M). La mezcla se agitó a TA durante 2-3 horas antes de que la mezcla se concentrara para dar el producto en bruto, que se usó en la siguiente etapa sin purificación adicional. MS (ESI) m/e ($M+H^+$): 510

Etapa 10

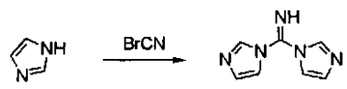


A una mezcla del producto en bruto de la etapa 9 (1,0 mmol), ácido (S)-2-(metoxicarbonilamino)-3-metilbutanoico (2,0 mmol) y DIPEA (8 mmol) en CH_3CN (10 ml) se le añadió BOP (2,2 mmol). La mezcla resultante se agitó a TA. Después de que el análisis por LCMS mostrara que el material de partida se había consumido, la mezcla se filtró, y el filtrado se purificó por HPLC para dar el compuesto deseado en forma de un sólido de color blanco. MS (ESI) m/e ($M+H^+$): 825. ^1H RMN (MeOD): □ 7,83-7,85 (m, 3 H), 7,72 (s, 1 H), 7,53 (s, 2 H), 7,46-7,48 (m, 1 H), 7,42 (s, 1 H), 5,92 (s, 2 H), 5,20-5,22 (m, 2 H), 4,20-4,23 (m, 2 H), 4,06-4,09 (m, 2 H), 3,86-3,88 (m, 2 H), 3,61 (s, 6 H), 2,50-2,52 (m, 2 H), 1,96-2,20 (m, 8 H), 0,90-0,98 (m, 12 H).

Ejemplo 190: (2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-(2-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1,3-benzoxazol-2-il}-1H-indol-5-il)pirrolidin-2-carboxamida

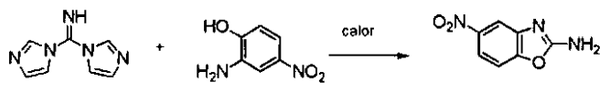


Etapa 1



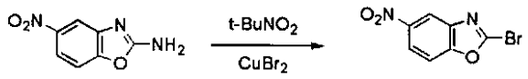
A una solución de imidazol (13,6 g, 0,2 mol) en 1 l de DCM se le añadió BrCN (7,4 g, 66 mmol) y la mezcla se calentó a reflujo durante 30 minutos. La mezcla se enfrió a TA, el precipitado de color blanco se retiró por filtración y el filtrado se concentró para dar 100 ml que se enfriaron a

0 °C durante 2 días. El sólido cristalizado se filtró, se lavó con DCM frío, después se secó al vacío para dar el producto deseado (8,8 g) en forma de un sólido de color blanco. *Etapa 2*



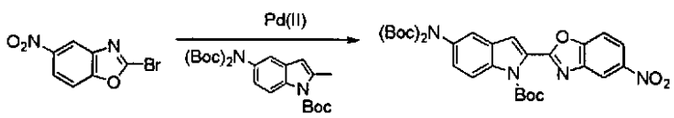
Una solución que contenía el producto de la etapa 1 (8,36 g, 54,2 mmol) y 2-amino-4-nitrofenol (8,74 g, 54,2 mmol) en THF anhidro (200 ml) se dejó a reflujo en una atmósfera de N_2 durante 14 horas. La mezcla se enfrió a TA, se filtró, el precipitado se lavó con THF (frío) y después se secó al vacío para proporcionar el producto deseado (9,0 g), en forma de un sólido de color amarillo. MS (ESI) m/e ($M+H^+$): 180. ^{1}H RMN (DMSO) □: 7,85~7,96(m, 3 H), 7,52(d, J = 8,8 Hz, 1H).

Etapa 3



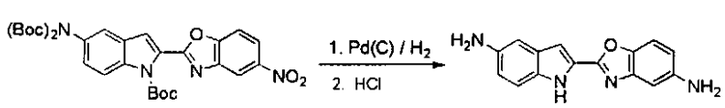
A una suspensión del producto de la etapa 2 (3,58 g, 20 mmol) en acetonitrilo (300 ml) se le añadió $CuBr_2$ (8,96 g, 40 mmol). La solución se volvió de color verde oscuro y se añadió nitrito de t-butilo (4,12 g, 40 mmol) a TA durante 5 minutos, después de lo cual la mezcla se calentó a 45 °C durante 2 horas. La mezcla de reacción se vertió en agua (800 ml) y DCM (800 ml) y las fases se separaron. La fase acuosa se extrajo con DCM (3 x 800 ml), se secó con Na_2SO_4 y se evaporó para proporcionar el producto en bruto. La purificación por cromatografía en columna proporcionó el producto deseado. MS (ESI) m/e ($M+H^+$): 243/245. ^{1}H RMN (DMSO) □: 8,71 (s, 1 H), 8,42(d, J = 9,2 Hz, 1H), 8,10 (d, J = 9,2 Hz, 1H).

Etapa 4



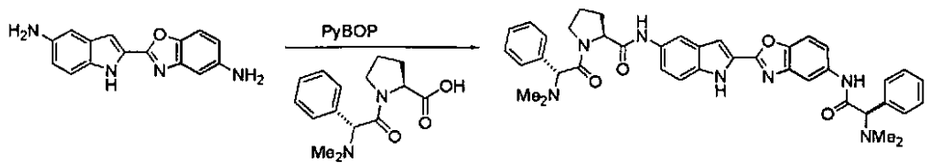
La mezcla del compuesto de la etapa 3 anterior (603 mg, 2,5 mmol), el ácido indol borónico del Ejemplo 42 (1,0 g, 2,75 mmol), $Pd(dppf)Cl_2$ (183 mg, 0,25 mmol), Na_2CO_3 (530 mg, 5,0 mmol) en 5 ml de dioxano-H_2O (5:1) se calentó a reflujo en una atmósfera de N_2 durante una noche. Cuando la reacción se completó, la mezcla se vertió en agua y se extrajo con DCM. La fase orgánica se secó sobre Na_2SO_4, se concentró y el residuo se purificó para dar el compuesto del producto deseado. MS (ESI) m/e ($M+H^+$): 596.

Etapa 5



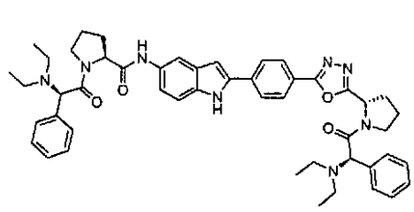
El producto de la etapa 4 (596 mg, 1,0 mmol) se disolvió en EtOAc y se trató con Pd/C (100 mg, 20%). Después, la mezcla se agitó a TA durante una noche en una atmósfera de H_2. Cuando la reacción se completó, el Pd/C se retiró por filtración, y la solución resultante se concentró para dar el producto en bruto MS (ESI) m/e ($M+H^+$): 565. Este material se cubrió con 5 ml de HCl 3 M y la mezcla se agitó a TA durante 2 horas. La evaporación del disolvente proporcionó el producto deseado, que se usó directamente sin purificación adicional. MS (ESI) m/e ($M+H^+$): 265.

Etapa 6

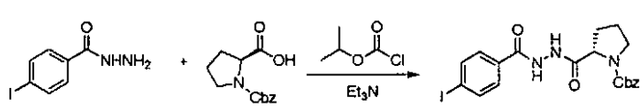


El compuesto se acopló usando un procedimiento similar al que se describió en el Ejemplo 40 partiendo de 265 mg (1,0 mmol) del producto de la etapa 5. ^{1}H RMN (MeOD) □: 8,12 (s, 1H), 7,97 (d, J = 2 Hz, 1H), 7,30~7,70 (m, 15H), 5,30~5,35 (m, 2H), 4,51~4,60 (m, 2H), 3,85~3,95 (m, 2H), 3,15~3,25 (m, 2H), 3,06 (s, 3H), 2,54 (s, 6H), 1,80~2,30 (m, 8H). MS (ESI) m/e ($M+H^+$): 781.

Ejemplo 191: 1-[(2R)-2-(dietilamino)-2-fenilacetil]-N-(2-[4-(5-{(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}-1,3,4-oxadiazol-2-il)fenil]-1H-indol-5-il}-L-prolinamida

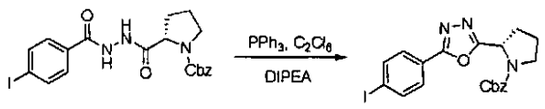


Etapa 1



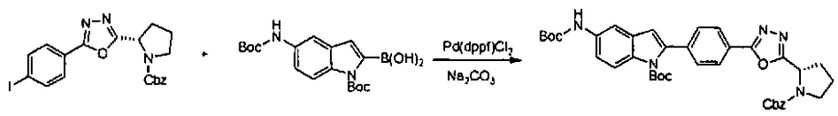
A una solución de N-Cbz-L-Pro (14,9 g, 0,06 mol) y TEA (8,08 g, 0,08 mol) en 100 ml de DCM se le añadió gota a gota cloroformiato de isopropilo (8,05 g, 0,066 mol) a 0 °C. Después de la adición, la solución continuó en agitación durante 1 hora antes de añadir la hidrazida (13,0 g, 0,05 mol) y la mezcla continuó en agitación durante 1 hora más. El disolvente se evaporó al vacío y el residuo se recristalizó en EtOH para dar un sólido de color blanco (22,1 g). ^{1}H RMN (DMSO) □: 10,47 (s, 1H), 10,03 (s, 1H), 7,86 (d, J = 8,0 Hz, 2H), 7,62 (d, J = 8,0 Hz, 2H), 7,31~7,61 (m, 5H), 4,91~5,14 (m, 2 H), 4,26~4,35 (m, 1 H), 3,30~3,4 (m, 2 H), 1,95~2,19 (s, 4H). MS (ESI) m/e ($M+H^+$): 494.

Etapa 2



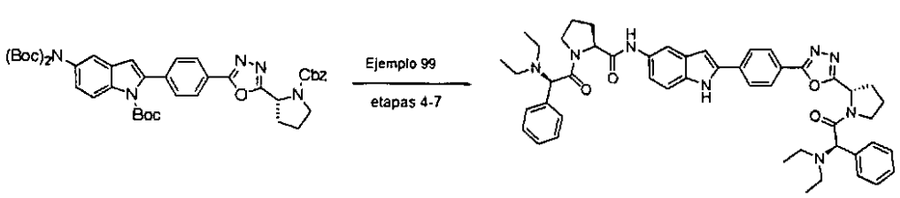
A una solución del producto de la etapa 1 (2,1 g, 4,26 mmol), DIPEA (2,3 ml, 17,7 mmol) y PPh_3 (1,71 g, 6,5 mmol) en 20 ml de MeCN se le añadió hexcloroetano (1,41 g, 5,97 mmol) y la mezcla se agitó a TA durante 1,5 horas. El disolvente se evaporó y el residuo se purificó por cromatografía para dar un sólido de color blanco (1,75 g). MS (ESI) m/e ($M+H^+$): 494.

Etapa 3



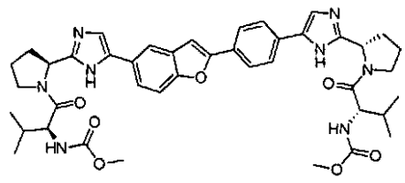
Una mezcla del producto de la etapa 2 anterior (494 mg, 1,0 mmol), ácido indol borónico del Ejemplo 42 (377 mg, 1,0 mmol), $Pd(dppf)Cl_2$ (73 mg, 0,10 mmol), Na_2CO_3 (318 mg, 3,0 mmol), THF (25 ml) y H_2O (5 ml) se calentó a reflujo en una atmósfera de N_2 durante una noche. La mezcla se vertió en agua y se extrajo con CH_2Cl_2. La fase orgánica se combinó, se secó sobre Na_2SO_4 y se filtró para dar el compuesto deseado, que se usó directamente en la siguiente etapa. MS (ESI) m/e ($M+H^+$): 680.

Etapa 4

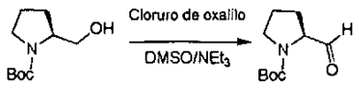


Siguiendo el procedimiento descrito en el Ejemplo 99, etapas 4-7, el oxadiazol de la etapa 3 anterior se convirtió en el producto deseado. ^1H RMN (MeOD) □: 8,09 (d, J = 8,8 Hz, 2H), 7,99 (d, J = 8,8 Hz, 2H), 7,83 (s, 1H), 7,66~7,68 (m, 4H), 7,55~7,58 (m, 6H), 7,38~7,40 (m, 1H), 7,22~7,24 (m, 1H), 6,98 (s, 1H), 5,39 (s, 1H), 5,37~5,39 (m, 2H), 4,52~4,54 (m, 1H), 4,12~4,14 (m, 1H), 3,94~3,96 (m, 1H), 3,10~3,41 (m, 8H), 2,72~2,76 (m, 2H), 1,84~2,24 (m, 8H), 1,34~1,41 (m, 6H), 1,16~1,19 (m, 6H). MS (ESI) m/e ($M+H^+$): 821.

Ejemplo 192: {(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(metoxi-carbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

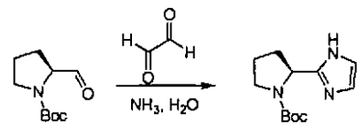


Etapa 1



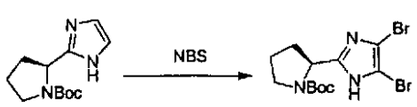
Un matraz de 2 l de fondo redondo y 3 bocas equipado con un agitador situado en la parte superior y una entrada de N_2 se cargó con una solución de cloruro de oxalilo (130 ml, 0,26 mol) en DCM (250 ml). La solución se enfrió a -78 °C y se añadió gota a gota una solución de DMSO (20 ml, 0,28 mol) en DCM (30 ml). Después de 30 minutos, se añadió gota a gota una solución de (S)-N-Boc-prolinol (40 g, 0,20 mol) en DCM (200 ml). Después de 30 minutos, a la solución se le añadió TEA (140 ml, 1,00 mol), y el matraz se transfirió a un baño de hielo/agua y se agitó durante 30 minutos más. La mezcla de reacción se diluyó con DCM (200 ml) y se lavó sucesivamente con H_2O, HCl 1 M, $NaHCO_3$ saturado y salmuera. La capa de DCM se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar éster terc-butílico del ácido *(S)*-2-formil-pirrolidin-1-carboxílico en bruto (40 g) en forma de un aceite, que se usó sin purificación adicional.

Etapa 2



Se añadió gota a gota glioxal (2,0 ml del 40% en agua) durante 11 minutos a una solución en metanol de NH_4OH (32 ml) y (S)-Boc-prolinal (8,564 g, 42,98 mmol) y se agitó a temperatura ambiente durante 19 horas. Los componentes volátiles se retiraron al vacío y el residuo se purificó por cromatografía ultrarrápida sobre gel de sílice (EtOAc) seguido de recristalización (EtOAc) para proporcionar el compuesto deseado en forma de un sólido esponjoso de color blanco (4,43 g). ^{1}H RMN (DMSO) □: 11,68, 11,59 (s a, 1H), 6,94 (s, 1H), 6,76 (s, 1H), 4,76 (m, 1H), 3,48 (m, 1H), 3,35-3,29 (m, 1H), 2,23-1,73 (m, 4H), 1,39/1,15 (s, 9H). MS (ESI) m/e ($M+H^+$): 238.

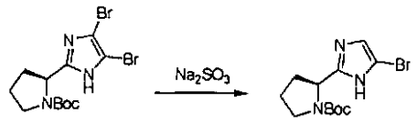
Etapa 3



A una suspensión del compuesto de la etapa 2 (140 g, 0,59 mol) en THF (2000 ml) se le añadió NBS (200 g, 1,1 mol). La mezcla se agitó a TA en una atmósfera protectora de N_2 durante

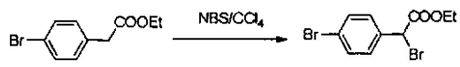
una noche antes de que el disolvente se retirara y el residuo se purificó por cromatografía sobre gel de sílice para dar 230 g del compuesto de dibromo deseado. MS (ESI) m/e ($M+H^+$): 396.

Etapa 4



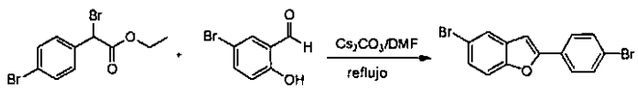
A una suspensión del compuesto de la etapa 3 (230 g, 0,58 mol) en $EtOH/H_2O$ (3000 ml) se le añadió Na_2SO_3 (733 g, 5,8 mol). La mezcla resultante se agitó a la temperatura de reflujo durante una noche. Después de enfriar a TA, la mezcla se extrajo con DCM y se concentró al vacío. El residuo resultante se purificó por cromatografía sobre gel de sílice para dar el bromo imidazol diana deseado. MS (ESI) m/e ($M+H^+$): 317.

Etapa 5



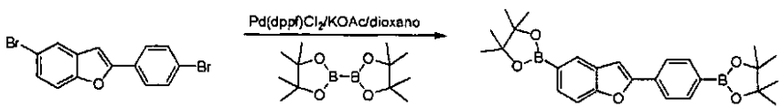
A una solución agitada de 4-bromofenilacetato de etilo (50 g, 205,8 mmol) en CCl_4 (500 ml) se le añadió NBS (38 g, 214,7 mmol) y después HBr acuoso al 48% (4 gotas). Después de la adición, la solución se agitó durante una noche a 80 °C en una atmósfera de argón. Después, la reacción se enfrió a TA, se filtró y se concentró. El aceite resultante se usó directamente en la siguiente etapa.

Etapa 6



A una solución del compuesto de la etapa 5 (2 g, 6,2 mmol) en DMF (20 ml) se le añadieron 5-bromosalicilaldehído (1,21 g, 6,0 mmol) y Cs_2CO_3 (2 g, 12,3 mmol) en una atmósfera protectora de N_2. La suspensión resultante se agitó durante 5 horas a 160 °C, después se enfrió y se trató con agua. El precipitado resultante se filtró y la torta de filtro se secó al vacío para dar el compuesto deseado, que se usó directamente en la siguiente etapa.

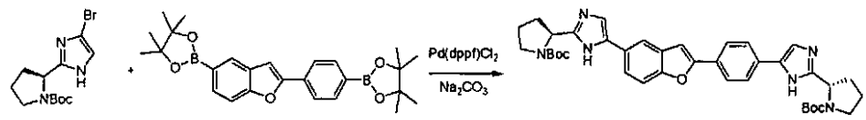
Etapa 7



Una suspensión del producto de la etapa 6 anterior (4,43 g, 12,58 mmol), bis(pinacolato)diboro (8,31 g, 32,72 mmol), AcOK (3,72 g, 37,7 mmol) y $Pd(dppf)Cl_2$ (921 mg, 1,26 mmol) en dioxano (100 ml) se calentó a reflujo durante 4 horas en una atmósfera de N_2. La mezcla se concentró, el residuo se repartió entre H_2O y DCM y la fase acuosa se extrajo con DCM.

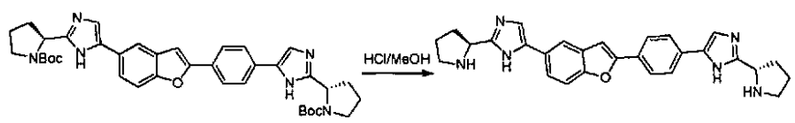
Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron. El residuo se purificó por cromatografía sobre gel de sílice para proporcionar el compuesto deseado (5 g).

Etapa 8



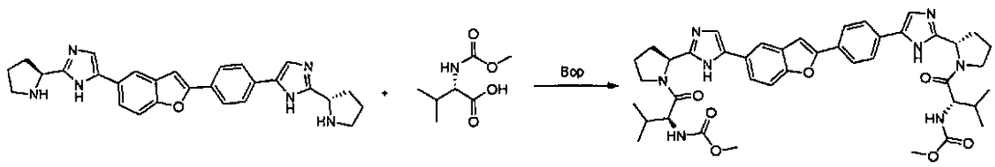
Una suspensión del producto de la etapa 4 (5 mmol), el éster boronato de la etapa 7 (2 mmol), $Pd(dppf)Cl_2$ (146 mg, 0,2 mmol) y Na_2CO_3 (636 mg, 6 mmol) se calentaron a reflujo en THF/H_2O (10:1, 33 ml) durante una noche en una atmósfera protectora de N_2. La mezcla se enfrió, se filtró, el filtrado se lavó con agua (50 ml), después se extrajo con EtOAc (100 ml), se lavó con salmuera y se secó sobre sulfato sódico anhidro. La solución se concentró y el residuo resultante se purificó por cromatografía en columna (PE/AE = 8:1 □ 5:1) para proporcionar el compuesto deseado. MS (ESI) m/z $(M+H)^+$: 641).

Etapa 9



El producto de la etapa 8 (1,3 mmol) se le añadió en HCl 3 M/CH_3OH (20 ml) y la mezcla se agitó a TA durante 2 a 3 horas. La mezcla se concentró y el producto en bruto se usó directamente en la siguiente etapa sin purificación adicional. MS (ESI) m/z $(M+H)^+$: 441.

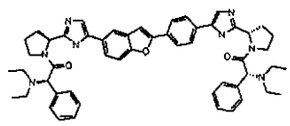
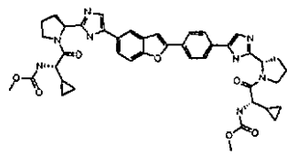
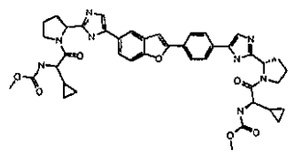
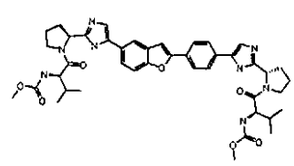
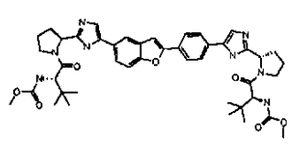
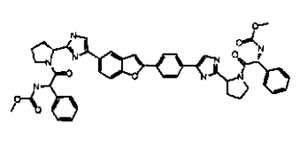
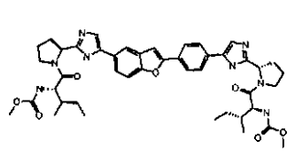
Etapa 10

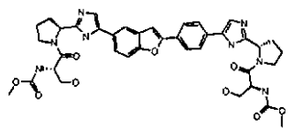
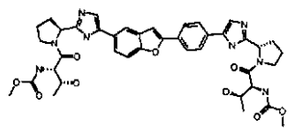
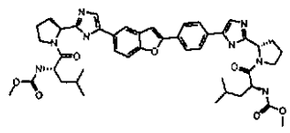


A una mezcla del producto de la etapa 9 (1 mmol), N-Moc-L-valina (2,1 mmol) y DIPEA (0,4 ml) en DMF (3 ml) se le añadió el reactivo BOP (2,2 mmol). La mezcla resultante se agitó a TA durante 16 horas. La solución se sometió directamente a RPLC para proporcionar el compuesto deseado. ^1H RMN (MeOD) □: 7,7-8,1 (m, 10 H), 7,4 (m, 1 H), 5,3 (m, 2 H), 4,3 (m, 2 H), 4,1 (d, J = 4,8 Hz, 2 H), 3,9 (m, 2 H), 3,7 (m, 6 H), 2,6 (d, J = 4,8 Hz, 2 H), 2,0-2,4 (m, 8 H), 1,3-1,4 (m, 2 H), 0,9-1,0 (m, 12 H). MS (ESI) m/z $(M+H)^+$: 780.

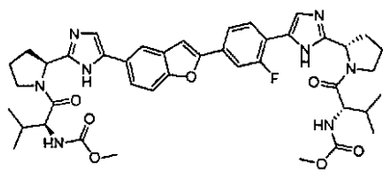
Ejemplos 193-202

Los compuestos de los Ejemplos 193-202 se prepararon de una manera similar a la que se ha descrito en el Ejemplo 192.

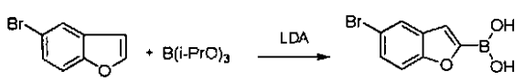
Ejemplo	Estructura	PM	Nombre
193		844	(2R)-2-(dietilamino)-1-[(2S)-2-(5-{4-[5-(2-{(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}-1H-imidazol-5-il)-1-benzofuran-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-2-feniletanona
194		775	{(1S)-1-ciclopropil-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-ciclopropil-2-[(metoxicarbonil)amino]acetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxoetil}carbamato de metilo
195		775	{(1R)-1-ciclopropil-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-ciclopropil-2-[(metoxicarbonil)amino]acetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxoetil}carbamato de metilo
196		780	{(2R)-1-[(2S)-2-{5-[2-(4-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo
197		806	{(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo
198		848	{(1R)-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-4-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo
199		806	{(2S,3R)-1-{(2S)-2-(5-{2-[4-(2-{(2S)-1-N-(metoxicarbonil)-L-aloisoleucil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1-benzofuran-5-il}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxopentan-2-il}carbamato de metilo

Ejemplo	Estructura	PM	Nombre
200		755	{(2S)-3-hidroxi-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-3-hidroxi-2-[(metoxicarbonil)amino]propanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-1-oxopropan-2-il}carbamato de metilo
201		783	{(2S,3R)-3-hidroxi-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S,3R)-3-hidroxi-2-[(metoxicarbonil)amino]butanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-1-oxobutan-2-il}carbamato de metilo
202		806	{(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-4-metilpentanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-4-metil-1-oxopentan-2-il}carbamato de metilo

Ejemplo 203: {(2S)-1-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo



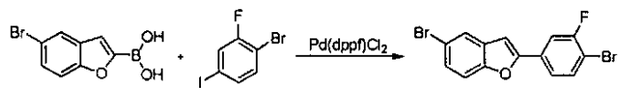
Etapa 1



Se añadió lentamente una solución de 5-bromobenzofurano (3,9 g, 20 mmol) en THF seco (□30 ml) enfriada a -78 °C en una atmósfera de LDA protegida con N_2 (preparada a partir de n-BuLi y iPr_2NH en THF (~30 mmol)). La mezcla se agitó a la misma temperatura durante 30 minutos y después a la mezcla se le añadió triisopropilborato (5,64 g, 30 mmol). La mezcla se dejó calentar a TA y se agitó durante 2 horas. Después, la mezcla se inactivó con HCl 1 N a pH = 3 y se

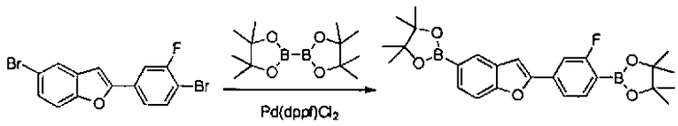
extrajo con EtOAc. Las fases orgánicas combinadas se combinaron, se secaron y se filtraron. El filtrado se concentró para proporcionar el producto deseado (4,3 g). MS (ESI) m/e ($M+H^+$): 241.

Etapa 2



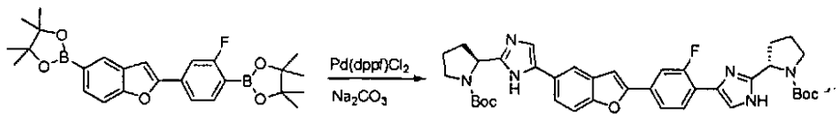
Una suspensión del ácido borónico de la etapa 1 (1,44 mg, 6,0 mmol), 2-fluoro-4-yodobromobenceno (1,8 g, 6,0 mmol), $Pd(dppf)Cl_2$ (600 mg), Na_2CO_3 (954 mg, 9,0 mmol) y en THF/H_2O (9:1, 100 ml) se calentó a reflujo a 75 °C durante una noche en una atmósfera protectora de N_2. La mezcla se enfrió y se filtró. El filtrado se lavó con agua (150 ml), se extrajo con EtOAc (200 ml), se lavó con salmuera y se secó sobre sulfato sódico anhidro. La solución se evaporó y el residuo se purificó por cromatografía en columna (PE/AE = 8:1 □ 5:1) para proporcionar el compuesto deseado. MS (ESI) m/e ($M+H^+$): 370.

Etapa 3



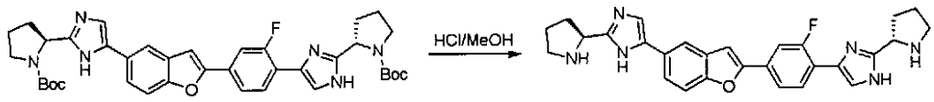
Una solución del producto de la etapa 2 (1,85 g, 5 mmol), bis(pinacolato)diboro (2,54 g, 10 mmol) y $Pd(dppf)Cl_2$ (80 mg) y KOAc (0,98 g, 10 mmol) se disolvieron en 1,4-dioxano (30 ml) y la mezcla de reacción se calentó a 110 °C durante 16 horas. El disolvente se evaporó y el residuo se purificó por cromatografía en columna con gel de sílice de elución con PE para proporcionar el producto deseado en forma de un sólido de color blanco (1,95 g). MS (ESI) m/e ($M+H^+$): 465.

Etapa 4



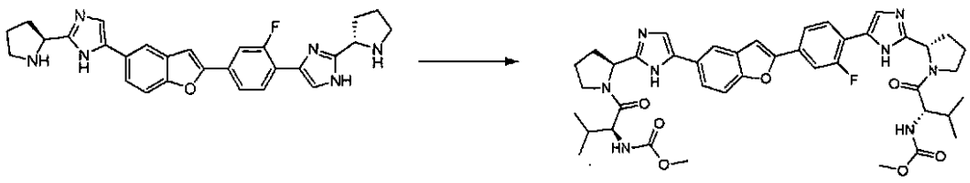
Una suspensión del bromoimidazol del Ejemplo 192 (5 mmol), el éster boronato de la etapa 3 (2 mmol), $Pd(dppf)Cl_2$ (146 mg, 0,2 mmol) y Na_2CO_3 (636 mg, 6 mmol) se calentó a reflujo en THF/H_2O (10:1, 33 ml) durante una noche en una atmósfera protectora de N_2. La mezcla se enfrió, se filtró, el filtrado se lavó con agua (50 ml), se extrajo con EtOAc (100 ml), se lavó con salmuera y se secó sobre sulfato sódico anhidro. La solución se concentró y el residuo resultante se purificó por cromatografía en columna (PE/EtOAc = 8:1) para proporcionar el compuesto deseado. MS (ESI) m/e ($M+H^+$): 683.

Etapa 5



El producto de la etapa 4 (682 mg, 1,0 mmol) se trató con HCl 3 M/CH_3OH (10 ml) y la mezcla se agitó a TA durante 3 horas. La mezcla de reacción se concentró y el producto en bruto se usó directamente en la siguiente etapa sin purificación adicional. MS (ESI) m/e ($M+H^+$): 483.

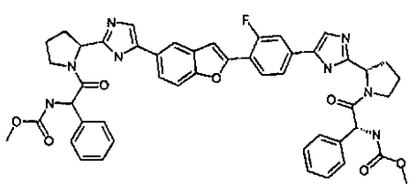
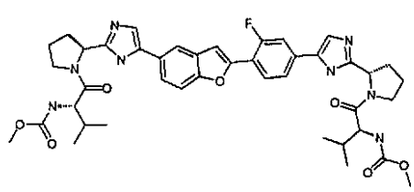
Etapa 6

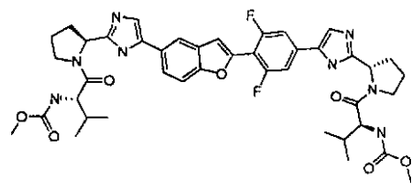
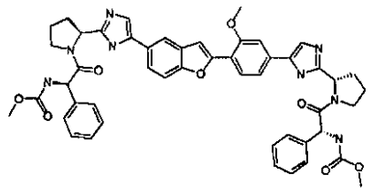
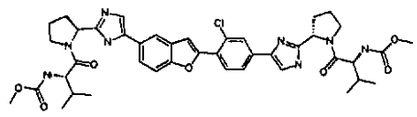
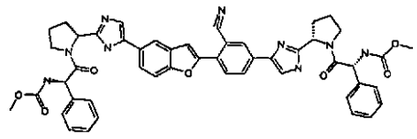
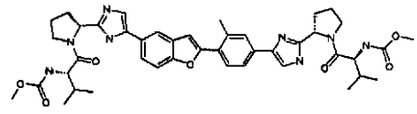


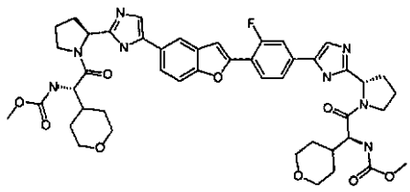
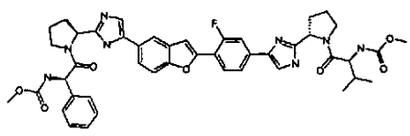
A una mezcla del producto de la etapa 5 (482 mg, 1,0 mmol), N-Moc-L-valina (2,1 mmol) y DIPEA (0,4 ml) en DMF (3 ml) se le añadió el reactivo BOP (977 mg, 2,2 mmol). La mezcla resultante se agitó a TA durante 16 horas. La solución se sometió directamente a RPLC para proporcionar el compuesto deseado en forma de un sólido de color blanco (40 mg). ^1H RMN (MeOD) □: 7,99 (s, 1 H), 7,89-7,80 (m, 5 H), 7,72-7,67 (m, 2 H), 7,47 (s, 1 H), 5,27-5,22 (m, 2 H), 4,22 (d, 2 H), 4,09 (d, 2 H), 3,89-3,84 (m, 2 H), 3,64 (s, 6 H), 2,55-2,02 (m, 10 H), 0,92 (d, 6 H), 0,88 (d, 6 H). MS (ESI) m/e ($M+H^+$): 797.

Ejemplos 204-212

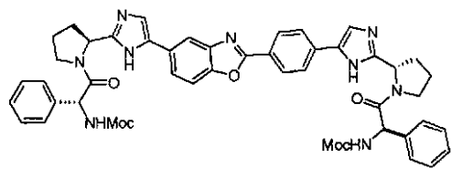
Los compuestos de los Ejemplos 204-212 se prepararon de una manera similar a la que se ha descrito en el Ejemplo 203.

Ejemplo	Estructura	M+1	Nombre
204		866	{(1R)-2-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(25)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo
205		797	{(2S)-1-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(25)-1-{(25)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

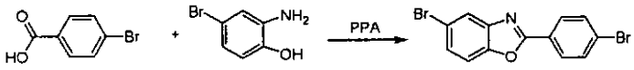
Ejemplo	Estructura	M+1	Nombre
206		816	{(2S)-1-[(2S)-2-{5-[2-(2,6-difluoro-4-{2-[(25)-1-{(25)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo
207		878	{(1R)-2-[(2S)-2-{5-[3-metoxi-4-(5-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo
208		814	{(2S)-1-[(2S)-2-{5-[2-(2-cloro-4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo
209		873	{(1R)-2-[(2S)-2-{4-[3-ciano-4-(5-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo
210		794	{(2S)-1-[(2S)-2-{5-[2-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}-2-metilfenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo	Estructura	M+1	Nombre
211			[(1S)-2-[(2S)-2-(5-{3-fluoro-4-[5-(2-{(2S)-1-[(2S)-2-[(metoxicarbonil)amino]-2-(tetrahidro-2/f-piran-4-il)acetil]pirrolidin-2-il}-1H-imidazol-5-il)-1-benzofuran-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-2-oxo-1-(tetrahidro-2H-piran-4-il)etil]carbamato de metilo
212		832	{(2S)-1-[(2S)-2-{4-[3-fluoro-4-(5-{2-[(25)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo

Ejemplo 213: {(1R)-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-[(metoxi-carbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1,3-benzoxazol-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo

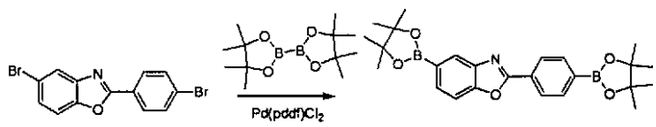


Etapa 1



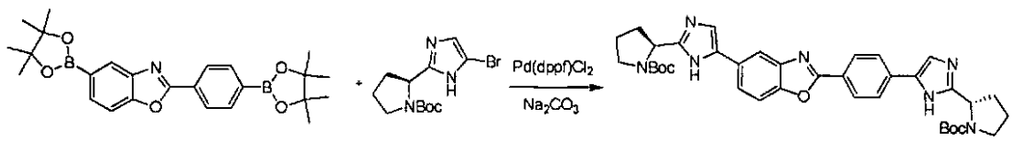
Se añadieron ácido 4-bromobenzoico (20 g, 0,1 mol) y 2-amino-4-bromofenol (18,8 g, 0,1 mol) en ácido polifosfórico (250 ml) y la mezcla se agitó a 140 °C durante 90 minutos. Después de la refrigeración en un baño de hielo, la mezcla de reacción se diluyó con agua (4000 ml) y se neutralizó con NaOH. El sólido resultante se retiró por filtración y se secó para proporcionar el benzoxazol deseado. MS (ESI) m/e ($M+H^+$): 354.

Etapa 2



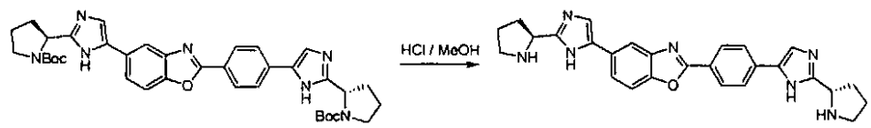
Una suspensión del producto de la etapa 1 anterior (10,6 g, 30 mmol), bis(pinacolato)diboro (30,3 g, 120 mmol), KOAc (7,6 g, 78 mmol) y $Pd(dppf)Cl_2$ (1,1 g, 1,5 mmol) en dioxano (300 ml) se agitó a 100 °C en una atmósfera protectora de N_2 durante una noche. La mezcla de reacción se enfrió, se concentró y después se sometió a cromatografía sobre gel de sílice dando el compuesto del producto. MS (ESI) m/e ($M+H^+$): 366.

Etapa 3



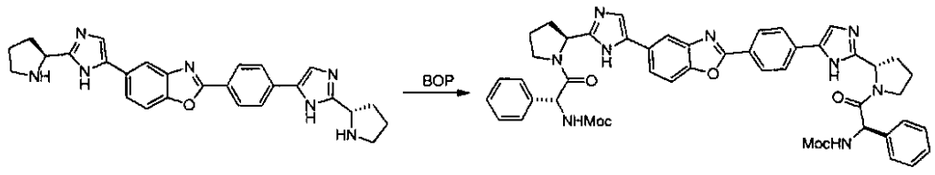
Una suspensión del producto de la etapa 2 (1,2 g, 2,6 mmol), bromoimidazol del Ejemplo 192 (2 g, 6,3 mmol), Na_2CO_3 (1,3 g, 12 mmol) y $Pd(dppf)Cl_2$ (220 mg, 0,3 mmol) en THF/H_2O (36 ml) se agitó a 100 °C en una atmósfera protectora de N_2 durante una noche. La mezcla de reacción se concentró y se purificó por cromatografía sobre gel de sílice para dar el compuesto deseado. MS (ESI) m/e ($M+H^+$): 666.

Etapa 4



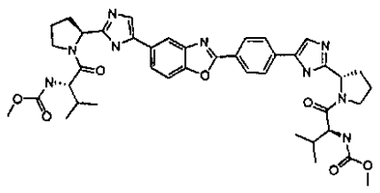
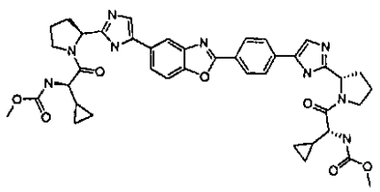
Una solución del producto de la etapa 3 (400 mg, 0,6 mmol) en HCl/MeOH (20 ml) se agitó a temperatura ambiente durante 3 horas, después se concentró y se secó a alto vacío para dar el producto deseado. MS (ESI) m/e ($M+H^+$): 466.

Etapa 5



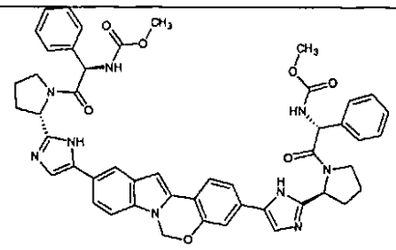
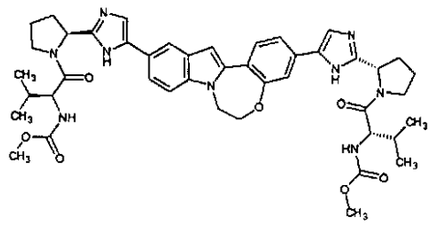
A una mezcla del producto de la etapa 4 (233 mg, 0,5 mmol), *N*-Moc-D-Phg (1,1 mmol) y DIPEA (0,2 ml) en DMF (3 ml) se le añadió el reactivo BOP (488 mg, 1,1 mmol). La mezcla resultante se agitó a TA durante 16 horas antes de someter la solución directamente a RPLC para proporcionar el compuesto deseado. ^1H RMN (MeOD) □: 8,4 (d, J = 8,4 Hz, 2 H), 8,2 (s, 1 H), 8,0 (m, 3 H), 7,9 (m, 3 H), 7,5-7,4 (m, 10 H), 5,5 (s, 2 H), 5,3 (m, 2 H), 4,1-4,0 (m, 2 H), 3,6 (d, J = 2,8 Hz, 6 H), 3,3 (m, 1 H), 3,3-3,1 (m, 1 H), 2,5-2,3 (m, 2 H), 2,2-2,1 (m, 4 H), 2,0 (m, 2 H). MS (ESI) m/e ($M+H^+$): 780.

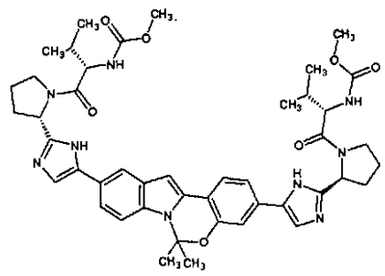
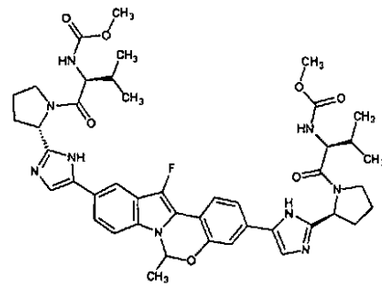
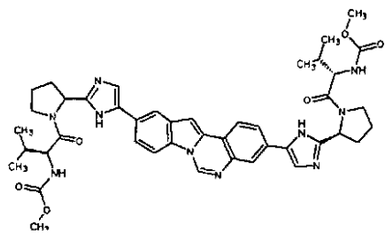
Ejemplos 214-215

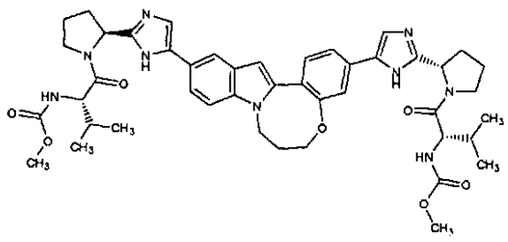
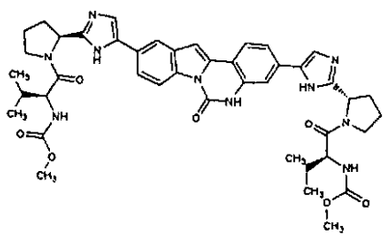
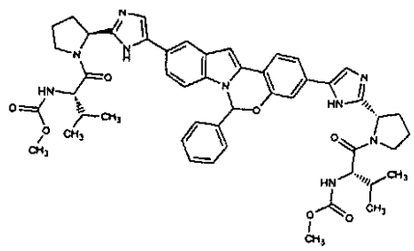
Ejemplo	Estructura	M+1	Nombre
214		848	{(2S)-1-[(2S)-2-{5-[2-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1,3-benzoxazol-5-il]-*1H*-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo
215		776	ciclopropil-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-ciclopropil-2-[(metoxicarbonil)amino]acetil}pirrolidin-2-il]-1H-imidazol-5-il}-1,3-benzoxazol-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxoetil}carbamato de metilo

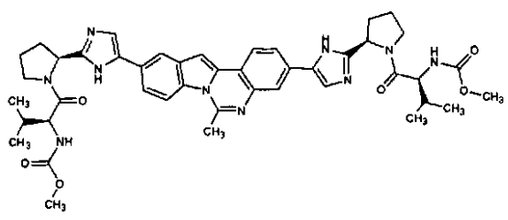
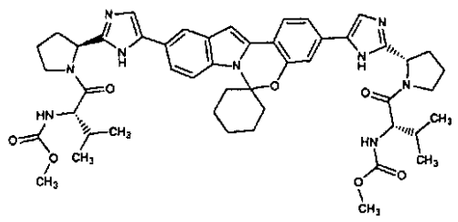
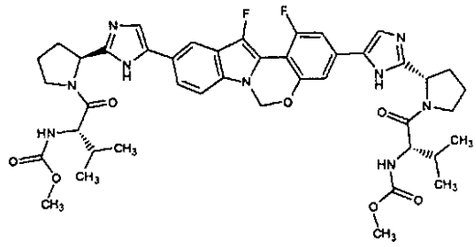
Ejemplos 216-227

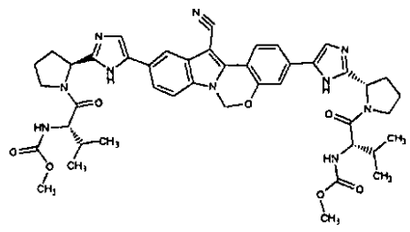
Los compuestos de los Ejemplos 216-227 se prepararon de una manera similar a la que se ha descrito en el Ejemplo 189b (Procedimiento Alternativo).

Ejemplo	Estructura	M+1	Nombre
216		875	(indolo[1,2-c][1,3]benzoxazina-3,10-diilbis{1H-imidazol-5,2-diil(2S)pirrolidin-2,1-diil[(1R)-2-oxo-1-feniletano-2,1-diil]})biscarbamato de dimetilo
217		821	[(2S)-1-{(2S)-2-[5-(11-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6,7-dihidroindolo[1,2-d][1,4]benzoxazepin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo	Estructura	M+1	Nombre
218		835	[(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6,6-dimetilindolo[1,2-c][1,3]benzoxazin-10-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo
219		839	[(2S)-1-{(2S)-2-[5-(12-fluoro-10-{2-[(2S)-1-{(2,S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6-metilindolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo
220		804	[(2S)-1-{(2,S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c]quinazolin-10-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo	Estructura	M+1	Nombre
221		835	[(2S)-1-{(2S)-2-[5-(12-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-7,8-dihidro-6H-indolo[1,2-e][1,5]benzoxazocin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo
222		820	[(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6-oxo-5,6-dihidroindolo[1,2-c]quinazolin-10-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo
223		883	[(2S)-1-{(2S)-2-[5-(10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6-fenilindolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo	Estructura	M+1	Nombre
224		818	[(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6-metilindolo[1,2-c]quinazolin-10-il)-1H-imidazol-2-il]pirrolidin-1-il}-3 -metil-1-oxobutan-2-il]carbamato de metilo
225		875,1	[(2S)-1-{(2S)-2-[5-(10'-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}espiro[ciclohexano-1,6'-indolo[1,2-c][1,3]benzoxazin]-3'-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo
226		842	[(2S)-1-{(2S)-2-[5-(1,12-difluoro-10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo	Estructura	M+1	Nombre
227		832	[(2S)-1-{(2S)-2-[5-(12-ciano-10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo

Ejemplo 228-Medición de la Potencia de Inhibición del Compuesto

La medición de la inhibición por los compuestos se realizó usando el sistema replicón del VHC. Se usaron varios replicones diferentes que codificaban genotipos o mutaciones del VHC. Además, las mediciones de potencia se hicieron usando diferentes formatos del ensayo de replicón, incluyendo diferentes maneras de medición y diferentes formatos de placas. Véase, Jan M. Vrolijk *et al., A replicons-based bioassay for the measurement of interferons in patients with chronic hepatitis C,* 110 J. VIROLOGICAL METHODS 201 (2003); Steven S. Carroll *et al., Inhibition of Hepatitis C Virus RNA Replication by 2'-ModifiedNucleoside Analogs,* 278(14) J. BIOLOGICAL CHEMISTRY 11979 (2003). Sin embargo, los principios subyacentes son comunes a todas estas determinaciones, y se indican a continuación.

Se usaron líneas celulares que albergaban el replicón que codificaba la fosfotransferasa de neomicina estable, por lo que todas las líneas celulares se mantuvieron en la selección G418 anterior al ensayo. En algunos casos, las líneas celulares codificaron una fusión luciferasa:Neor y pueden ensayarse directamente por determinación del número de copia de ARN, o indirectamente a través de la medición de la actividad luciferasa.

Para iniciar un ensayo, las células replicón se colocaron en placas en presencia de una serie de diluciones del compuesto de ensayo en ausencia de G418. Típicamente, los ensayos se realizaron en un formato de placas de 96 pocillos para la operación manual, o una placa de 384 pocillos en un ensayo automatizado. Las células replicón y el compuesto se incubaron durante 24 a 72 horas. Al final del ensayo, las células se lavaron sin el medio y el compuesto y después se lisaron. La actividad luciferasa se midió usando un ensayo de luciferasa convencional. Las determinaciones CE_{50} se calcularon como un porcentaje de un control de DMSO ajustando los datos a una función de ajuste de cuatro parámetros.

La tabla de actividad que se muestra a continuación proporciona datos representativos que ilustran la actividad observada frente al genotipo 1b.

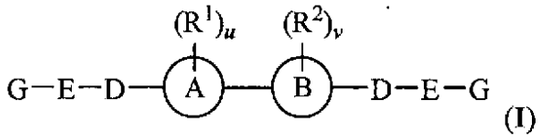
Tabla de Actividad			
Ejemplo	**CE_{50} (nM)**	**Ejemplo**	**CE_{50} (nM)**
2	9	105	0,08
6	200	107	0,04
14	10	116	0,065
15	0,045	119	0,013
19	25	125	0,016
26	0,063	129	0,7
30	26	130	0,05
39	0,24	131	17
40	0,026	137	0,009
41	0,05	138	8,5
42	14	144	0,036
45	0,02	155	0,9
49	0,072	158	0,5
58	0,97	159	0,002
60	0,13	169	0,004
62	0,067	178	317
72	0,17	186	0,015
94	0,006	189a	0,15
95	0,01	189b	0,001
96	0,015	190	0,067
99	0,038	191	0,02
100	0,031	192	0,002
101	0,5	193	0,05
102	8,3	203	0,004
103	5,7	213	0,009

Se apreciará que diversas de las características y funciones que se han analizado anteriormente, o alternativas de las mismas, pueden combinarse de forma deseable en muchos otros sistemas o aplicaciones diferentes. También se apreciará que, posteriormente, pueden hacerse diversas alternativas, modificaciones, variaciones o mejoras imprevisibles o imprevistas en la actualidad en el mismo, también con la intención de incluirse por las siguientes reivindicaciones, por los expertos en la técnica.

217.

REIVINDICACIONES

1. Un compuesto que tiene la fórmula estructural **(I):**



(I)

y/o una sal farmacéuticamente aceptable del mismo, en la que:

(A) se elige entre el grupo que consiste en sistemas de anillos arilo bicíclicos de 9 miembros que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que están sustituidos en los átomos de C o N con ***u*** sustituyentes R^1,

cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{3a}, -CN, -$(CH_2)_{0-6}C(O)R^3$, -CO_2R^{3a}, -$C(O)N(R^{3a})_2$, -SR^{3a}, -$S(O)R^{3a}$, -$S(O_2)R^{3a}$, -$(CH_2)_{0-6}N(R^{3a})_2$, -$N(R^{3a})SO_2R^{3a}$, -$N(R^{3a})CO_2R^{3a}$, -$N(R^{3a})C(O)R^3$, -$N(R^{3a})COR^{3a}$, -$N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-6}, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, -OR^{3a}, -CN, -CO_2R^{3a}, -$C(O)N(R^{3a})_2$, -$N(R^{3a})_2$, -$N(R^{3a})CO_2R^{3a}$, -SR^{3a}, -$S(O)R^{3a}$, -$S(O_2)R^{3a}$, -$N(R^{3a})SO_2R^{3a}$, -$N(R^{3a})CO_2R^{3a}$, -$N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6} y cicloalquilo C_{3-8},

u es de 0 a 4,

cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

(B) es un grupo elegido entre el grupo que consiste en

(a) -C≡C- y

(b) sistemas de anillos arilo B' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo B' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con ***v*** sustituyentes R^2,

cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{4a}, -CN, -CO_2R^{4a}, -$C(O)R^{4a}$, -$C(O)N(R^{4a})_2$, -$N(R^{4a})_2$, -$N(R^{4a})COR^4$, -$N(R^{4a})CO_2R^{4a}$, -

$N(R^{4a})C(O)N(R^{4a})$, $-N(R^{4a})SO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4,

v es de 0 a 4,

cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada R^{4a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

R^1 y R^2 pueden tomarse junto con (A) y (B) para formar un anillo carbocíclicos de 5 a 9 miembros que contiene 1 ó 2 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S;

cada D es un grupo independientemente elegidos entre el grupo que consiste en:

(a) un enlace sencillo,

(b) $-C(O)N(R^5)-$,

(c) $-N(R^5)C(O)-$, y

(d) un sistema de anillos arilo de 5 ó 6 miembros D' que contiene de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 2 sustituyentes R^5,

cada R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^6$, -CN, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, alquilo C_{1-6} sustituido con 0 a 3 R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 R^6, y

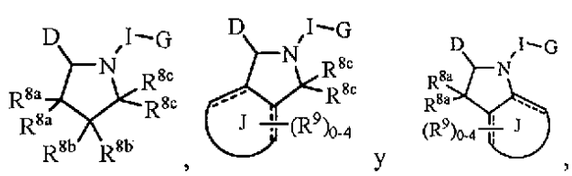
cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada E es un grupo independientemente elegidos entre el grupo que consiste en:

(a) un enlace sencillo,

(b) $-(C(R^7)_2)_{0-2}NR^7C(O)O_{0-1}-$, y

(c) un derivado de pirrolidinilo elegido entre el grupo que consiste en:



I es un grupo bivalente elegido entre -C(O)-, $-CO_2-$ y $-C(O)N(R^7)-$,

J es un sistema de anillos condensado elegido entre el grupo que consiste en carbociclos de 3 a 7 miembros y anillos arilo de 5 ó 6 miembros que contienen de 0 a 4 heteroátomos

independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con sustituyentes R^9,

cada R^{8a} se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OH, -Oalquilo C_{1-6} y alquilo C_{1-6}, o dos R^{8a} pueden tomarse juntos para formar oxo,

cada R^{8b} se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OH, -Oalquilo C_{1-6} y alquilo C_{1-6}, o dos R^{8b} pueden tomarse juntos para formar oxo,

cada R^{8c} se elige independientemente entre el grupo que consiste en hidrógeno y alquilo C_{1-6},

o dos grupos cualquiera seleccionados entre R^{8a}, R^{8b} y R^{8c} pueden tomarse juntos para formar un anillo espiro-bicíclico o bicíclico puenteado;

cada R^9 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, -NH-alquilo C_{1-6} y -NHC(O)-alquilo C_{1-6},

cada R^7 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y fenilo, y el alquilo C_{1-6} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

cada G se elige independientemente entre el grupo que consiste en:

(a) hidrógeno,

(b) $-OR^{10a}$,

(c) -CN,

(d) $-CO_2R^{10a}$,

(e) $-C(O)N(R^{10})_2$,

(f) $-SR^{10a}$,

(g) $-S(O)R^{10a}$,

(h) $-S(O_2)R^{10a}$,

(i) $-N(R^{10})_2$,

(j) $-N(R^{10})SO_2R^{10a}$, (k) $-NCO_2R^{10a}$, (l) $-NC(O)N(R^{10})_2$,

(m) alquilo C_{1-6} que tiene de 0 a 4 sustituyentes R^{11},

cada R^{11} se elige independientemente entre el grupo que consiste en:

(i) -OH,

(ii) $-N(R^{10})_2$,

(iii) $=NR^{10}$,

(iv) -O-alquilo C_{1-6},

(v) $-C(O)R^{10}$,

(vi) -S-alquilo C_{1-6},

(vii) $-SO_2$-alquilo C_{1-6},

(viii) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{12} en los átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} que tiene de 0 a 3 sustituyentes elegidos entre R^{10}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, $-OR^{10a}$, -CN, $-C(O)R^{10}$, $-CO_2R^{10a}$, $-C(O)N(R^{10})_2$, $-SR^{10a}$, $-S(O)R^{10a}$, $-S(O_2)R^{10a}$, $-N(R^{10})SO_2R^{10a}$, $-NCO_2R^{10a}$, $-NC(O)N(R^{10})_2$ y $-N(R^{10})_2$, o dos R^{12} se toman juntos para formar oxo, y

(ix) arilo de 5 ó 6 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tiene de 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6} y carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

(n) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C; y

(o) sistemas de anillos arilo G' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo G' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 3 sustituyentes R^{10};

cada R^{10} se elige independientemente entre el grupo que consiste en

(i) hidrógeno,

(ii) -CN,

(iii) alquilo C_{1-6},

(iv) -O-alquilo C_{0-6},

(v) -S-alquilo C_{0-6},

(vi) alquil C_{1-6}-O-R^{14},

(vii) $-C(O)R^{14}$,

(viii) $-CO_2R^{14}$,

(ix) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

(xiii) $-NC(O)N(R^{14})_2$, y

(xiv) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

o dos R^{10} pueden tomarse juntos para formar oxo;

cada R^{10a} se elige independientemente entre el grupo que consiste en

(i) hidrógeno,

(ii) -CN,

(iii) alquilo C_{1-6},

(iv) alquil C_{1-6}-O-R^{14},

(v) -$C(O)R^{14}$,

(vi) -CO_2R^{14},

(vii) -SO_2R^{14},

(x) -$N(R^{14})_2$,

(xi) -$N(R^{14})SO_2R^{14}$,

(xii) -NCO_2R^{14},

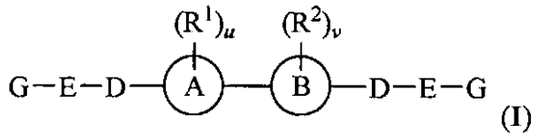
(xiii) -$NC(O)N(R^{14})_2$, y

(xiv) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

y dos grupos R^{10} o R^{10a} pueden tomarse junto con el N al que están unidos para formar un anillo, que puede estar sustituido con 0 a 3 sustituyentes R^{14}, y

cada R^{14} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-8}, -$(CH_2)_{0-3}$cicloalquilo C_{3-8} y fenilo.

2. Un compuesto que tiene la fórmula estructural **(I)**:



(I)

y/o una sal farmacéuticamente aceptable de los mismos, en la que:

(A) se elige entre el grupo que consiste en sistemas de anillos arilo bicíclicos de 9 miembros que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que están sustituidos en los átomos de C o N con ***u*** sustituyentes R^1,

cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{3a}, -CN, -$C(O)R^3$, -CO_2R^{3a}, -$C(O)N(R^{3a})_2$, -SR^{3a}, -$S(O)R^{3a}$, -$S(O_2)R^{3a}$, -$(CH_2)_{0-6}N(R^{3a})_2$, -$N(R^{3a})SO_2R^{3a}$, -$N(R^{3a})CO_2R^{3a}$, -$N(R^{3a})C(O)R^3$, -$N(R^{3a})COR^{3a}$, -$N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-}

$_{6}$, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6},

u es de 0 a 4,

cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

(B) es un grupo elegido entre el grupo que consiste en

(a) -C≡C- y

(b) sistemas de anillos arilo B' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo B' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con *v* sustituyentes R^2,

cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})COR^4$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, $-N(R^{4a})SO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4,

v es de 0 a 4,

cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada R^{4a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

R^1 y R^2 pueden tomarse junto con (A) y (B) para formar un anillo carbocíclicos de 5 a 9 miembros que contiene 1 ó 2 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S;

cada D es un grupo independientemente elegidos entre el grupo que consiste en:

(a) un enlace sencillo,

(b) $-C(O)N(R^5)-$,

(c) $-N(R^5)C(O)-$, y

(d) un sistema de anillos arilo de 5 ó 6 miembros D' que contiene de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 2 sustituyentes R^5,

cada R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^6, -CN, -CO_2R^6, -$C(O)N(R^6)_2$, -$N(R^6)_2$, -$N(R^6)COR^6$, -SR^6, -$S(O)R^6$, -$S(O_2)R^6$, -$N(R^6)SO_2R^6$, -NCO_2R^6, -$NC(O)N(R^6)_2$, alquilo C_{1-6} sustituido con 0 a 3 R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 R^6, y

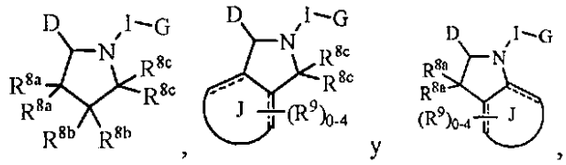
cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada E es un grupo independientemente elegidos entre el grupo que consiste en:

(a) un enlace sencillo,

(b) -$(C(R^7)_2)_{0-2}NR^7C(O)O_{0-1}$-, y

(c) un derivado de pirrolidinilo elegido entre el grupo que consiste en:



I es un grupo bivalente elegido entre -C(O)-, -CO_2- y -$C(O)N(R^7)$-,

J es un sistema de anillos condensado elegido entre el grupo que consiste en carbociclos de 3 a 7 miembros y anillos arilo de 5 ó 6 miembros que contiene de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con sustituyentes R^9,

cada R^{8a} se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OH, -Oalquilo C_{1-6} y alquilo C_{1-6}, o dos R^{8a} pueden tomarse juntos para formar oxo,

cada R^{8b} se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OH, -Oalquilo C_{1-6} y alquilo C_{1-6}, o dos R^{8b} pueden tomarse juntos para formar oxo,

cada R^{8c} se elige independientemente entre el grupo que consiste en hidrógeno y alquilo C_{1-6},

o dos grupos cualquiera seleccionados entre R^{8a}, R^{8b} y R^{8c} pueden tomarse juntos para formar un anillo espiro-bicíclico o bicíclico puenteado;

cada R^9 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, -NH-alquilo C_{1-6} y -NHC(O)-alquilo C_{1-6},

cada R^7 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y fenilo, y el alquilo C_{1-6} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

cada G se elige independientemente entre el grupo que consiste en:

(a) hidrógeno,

(b) $-OR^{10a}$,

(c) -CN,

(d) $-CO_2R^{10a}$,

(e) $-C(O)N(R^{10})_2$,

(f) $-SR^{10a}$,

(g) $-S(O)R^{10a}$,

(h) $-S(O_2)R^{10a}$,

(i) $-N(R^{10})_2$,

(j) $-N(R^{10})SO_2R^{10a}$, (k) $-NCO_2R^{10a}$, (l) $-NC(O)N(R^{10})_2$,

(m) alquilo C_{1-6} que tiene de 0 a 4 sustituyentes R^{11},

cada R^{11} se elige independientemente entre el grupo que consiste en:

(i) -OH,

(ii) $-N(R^{10})_2$,

(iii) $=NR^{10}$,

(iv) -O-alquilo C_{1-6},

(v) $-C(O)R^{10}$,

(vi) -S-alquilo C_{1-6},

(vii) $-SO_2$-alquilo C_{1-6},

(viii) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{12} en los átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} que tiene de 0 a 3 sustituyentes elegidos entre R^{10}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, $-OR^{10a}$, -CN, $-C(O)R^{10}$, $-CO_2R^{10a}$, $-C(O)N(R^{10})_2$, $-SR^{10a}$, $-S(O)R^{10a}$, $-S(O_2)R^{10a}$, $-N(R^{10})SO_2R^{10a}$, $-NCO_2R^{10a}$, $-NC(O)N(R^{10})_2$ y $-N(R^{10})_2$, o dos R^{12} se toman juntos para formar oxo, y

(ix) arilo de 5 ó 6 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tiene de 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6} y carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

(n) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C; y

(o) sistemas de anillos arilo G' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo G' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 3 sustituyentes R^{10};

cada R^{10} se elige independientemente entre el grupo que consiste en

(i) hidrógeno,

(ii) -CN,

(iii) alquilo C_{1-6},

(iv) -O-alquilo C_{0-6},

(v) -S-alquilo C_{0-6},

(vi) alquil C_{1-6}-O-R^{14},

(vii) -C(O)R^{14},

(viii) -CO_2R^{14},

(ix) -SO_2R^{14},

(x) -N(R^{14})$_2$,

(xi) -N(R^{14})SO_2R^{14},

(xii) -NCO_2R^{14},

(xiii) -NC(O)N(R^{14})$_2$, y

(xiv) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

o dos R^{10} pueden tomarse juntos para formar oxo;

cada R^{10a} se elige independientemente entre el grupo que consiste en

(i) hidrógeno,

(ii) -CN,

(iii) alquilo C_{1-6},

(iv) alquil C_{1-6}-O-R^{14},

(v) -C(O)R^{14},

(vi) -CO_2R^{14},

(vii) -SO_2R^{14},

(x) -N(R^{14})$_2$,

(xi) -N(R^{14})SO_2R^{14},

(xii) -NCO_2R^{14},

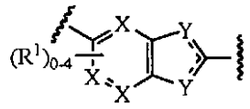
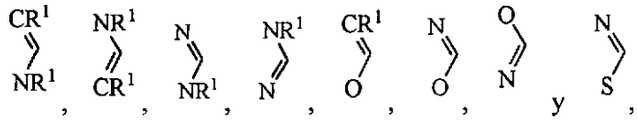
(xiii) -NC(O)N(R^{14})$_2$, y

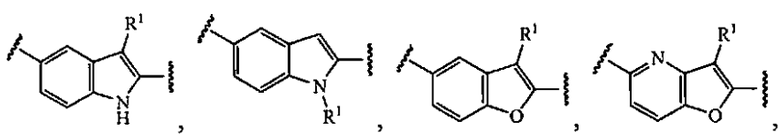
(xiv) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

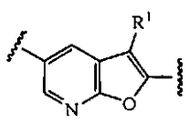
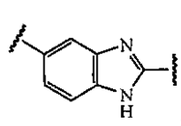
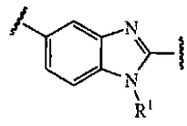
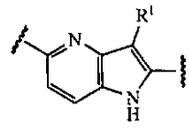
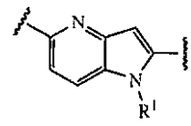
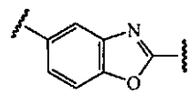
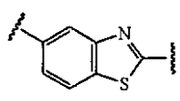
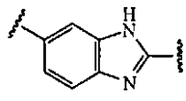
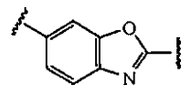
y dos grupo R^{10} o R^{10a} pueden tomarse junto con el N al que están unidos para formar un anillo, que puede estar sustituido con 0 a 3 sustituyentes R^{14}, y

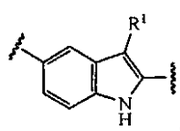
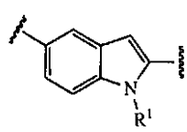
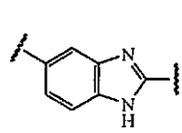
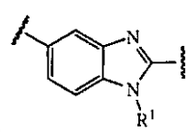
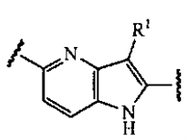
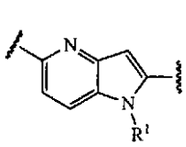
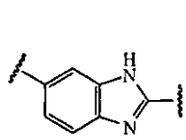
cada R^{14} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-8}, $-(CH_2)_{0-3}$cicloalquilo C_{3-8} y fenilo.

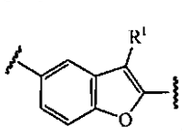
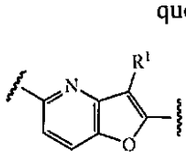
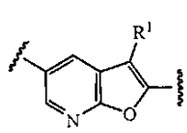
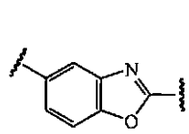
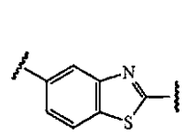
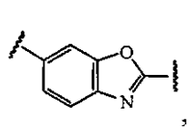
3. El compuesto de acuerdo con la reivindicación 1 ó 2, en el que

dicho (A) se elige entre el grupo que consiste en  , en la que cada X se elige independientemente entre el grupo que consiste en CR^1 y N,  se elige entre el grupo que consiste en  , cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-6}, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3A})_2$, $-N(R^{3A})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}, cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8}.

4. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1-3, en el que dicho (A) se elige entre el grupo que consiste en 


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y

, en el que dicho (A) está sustituido de 0 a 3 R^1 más.

5. El compuesto de acuerdo con la reivindicación 4, en el que dicho (A) se elige entre el grupo que consiste en

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y

; en el que dicho (A) está sustituido con 0 a 3 R^1 más.

6. El compuesto de acuerdo con la reivindicación 4, en el que dicho (A) se elige entre el grupo que consiste en

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y

, en el que dicho (A) está sustituido con 0 a 3 R^1 más.

7. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1-6, en el que cada R^1 se elige entre el grupo que consiste en hidrógeno, halógeno, -CN y alquilo C_{1-6}.

8. El compuesto de acuerdo con la reivindicación 7, en el que cada R^1 se elige entre el grupo que consiste en hidrógeno, flúor y -CN.

9. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1-8, en el que

dicho (B) se elige entre el grupo que consiste en -C≡C-, fenilo, piridinilo, pirazinilo, pirimidilo, 1,2,4-triazinilo, piridazinilo, tiazilo y sistemas de anillos bicíclicos de 9 miembros que contienen de 1 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, *v* es de 0 a 4, cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a}h$, $-N(R^{4a})_2$, $-N(R^{4a})CO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, $-N(R^{4a})SO_2R^{4a}$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4, cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8}, y cada R^{4a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8}.

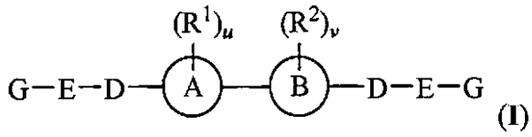
10. El compuesto de acuerdo con la reivindicación 9, en el que

dicho (B) es fenilo,

v es de 0 a 2, y

cada R^2 se elige independientemente entre el grupo que consiste en flúor, cloro, -OH, $-CH_3$, $-OCH_3$ y -CN.

11. Un compuesto que tiene la fórmula estructural (**I**):



(I)

y/o una sal farmacéuticamente aceptable del mismo, en la que:

(A) se elige entre el grupo que consiste en sistemas de anillos arilo bicíclicos de 9 miembros que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que están sustituidos en los átomos de C o N con *u* sustituyentes R^1,

cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-(CH_2)_{0-6}C(O)R^3$, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-(CH_2)_{0-6}N(R^{3a})_2$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)R^3$, $-N(R^{3a})COR^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-6}, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3a})_2$, $-N(R^{3a})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6} y cicloalquilo C_{3-8},

u es de 0 a 4,

cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

(B) es un grupo elegido entre el grupo que consiste en

(a) -C≡C- y

(b) sistemas de anillos arilo B' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo B' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con v sustituyentes R^2,

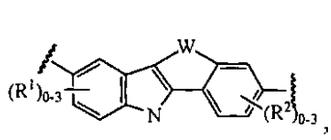
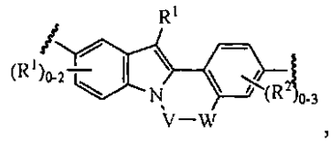
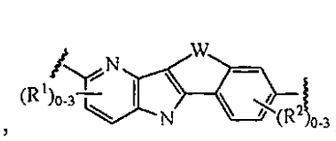
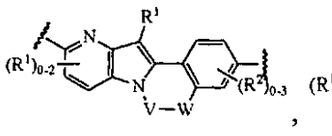
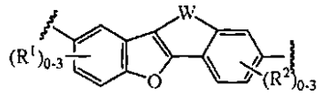
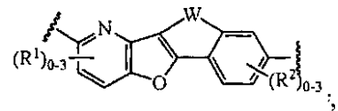
cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{4a}, -CN, -CO_2R^{4a}, -$C(O)R^{4a}$, -$C(O)N(R^{4a})_2$, -$N(R^{4a})_2$, -$N(R^{4a})COR^4$, -$N(R^{4a})CO_2R^{4a}$, -$N(R^{4a})C(O)N(R^{4a})$, -$N(R^{4a})SO_2R^{4a}$, -SR^{4a}, -$S(O)R^{4a}$, -$S(O_2)R^{4a}$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4,

v es de 0 a 4,

cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada R^{4a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

en el que dicho (A) y dicho (B), tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por un grupo elegido entre el grupo que consiste en:

que

W se elige entre el grupo que consiste en -$(CH_2)_{1-3}$-, -$(CH_2)_{0-2}NH(CH_2)_{0-2}$-, -$(CH_2)_{0-2}N$(alquil C_{1-6})$(CH_2)_{0-2}$-, -$(CH_2)_{0-2}O(CH_2)_{0-2}$- y -$(CH_2)_{0-2}C(O)(CH_2)_{0-2}$-, en el que W está sustituido

con 0 a 4 R^w, en el que cada R^w se selecciona independientemente entre alquilo C_{1-6} y cicloalquilo C_{3-8}; y

V se elige entre el grupo que consiste en -C(O)- y $-CH_2-$, y en el que V es $-CH_2-$, V está sustituido con 0 a 2 R^v, en el que cada R^v se selecciona independientemente entre el grupo que consiste en alquilo C_{1-6} y cicloalquilo C_{3-8}.

cada D es un grupo independientemente elegidos entre el grupo que consiste en:

(a) un enlace sencillo,

(b) $-C(O)N(R^5)-$,

(c) $-N(R^5)C(O)-$, y

(d) un sistema de anillos arilo de 5 ó 6 miembros D' que contiene de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 2 sustituyentes R^5,

cada R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^6$, -CN, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, alquilo C_{1-6} sustituido con 0 a 3 R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 R^6, y

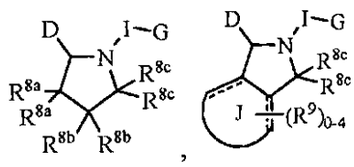
cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada E es un grupo independientemente elegidos entre el grupo que consiste en:

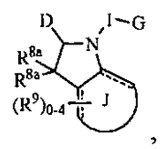
(a) un enlace sencillo,

(b) $-(C(R^7)_2)_{0-2}NR^7C(O)O_{0-1}-$, y

(c) un derivado de pirrolidinilo elegido entre el grupo que consiste en:



y



I es un grupo bivalente elegido entre -C(O)-, $-CO_2-$ y $-C(O)N(R^7)-$,

J es un sistema de anillos condensado elegido entre el grupo que consiste en carbociclos de 3 a 7 miembros y anillos arilo de 5 ó 6 miembros que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con sustituyentes R^9,

cada R^{8a} se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OH, -Oalquilo C_{1-6} y alquilo C_{1-6}, o dos R^{8a} pueden tomarse juntos para formar oxo,

cada R^{8b} se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OH, -Oalquilo C_{1-6} y alquilo C_{1-6}, o dos R^{8b} pueden tomarse juntos para formar oxo,

cada R^{8c} se elige independientemente entre el grupo que consiste en hidrógeno y alquilo C_{1-6},

o dos grupos cualquiera seleccionados entre R^{8a}, R^{8b} y R^{8c} pueden tomarse juntos para formar un anillo espiro-bicíclico o bicíclico puenteado;

cada R^9 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, -NH-alquilo C_{1-6} y -NHC(O)-alquilo C_{1-6},

cada R^7 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y fenilo, y el alquilo C_{1-6} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

cada G se elige independientemente entre el grupo que consiste en:

(a) hidrógeno,

(b) $-OR^{10a}$,

(c) -CN,

(d) $-CO_2R^{10a}$,

(e) $-C(O)N(R^{10})_2$,

(f) $-SR^{10a}$,

(g) $-S(O)R^{10a}$,

(h) $-S(O_2)R^{10a}$,

(i) $-N(R^{10})_2$,

(j) $-N(R^{10})SO_2R^{10a}$, (k) $-NCO_2R^{10a}$, (l) $-NC(O)N(R^{10})_2$,

(m) alquilo C_{1-6} que tiene de 0 a 4 sustituyentes R^{11},

cada R^{11} se elige independientemente entre el grupo que consiste en:

(i) -OH,

(ii) $-N(R^{10})_2$,

(iii) $=NR^{10}$,

(iv) -O-alquilo C_{1-6},

(v) $-C(O)R^{10}$,

(vi) -S-alquilo C_{1-6},

(vii) $-SO_2$-alquilo C_{1-6},

(viii) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{12} en los átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} que tiene de 0 a 3 sustituyentes elegidos entre R^{10}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, $-OR^{10a}$, -CN, $-C(O)R^{10}$, $-CO_2R^{10a}$, $-C(O)N(R^{10})_2$, $-SR^{10a}$, -

$S(O)R^{10a}$, $-S(O_2)R^{10a}$, $-N(R^{10})SO_2R^{10a}$, $-NCO_2R^{10a}$, $-NC(O)N(R^{10})_2$ y $-N(R^{10})_2$, o dos R^{12} se toman juntos para formar oxo, y

(ix) arilo de 5 ó 6 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tiene de 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6}, -O-alquilo C_{1-6} y carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

(n) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C; y

(o) sistemas de anillos arilo G' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos bicíclicos de 8 a 10 miembros,

y los sistemas de anillos arilo G' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 3 sustituyentes R^{10};

cada R^{10} se elige independientemente entre el grupo que consiste en

(i) hidrógeno,

(ii) -CN,

(iii) alquilo C_{1-6},

(iv) -O-alquilo C_{0-6},

(v) -S-alquilo C_{0-6},

(vi) alquil C_{1-6}-O-R^{14},

(vii) $-C(O)R^{14}$,

(viii) $-CO_2R^{14}$,

(ix) $-SO_2R^{14}$,

(x) $-N(R^{14})_2$,

(xi) $-N(R^{14})SO_2R^{14}$,

(xii) $-NCO_2R^{14}$,

(xiii) $-NC(O)N(R^{14})_2$, y

(xiv) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

o dos R^{10} pueden tomarse juntos para formar oxo;

cada R^{10a} se elige independientemente entre el grupo que consiste en

(i) hidrógeno,

(ii) -CN,

(iii) alquilo C_{1-6},

(iv) alquil C_{1-6}-O-R^{14},

(v) -C(O)R^{14},

(vi) -CO_2R^{14},

(vii) -SO_2R^{14},

(x) -$N(R^{14})_2$,

(xi) -$N(R^{14})SO_2R^{14}$,

(xii) -NCO_2R^{14},

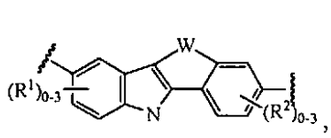
(xiii) -$NC(O)N(R^{14})_2$, y

(xiv) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

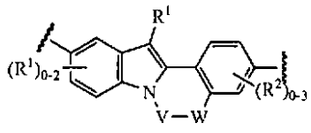
y dos grupos R^{10} o R^{10a} pueden tomarse junto con el N al que están unidos para formar un anillo, que puede estar sustituido con 0 a 3 sustituyentes R^{14}, y

cada R^{14} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, cicloalquilo C_{3-8}, -$(CH_2)_{0-3}$cicloalquilo C_{3-8} y fenilo.

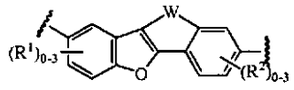
12. El compuesto de acuerdo con la reivindicación 11, en el que dicho (A) y dicho (B), tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por un grupo elegido entre el grupo que consiste en:



,

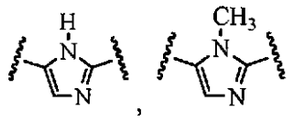
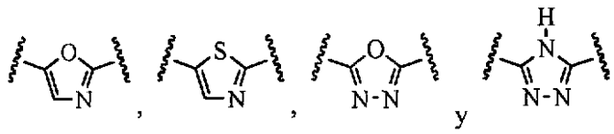


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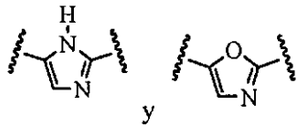
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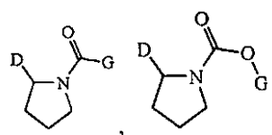
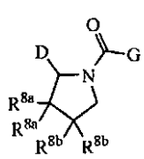
13. El compuesto de acuerdo con la reivindicación 12, en el que W se elige entre el grupo que consiste en -CH_2-, -NH-, -N(alquil C_{1-6})-, -C(O)-, -CH_2NH-, -CH_2N(alquil C_{1-6})-, -CH_2CH_2-, -C(O)CH_2-, -CH_2C(O)-, -CH_2O-, -$CH_2CH_2CH_2$-, -C(O)CH_2CH_2-, -CH_2C(O)CH_2-, -CH_2OCH_2-, -CH_2CH_2C(O)-, -CH_2CH_2O-, -CH_2CH_2NH-, -CH_2CH_2N(alquil C_{1-6})-, -CH_2NHCH_2-, -CH_2N(alquil C_{1-6})CH_2-, -$NHCH_2CH_2$- y -N(alquil C_{1-6})CH_2CH_2-.

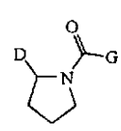
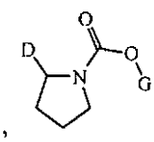
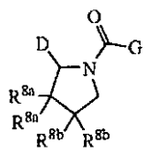
14. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1-13, en el que cada D se e elige independientemente entre el grupo que consiste en un enlace sencillo, -C(O)N(R^5)-, -NR^5C(O)-,   y , en el que

R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno -OR^6, -CN, -CO_2R^6, -C(O)N(R^6)$_2$, -N(R^6)$_2$, -N(R^6)COR^6, -SR^6, -S(O)R^6, -S(O_2)R^6, -N(R^6)SO_2R^6, -NCO_2R^6, -NC(O)N(R^6)$_2$, alquilo C_{1-6} sustituido con 0 a 3 sustituyentes R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 sustituyentes R^6, y

cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8}.

15. El compuesto de acuerdo con la reivindicación 14, en el que cada D se elige independientemente entre el grupo que consiste en  y .

16. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1-15, en el que cada E se elige independientemente entre el grupo que consiste en un enlace sencillo, -CH_2NHC(O)-, -CH_2N(CH_3)C(O)-, -C(CH_3)HNHC(O)-, -C(CH_3)HN(CH_3)C(O)-, -C(CH_3)$_2$NHC(O)-, -C(CH_3)$_2$N(CH_3)C(O)-, -CH_2NHC(O)O-, -CH_2N(CH_3)C(O)O-, -C(CH_3)HNHC(O)O-, -C(CH_3)HN(CH_3)C(O)O-, -C(CH_3)$_2$NHC(O)O-, C(CH_3)$_2$N(CH_3)C(O)O-,  y  , en los que uno de R^{8a} y R^{8b} es -OH o flúor.

17. El compuesto de acuerdo con la reivindicación 16, en el que cada E se elige independientemente entre el grupo que consiste en un enlace sencillo,  ,  y  , en los que uno de R^{8a} y R^{8b} es -OH o flúor.

18. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1-17, en el que cada G se elige independientemente entre el grupo que consiste en:

(a) alquilo C_{1-6} que tiene de 0 a 4 sustituyentes R^{11},

(b) carbociclos de 3 a 8 miembros que contienen de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C; y

(c) sistemas de anillos arilo G' elegidos entre el grupo que consiste en:

(i) sistemas de anillos monocíclicos de 5 a 7 miembros y

(ii) sistemas de anillos biciclicos de 8 a 10 miembros,

y los sistemas de anillos arilo G' que contienen de 0 a 4 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S, y están sustituidos en los átomos de C o N con 0 a 3 sustituyentes R^{10}.

19. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1-17, en el que cada G se elige independientemente entre el grupo que consiste en:

(a) hidrógeno,

(b) -CN,

(c) alquilo C_{1-5} que tiene de 1 a 3 sustituyentes R^{11},

cada R^{11} se elige independientemente entre el grupo que consiste en -OH, $-NH_2$, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, =NH, $=NCH_3$, -C(O)H, -C(O)OH, $-C(O)CH_3$, $-C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, $-NHC(O)CH_3$, $-NHC(O)OCH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo, fenilo, piridinilo, pirimidinilo y pirrolilo, en el que

el ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo están sustituidos con 0 a 2 sustituyentes R^{12} en los

átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

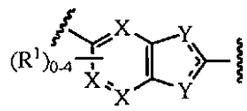
el fenilo, piridinilo, pirimidinilo y pirrolilo están sustituidos con 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} y cicloalquilo de 3 a 8 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

(d) ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C, el R^{10} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, fenilo y bencilo, y

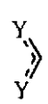
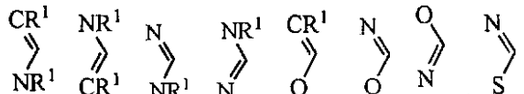
(e) sistemas de anillos arilo G' elegidos entre el grupo que consiste en: fenilo, piridinilo y sistemas de anillos bicíclicos de 9 miembros que contienen de 0 a 2 heteroátomos independientemente elegidos entre el grupo que consiste en N y O.

20. El compuesto de acuerdo con la reivindicación 19, en el que cada G se elige independientemente entre el grupo que consiste en alquilo C_{1-4} que tiene de 1 a 2 sustituyentes R^{11}, en el que cada R^{11} se elige independientemente entre el grupo que consiste en -OH, -NH2, -NCH_3H, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, -$C(O)OCH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo, oxaciclohexilo, fenilo, piridinilo, pirimidinilo y pirrolilo.

21. El compuesto de acuerdo con la reivindicación 1 ó 2, en el que

dicho se elige entre el grupo consiste en:  , en la que

cada X se elige independientemente entre el grupo que consiste en CR^1 y N,

 se elige entre el grupo que consiste en  ,

cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{3a}, -CN, -$C(O)R^3$, -CO_2R^{3a}, -$C(O)N(R^{3a})_2$, -SR^{3a}, -$S(O)R^{3a}$, -$S(O_2)R^{3a}$, -$(CH_2)_{0-6}N(R^{3a})_2$, -$N(R^{3a})SO_2R^{3a}$, -$N(R^{3a})CO_2R^{3a}$, -$N(R^{3a})C(O)R^3$, -$N(R^{3a})COR^{3a}$, -$N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-6}, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes elegidos independientemente entre el grupo que consiste en hidrógeno, halógeno, -OR^{3a}, -CN, -CO_2R^{3a}, -$C(O)N(R^{3a})_2$, -$N(R^{3a})_2$, -

$N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6},

cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

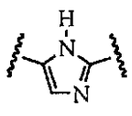
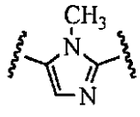
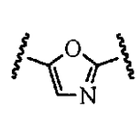
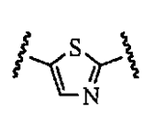
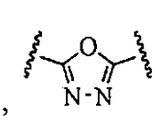
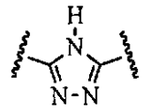
dicho (B) se elige entre el grupo que consiste en -C≡C-, fenilo, piridinilo, pirazinilo, pirimidilo, 1,2,4-triazinilo, piridazinilo, tiazilo y sistemas de anillos bicíclicos de 9 miembros que contienen de 1 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

v es de 0 a 4,

cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4a})_2$, $-N(R^{4a})_2$, $-N(R^{4a})CO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, $-N(R^{4a})SO_2R^{4a}$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4,

cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{4a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

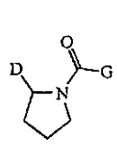
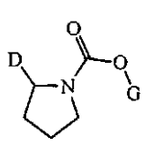
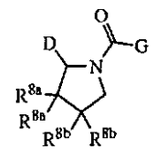
en los que cada D se elige independientemente entre el grupo que consiste en un enlace sencillo,  ,  ,  ,  ,  y  , en los que

R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^6$, -CN, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, alquilo C_{1-6} sustituido con 0 a 3 sustituyentes R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 sustituyentes R^6, y

cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

en el que cada E se elige independientemente entre el grupo que consiste en un enlace sencillo, $-CH_2NHC(O)-$, $-CH_2N(CH_3)C(O)-$, $-C(CH_3)HNHC(O)-$, $-C(CH_3)HN(CH_3)C(O)-$, $-C(CH_3)_2NHC(O)-$, $-C(CH_3)_2N(CH_3)C(O)-$, $-CH_2NHC(O)O-$, $-CH_2N(CH_3)C(O)O-$, -

$C(CH_3)HNHC(O)O$-, -$C(CH_3)HN(CH_3)C(O)O$-, -$C(CH_3)_2NHC(O)O$-, -$C(CH_3)_2N(CH_3)C(O)O$-,


, 
y 
, en los que uno de R^{8a} y R^{8b} es -OH o flúor;

en los que cada G se elige independientemente entre el grupo que consiste en

(a) hidrógeno,

(b) -CN,

(c) alquilo C_{1-5} que tiene de 1 a 3 sustituyentes R^{11},

cada R^{11} se elige independientemente entre el grupo que consiste en -OH, -NH2, -NCH_3H, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, =NH, =NCH_3, -C(O)H, -C(O)OH, -$C(O)CH_3$, -$C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo, y oxaciclohexilo, fenilo, piridinilo, pirimidinilo y pirrolilo, en el que

el ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo están sustituidos con 0 a 2 sustituyentes R^{12} en los átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

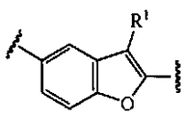
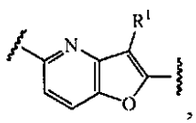
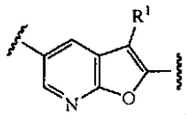
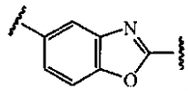
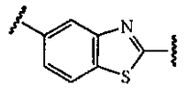
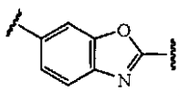
el fenilo, piridinilo, pirimidinilo y pirrolilo están sustituidos con 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} y cicloalquilo de 3 a 8 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

(d) ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C, el R^{10} seleccionado independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, fenilo y bencilo, y

(e) sistemas de anillos arilo G' elegidos entre el grupo que consiste en: fenilo, piridinilo y sistemas de anillos bicíclicos de 9 miembros que contienen de 0 a 2 heteroátomos independientemente elegidos entre el grupo que consiste en N y O.

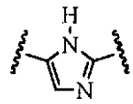
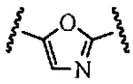
22. El compuesto de acuerdo con la reivindicación 1 o la reivindicación 2, en el que

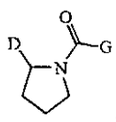
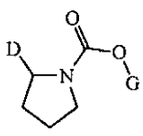
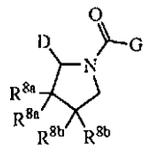
dicho  se elige entre el grupo que consiste en






y

; en los dicho (A) está sustituido con 0 a 3 R^1 más;

dicho (B) es fenilo;

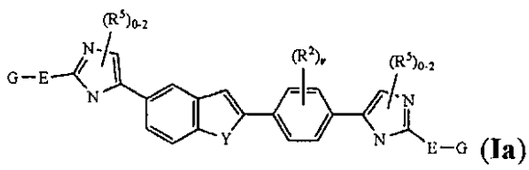
v es de 0 a 2; cada R^2 se elige independientemente entre el grupo que consiste en flúor, cloro, -OH, $-CH_3$, $-OCH_3$ y -CN;

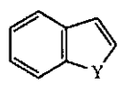
cada D se elige independientemente entre el grupo que consiste en  y  ;

cada E se elige independientemente entre el grupo que consiste en un enlace sencillo,  ,  y  , en el que uno de R^{8a} y R^{8b} es -OH o flúor; y

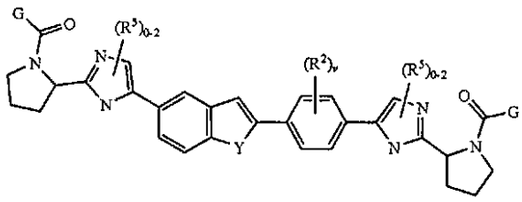
cada G se elige independientemente entre el grupo que consiste en alquilo C_{1-4} que tiene de 1 a 2 sustituyentes R^{11}, en el que cada R^{11} se elige independientemente entre el grupo que consiste en -OH, -NH2, $-NCH_3H$, $-N(CH_3)_2$, $-N(CH_2CH_3)_2$, $-C(O)OCH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo, oxaciclohexilo, fenilo, piridinilo, pirimidinilo y pirrolilo.

23. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1-22, en el que el compuesto que tiene la fórmula estructural (**I**) es un compuesto que tiene una fórmula estructural (**Ia**):

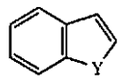
 **(Ia)**

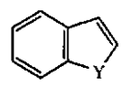
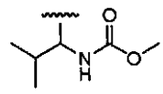
o una sal farmacéuticamente aceptable del mismo, en la que dicho  está sustituido con ***u*** sustituyentes R^1, e Y se selecciona entre el grupo que consiste en O y NR^1.

24. El compuesto de acuerdo con la reivindicación 23, en el que el compuesto que tiene la fórmula estructural **(Ia)** es un compuesto que tiene la fórmula estructural **(Ib):**

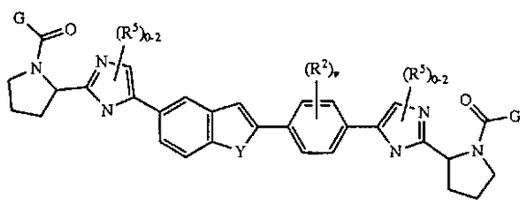


(Ib)

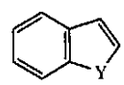
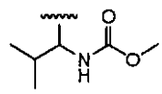
o una sal farmacéuticamente aceptable del mismo, en la que dicho  está sustituido con ***u*** sustituyentes R^1, e Y se selecciona entre el grupo que consiste en O y NR^1.

25. El compuesto de acuerdo con la reivindicación 24, en el que dicho  está sustituido con ***u*** sustituyentes R^1, Y es O, y ambos casos de G son  .

26. El compuesto de acuerdo con la reivindicación 1 o la reivindicación 2, en el que el compuesto que tiene la fórmula estructural **(Ia)** es un compuesto que tiene la fórmula estructural **(Ib):**

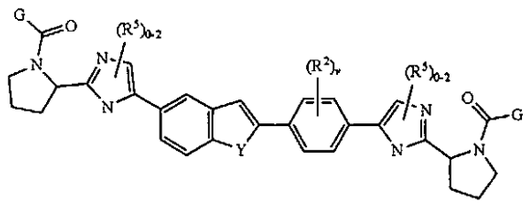


(Ib)

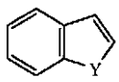
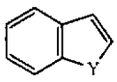
o una sal farmacéuticamente aceptable del mismo, en la que dicho  está sustituido con ***u*** sustituyentes R^1, Y es O, y ambos casos de G son  .

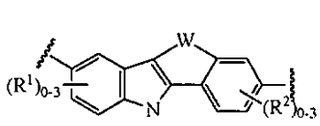
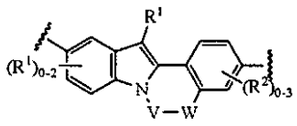
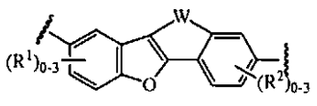
229

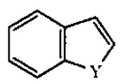
27. El compuesto de acuerdo con la reivindicación 1-23, en el que el compuesto que tiene la fórmula estructural **(Ia)** es un compuesto que tiene la fórmula estructural **(Ib):**

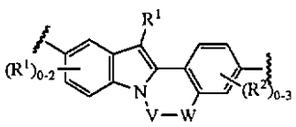
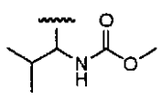


(Ib)

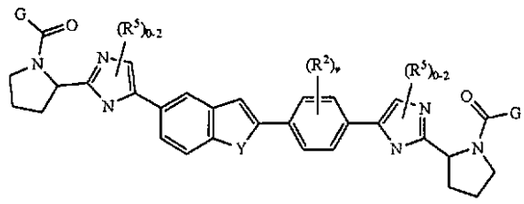
o una sal farmacéuticamente aceptable del mismo, en la que dicho  está sustituido con ***u*** sustituyentes R^1, y dicho  y dicho  , tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por un grupo elegido entre el grupo que consiste en

 ,  y  .

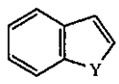
28. El compuesto de acuerdo con la reivindicación 27, en el que dicho  y dicho  , tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por

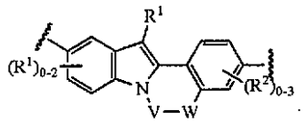
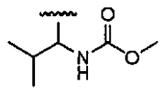
 , en la que V es $-CH_2-$, W es $-(CH_2)_{0-2}O(CH_2)_{0-2}-$, R^1 es flúor, y ambos casos de G son  .

29. El compuesto de acuerdo con la reivindicación 1 a la reivindicación 11, en el que el compuesto que tiene la fórmula estructural **(Ia)** es un compuesto que tiene la fórmula estructural **(Ib):**

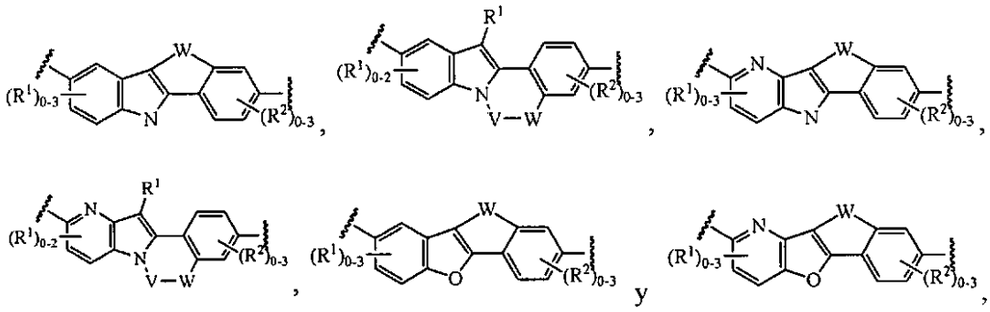


(Ib)

o una sal farmacéuticamente aceptable del mismo, en la que dicho  y dicho  , tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por

 , en la que V es $-CH_2-$, W es $-(CH_2)_{0-2}O(CH_2)_{0-2}-$, R^1 es flúor, y ambos casos de G son  .

30. El compuesto de acuerdo con la reivindicación 1 o la reivindicación 11, en el que dicho  y dicho  , tomados junto con un sustituyente R^1 y un sustituyente R^2, se representan por un grupo elegido entre el grupo que consiste en:



que

W se elige entre el grupo que consiste en $-(CH_2)_{1-3}-$, $-(CH_2)_{0-2}NH(CH_2)_{0-2}-$, $-(CH_2)_{0-2}N(\text{alquil } C_{1-6})(CH_2)_{0-2}-$, $-(CH_2)_{0-2}O(CH_2)_{0-2}-$ y $-(CH_2)_{0-2}C(O)(CH_2)_{0-2}-$, en el que W está sustituido con 0 a 4 R^w, en el que cada R^w se selecciona independientemente entre alquilo C_{1-6} y cicloalquilo C_{3-8}; y

V se elige entre el grupo que consiste en -C(O)- y $-CH_2-$, y en el que V es $-CH_2-$, V está sustituido con 0 a 2 R^v, en el que cada R^v se selecciona independientemente entre el grupo que consiste en alquilo C_{1-6} y cicloalquilo C_{3-8};

cada R^1 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^3$, -CN, $-C(O)R^3$, $-CO_2R^3$, $-C(O)N(R^{3A})_2$, $-SR^3$, $-S(O)R^3$, $-S(O_2)R^3$, $-N(R^{3A})_2$, $-(CH_2)_{0-6}N(R^{3A})_2$, -

$N(R^{3a})SO_2R^3$, $-N(R^{3a})CO_2R^3$, $-N(R^{3a})COR^3$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, carbociclo C_{3-8} que contiene de 0 a 3 heteroátomos elegidos entre N, O y S, y fenilo, y el alquilo C_{1-6}, carbociclo C_{3-8} y fenilo están sustituidos con 0 a 3 sustituyentes independientemente elegidos entre el grupo que consiste en hidrógeno, halógeno, $-OR^{3a}$, -CN, $-CO_2R^{3a}$, $-C(O)N(R^{3A})_2$, $-N(R^{3A})_2$, $-N(R^{3a})CO_2R^{3a}$, $-SR^{3a}$, $-S(O)R^{3a}$, $-S(O_2)R^{3a}$, $-N(R^{3a})SO_2R^{3a}$, $-N(R^{3a})CO_2R^{3a}$, $-N(R^{3a})C(O)N(R^{3a})$, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6},

cada R^3 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6}, -OH, -O-alquilo C_{1-6} y cicloalquilo C_{3-8}, y

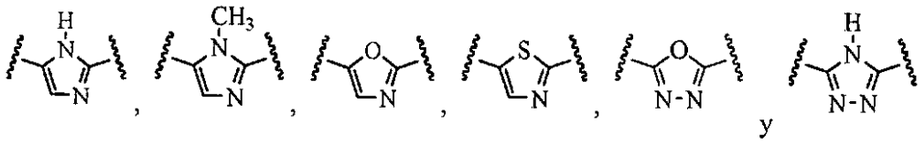
cada R^{3a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

cada R^2 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno, $-OR^{4a}$, -CN, $-CO_2R^{4a}$, $-C(O)N(R^{4A})_2$, $-N(R^{4A})_2$, $-N(R^{4a})CO_2R^{4a}$, $-SR^{4a}$, $-S(O)R^{4a}$, $-S(O_2)R^{4a}$, $-N(R^{4a})SO_2R^{4a}$, $-N(R^{4a})CO_2R^{4a}$, $-N(R^{4a})C(O)N(R^{4a})$, alquilo C_{1-6} sustituido con 0 a 4 R^4 y cicloalquilo C_{3-8} sustituido con 0 a 4 R^4,

cada R^4 se elige independientemente entre el grupo que consiste en hidrógeno, -OH, alquilo C_{1-6} y cicloalquilo C_{3-8}, y

cada R^{4a} se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

en el que cada D se elige independientemente entre el grupo que consiste en un enlace sencillo, $-C(O)N(R^5)-$, $-NR^5C(O)-$,



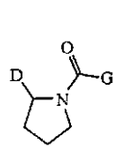
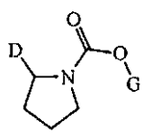
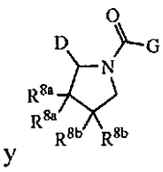
y , en las que

R^5 se elige independientemente entre el grupo que consiste en hidrógeno, halógeno $-OR^6$, -CN, $-CO_2R^6$, $-C(O)N(R^6)_2$, $-N(R^6)_2$, $-N(R^6)COR^6$, $-SR^6$, $-S(O)R^6$, $-S(O_2)R^6$, $-N(R^6)SO_2R^6$, $-NCO_2R^6$, $-NC(O)N(R^6)_2$, alquilo C_{1-6} sustituido con 0 a 3 sustituyentes R^6 y cicloalquilo C_{3-8} sustituido con 0 a 3 sustituyentes R^6, y

cada R^6 se elige independientemente entre el grupo que consiste en hidrógeno, alquilo C_{1-6} y cicloalquilo C_{3-8};

en el que cada E se elige independientemente entre el grupo que consiste en un enlace sencillo, $-CH_2NHC(O)-$, $-CH_2N(CH_3)C(O)-$, $-C(CH_3)HNHC(O)-$, $-C(CH_3)HN(CH_3)C(O)-$, $-C(CH_3)_2NHC(O)-$, $-C(CH_3)_2N(CH_3)C(O)-$, $-CH_2NHC(O)O-$, $-CH_2N(CH_3)C(O)O-$, -

$C(CH_3)HNHC(O)O$-, -$C(CH_3)HN(CH_3)C(O)O$-, -$C(CH_3)_2NHC(O)O$-, -$C(CH_3)_2N(CH_3)C(O)O$-,



y  , en el que uno de R^{8a} y R^{8b} es -OH o flúor;

en el que cada G se elige independientemente entre el grupo que consiste en

(a) hidrógeno,

(b) -CN,

(c) alquilo C_{1-5} que tiene de 1 a 3 sustituyentes R^{11},

cada R^{11} se elige independientemente entre el grupo que consiste en -OH, -NH2, -NCH_3H, -$N(CH_3)_2$, -$N(CH_2CH_3)_2$, =NH, =NCH_3, -C(O)H, -C(O)OH, -$C(O)CH_3$, -$C(O)OCH_3$, -NHC(O)H, -NHC(O)OH, -$NHC(O)CH_3$, -$NHC(O)OCH_3$, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo, y oxaciclohexilo, fenilo, piridinilo, pirimidinilo y pirrolilo, en el que

el ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo están sustituidos con 0 a 2 sustituyentes R^{12} en los átomos de N o C, y cada R^{12} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6} y -S-alquilo C_{1-6}; y

el fenilo, piridinilo, pirimidinilo y pirrolilo están sustituidos con 0 a 3 sustituyentes R^{13} en los átomos de N o C, y cada R^{13} se selecciona independientemente entre el grupo que consiste en hidrógeno, halógeno, alquilo C_{1-6} y cicloalquilo de 3 a 8 miembros que contiene de 0 a 3 heteroátomos independientemente elegidos entre el grupo que consiste en N, O y S,

(d) ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, piranilo, pirrolidinilo, piperidinilo, oxaciclopentilo y oxaciclohexilo que tienen de 0 a 3 sustituyentes R^{10} en los átomos de N o C, el R^{10} seleccionado independientemente entre el grupo que consiste en hidrógeno, halógeno, carboxi, alquilo C_{1-6}, -O-alquilo C_{1-6}, -S-alquilo C_{1-6}, fenilo y bencilo, y

(e) sistemas de anillos arilo G' elegidos entre el grupo que consiste en: fenilo, piridinilo y sistemas de anillos bicíclicos de 9 miembros que contienen de 0 a 2 heteroátomos independientemente elegidos entre el grupo que consiste en N y O.

31. Un compuesto de acuerdo con la reivindicación 1, reivindicación 2 o reivindicación 11, elegido entre el grupo que consiste en:

N-{4-[5-(acetilamino)-1H-pirrolo[3,2-b]piridin-2-il]fenil}-1-(fenilacetil)-L-prolinamida;

(2S)-1-(fenilacetil)-N-{2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-pirrolo[3,2-b]piridin-5-il}pirrolidin-2-carboxamida;

(2S)-2-[(2-{4-[({(2S)-1-[(benciloxi)carbonil]pirrolidin-2-il}carbonil)amino]fenil}-1H-pirrolo[3,2-b]piridin-5-il)carbamoil]pirrolidin-1-carboxilato de bencilo;

(1S)-2-[(2S)-2-{[4-(5-bromo-1H-pirrolo[3,2-b]piridin-2-il)fenil]carbamoil}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-N-{3-cloro-2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-pirrolo[2,3-c]piridin-5-il}-1-(fenilacetil)pirrolidin-2-carboxamida;

(2S)-N-{3-cloro-2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-pirrolo[2,3-b]piridin-5-il}-1-(fenilacetil)pirrolidin-2-carboxamida;

N-[4-(3-oxo-7-{2-oxo-2-[(2S)-1-(fenilacetil)pirrolidin-2-il]etil}-3,7-dihidroimidazo[1,2-a]pirazin-2-il)fenil]-1-(fenilacetil)-L-prolinamida;

(2S)-1-(ciclobutilcarbonil)-N-{2-[4-({[(2S)-1-(piridin-3-ilcarbonil)pirrolidin-2-il]carbonil}amino)fenil]-1H-bencimidazol-5-il}pirrolidin-2-carboxamida;

(2S)-1-(fenilcarbonil)-N-{4-[5-({[(2S)-1-(fenilcarbonil)pirrolidin-2-il]carbonil}amino)-1H-bencimidazol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-[(4Z,5Z)-4-etilidenohept-5-enoil]-N-{2-[4-({[(2S)-1-(3-fenilpropanoil)pirrolidin-2-il]carbonil}amino)fenil]-1H-bencimidazol-5-il}pirrolidin-2-carboxamida;

(2S)-1-[(4Z,5Z)-4-etilidenohept-5-enoil]-N-{2-[3-({[(2S)-1-(3-fenilpropanoil)pirrolidin-2-il]carbonil}amino)fenil]-1H-bencimidazol-5-il}pirrolidin-2-carboxamida;

(2S)-1-[(2R)-2-hidroxi-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-hidroxi-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-bencimidazol-2-il}fenil)pirrolidin-2-carboxamida;

(2S)-1-(fenilacetil)-N-{4-[5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-bencimidazol-2-il]fenil}pirrolidin-2-carboxamida;

{(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2S)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-bencimidazol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-bencimidazol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-2-{[4-(4-{[(4-metilfenil)sulfonil]amino}-1H-bencimidazol-2-il)fenil]carbamoil}pirrolidin-1-carboxilato de bencilo;

(2S)-1-(3-fenilpropanoil)-N-{4-[5-({[(2S)-1-(3-fenilpropanoil)pirrolidin-2-il]carbonil}amino)-1,3-benzoxazol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-(3-fenilpropanoil)-N-{4-[5-({[(2S)-1-(3-fenilpropanoil)pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}pirrolidin-2-carboxamida;

N-{2-[4-(acetilamino)fenil]-1-benzofuran-5-il}-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}-L-prolinamida;

(2S)-1-(fenilacetil)-N-{4-[5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}pirrolidin-2-carboxamida;

{(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2S)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

[(1R)-2-oxo-1-fenil-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)carbamoil]pirrolidin-1-il}etil]carbamato de propan-2-ilo;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;

(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)pirrolidin-2-carboxamida;

(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)pirrolidin-2-carboxamida;

[(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de propan-2-ilo;

N-[2-(4-aminofenil)-1-benzofuran-5-il]-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolinamida;

(2S)-1-{(2R)-2-[metil(3-metilbutil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[metil(3-metilbutil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}pirrolidin-2-carboxamida;

N-{2-[4-(acetilamino)fenil]-1-benzofuran-5-il}-1-[(2R)-2-(dietilamino)-2-fenilacetil]-L-prolinamida;

(2S)-1-acetil-N-(2-{4-[({(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]fenil}-1-benzofuran-5-il)pirrolidin-2-carboxamida;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-acetilpirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-1-acetil-N-(2-{4-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]fenil}-1-benzofuran-5-il)pirrolidin-2-carboxamida;

N-{4-[5-(acetilamino)-1-benzofuran-2-il]fenil}-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}-L-prolinamida;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-7-metil-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;

(2S)-1-{(2R)-2-[etil(propil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[etil(propil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-(fenilacetil)-N-{4-[6-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)imidazo[1,2-a]pirimidin-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-(fenilacetil)-N-{4-[6-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)imidazo[1,2-a]piridin-2-il]fenil}pirrolidin-2-carboxamida;

(2S,2'S)-N,N'-1H,1'H-2,2'-biindolo-5,5'-diilbis[1-(fenilacetil)pirrolidin-2-carboxamida];

(1H,1'H-2,2'-biindolo-5,5'-diilbis{carbamoil(2S)pirrolidin-2,1-diil[(1R)-2-oxo-1-feniletano-2,1-diil]})biscarbamato de di-terc-butilo;

{(1R)-2-oxo-1-fenil-2-[(2S)-2-({2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]etil}carbamato de terc-butilo;

(2S)-1-(fenilacetil)-N-{2-[5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]pirimidin-5-il}pirrolidin-2-carboxamida;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;

(2S)-1-[(2R)-2-fenil-2-(pirrolidin-1-il)acetil]-N-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-(pirrolidin-1-il)acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

(2S)-1-{(2R)-2-[(ciclopropilacetil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[(ciclopropilacetil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-{(2R)-2-[(3-metilbutanoil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[(3-metilbutanoil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-[(2R)-2-(morfolin-4-il)-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-(morfolin-4-il)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

(2S)-1-(2,3-difenilpropanoil)-N-{4-[5-({[(2S)-1-(2,3-difenilpropanoil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-[(2R)-2-{[(4-metilfenil)sulfonil]amino}-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-{[(4-metilfenil)sulfonil]amino}-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

(2S)-1-{(2R)-2-[(ciclohexilcarbonil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[(ciclohexilcarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

{(1R)-2-[(2S)-2-({2-[4-(acetilamino)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;

{(1R)-2-[(2S)-2-({4-[5-(acetilamino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

N-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1-[(2R)-2-(morfolin-4-il)-2-fenilacetil]-L-prolinamida;

{(1R)-2-[(2S)-2-({2-[4-(acetilamino)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo;

(2S)-1-{(2R)-2-[(ciclopentilcarbamoil)amino]-2-fenilacetil}-N-(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

{(2R)-1-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de terc-butilo;

N-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1-[(2R)-2-fenil-2-(pirrolidin-1-il)acetil]-L-prolinamida;

(2S)-1-[(2R)-2-(dimetilamino)-4-metilpentanoil]-N-(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-4-metilpentanoil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

(2S)-1-[(2R)-2-fenil-2-(piperidin-1-il)acetil]-N-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-(piperidin-1-il)acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

(2S)-1-[(2R)-2-(1H-imidazol-1-il)-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-(1H-imidazol-1-il)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]-N-(4-{5-[({(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

{(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-acetilpirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-acetilpirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-oxo-1-fenil-2-[(2S)-2-({2-[4-({[(2S)-1-(propan-2-il)pirrolidin-2-il]carbonil}amino)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]etil}carbamato de terc-butilo;

N-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolinamida;

N-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1-[(2R)-2-fenil-2-(piperidin-1-il)acetil]-L-prolinamida;

[(1R)-2-{(2S)-2-[(2-{4-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]fenil}-1H-indol-5-il)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de terc-butilo;

[(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de terc-butilo;

(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-{4-[5-({[(2S)-1-{(2R)-2-[(3,3-dimetilbutanoil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-(ciclopropilacetil)-N-(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-(2-{4-[({(2S)-1-[(2R)-tetrahidrofurano-2-ilcarbonil]pirrolidin-2-il}carbonil)amino]fenil}-1H-indol-5-il)pirrolidin-2-carboxamida;

[(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-[(terc-butoxicarbonil)amino]-2-(4-fluorofenil)acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)carbamoil]pirrolidin-1-il}-1-(4-fluorofenil)-2-oxoetil]carbamato de terc-butilo;

(2S)-1-{(2R)-2-[metil(3-metilbutil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2R)-2-[metil(3-metilbutil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-[(2S)-tetrahidrofurano-2-ilcarbonil]-N-(4-{5-[({(2S)-1-[(2S)-tetrahidrofurano-2-ilcarbonil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

N-(terc-butoxicarbonil)-D-valil-N-{4-[5-({1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolil}amino)-1H-indol-2-il]fenil}-L-prolinamida;

(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-{2-[4-({[(2S)-1-(1,3-oxazol-2-ilcarbonil)pirrolidin-2-il]carbonil}amino)fenil]-1H-indol-5-il}pirrolidin-2-carboxamida;

[(1R)-2-{[(2S)-1-({4-[5-({(2S)-2-[{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}(metil)amino]propanoil}amino)-1H-indol-2-il]fenil}amino)-1-oxopropan-2-il](metil)amino}-2-oxo-1-feniletil]carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({2-[4-(metilamino)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-{2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-indol-5-il}pirrolidin-2-carboxamida;

(2S)-1-{[(3R)-1-bencilpirrolidin-3-il]carbonil}-N-(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

(2S)-1-{[(3S)-1-bencilpirrolidin-3-il]carbonil}-N-(4-{5-[({(2S)-1-[(2R)-2-

(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)pirrolidin-2-carboxamida;

N,N-dimetil-D-leucil-N-{4-[5-({1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolil}amino)-1H-indol-2-il]fenil}-L-prolinamida;

N-(2-{4-[(ciclopentilcarbonil)amino]fenil}-1H-indol-5-il)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolinamida;

[(2S)-1-({4-[5-({1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolil}amino)-1H-indol-2-il]fenil}amino)-1-oxopropan-2-il]carbamato de terc-butilo;

[(1S)-2-({4-[5-({1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolil}amino)-1H-indol-2-il]fenil}amino)-2-oxo-1-feniletil]carbamato de terc-butilo;

[(2R)-1-({4-[5-({1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolil}amino)-1H-indol-2-il]fenil}amino)-3-metil-1-oxobutan-2-il]carbamato de terc-butilo;

(2S,2'S)-N,N'-5,6,7,12-tetrahidrobenzo[6,7]ciclohepta[1,2-b]indolo-3,9-diilbis[1-(fenilacetil)pirrolidin-2-carboxamida];

(2S,2'S)-N,N'-6,11-dihidro-5H-benzo[a]carbazol-3,8-diilbis[1-(fenilacetil)pirrolidin-2-carboxamida];

dibencilo(2S,2'S)-2,2'-(6,11-dihidro-5H-benzo[a]carbazol-3,8-diildicarbamoil)dipirrolidin-1-carboxilato;

N-(8-bromo-6,11-dihidro-5H-benzo[a]carbazol-3-il)-1-(fenilacetil)-L-prolinamida;

(6,11-dihidro-5H-benzo[a]carbazol-3,8-diilbis{carbamoil(2S)pirrolidin-2,1-diil[(1S)-2-oxo-1-feniletano-2,1-diil]})biscarbamato de di-terc-butilo;

[(1S)-2-{(2S)-2-[(8-bromo-6,11-dihidro-5H-benzo[a]carbazol-3-il)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de terc-butilo;

(2S,2'S)-N,N'-6,11-dihidro-5H-benzo[a]carbazol-3,8-diilbis{1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-carboxamida};

(2S,2'S)-N,N'-5,6,7,12-tetrahidrobenzo[6,7]ciclohepta[1,2-b]indolo-3,9-diilbis{1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-carboxamida};

N-(6,11-dihidro-5H-benzo[a]carbazol-3-il)-1-{(2S)-2-[(3,3-dimetilbutanoil)amino]-2-fenilacetil}-L-prolinamida;

{(1R)-2-[(2S)-2-(6,11-dihidro-5H-benzo[a]carbazol-3-ilcarbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(5,6,7,12-tetrahidrobenzo[6,7]ciclohepta[1,2-b]indolo-3,9-diilbis{carbamoil(2S)pirrolidin-2,1-diil[(1R)-2-oxo-1-feniletano-2,1-diil]})biscarbamato de di-terc-butilo;

{(1R)-2-[(2S)-2-(5-{4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-2-[5-(4-{5-[(1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}-L-prolil)amino]-1H-indol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-carboxilato de bencilo;

1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-{2-[4-(2-{(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1H-indol-5-il}-L-prolinamida;

{(1R)-2-[(2S)-2-({2-[4-(1H-imidazol-4-il)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

1-[(2S)-2-(dimetilamino)-2-fenilacetil]-N-{2-[4-(2-{(2S)-1-[(2S)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1H-indol-5-il}-L-prolinamida;

{(1R)-2-oxo-1-fenil-2-[(2S)-2-{[2-(4-{2-[(2S)-1-(fenilacetil)pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-indol-5-il]carbamoil}pirrolidin-1-il]etil}carbamato de terc-butilo;

terc-butil{(1R)-2-[(2S)-2-{[2-(4-{2-[(2S)-1-acetilpirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-indol-5-il]carbamoil}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato;

(2S)-2-(5-{4-[5-({1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]-L-prolil}amino)-1H-indol-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-carboxilato de bencilo;

{(1R)-2-[(2S)-2-({2-[4-(2-{(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

[(1R)-2-{(2S)-2-[1-metil-4-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de propan-2-ilo;

{(1R)-2-[(2S)-2-{[2-(4-{2-[(2S)-1-acetilpirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-indol-5-il]carbamoil}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo;

{(1R)-2-oxo-1-fenil-2-[(2S)-2-{[2-(4-{2-[(2S)-pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1H-indol-5-il]carbamoil}pirrolidin-1-il]etil}carbamato de propan-2-ilo;

{(1R)-2-[(2S)-2-{5-[4-(1H-indol-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo;

(2R)-2-(dimetilamino)-1-[(2S)-2-{5-[4-(1H-indol-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-feniletanona;

[(1R)-2-oxo-1-fenil-2-{(2S)-2-[5-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1H-imidazol-2-il]pirrolidin-1-il}etil]carbamato de propan-2-ilo;

{(1R)-2-[(2S)-2-({2-[4-(2-{(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo;

{(1R)-2-[(2S)-2-{4-[4-(3-cloro-1H-indol-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo;

N-(metoxicarbonil)-L-valil-N-{2-[4-(2-{(2S)-1-[N-(metoxicarbonil)-L-valil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1H-indol-5-il}-L-prolinamida;

[(1R)-2-oxo-1-fenil-2-{(2S)-2-[3-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1H-pirazol-5-il]pirrolidin-1-il}etil]carbamato de propan-2-ilo;

[(1R)-2-oxo-1-fenil-2-{(2S)-2-[5-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1,3-tiazol-2-il]pirrolidin-1-il}etil]carbamato de propan-2-ilo;

[(1R)-2-oxo-1-fenil-2-{(2S)-2-[2-(4-{5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1H-imidazol-5-il]pirrolidin-1-il}etil]carbamato de propan-2-ilo;

1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]-N-{4-[5-(2-{(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}-1H-imidazol-5-il)-1-benzofuran-2-il]fenil}-L-prolinamida;

{(1R)-2-[(2S)-2-(5-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1,3,4-oxadiazol-2-il)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo;

(2S)-1-(fenilacetil)-N-{3-[5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-(fenilacetil)-N-{4-[6-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-(fenilacetil)-N-{3-[6-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

[(1R)-2-{(2S)-2-[(2-{2-[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-bencimidazol-5-il}-1H-indol-5-il)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de terc-butilo;

(2S)-N-{4-[3-bromo-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

{(1S)-2-[(2S)-2-({2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-N-{4-[3-cloro-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

(2S)-N-{4-[3-fluoro-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

{(1S)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2S)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-fluoro-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1S)-2-[(2S)-2-({2-[4-(acetilamino)fenil]-3-cloro-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-N-{4-[3-yodo-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

{(1S)-2-[(2S)-2-({2-[4-({[(2S)-1-acetilpirrolidin-2-il]carbonil}amino)fenil]-3-fluoro-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-1-{(2S)-2-[(3,3-dimetilbutanoil)amino]-2-fenilacetil}-N-{4-[5-({[(2S)-1-{(2S)-2-[(3,3-dimetilbutanoil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-fluoro-1H-indol-2-il]fenil} pirrolidin-2-carboxamida;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-fluoro-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({2-[4-({[(2S)-1-acetilpirrolidin-2-il]carbonil}amino)fenil]-3-fluoro-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({3-fluoro-2-[4-(2-oxopirrolidin-1-il)fenil]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

N-{2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-il}-1-[(2R)-2-fenil-2-(pirrolidin-1-il)acetil]-L-prolinamida;

N-(terc-butoxicarbonil)-D-alanil-N-{2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-il}-L-prolinamida;

N-{2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-il}-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolinamida;

N-(terc-butoxicarbonil)-D-leucil-N-{2-[4-(acetilamino)fenil]-3-fluoro-1H-indol-5-il}-L-prolinamida;

[(1R)-2-{(2S)-2-[(4-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-3-fluoro-1H-indol-2-il}fenil)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato) de propan-2-ilo;

(2S)-2-[(3-fluoro-2-{4-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]fenil}-1H-indol-5-il)carbamoil]pirrolidin-1-carboxilato de terc-butilo;

[(1R)-2-{(2S)-2-[(4-{3-bromo-5-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)carbamoil]pirrolidin-1-il}-2-oxo-1-feniletil]carbamato de propan-2-ilo;

(2S)-N-(4-{3-bromo-5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-carboxamida;

{(1R)-2-[(2S)-2-({4-[3-bromo-5-({[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;

{(2S)-1-[(2S)-2-({4-[3-fluoro-5-({[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;

N-{2-[4-(acetilamino)fenil]-3-bromo-1-benzofuran-5-il}-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-L-prolinamida;

(2S)-N-(4-{3-bromo-5-[({(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-carboxamida;

(2S)-1-acetil-N-(4-{3-bromo-5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1-benzofuran-2-il}fenil)pirrolidin-2-carboxamida;

{(1S)-2-[(2S)-2-({4-[3-bromo-5-({[(2S)-1-{(2S)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo);

(2S)-N-{4-[3-bromo-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

{(1R)-2-[(2S)-2-({4-[3-bromo-5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-1-benzofuran-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-N-{4-[3-ciano-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

(2S)-N-{4-[3-(2,2-dimetilpropanoil)-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-1H-indolo-3-carboxamida;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-(ciclopropilcarbamoil)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxi-carbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-(4-metoxifenil)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-1-(fenilacetil)-N-{4-[3-fenil-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-N-{4-[3-etil-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

(2S)-N-{4-[3-acetil-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

(2S)-1-(fenilacetil)-N-{4-[5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-3-(fenilcarbonil)-1H-indol-2-il]fenil}pirrolidin-2-carboxamida;

(2S)-1-(fenilacetil)-N-{2-[4-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)fenil]-3-(piridin-4-il)-1H-indol-5-il}pirrolidin-2-carboxamida;

(2S)-2-[(4-{5-[({(2S)-1-[(benciloxi)carbonil]pirrolidin-2-il}carbonil)amino]-3-fenil-1H-indol-2-il}fenil)carbamoil]pirrolidin-1-carboxilato de bencilo;

(2S)-N-{4-[3-ciano-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

(2S)-N-{4-[3-ciclopropil-5-({[(2S)-1-(fenilacetil)pirrolidin-2-il]carbonil}amino)-1H-indol-2-il]fenil}-1-(fenilacetil)pirrolidin-2-carboxamida;

(2S)-2-[(4-{5-[({(2S)-1-[(benciloxi)carbonil]pirrolidin-2-il}carbonil)amino]-3-(3-metoxifenil)-1H-indol-2-il}fenil)carbamoil]pirrolidin-1-carboxilato de bencilo;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-(3-metilfenil)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-(2-metilfenil)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({2-[4-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)fenil]-3-(piridin-4-il)-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-ciano-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

(2S)-N-(4-{3-ciano-5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1H-indol-2-il}fenil)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-carboxamida;

{(1R)-2-[(2S)-2-({2-[4-(acetilamino)fenil]-3-ciano-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

{(1R)-2-[(2S)-2-({4-[5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-3-(dimetilcarbamoil)-1H-indol-2-il]fenil}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-2-[4-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)fenil]-1H-indolo-3-carboxilato de metilo;

ácido 5-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)-2-[4-({[(2S)-1-{(2R)-2-[(terc-butoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]carbonil}amino)fenil]-1H-indolo-3-carboxílico;

{(1R)-2-[(2S)-2-({2-[3-(acetilamino)prop-1-in-1-il]-1H-indol-5-il}carbamoil)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

N-{4-[5-(furan-3-il)-1H-indol-2-il]fenil}-1-(fenilacetil)-L-prolinamida;

N-(4-{5-[6-(dimetilamino)-4-metilpiridin-3-il]-1H-indol-2-il}fenil)-1-(fenilacetil)-L-prolinamida;

N-{4-[5-(1-benzotiofen-3-il)-1H-indol-2-il]fenil}-1-(fenilacetil)-L-prolinamida;

N-{4-[5-(1-bencil-1H-pirazol-4-il)-1H-indol-2-il]fenil}-1-(fenilacetil)-L-prolinamida;

N-{4-[5-(2,3-dihidro-1,4-benzodioxin-6-il)-1H-indol-2-il]fenil}-1-(fenilacetil)-L-prolinamida;

1-(fenilacetil)-N-{4-[5-(quinolin-8-il)-1H-indol-2-il]fenil}-L-prolinamida;

1-(fenilacetil)-N-{4-[5-(tiofen-3-il)-1H-indol-2-il]fenil}-L-prolinamida;

{(1S)-2-[(2S)-2-{[4-(5-ciano-1H-indol-2-il)fenil]carbamoil}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de terc-butilo;

[(1R)-2-oxo-1-fenil-2-{(2S)-2-[4-(2-{4-[({(2S)-1-[(2R)-2-fenil-2-{[(propan-2-iloxi)carbonil]amino}acetil]pirrolidin-2-il}carbonil)amino]fenil}-1H-indol-5-il)-1H-imidazol-2-il]pirrolidin-1-il}etil]carbamato de propan-2-ilo;

{(1R)-2-[(2S)-2-(5-{2-[4-(acetilamino)fenil]-1H-indol-5-il}-1,3,4-oxadiazol-2-il)pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de propan-2-ilo;

N-{4-[5-(5-{(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}-1,3,4-oxadiazol-2-il)-1H-indol-2-il]fenil}acetamida;

[(2S)-1-{(2S)-2-[5-(10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(12-fluoro-10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]-N-(2-{5-[({(2S)-1-[(2R)-2-(dimetilamino)-2-fenilacetil]pirrolidin-2-il}carbonil)amino]-1,3-benzoxazol-2-il}-1H-indol-5-il)pirrolidin-2-carboxamida;

1-[(2R)-2-(dietilamino)-2-fenilacetil]-N-{2-[4-(5-{(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}-1,3,4-oxadiazol-2-il)fenil]-1H-indol-5-il}-L-prolinamida;

{(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(metoxi-carbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;

(2R)-2-(dietilamino)-1-[(2S)-2-(5-{4-[5-(2-{(2S)-1-[(2R)-2-(dietilamino)-2-fenilacetil]pirrolidin-2-il}-1H-imidazol-5-il)-1-benzofuran-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-2-feniletanona;

{(1S)-1-ciclopropil-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-ciclopropil-2-[(metoxicarbonil)amino]acetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxoetil}carbamato de metilo;

{(1R)-1-ciclopropil-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-ciclopropil-2-[(metoxicarbonil)amino]acetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxoetil}carbamato de metilo;

{(2R)-1-[(2S)-2-{5-[2-(4-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;

{(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3,3-dimetilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3,3-dimetil-1-oxobutan-2-il}carbamato de metilo;

{(1R)-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-4-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;

{(2S,3R)-1-[(2S)-2-(5-{2-[4-(2-{(2S)-1-[N-(metoxicarbonil)-L-aloisoleucil]pirrolidin-2-il}-1H-imidazol-5-il)fenil]-1-benzofuran-5-il}-1H-imidazol-2-il)pirrolidin-1-il]-3-metil-1-oxopentan-2-il}carbamato de metilo;

{(2S)-3-hidroxi-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-3-hidroxi-2-[(metoxicarbonil)amino]propanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-1-oxopropan-2-il}carbamato de metilo;

{(2S,3R)-3-hidroxi-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S,3R)-3-hidroxi-2-[(metoxicarbonil)amino]butanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-1-oxobutan-2-il}carbamato de metilo;

{(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-4-metilpentanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-4-metil-1-oxopentan-2-il}carbamato de metilo;

{(2S)-1-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;

{(1R)-2-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;

{(2S)-1-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;

{(2S)-1-[(2S)-2-{5-[2-(2,6-difluoro-4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;

{(1R)-2-[(2S)-2-{5-[3-metoxi-4-(5-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;

{(2S)-1-[(2S)-2-{5-[2-(2-cloro-4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;

{(1R)-2-[(2S)-2-{4-[3-ciano-4-(5-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;

{(2S)-1-[(2S)-2-{5-[2-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}-2-metilfenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;

[(1S)-2-[(2S)-2-(5-{3-fluoro-4-[5-(2-{(2S)-1-[(2S)-2-[(metoxicarbonil)amino]-2-(tetrahidro-2H-piran-4-il)acetil]pirrolidin-2-il}-1H-imidazol-5-il)-1-benzofuran-2-il]fenil}-1H-imidazol-2-il)pirrolidin-1-il]-2-oxo-1-(tetrahidro-2H-piran-4-il)etil]carbamato de metilo;

{(2S)-1-[(2S)-2-{4-[3-fluoro-4-(5-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;

{(1R)-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2[(metoxi-carbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1,3-benzoxazol-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;

{(2S)-1-[(2S)-2-{5-[2-(4-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1,3-benzoxazol-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;

{(1R)-1-ciclopropil-2-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2R)-2-ciclopropil-2-[(metoxicarbonil)amino]acetil}pirrolidin-2-il]-1H-imidazol-5-il}-1,3-benzoxazol-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxoetil}carbamato de metilo;

(indolo[1,2-c][1,3]benzoxazina-3,10-diilbis{1H-imidazol-5,2-diil(2S)pirrolidin-2,1-diil[(1R)-2-oxo-1-feniletano-2,1-diil]})biscarbamato de dimetilo;

[(2S)-1-{(2S)-2-[5-(11-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6,7-dihidroindolo[1,2-d][1,4]benzoxazepin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6,6-dimetilindolo[1,2-c][1,3]benzoxazin-10-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(12-fluoro-10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6-metilindolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c]quinazolin-10-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(12-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-7,8-dihidro-6H-indolo[1,2-c][1,5]benzoxazocin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6-oxo-5,6-dihidroindolo[1,2-c]quinazolin-10-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6-fenilindolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(3-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6-metilindolo[1,2-c]quinazolin-10-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(10'-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}espiro[ciclohexano-1,6'-indolo[1,2-c][1,3]benzoxazin]-3'-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(1,12-difluoro-10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;

[(2S)-1-{(2S)-2-[5-(12-ciano-10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo; y
sales farmacéuticamente aceptables de los mismos.

32. Un compuesto de acuerdo con la reivindicación 1 o la reivindicación 2, elegido entre el grupo que consiste en:
{(25)-1-[(25)-2-{5-[4-(5-{2-[(25)-1-{(2^)-2-[(metoxi-carbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;
{(2R)-1-[(2S)-2-{5-[2-(4-{2-[(2S)-1-{(2R)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;
{(2S)-1-[(2S)-2-{5-[4-(5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-4-metilpentanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-4-metil-1-oxopentan-2-il}carbamato de metilo;
{(2S)-1-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;
{(2S)-1-[(2S)-2-{5-[3-fluoro-4-(5-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;
{(2*S*)-1-[(2*S*)-2-{5-[2-(2,6-difluoro-4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}fenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;
{(2*S*)-1-[(2*S*)-2-{5-[2-(2-cloro-4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}fenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo;
{(1*R*)-2-[(2*S*)-2-{4-[3-ciano-4-(5-{2-[(2*S*)-1-{(2*R*)-2-[(metoxicarbonil)amino]-2-fenilacetil}pirrolidin-2-il]-1H-imidazol-5-il}-1-benzofuran-2-il)fenil]-1H-imidazol-2-il}pirrolidin-1-il]-2-oxo-1-feniletil}carbamato de metilo;
{(2*S*)-1-[(2*S*)-2-{5-[2-(4-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-4-il}-2-metilfenil)-1-benzofuran-5-il]-1H-imidazol-2-il}pirrolidin-1-il]-3-metil-1-oxobutan-2-il}carbamato de metilo; y
sales farmacéuticamente aceptables de los mismos.

33. Un compuesto de acuerdo con la reivindicación 1 o la reivindicación 11, elegido entre el grupo que consiste en:
[(2*S*)-1-{(2*S*)-2-[5-(12-fluoro-10-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;
[(2*S*)-1-{(2*S*)-2-[5-(3-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1*H*-imidazol-5-il}-6,6-dimetilindolo[1,2-c][1,3]benzoxazin-10-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;
[(2*S*)-1-{(2S)-2-[5-(12-fluoro-10-{2-[(2*S*)-1-{(2*S*)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6-metilindolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;
[(2S)-1-{(2S)-2-[5-(10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}-6-fenilindolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;
[(2S)-1-{(2S)-2-[5-(10'-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}espiro[ciclohexano-1,6'-indolo[1,2-c][1,3]benzoxazin]-3'-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;
[(2S)-1-{(2S)-2-[5-(1,12-difluoro-10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo;
[(2S)-1-{(2S)-2-[5-(12-ciano-10-{2-[(2S)-1-{(2S)-2-[(metoxicarbonil)amino]-3-metilbutanoil}pirrolidin-2-il]-1H-imidazol-5-il}indolo[1,2-c][1,3]benzoxazin-3-il)-1H-imidazol-2-il]pirrolidin-1-il}-3-metil-1-oxobutan-2-il]carbamato de metilo; y
sales farmacéuticamente aceptables de los mismos.

34. Una composición farmacéutica que comprende una cantidad eficaz del compuesto de acuerdo con una cualquiera de las reivindicaciones 1-33, y un vehículo farmacéuticamente aceptable.

35. La composición farmacéutica de acuerdo con la reivindicación 34, que comprende adicionalmente un segundo agente terapéutico seleccionado entre el grupo que consiste en agentes antivirales del VHC, inmunomoduladores y agentes anti-infecciosos.

36. La composición farmacéutica de acuerdo con la reivindicación 34, que comprende adicionalmente un segundo agente terapéutico seleccionado entre el grupo que consiste en inhibidores de proteasa del VHC e inhibidores de polimerasa NS5B del VHC.

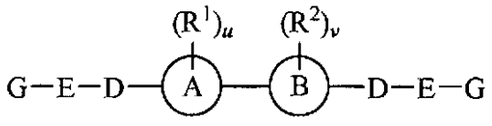
37. Un uso del compuesto de acuerdo con una cualquiera de las reivindicaciones 1-33 en la preparación de un medicamento para prevenir y/o tratar una infección por VHC en un sujeto que necesita el mismo.

38. Un procedimiento para tratar un paciente infectado con VHC que comprende la etapa de administrar una cantidad del compuesto de acuerdo con una cualquiera de las reivindicaciones 1-33 eficaz para prevenir y/o tratar la infección por VHC en un sujeto que necesita el mismo.

39. Un procedimiento para tratar un paciente infectado con VHC que comprende la etapa de administrar una cantidad del compuesto de acuerdo con una cualquiera de las reivindicaciones 1-33 eficaz para inhibir la replicación viral y/o la producción viral del VHC.

RESUMEN DE LA DESCRIPCIÓN

La presente invención se refiere a compuestos de fórmula **(I)** que son útiles como inhibidores de NS5A del virus de la hepatitis C (VHC), la síntesis de dichos compuestos, y el uso de dichos compuestos para inhibir la actividad NS5A del VHC, para tratar o prevenir infecciones por VHC y para inhibir la replicación viral y/o la producción viral del VHC en un sistema basado en células.



(I)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference MRLIFD00018	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 10/28653	International filing date *(day/month/year)* 25 March 2010 (25.03.2010)	(Earliest) Priority Date *(day/month/year)* 27 March 2009 (27.03.2009)
Applicant MERCK SHARP & DOHME CORP.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 10/28653

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.: 4-10, 14-20, 23-25, 27-28 and 34-39
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

2. ☐ As all searchable claims could be searched without effort justifying 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.:

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

International application No.
PCT/US 10/28653

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 37/18; A61K 31/16 (2010.01)
USPC - 514/613
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)
USPC - 514/613

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/265.1, 427, 563, 630 (see search terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWest (PGPB,USPT,USOC,EPAB,JPAB); Google
Search Terms Used:
polycyclic fused rings hcv inhibitor, viramidine, benzofuran, tetracycle

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X – Y	US 2006/0019974 A1 (MEDERSKI et al.) 26 January 2006 (26.01.2006) para [0001]-[0016]	1-3 and 21 --- 22, 26, 32
X – Y	US 2007/0049593 A1 (OKA et al.) 01 March 2007 (01.03.2007) para [0042]-[0051]	11-13, 30-31 --- 29, 33
Y	US 2007/0185175 A1 (LIU et al.) 09 August 2007 (09.08.2007) para [0008]-[0089]	22, 26, 29, 32, 33
Y	US 2006/0258682 A1 (LIAO et al.) 16 November 2006 (16.11.2006) para [0003]-[0047]	26

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

* 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 application or patent 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
02 May 2010 (02.05.2010)	12 MAY 2010
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-124967- -00000-0000
Fecha: 2011-09-23 16:50:24 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 243

PATENTE DE INVENCIÓN ☐ **MODELO DI**

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

Completa ☐ Incompleta ☐

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

- ☒ Indicación que se solicita una PCT
- ☒ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☒ Dibujos de ser estos pertinentes
- ☒ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☒ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐