08-108182

Organizacion y Digitalizacion CSA Ltda.

CSA220520

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QF

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

Industria y Comercio

SUPERINTENDENCIA

PCT

**DELEGATURA DE PROPIEDAD INDUSTRIAL**

**DIVISIÓN DE NUEVAS CREACIONES**

**SOLICITUD DE PATENTE DE INVENCIÓN**

08-108182

**TITULO:** COMPUESTOS ORGANICOS Y SUS USOS

**SOLICITANTE:** NOVARTIS AG

**DIRECCIÓN:** Lichtstrasse 35, CH- 4056 Basel, Suiza

**APODERADO:** CARLOS R. OLARTE

**BOGOTÁ:** 09 Octubre de 2008

P2008/000172

# OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-108182- -00000-0000
Fecha: 2008-10-09 16:33:16 Dep: 2020 NUEVA CREACION
Tra: 11 PATENTE Y II Eve: 378 FASE NACIONAL I
Act: 411 PRESENTACION Folios: 829

**PETITORIO - FORMULARIO ÚNICO DE SOLICITUD**
**PATENTE PCT**
**ENTRADA EN FASE NACIONAL** **P2008/000172**

**SOLICITUD DE:**

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

[X] Capítulo I. [ ] Capítulo II.

(2) **SOLICITANTE (71)**

**Nombre:** NOVARTIS AG
**Dirección:** Lichtstrasse 35, CH-4056 Basel
**Nacionalidad o Domicilio:** Suiza
**Lugar de Constitución:** Suiza
**Teléfono:** **Fax:**
**E-mail:**

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

**REPRESENTANTE O APODERADO**

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

**IDENTIFICACIÓN**
**C.C.** [X] **NIT** [ ]
**C.E.** [ ] **Otro** [ ]
**Cual**
**Número** 79782747Bta
**TP** 74.295

**INVENTOR (ES) (72)**

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

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2007/066204 Fecha Abril 9 2007

Publicación Internacional No. WO 2007/113865 Fecha Noviembre 22, 2007

(6) **Título (54)** **COMPUESTOS ORGANICOS Y SUS USOS**

**Clasificación Internacional (51)** C07K 5/06, C07K 5/078, C07K 5/083 C07K 5/087, C07K 5/10, C07K 5/103, C07K 5/107, A61K 38/05, A61K 38/06, A61K 38/07, A61P 31/12 A61P 31/14, A61P 31/18

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

| (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|
| US | Abril 11, 2006 | 60/791,318 |
| US | Noviembre 22, 2006 | 60/866,874 |
| | | |
| | | |
| | | |

(9) **Comprobante de pago No.** 08-80,096 **Fecha** Octubre 8 de 2008

## ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 07-026.397
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

## LISTA DE INVENTORES

PCT/US2007/066204

1. **Trixi BRANDL,**
   Murbacherstrasse 27,
   CH-4056 Basel
   Suiza
   Nacionalidad: Alemana

2. **Jiping FU,**
   74 Cutter Hill Road,
   Arlington, Massachusetts 02474
   Estados Unidos de America
   Nacionalidad: China

3. **Francois LENOIR,**
   5101 Stearns Hill Road,
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   Nacionalidad: Canadiense

4. **David Thomas PARKER,**
   541 Bedford Street, Lexington,
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   Nacionalidad: Estadounidense

5. **Michael PATANE,**
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   Estados Unidos
   Nacionalidad: Estadounidense

6. **Branko RADETICH,**
   1 Saint Charles Street,
   Apartment 4, Boston, Massachusetts 02116
   Estados Unidos
   Nacionalidad: Rusa

## LISTA DE INVENTORES

PCT/US2007/066204

7. **Prakash RAMAN,**
125 Summer Street, Acton,
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Estados Unidos
Nacionalidad: India

8. **Pascal RIGOLLIER,**
4 bis, Avenue de la Première Division Blindée,
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Francia
Nacionalidad: Francesa

9. **Mohindra SEEPERSAUD,**
3 Colby Street, Belmont,
Massachusetts 02478
Estados Unidos
Nacionalidad: Estadounidense

10. **Oliver SIMIC,**
Gundeldingerstrasse 209,
CH-4053 Basel
Suiza
Nacionalidad: Alemana

11. **Aregahegn YIFRU,**
14 Murdock Street, Apartment 2-7,
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Estados Unidos de America
Nacionalidad: Canadiense

12. **Rui ZHENG,**
38 Varnum Street, Arlington,
Massachusetts 02474
Estados Unidos de America
Nacionalidad: China

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-108182- -00000-0000

Fec Rad 2008-10-08 16:14:16 Dep 2023 NUEVA CREACION
Fol 11 PATENTE(S) Eva 378 PASEN NACIONAL
Act 411 PRESENTACION Folios 829

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 80,096
FECHA : OCTUBRE 8 DE 2008

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

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| OLARTE RAISBEK | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 11593525 | 07/10/2008 | 3,568,000.00 |

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

| CANT. | RENTISTICO | CONCEPTO | | TOTAL CONCEPTO |
|---|---|---|---|---|
| 1 | 50005-01-01 SOLICITUDES | 1 | TRAMITES DE SOL. DE PATENTE DE IN | 501,000.00 |
| | | | TOTAL : $ | 501,000.00 |

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

*Nota del traductor:*

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

Traductor Ofici
JORGE E. SIERRA
Licencia 376 - 1993 A

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

*Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.*

Traductor Oficia
JORGE E. SIERRA P
Licencia

*Certificación:*

*Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"*

*Fecha: 12 de Septiembre de 2006.*

*Traductor: Jorge Enrique Sierra Reyes.*

*Licencia No. 376 de 1993, del Ministerio de Justicia.*

*Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.*

*Teléfono: (57-1) 2182308, (57-1) 6232925.*

*E-mail: treseser1@yahoo.com. No. 8346*

Traductor Ofic
JORGE E. SIERRA
Licencia 376 - 1993

OLARTE RAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frier
Juan Guillermo Moure
Natalia Castro

Zayde Chalhu
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoz
Simón Salina

Of Counse
Guillermo Chalhu
Graciela Mele

# Power of Attorney

# Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las **Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:

Arthur Canonica

Pascal Thaub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

10

**Attestation**

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

M. Staehelin Notar

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Leg.Prot.Nr. 975 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by .....
3. in his/her function as .....
4. and certified by the seal of the .....

Certified 18. Aug. 2010

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. .....
9. Seal/stamp: 10. Signature:

Heidi Fischer

STATE CHANCERY * BASLE-CITY *

P2008/172

Caso de Patente: 34769-US-PCT

# CESIÓN

Por buena y onerosa consideración, del cual se acusa recibo suficiente, nosotros

| | | |
|---|---|---|
| David Thomas PARKER | Residente en | 541 Bedford Street<br>Lexington, MA 02420 |
| Mohindra SEEPERSAUD | Residente en | 3 Colby Street<br>Belmont, MA 02478 |
| Branko RADETICH | Residente en | 1 Saint Charles Street, Apt. 4<br>Boston, MA 01720 |
| Aregahegn YIFRU | Residente en | 14 Murdock Street, Apt. 2-7<br>Somerville, MA 02145 |
| Prakash RAMAN | Residente en | 125 Summer Street<br>Acton, MA 01720 |
| Jiping FU | Residente en | 74 Cutter Hill Road<br>Arlington, MA 01867 |
| Michael PATENE | Residente en | 273 Forest Street<br>Reading, MA 02474 |
| Rui ZHENG | Residente en | 38 Varnum Street<br>Rading, MA 01867 |
| Oliver SIMIC | Residente en | Gundeldingerstrassse 209<br>4053 Basel<br>Suiza |
| Trixi BRANDL | Residente en | Murbachestrasse 27<br>4056 Basel<br>Suiza |
| Pascasl RIGOLLIER | Residente en | 4 bis, Avenue de la Premiere<br>Division Blindèe<br>68100 Mulhouse<br>Francia |
| Francois LENOIR | Resdiente en | 5101 Stearns Hill Road<br>Waltham, MA 02451 |

MAURICE URI[illegible]
TRADUCTOR E INTERPRETE OF[illegible]
INGLES • ESPAÑOL - ESPAÑOL
RES. MINJUSTICIA [illegible]

Por medio de la presente vendemos y transferimos a NOVARTIS AG, una compañía constituida bajo las leyes de la confederación Suiza, de Lichstrasse 35, 4056 Basilea, Suiza y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para todos los países del mundo, excepto Austria, y Novartis Pharma GmbH, una compañía constituida bajo las Leyes de Austria de Bruner Strasse 59, 1230 Vienna, Austria y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para Austria (Novartis AG y Novartis Pharma GmbH, llamados de ahora en adelante colectivamente los CESIONARIOS) en y para (1) todos nuestros inventos y descubrimientos descritos en la solicitud de patente titulada:

**COMPUESTOS ORGANICOS Y SUS USOS**

Y presentada en la Oficina de Patentes y Marcas Registradas de Los Estados Unidos De América el 09 abril_____, 2007___ y de acuerdo con la Solicitud número_____* y/o archivada bajo el número **PCT/US2007/066204**, (2) la solicitud de Patente identificada en (1), (3) todas las fases nacionales de dicha solicitud de patente internacional identificada en, (1), (4) todas las demás solicitudes de patentes en todas las regiones y países que reivindiquen prioridad de la(s) solicitud(es) de Patentes Provisionales o no provisionales presentada(s) en la Oficina de Patentes y Marcas Registradas de Los Estados Unidos el **11 de abril de 2006** y de acuerdo con la solicitud numero **60/791,318**, (5) por todas las solicitudes de Patentes, todos los derechos de prioridad basados en la solicitud de Patente en Los Estados Unidos identificada en (4) en todos los países y regiones bajo la convención de Paris para la protección de la propiedad industrial, la Convención Inter-Americana relacionado con Patentes, Invenciones Diseños y Modelos Industriales y todos los demás convenios internacionales a los cuales esté suscrito o que intente hacerlo, y si la Patente de los Estados Unidos identificada en (4) es una solicitud de Patente provisional, bajo 35USC 119(e) (incluyendo el derecho a presentar solicitud de Patente en dichas invenciones y descubrimientos en nombre de los CESIONARIOS o sus designados o en nuestros nombres, a su elección y de acuerdo a las leyes aplicables en todos los países o regiones), (6) Todas las continuaciones o divisiones de cualquiera de las solicitudes de Patente en Los Estados Unidos o de solicitud de Patente Internacional identificada en (1) y cualquier solicitud de Patente dentro del rango de (4) (incluyendo futuras continuaciones y divisiones tales como, pero no limitadas a, continuaciones de continuaciones de divisiones), (7) todas las Patentes que sean otorgadas en cualquiera de dichas solicitudes de Patente, (8) todas los registros de y confirmaciones de, y certificados de importación basados en, una o mas dichas Patentes y (9) todos los re-otorgamientos, renovaciones, y extensiones de dichas patentes, registros, confirmaciones y certificados de importación y certificados de re reexaminación, expedidos para dichas patentes y certificados de protección basados en dichas patentes y solicitudes para tales re otorgamientos, renovaciones, extensiones, certificados de re-exanimación y certificados de protección, así mismo para ser conservada y disfrutada por dichos CESIONARIOS y sus sucesores, asignados y representantes legales, en su totalidad por dichas patentes, registros, confirmaciones, certificados de importación, certificados de reexaminación, certificados suplementarios de protección, re otorgamientos, renovaciones y extensiones que puedan ser expedidas, proporcionar todos los términos para que todas las patentes puedan ser concedidas, para conservar y disfrutar plenamente y totalmente por nosotros, así mismo como lo haríamos si esta cesión no hubiera sido vendida y transferida.

MAURICE URI...
TRADUCTOR E INTERPRETE OFICIAL
INGLÉS • ESPAÑOL - ESPAÑOL - INGLÉS
RES. MINJUSTICIA ...

*Nosotros por medio del presente autorizamos al CESIONARIO y sus representantes para incorporar en este instrumento el número de la solicitud y la fecha de presentación de dicha solicitud cuando esta sea notificada.

Y por medio de la presente nosotros convenimos y acordamos que en cualquier momento, al requerirse y a expensas del CESIONARIO o sus sucesores asignados o representantes legales, ejecutaremos y entregaremos cualquier y todos los documentos necesarios y deseables para perfeccionar el titulo de los anteriores inventos o descubrimientos, solicitudes de patente, registros confirmaciones, certificados de importación, re-otorgamientos, renovaciones, extensiones, certificados de reexaminación, certificados de protección adicional dentro del rango de (8) y (9) a nombre del CESIONARIO, sus cesionarios, sucesores, u otros representantes legales, incluyendo la ejecución y consecución de cualquier y todo documento adicional que evidencie esta cesión y venta según sea necesario o deseable en la Oficina de Patentes u otra Oficina o Agencia para la Propiedad Intelectual o similar de cualquier país o región, (ii) al requerirse, pero a expensas del CESIONARIO o de sus sucesores, asignados, o representantes legales ejecutaremos todas las solicitudes dentro del rango de adicionales de Patente (3), (4) y (6) y todas las solicitudes dentro del rango (8) o (9) y (iii) y realizaremos las declaraciones necesarias juramentadas y realizaremos todos los actos jurídicos necesarios para ello, sin compensación adicional, pero a expensas del CESIONARIO, sus sucesores, cesionarios, u otros representantes legales.

Ejecutado el 23 de Marzo de 2007.

David Thomas PARKER, (firma ilegible) L.S.

**RECONOCIMIENTO**

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

El día 23 de Marzo del 2007, se presento ante mí personalmente **David Thomas PARKER** demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

Ejecutado el 23 de marzo de 2007.

Mohindra SEEPERSAUD, (firma ilegible) L.S.

**RECONOCIMIENTO**

MAURICE UR... TRADUCTOR E INTERPRETE OF... INGLES - ESPAÑOL / ESPAÑOL - ... RES. MINJUS...

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

El día 23 de Marzo del 2007, se presento ante mí personalmente **Mohindra SEEPERSAUD**demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

Ejecutado el 4 de Abril de 2007.

Bronko RADETICH, (firma ilegible) L.S.

**RECONOCIMIENTO**

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

El día 4 de Abril del 2007, se presento ante mí personalmente **Bronko RADETICH** demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

Ejecutado el 23 de marzo de 2007.

Aregahegn YIFRU, (firma ilegible) L.S.

**RECONOCIMIENTO**

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

El día 23 de Marzo del 2007, se presento ante mí personalmente **Aregahegn YIFRU** demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

MAURICE [illegible]
TRADUCTOR E INTERPRETE OF[illegible]
INGLES - ESPAÑOL - ESPAÑOL - INGLES
RES. MINJUSTIC[illegible]

Firma ilegible
Notario Público.

Ejecutado el 23 de marzo de 2007.

Prakash RAMAN, (firma ilegible) L.S.

**RECONOCIMIENTO**

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

El día 23 de Marzo del 2007, se presento ante mí personalmente **Prakash RAMAN** demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

Ejecutado el 23 de marzo de 2007.

Jiping FU, (firma ilegible) L.S.

**RECONOCIMIENTO**

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

El día 23 de Marzo del 2007, se presento ante mí personalmente **Jiping FU** demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

Ejecutado el 23 de marzo de 2007.

Rui ZHENG, (firma ilegible) L.S.

**RECONOCIMIENTO**

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

MARIDIC [illegible] V.
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL / ESPAÑOL - INGLES
RES. MINJUST [illegible]

El día 23 de Marzo del 2007, se presento ante mí personalmente **Rui ZHENG** demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

Ejecutado el 5 de abril de 2007.

Francois LENOIR, (firma ilegible) L.S.

**RECONOCIMIENTO**

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

El día 5 de Abril del 2007, se presento ante mí personalmente **Francois LENOIR** demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

MAURICE URI[illegible]
TRADUCTOR E INTERPRETE OF[illegible]
INGLES • ESPAÑOL - ESPAÑOL - IN[illegible]S
RES. MINJUSTICIA 1790 - [illegible]

Caso de Patente: 34769-US-PCT

# CESIÓN

Por buena y onerosa consideración, del cual se acusa recibo suficiente, nosotros

| | | |
|---|---|---|
| David Thomas PARKER | Residente en | 541 Bedford Street<br>Lexington, MA 02420 |
| Mohindra SEEPERSAUD | Residente en | 3 Colby Street<br>Belmont, MA 02478 |
| Branko RADETICH | Residente en | 1 Saint Charles Street, Apt. 4<br>Boston, MA 01720 |
| Aregahegn YIFRU | Residente en | 14 Murdock Street, Apt. 2-7<br>Somerville, MA 02145 |
| Prakash RAMAN | Residente en | 125 Summer Street<br>Acton, MA 01720 |
| Jiping FU | Residente en | 74 Cutter Hill Road<br>Arlington, MA 01867 |
| Michael PATENE | Residente en | 273 Forest Street<br>Reading, MA 02474 |
| Rui ZHENG | Residente en | 38 Varnum Street<br>Rading, MA 01867 |
| Oliver SIMIC | Residente en | Gundeldingerstrassse 209<br>4053 Basel<br>Suiza |
| Trixi BRANDL | Residente en | Murbachestrasse 27<br>4056 Basel<br>Suiza |
| Pascasl RIGOLLIER | Residente en | 4 bis, Avenue de la Premiere<br>Division Blindèe<br>68100 Mulhouse<br>Francia |
| Francois LENOIR | Resdiente en | 5101 Stearns Hill Road<br>Waltham, MA 02451 |

MAURICE UR[illegible]
TRADUCTOR E INTERPRETE OF[illegible]
INGLES - ESPAÑOL - ESPAÑOL - ING[illegible]
RES. MINJUSTICIA 1790 - [illegible]

Por medio de la presente vendemos y transferimos a NOVARTIS AG, una compañía constituida bajo las leyes de la confederación Suiza, de Lichstrasse 35, 4056 Basilea, Suiza y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para todos los países del mundo, excepto Austria, y Novartis Pharma GmbH, una compañía constituida bajo las Leyes de Austria de Bruner Strasse 59, 1230 Vienna, Austria y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para Austria (Novartis AG y Novartis Pharma GmbH, llamados de ahora en adelante colectivamente los CESIONARIOS) en y para (1) todos nuestros inventos y descubrimientos descritos en la solicitud de patente titulada:

**COMPUESTOS ORGANICOS Y SUS USOS**

Y presentada en la Oficina de Patentes y Marcas Registradas de Los Estados Unidos De América el _____, 20___ y de acuerdo con la Solicitud número_____* y/o archivada bajo el número **PCT/US2007/066204**, (2) la solicitud de Patente identificada en (1), (3) todas las fases nacionales de dicha solicitud de patente internacional identificada en, (1), (4) todas las demás solicitudes de patentes en todas las regiones y países que reivindiquen prioridad de la(s) solicitud(es) de Patentes Provisionales o no provisionales presentada(s) en la Oficina de Patentes y Marcas Registradas de Los Estados Unidos el 22 **de noviembre de 2006** y de acuerdo con la solicitud numero **60/866,874**, (5) por todas las solicitudes de Patentes, todos los derechos de prioridad basados en la solicitud de Patente en Los Estados Unidos identificada en (4) en todos los países y regiones bajo la convención de Paris para la protección de la propiedad industrial, la Convención Inter-Americana relacionado con Patentes, Invenciones Diseños y Modelos Industriales y todos los demás convenios internacionales a los cuales esté suscrito o que intente hacerlo, y si la Patente de los Estados Unidos identificada en (4) es una solicitud de Patente provisional, bajo 35USC 119(e) (incluyendo el derecho a presentar solicitud de Patente en dichas invenciones y descubrimientos en nombre de los CESIONARIOS o sus designados o en nuestros nombres, a su elección y de acuerdo a las leyes aplicables en todos los países o regiones), (6) Todas las continuaciones o divisiones de cualquiera de las solicitudes de Patente en Los Estados Unidos o de solicitud de Patente Internacional identificada en (1) y cualquier solicitud de Patente dentro del rango de (4) (incluyendo futuras continuaciones y divisiones tales como, pero no limitadas a, continuaciones de continuaciones de divisiones), (7) todas las Patentes que sean otorgadas en cualquiera de dichas solicitudes de Patente, (8) todas los registros de y confirmaciones de, y certificados de importación basados en, una o mas dichas Patentes y (9) todos los re-otorgamientos, renovaciones, y extensiones de dichas patentes, registros, confirmaciones y certificados de importación y certificados de re reexaminación, expedidos para dichas patentes y certificados de protección basados en dichas patentes y solicitudes para tales re otorgamientos, renovaciones, extensiones, certificados de re-exanimación y certificados de protección, así mismo para ser conservada y disfrutada por dichos CESIONARIOS y sus sucesores, asignados y representantes legales, en su totalidad por dichas patentes, registros, confirmaciones, certificados de importación, certificados de reexaminación, certificados suplementarios de protección, re otorgamientos, renovaciones y extensiones que puedan ser expedidas, proporcionar todos los términos para que todas las patentes puedan ser concedidas, para conservar y disfrutar plenamente y totalmente por nosotros, así mismo como lo haríamos si esta cesión no hubiera sido vendida y transferida.

TRADUCTOR E INTÉRPRETE OFICIAL
INGLÉS • ESPAÑOL - ESPAÑOL - INGLÉS
RES. MINJUSTICIA 1780

*Nosotros por medio del presente autorizamos al CESIONARIO y sus representantes para incorporar en este instrumento el número de la solicitud y la fecha de presentación de dicha solicitud cuando esta sea notificada.

Y por medio de la presente nosotros convenimos y acordamos que en cualquier momento, al requerirse y a expensas del CESIONARIO o sus sucesores asignados o representantes legales, ejecutaremos y entregaremos cualquier y todos los documentos necesarios y deseables para perfeccionar el titulo de los anteriores inventos o descubrimientos, solicitudes de patente, registros confirmaciones, certificados de importación, re-otorgamientos, renovaciones, extensiones, certificados de reexaminación, certificados de protección adicional dentro del rango de (8) y (9) a nombre del CESIONARIO, sus cesionarios, sucesores, u otros representantes legales, incluyendo la ejecución y consecución de cualquier y todo documento adicional que evidencie esta cesión y venta según sea necesario o deseable en la Oficina de Patentes u otra Oficina o Agencia para la Propiedad Intelectual o similar de cualquier país o región, (ii) al requerirse, pero a expensas del CESIONARIO o de sus sucesores, asignados, o representantes legales ejecutaremos todas las solicitudes dentro del rango de adicionales de Patente (3), (4) y (6) y todas las solicitudes dentro del rango (8) o (9) y (iii) y realizaremos las declaraciones necesarias juramentadas y realizaremos todos los actos jurídicos necesarios para ello, sin compensación adicional, pero a expensas del CESIONARIO, sus sucesores, cesionarios, u otros representantes legales.

Ejecutado el 28 de Marzo de 2007.

Michael PATANE, (firma ilegible) L.S.

**RECONOCIMIENTO**

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

El día 28 de Marzo del 2007, se presento ante mí personalmente **Michael PATANE**demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

MAURICE LIR...
TRADUCTOR E INTERPRETE OF...
INGLES - ESPAÑOL - ESPAÑOL - IN...
RES. MINJUSTICIA 1990 - ...

# CESIÓN

Por buena y onerosa consideración, del cual se acusa recibo suficiente, nosotros

| | | |
|---|---|---|
| David Thomas PARKER | Residente en | 541 Bedford Street<br>Lexington, MA 02420 |
| Mohindra SEEPERSAUD | Residente en | 3 Colby Street<br>Belmont, MA 02478 |
| Branko RADETICH | Residente en | 1 Saint Charles Street, Apt. 4<br>Boston, MA 01720 |
| Aregahegn YIFRU | Residente en | 14 Murdock Street, Apt. 2-7<br>Somerville, MA 02145 |
| Prakash RAMAN | Residente en | 125 Summer Street<br>Acton, MA 01720 |
| Jiping FU | Residente en | 74 Cutter Hill Road<br>Arlington, MA 01867 |
| Michael PATENE | Residente en | 273 Forest Street<br>Reading, MA 02474 |
| Rui ZHENG | Residente en | 38 Varnum Street<br>Rading, MA 01867 |
| Oliver SIMIC | Residente en | Gundeldingerstrassse 209<br>4053 Basel<br>Suiza |
| Trixi BRANDL | Residente en | Murbachestrasse 27<br>4056 Basel<br>Suiza |
| Pascasl RIGOLLIER | Residente en | 4 bis, Avenue de la Premiere<br>Division Blindée<br>68100 Mulhouse<br>Francia |
| Francois LENOIR | Resdiente en | 5101 Stearns Hill Road<br>Waltham, MA 02451 |

MARIA RICE
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL - ESPAÑOL - INGLES
RES. MINJUSTICIA 1790 - 2001

Por medio de la presente vendemos y transferimos a NOVARTIS AG, una compañía constituida bajo las leyes de la confederación Suiza, de Lichstrasse 35, 4056 Basilea, Suiza y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para todos los países del mundo, excepto Austria, y Novartis Pharma GmbH, una compañía constituida bajo las Leyes de Austria de Bruner Strasse 59, 1230 Vienna, Austria y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para Austria (Novartis AG y Novartis Pharma GmbH, llamados de ahora en adelante colectivamente los CESIONARIOS) en y para (1) todos nuestros inventos y descubrimientos descritos en la solicitud de patente titulada:

**COMPUESTOS ORGANICOS Y SUS USOS**

Y presentada en la Oficina de Patentes y Marcas Registradas de Los Estados Unidos De América el _____, 20___ y de acuerdo con la Solicitud número_____* y/o archivada bajo el número **PCT/US2007/066204**, (2) la solicitud de Patente identificada en (1). (3) todas las fases nacionales de dicha solicitud de patente internacional identificada en. (1). (4) todas las demás solicitudes de patentes en todas las regiones y países que reivindiquen prioridad de la(s) solicitud(es) de Patentes Provisionales o no provisionales presentada(s) en la Oficina de Patentes y Marcas Registradas de Los Estados Unidos el **22 de noviembre de 2006** y de acuerdo con la solicitud numero **60/866,874**, (5) por todas las solicitudes de Patentes, todos los derechos de prioridad basados en la solicitud de Patente en Los Estados Unidos identificada en (4) en todos los países y regiones bajo la convención de Paris para la protección de la propiedad industrial, la Convención Inter-Americana relacionado con Patentes, Invenciones Diseños y Modelos Industriales y todos los demás convenios internacionales a los cuales esté suscrito o que intente hacerlo, y si la Patente de los Estados Unidos identificada en (4) es una solicitud de Patente provisional, bajo 35USC 119(e) (incluyendo el derecho a presentar solicitud de Patente en dichas invenciones y descubrimientos en nombre de los CESIONARIOS o sus designados o en nuestros nombres, a su elección y de acuerdo a las leyes aplicables en todos los países o regiones), (6) Todas las continuaciones o divisiones de cualquiera de las solicitudes de Patente en Los Estados Unidos o de solicitud de Patente Internacional identificada en (1) y cualquier solicitud de Patente dentro del rango de (4) (incluyendo futuras continuaciones y divisiones tales como, pero no limitadas a, continuaciones de continuaciones de divisiones), (7) todas las Patentes que sean otorgadas en cualquiera de dichas solicitudes de Patente, (8) todas los registros de y confirmaciones de, y certificados de importación basados en, una o mas dichas Patentes y (9) todos los re-otorgamientos, renovaciones, y extensiones de dichas patentes, registros, confirmaciones y certificados de importación y certificados de re reexaminación, expedidos para dichas patentes y certificados de protección basados en dichas patentes y solicitudes para tales re otorgamientos, renovaciones, extensiones, certificados de re-exanimación y certificados de protección, así mismo para ser conservada y disfrutada por dichos CESIONARIOS y sus sucesores, asignados y representantes legales, en su totalidad por dichas patentes, registros, confirmaciones, certificados de importación, certificados de reexaminación, certificados suplementarios de protección, re otorgamientos, renovaciones y extensiones que puedan ser expedidas, proporcionar todos los términos para que todas las patentes puedan ser concedidas, para conservar y disfrutar plenamente y totalmente por nosotros, así mismo como lo haríamos si esta cesión no hubiera sido vendida y transferida.

MAURICE UR[illegible]
TRADUCTOR E INTERPRETE OF.
INGLES - ESPAÑOL - ESPAÑOL - IN[illegible]
RES. MINJUSTICIA 1790 - 18[illegible]

*Nosotros por medio del presente autorizamos al CESIONARIO y sus representantes para incorporar en este instrumento el número de la solicitud y la fecha de presentación de dicha solicitud cuando esta sea notificada.

Y por medio de la presente nosotros convenimos y acordamos que en cualquier momento, al requerirse y a expensas del CESIONARIO o sus sucesores asignados o representantes legales, ejecutaremos y entregaremos cualquier y todos los documentos necesarios y deseables para perfeccionar el titulo de los anteriores inventos o descubrimientos, solicitudes de patente, registros confirmaciones, certificados de importación, re-otorgamientos, renovaciones, extensiones, certificados de reexaminación, certificados de protección adicional dentro del rango de (8) y (9) a nombre del CESIONARIO, sus cesionarios, sucesores, u otros representantes legales, incluyendo la ejecución y consecución de cualquier y todo documento adicional que evidencie esta cesión y venta según sea necesario o deseable en la Oficina de Patentes u otra Oficina o Agencia para la Propiedad Intelectual o similar de cualquier país o región, (ii) al requerirse, pero a expensas del CESIONARIO o de sus sucesores, asignados, o representantes legales ejecutaremos todas las solicitudes dentro del rango de adicionales de Patente (3), (4) y (6) y todas las solicitudes dentro del rango (8) o (9) y (iii) y realizaremos las declaraciones necesarias juramentadas y realizaremos todos los actos jurídicos necesarios para ello, sin compensación adicional, pero a expensas del CESIONARIO, sus sucesores, cesionarios, u otros representantes legales.

Ejecutado el 14 de Marzo de 2007.

Oliver SIMIC, (firma ilegible) L.S.

**RECONOCIMIENTO**

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

El día_____de____ del 2007, se presento ante mí personalmente _____demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

Ejecutado el 14 de marzo de 2007.

Trixi BRANDL, (firma ilegible) L.S.

**RECONOCIMIENTO**

MAURICE UR[illegible]
TRADUCTOR E INTERPRETE OF[illegible]
INGLES - ESPAÑOL - ESPAÑOL - ING[illegible]
RES. MINJUSTICIA 1790 - 19[illegible]

Estado de Massachusetts )
) S.S.:
Condado se Middlesex )

El día__ de ___ del 2007, se presento ante mí personalmente _____demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

Ejecutado el 30 de marzo de 2007.

Pascal RIGOLLIER, (firma ilegible) L.S.

**RECONOCIMIENTO**

Estado de _____ )
) S.S.:
Condado se _____ )

El día__ de ___ del 2007, se presento ante mí personalmente _____demostrando ante mi ser la misma persona descrita aquí y de ser quien ejecuto este documento y reconoce haberlo hecho por su propia voluntad con el propósito aquí descrito.

Sellado.

Firma ilegible
Notario Público.

MAURICE URI[illegible]
TRADUCTOR E INTERPRETE OFI[illegible]
INGLES - ESPAÑOL - ESPAÑOL - INGLES
RES. MINJUSTICIA 1790 - 1966

# TESTIFICACION

Yo, el suscrito notario público de Basilea, Suiza, certifico por medio del presente la autenticidad de las firmas del **Dr. Oliver Simic**, ciudadano Alemán, residente en Basilea, Suiza; el Sr. Trixi Brandl, ciudadano Alemán, residente en Basilea, Suiza y el Sr. Pascal Roglier, ciudadano Francés, resiente en Mulhouse, Francia

La autenticidad de la firma fue demostrada bajo comparación.

BASILEA, Suiza, 10 días del mes de Abril de 2007

(Firma) Ilegible

Leg.Prot.Nr. 113/2007

## POR COPIA CERTIFICADA

Yo. El firmante Notario Civil, Dr. Thomas Gelzer, por este medio certifico que el documento aquí adjunto es una copia fiel del documento original.

Basilea Suiza. este 24 de Septiembre de 2008

Firma ilegible
Notario

Leg. Prot. 844/2008

TRADUCTOR E INTERPRETE OF.
INGLES o ESPAÑOL - ESPAÑOL - IN
RES. MINJUSTICIA 1790 - 1811

**APOSTILLA**

**(CONVENCION DE LA HAYA DEL 5 DE OCTUBRE DE 1961)**

1. PAÍS: SUIZA
2. ESTE DOCUMENTO PÚBLICO HA SIDO FIRMADO POR: Thomas Gelzer.
3. EN CALIDAD DE: NOTARIO PÚBLICO OFICIAL
4. CERTIFICADO CON EL SELLO DE: NOTARIO PÚBLICO

CERTIFICÓ

5. EN BASILEA
6. EL 25 DE SEPTIEMBRE DE 2008
7. POR: LA CANCILLERÍA DEL ESTADO DE CANTON DE BASILEA
8. No. 8519/14342
9. SELLO: DE LA CANCILLERÍA DE ESTADO CIUDAD DE BASILEA
10. FIRMA: (ILEGIBLE)
    Helena Schaffner

2008 OCT -9 P 3:43

JEFE DE LEGALIZACIONES
BOGOTA D.C.

MINISTERIO DE
RELACIONES EXTERIORES

829387

NO SE ASUME
RESPONSABILIDAD
DEL TEXTO

EN EL CUMPLIMIENTO DE
LAS FUNCIONES INDICADAS

MAURICE URREGO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL - ESPAÑOL - INGLES
RES. MINJUSTICIA 1790 - 1998

P2008/172 836 CO

Patent Case 34769-US-PCT

## ASSIGNMENT

good and valuable consideration, the receipt and adequacy of which are hereby acknowledged, we

| | | |
|---|---|---|
| David Thomas PARKER | residing at | 541 Bedford Street<br>Lexington, MA 02420 |
| Mohindra SEEPERSAUD | residing at | 3 Colby Street<br>Belmont, MA 02478 |
| Branko RADETICH | residing at | 1 Saint Charles Street, Apt. 4<br>Boston, MA 01720 |
| Aregahegn YIFRU | residing at | 14 Murdock Street, Apt. 2-7<br>Somerville, MA 02145 |
| Prakash RAMAN | residing at | 125 Summer Street<br>Acton, MA 01720 |
| Jiping FU | residing at | 74 Cutter Hill Road<br>Arlington, MA 02474 |
| Michael PATANE | residing at | 273 Forest Street<br>Reading, MA 01867 |
| Rui ZHENG | residing at | 38 Varnum Street<br>Arlington, MA 02474 |
| Oliver SIMIC | residing at | Gundeldingerstrassse 209<br>4053 Basel<br>Switzerland |
| Trixi BRANDL | residing at | Murbachestrasse 27<br>4056 Basel<br>Switzerland |
| Pascal RIGOLLIER | residing at | 4 bis, Avenue de la Première<br>Division Blindée<br>68100 Mulhouse<br>France |
| Francois LENOIR | residing at | 5101 Stearns Hill Road<br>Waltham, MA 02451 |

do hereby sell, assign and transfer to **Novartis AG**, a company organized under the laws of the Swiss Confederation, of Lichtstrasse 35, Basel, Switzerland 4056, and its successors, assigns and legal representatives, all of our right, title and interest for all countries of the world except Austria and to Novartis Pharma GmbH, a company organized under the laws of Austria, of Brunner Strasse 59, 1230 Vienna, Austria, and its successors, assigns and legal representatives, all of our right, title and interest for Austria (Novartis AG and Novartis Pharma GmbH) hereinafter referred to collectively as the "**ASSIGNEES**" in and to (1) all of our inventions and discoveries described in the patent provisional or non-provisional patent application(s) titled

**ORGANIC COMPOUNDS AND THEIR USES**

filed in the United States Patent and Trademark Office on _____, 20___ and accorded Application Number _____* and/or filed in the RO/ EP on 09 April, 2007 and accorded International Patent Application Number PCT/US2007/066204*, (2) the patent application(s) identified in (1), (3) all national stages of any international patent application identified in (1), (4) all other patent applications in all countries and regions claiming the priority of the provisional or non-provisional patent application filed in the United States Patent and Trademark Office on **April 11, 2006** and accorded **Application Number 60/791,318** and on **November 22, 2006** and accorded **Application Number 60/866,874**, (5) for all patent applications, all rights of priority based upon the United States patent application identified in (4) in all countries and regions under the Paris Convention for the Protection of Industrial Property, the Inter-American Convention relating to Inventions, Patents, Designs, and Industrial Models and all other international agreements to which the United States now is or hereafter becomes a signatory and, if the United States patent application identified in (4) is a provisional patent application, under 35 USC 119(e) (including the right to file patent applications on said inventions and discoveries in the names of **ASSIGNEES** or their designees or in our names, at their election and in accordance with applicable law in all countries and regions), (6) all continuations and divisions of any United States patent application or international patent application designating the United States identified in (1), any national stages of any international application identified in (1) and any patent applications within the scope of (4) (including further continuations and divisions such as, but not limited to, continuations of continuations and continuations of divisions), ((2)-(4) and (6) hereinafter referred to collectively as "patent applications"), (7) all patents that are granted on any of said patent applications, (8) all registrations and confirmations of, and importation certificates based upon, one or more of said patents and applications for such registrations, confirmations and importation certificates and (9) all reissues, renewals and extensions of said patents, registrations, confirmations and importation certificates, reexamination certificates issued for said patents and supplementary protection certificates based upon said patents and applications for such reissues, renewals, extensions, reexamination certificates and supplementary protection certificates, the same to be held and enjoyed by said **ASSIGNEES** and their successors, assigns and legal representatives to the full ends of the terms for which said patents, registrations, confirmations, importation certificates, reexamination certificates, supplementary protection certificates, reissues, renewals and extensions may be granted, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made.

And we hereby covenant and agree that we will, at any time, (i) upon the request, but at the expense, of **ASSIGNEES** or their successors, assigns or legal representatives execute and deliver all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, patents, registrations, confirmations, importation certificates, reissues, renewals, extensions, reexamination certificates, supplementary protection certificates and applications within the scope of (8) and (9) in **ASSIGNEES** or their successors, assigns or legal representatives, including the execution and procurement of all further documents evidencing this sale, assignment and transfer as may be necessary or desirable for recording the same in the patent office or other intellectual property office, agency or the like of any country or region, (ii) upon the request, but at the expense, of **ASSIGNEES** or their successors, assigns or legal representatives execute all additional patent applications within the scope of (3), (4) and (6) and all applications within the scope of (8) or (9) and (iii) make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of **ASSIGNEES** or their successors, assigns or legal representatives.

*We hereby authorize **ASSIGNEES** and their representatives to insert in this Assignment the filing date(s) and Application Number(s) of said patent application(s) when notified thereof.

cuted this 23 day of March, 2007.

David T Parker L.S.

David Thomas PARKER

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of Middlesex )

On this 23 day of March, 2007, personally appeared before me **David Thomas PARKER** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

Elizabeth Sweeney
Notary Public

Executed this 23 day of March, 2007.

Mohd Seepersaud L.S.

Mohindra SEEPERSAUD

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of Middlesex )

On this 23 day of March, 2007, personally appeared before me **Mohindra SEEPERSAUD** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

Elizabeth Sweeney
Notary Public

30

Executed this 4th day of April, 2007.

Branko Radetich L.S.
**Branko RADETICH**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of Middlesex )

On this 4th day of April, 2007, personally appeared before me **Branko RADETICH** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

Elyabeth Sweeny
Notary Public

Executed this 23 day of March, 2007.

_____ L.S.
**Aregahegn YIFRU**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of Middlesex )

On this 23 day of March 2007, personally appeared before me **Aregahegn YIFRU** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

Elyabeth Sweeny
Notary Public

Executed this 23 day of March, 2007.

R. Prakash L.S.

**Prakash RAMAN**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of Middlesex )

On this 23 day of March, 2007, personally appeared before me **Prakash RAMAN** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

Notary Public

Executed this 23 day of March, 2007.

L.S.

**Jiping FU**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of Middlesex )

On this 23 day of March, 2007, personally appeared before me **Jiping FU** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

Notary Public

Executed this _____ day of_____, 20____.

_____ L.S.
**Michael PATANE**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Michael PATANE** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 23 day of March, 2007.

Rui Zheng _____ L.S.
**Rui ZHENG**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of Middlesex )

On this 23 day of March, 2007, personally appeared before me **Rui ZHENG** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

Elizabeth Sweeney
Notary Public

cuted this _____ day of_____, 20____.

_____ L.S.
**Oliver SIMIC**

**ACKNOWLEDGEMENT**

State of _____ )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Oliver SIMIC** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20____.

_____ L.S.
**Trixi BRANDL**

**ACKNOWLEDGEMENT**

State of _____ )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Trixi BRANDL** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20____.

_____ L.S.
**Pascal RIGOLLIER**

**ACKNOWLEDGEMENT**

State of _____ )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Pascal RIGOLLIER** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 5 day of April, 2007.

Francois Lenoir L.S.
**Francois LENOIR**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of Middlesex )

On this 5 day of April, 2007, personally appeared before me **Francois LENOIR** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

Elizabeth Lowery
Notary Public

# ASSIGNMENT

good and valuable consideration, the receipt and adequacy of which are hereby acknowledged, we

| | | |
|---|---|---|
| David Thomas PARKER | residing at | 541 Bedford Street<br>Lexington, MA 02420 |
| Mohindra SEEPERSAUD | residing at | 3 Colby Street<br>Belmont, MA 02478 |
| Branko RADETICH | residing at | 1 Saint Charles Street, Apt. 4<br>Boston, MA 01720 |
| Aregahegn YIFRU | residing at | 14 Murdock Street, Apt. 2-7<br>Somerville, MA 02145 |
| Prakash RAMAN | residing at | 125 Summer Street<br>Acton, MA 01720 |
| Jiping FU | residing at | 74 Cutter Hill Road<br>Arlington, MA 02474 |
| Michael PATANE | residing at | 273 Forest Street<br>Reading, MA 01867 |
| Rui ZHENG | residing at | 38 Varnum Street<br>Arlington, MA 02474 |
| Oliver SIMIC | residing at | Gundeldingerstrassse 209<br>4053 Basel<br>Switzerland |
| Trixi BRANDL | residing at | Murbachestrasse 27<br>4056 Basel<br>Switzerland |
| Pascal RIGOLLIER | residing at | 4 bis, Avenue de la Première<br>Division Blindée<br>68100 Mulhouse<br>France |
| Francois LENOIR | residing at | 5101 Stearns Hill Road<br>Waltham, MA 02451 |

do hereby sell, assign and transfer to **Novartis AG**, a company organized under the laws of the Swiss Confederation, of Lichtstrasse 35, Basel, Switzerland 4056, and its successors, assigns and legal representatives, all of our right, title and interest for all countries of the world except Austria and to Novartis Pharma GmbH, a company organized under the laws of Austria, of Brunner Strasse 59, 1230 Vienna, Austria, and its successors, assigns and legal representatives, all of our right, title and interest for Austria (Novartis AG and Novartis Pharma GmbH) hereinafter referred to collectively as the "**ASSIGNEES**" in and to (1) all of our inventions and discoveries described in the patent provisional or non-provisional patent application(s) titled

36

**ORGANIC COMPOUNDS AND THEIR USES**

I filed in the United States Patent and Trademark Office on _____, 20___ and accorded Application Number _____* and/or filed in the RO/ EP on 09 April, 2007 and accorded International Patent Application Number PCT/US2007/066204*, (2) the patent application(s) identified in (1), (3) all national stages of any international patent application identified in (1), (4) all other patent applications in all countries and regions claiming the priority of the provisional or non-provisional patent application filed in the United States Patent and Trademark Office on **April 11, 2006** and accorded **Application Number 60/791,318** and on **November 22, 2006** and accorded **Application Number 60/866,874**, (5) for all patent applications, all rights of priority based upon the United States patent application identified in (4) in all countries and regions under the Paris Convention for the Protection of Industrial Property, the Inter-American Convention relating to Inventions, Patents, Designs, and Industrial Models and all other international agreements to which the United States now is or hereafter becomes a signatory and, if the United States patent application identified in (4) is a provisional patent application, under 35 USC 119(e) (including the right to file patent applications on said inventions and discoveries in the names of **ASSIGNEES** or their designees or in our names, at their election and in accordance with applicable law in all countries and regions), (6) all continuations and divisions of any United States patent application or international patent application designating the United States identified in (1), any national stages of any international application identified in (1) and any patent applications within the scope of (4) (including further continuations and divisions such as, but not limited to, continuations of continuations and continuations of divisions), ((2)-(4) and (6) hereinafter referred to collectively as "patent applications"), (7) all patents that are granted on any of said patent applications, (8) all registrations and confirmations of, and importation certificates based upon, one or more of said patents and applications for such registrations, confirmations and importation certificates and (9) all reissues, renewals and extensions of said patents, registrations, confirmations and importation certificates, reexamination certificates issued for said patents and supplementary protection certificates based upon said patents and applications for such reissues, renewals, extensions, reexamination certificates and supplementary protection certificates, the same to be held and enjoyed by said **ASSIGNEES** and their successors, assigns and legal representatives to the full ends of the terms for which said patents, registrations, confirmations, importation certificates, reexamination certificates, supplementary protection certificates, reissues, renewals and extensions may be granted, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made.

And we hereby covenant and agree that we will, at any time, (i) upon the request, but at the expense, of **ASSIGNEES** or their successors, assigns or legal representatives execute and deliver all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, patents, registrations, confirmations, importation certificates, reissues, renewals, extensions, reexamination certificates, supplementary protection certificates and applications within the scope of (8) and (9) in **ASSIGNEES** or their successors, assigns or legal representatives, including the execution and procurement of all further documents evidencing this sale, assignment and transfer as may be necessary or desirable for recording the same in the patent office or other intellectual property office, agency or the like of any country or region, (ii) upon the request, but at the expense, of **ASSIGNEES** or their successors, assigns or legal representatives execute all additional patent applications within the scope of (3), (4) and (6) and all applications within the scope of (8) or (9) and (iii) make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of **ASSIGNEES** or their successors, assigns or legal representatives.

*We hereby authorize **ASSIGNEES** and their representatives to insert in this Assignment the filing date(s) and Application Number(s) of said patent application(s) when notified thereof.

cuted this _____ day of_____, 20_____.

_____ L.S.
**David Thomas PARKER**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **David Thomas PARKER** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Mohindra SEEPERSAUD**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Mohindra SEEPERSAUD** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Branko RADETICH**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Branko RADETICH** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Aregahegn YIFRU**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Aregahegn YIFRU** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Prakash RAMAN**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Prakash RAMAN** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Jiping FU**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Jiping FU** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

10

Executed this 28th day of March, 2007.

L.S.

Michael PATANE

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of Middlesex )

On this 28th day of March, 2007, personally appeared before me **Michael PATANE** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

Notary Public

**Joseph C. Andrade**
**Notary Public**
**My Commission Expires August 23, 2013**
**Commonwealth of Massachusetts**

Executed this _____ day of_____, 20_____.

_____ L.S.

**Rui ZHENG**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Rui ZHENG** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

cuted this _____ day of_____, 20_____.

_____ L.S.
**Oliver SIMIC**

**ACKNOWLEDGEMENT**

State of _____ )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Oliver SIMIC** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Trixi BRANDL**

**ACKNOWLEDGEMENT**

State of _____ )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Trixi BRANDL** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Pascal RIGOLLIER**

**ACKNOWLEDGEMENT**

State of _____ )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Pascal RIGOLLIER** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Francois LENOIR**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Francois LENOIR** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

## ASSIGNMENT

good and valuable consideration, the receipt and adequacy of which are hereby acknowledged, we

| | | |
|---|---|---|
| David Thomas PARKER | residing at | 541 Bedford Street<br>Lexington, MA 02420 |
| Mohindra SEEPERSAUD | residing at | 3 Colby Street<br>Belmont, MA 02478 |
| Branko RADETICH | residing at | 1 Saint Charles Street, Apt. 4<br>Boston, MA 01720 |
| Aregahegn YIFRU | residing at | 14 Murdock Street, Apt. 2-7<br>Somerville, MA 02145 |
| Prakash RAMAN | residing at | 125 Summer Street<br>Acton, MA 01720 |
| Jiping FU | residing at | 74 Cutter Hill Road<br>Arlington, MA 02474 |
| Michael PATANE | residing at | 273 Forest Street<br>Reading, MA 01867 |
| Rui ZHENG | residing at | 38 Varnum Street<br>Arlington, MA 02474 |
| Oliver SIMIC | residing at | Gundeldingerstrassse 209<br>4053 Basel<br>Switzerland |
| Trixi BRANDL | residing at | Murbacherstrasse 27<br>4056 Basel<br>Switzerland |
| Pascal RIGOLLIER | residing at | 4 bis, Avenue de la Première<br>Division Blindée<br>68100 Mulhouse<br>France |
| Francois LENOIR | residing at | 5101 Stearns Hill Road<br>Waltham, MA 02451 |

do hereby sell, assign and transfer to **Novartis AG**, a company organized under the laws of the Swiss Confederation, of Lichtstrasse 35, Basel, Switzerland 4056, and its successors, assigns and legal representatives, all of our right, title and interest for all countries of the world except Austria and to Novartis Pharma GmbH, a company organized under the laws of Austria, of Brunner Strasse 59, 1230 Vienna, Austria, and its successors, assigns and legal representatives, all of our right, title and interest for Austria (Novartis AG and Novartis Pharma GmbH) hereinafter referred to collectively as the "**ASSIGNEES**" in and to (1) all of our inventions and discoveries described in the patent provisional or non-provisional patent application(s) titled

**ORGANIC COMPOUNDS AND THEIR USES**

I filed in the United States Patent and Trademark Office on _____, 20___ and accorded Application Number _____* and/or filed in the RO/ EP _____ on 09 April, 2007 and accorded International Patent Application Number PCT/ US 2007/066 204*, (2) the patent application(s) identified in (1), (3) all national stages of any international patent application identified in (1), (4) all other patent applications in all countries and regions claiming the priority of the provisional or non-provisional patent application filed in the United States Patent and Trademark Office on **April 11, 2006** and accorded **Application Number 60/791,318** and on **November 22, 2006** and accorded **Application Number 60/866,874**, (5) for all patent applications, all rights of priority based upon the United States patent application identified in (4) in all countries and regions under the Paris Convention for the Protection of Industrial Property, the Inter-American Convention relating to Inventions, Patents, Designs, and Industrial Models and all other international agreements to which the United States now is or hereafter becomes a signatory and, if the United States patent application identified in (4) is a provisional patent application, under 35 USC 119(e) (including the right to file patent applications on said inventions and discoveries in the names of **ASSIGNEES** or their designees or in our names, at their election and in accordance with applicable law in all countries and regions), (6) all continuations and divisions of any United States patent application or international patent application designating the United States identified in (1), any national stages of any international application identified in (1) and any patent applications within the scope of (4) (including further continuations and divisions such as, but not limited to, continuations of continuations and continuations of divisions), ((2)-(4) and (6) hereinafter referred to collectively as "patent applications"), (7) all patents that are granted on any of said patent applications, (8) all registrations and confirmations of, and importation certificates based upon, one or more of said patents and applications for such registrations, confirmations and importation certificates and (9) all reissues, renewals and extensions of said patents, registrations, confirmations and importation certificates, reexamination certificates issued for said patents and supplementary protection certificates based upon said patents and applications for such reissues, renewals, extensions, reexamination certificates and supplementary protection certificates, the same to be held and enjoyed by said **ASSIGNEES** and their successors, assigns and legal representatives to the full ends of the terms for which said patents, registrations, confirmations, importation certificates, reexamination certificates, supplementary protection certificates, reissues, renewals and extensions may be granted, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made.

And we hereby covenant and agree that we will, at any time, (i) upon the request, but at the expense, of **ASSIGNEES** or their successors, assigns or legal representatives execute and deliver all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, patents, registrations, confirmations, importation certificates, reissues, renewals, extensions, reexamination certificates, supplementary protection certificates and applications within the scope of (8) and (9) in **ASSIGNEES** or their successors, assigns or legal representatives, including the execution and procurement of all further documents evidencing this sale, assignment and transfer as may be necessary or desirable for recording the same in the patent office or other intellectual property office, agency or the like of any country or region, (ii) upon the request, but at the expense, of **ASSIGNEES** or their successors, assigns or legal representatives execute all additional patent applications within the scope of (3), (4) and (6) and all applications within the scope of (8) or (9) and (iii) make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of **ASSIGNEES** or their successors, assigns or legal representatives.

*We hereby authorize **ASSIGNEES** and their representatives to insert in this Assignment the filing date(s) and Application Number(s) of said patent application(s) when notified thereof.

cuted this _____ day of_____, 20_____.

_____ L.S.
**David Thomas PARKER**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **David Thomas PARKER** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Mohindra SEEPERSAUD**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Mohindra SEEPERSAUD** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Branko RADETICH**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Branko RADETICH** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Aregahegn YIFRU**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Aregahegn YIFRU** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Prakash RAMAN**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Prakash RAMAN** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Jiping FU**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Jiping FU** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Michael PATANE**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Michael PATANE** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.
**Rui ZHENG**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Rui ZHENG** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

ıted this 14th day of March, 2007.

Oliver Simic L.S.

Oliver SIMIC

**ACKNOWLEDGEMENT**

State of _____ )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Oliver SIMIC** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 19th day of March, 2007.

Trixi Brandl L.S.

**Trixi BRANDL**

**ACKNOWLEDGEMENT**

State of _____ )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Trixi BRANDL** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

Executed this 30 day of March, 2007.

Pascal Rigollier L.S.

Pascal RIGOLLIER

**ACKNOWLEDGEMENT**

State of _____ )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Pascal RIGOLLIER** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

eal)

_____
Notary Public

Executed this _____ day of_____, 20_____.

_____ L.S.

**Francois LENOIR**

**ACKNOWLEDGEMENT**

Commonwealth of Massachusetts )
) s.s.:
County of _____ )

On this _____ day of_____, 2007, personally appeared before me **Francois LENOIR** to me known and known by me to be the same person described in and who executed the foregoing Assignment and acknowledged that (s)he executed the same of his (her) own free will for the purpose set forth.

(Seal)

_____
Notary Public

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**Attestation**

I, the undersigned notary public of Basel, Switzerland, certify herewith the authenticity of the signatures of **Mr. Oliver Simic**, German citizen, residing in Basel, Switzerland; of **Ms. Trixi Brandl**, German citizen, residing in Basel, Switzerland; and of **Mr. Pascal Rigollier**, French citizen, residing in Mulhouse, France.

The authenticity of the signatures was established by comparison.

BASEL, Switzerland, this 10th (tenth) day of April 2007 (twothousandandseven).

S. Burkhardt

Leg.Prot.Nr. 113 /2007

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**FOR CERTIFIED COPY**

I, the undersigned Civil Law Notary, Dr. Thomas Gelzer, hereby certify that the document attached heretofore is a true and authentic photocopy of the original.

BASEL, Switzerland, this 24th (twenty-fourth) day of September 2008 (twothousandandeight)

Leg. Prot. 844 /2008

APOSTILLE

(Hague Convention of October 5th, 1961)

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(54) Title: ORGANIC COMPOUNDS AND THEIR USES

(57) Abstract: The present application describes organic compounds that are useful for the treatment, prevention and/or amelioration of human diseases.

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# ORGANIC COMPOUNDS AND THEIR USES

## *Background*

Hepatitis C virus (HCV) is a (+)-sense single-stranded RNA virus that has been implicated as the major causative agent in non-A, non-B hepatitis (NANBH), particularly in blood-associated NANBH (BB-NANBH). NANBH is to be distinguished from other types of viral-induced liver disease, such as hepatitis A virus (HAV), hepatitis B virus (HBV), delta hepatitis virus (HDV), cytomegalovirus (CMV) and Epstein-Barr virus (EBV), as well as from other forms of liver disease such as alcoholism and primary biliar cirrhosis.

Recently, an HCV protease necessary for polypeptide processing and viral replication has been identified, cloned and expressed. (See, *e.g.*, U.S. Pat. No. 5,712,145). This approximately 3000 amino acid polyprotein contains, from the amino terminus to the carboxy terminus, a nucleocapsid protein (C), envelope proteins (E1 and E2) and several non-structural proteins (NS1, 2, 3, 4a, 5a and 5b). NS3 is an approximately 68 kda protein, encoded by approximately 1893 nucleotides of the HCV genome, and has two distinct domains: (a) a serine protease domain consisting of approximately 200 of the N-terminal amino acids; and (b) an RNA-dependent ATPase domain at the C-terminus of the protein. The NS3 protease is considered a member of the chymotrypsin family because of similarities in protein sequence, overall three-dimensional structure and mechanism of catalysis. The HCV NS3 serine protease is responsible for proteolysis of the polypeptide (polyprotein) at the NS3/NS4a, NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions and is thus responsible for generating four viral proteins during viral replication. This has made the HCV NS3 serine protease an attractive target for antiviral chemotherapy.

It has been determined that the NS4a protein, an approximately 6 kda polypeptide, is a co-factor for the serine protease activity of NS3. Autocleavage of the NS3/NS4a junction by the NS3/NS4a serine protease occurs intramolecularly (*i.e.*, cis) while the other cleavage sites are processed intermolecularly (*i.e.*, trans).

HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is

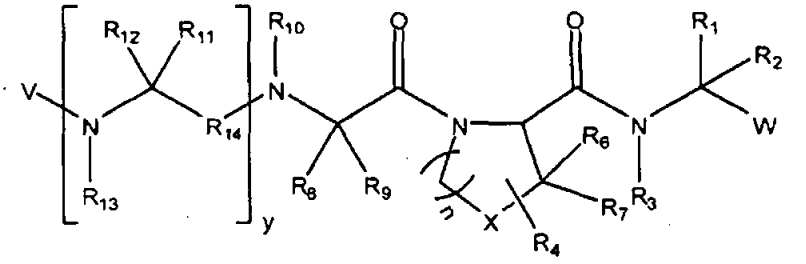
currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV infection. Current data indicates a less than 50% survival rate at four years post cirrhosis diagnosis. Patients diagnosed with localized resectable hepatocellular carcinoma have a five-year survival rate of 10-30%, whereas those with localized unresectable hepatocellular carcinoma have a five-year survival rate of less than 1%.

Current therapies for hepatitis C include interferon-α ($INF_\alpha$) and combination therapy with ribavirin and interferon. See, *e.g.*, Beremguer et al. (1998) Proc. Assoc. Am. Physicians 110(2):98-112. These therapies suffer from a low sustained response rate and frequent side effects. See, *e.g.*, Hoofnagle et al. (1997) N. Engl. J. Med. 336:347. Currently, no vaccine is available for HCV infection.

### *Summary of the Invention*

There remains a need for new treatments and therapies for HCV infection, as well as HCV-associated disorders. There is also a need for compounds useful in the treatment or prevention or amelioration of one or more symptoms of HCV, as well as a need for methods of treatment or prevention or amelioration of one or more symptoms of HCV. Furthermore, there is a need for methods for modulating the activity of HCV-serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

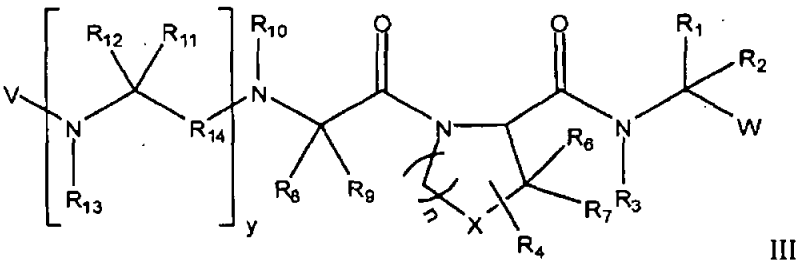
In one aspect, the invention provides compounds of Formula I:



I

and pharmaceutically acceptable salts and stereoisomers thereof.

In another aspect, the invention provides compounds of Formula III:



III

and pharmaceutically acceptable salts and stereoisomers thereof wherein X or $R_6$ and $R_7$, taken in combination, comprise a spirocyclic ring system which is spiro to the ring comprising the X variable.

In one embodiment, the invention provides a method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention, such that the HCV-associated disorder is treated.

In another embodiment, the invention provides a method of treating an HIV infection comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention.

In still another embodiment, the invention provides a method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention. In one embodiment, the compounds of the invention inhibit the activity of the NS2 protease, the NS3 protease, the NS3 helicase, the NS5a protein, and/or the NS5b polymerase. In another embodiment, the interaction between the NS3 protease and NS4A cofactor is disrupted. In yet another embodiment, the compounds of the invention prevent or alter the severing of one or more of the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions of the HCV. In another embodiment, the invention provides a method of inhibiting the activity of a serine protease, comprising the step of contacting said serine protease with a compound of the invention. In another embodiment, the invention provides a method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention, wherein the compound interacts with any target in the HCV life cycle. In one embodiment, the target of the HCV life cycle is

selected from the group consisting of NS2 protease, NS3 protease, NS3 helicase, NS5a protein andNS5b polymerase.

In another embodiment, the invention provides a method of decreasing the HCV RNA load in a subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention.

In another embodiment, the compounds of the invention exhibit HCV protease activity. In one embodiment, the compounds are an HCV NS3-4A protease inhibitor.

In another embodiment, the invention provides a method of treating an HCV-associated disorder in a subject, comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of the invention, and a pharmaceutically acceptable carrier, such that the HCV-associated disorder is treated.

In still another embodiment, the invention provides a method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically effective amount of a compound of the invention, in combination with a pharmaceutically effective amount of an additional HCV-modulating compound, such as interferon or derivatized interferon, or a cytochrome P450 monooxygenase inhibitor, such that the HCV-associated disorder is treated. In one embodiment, the additional HCV-modulating compound is selected from the group consisting of Sch 503034 and VX-950.

In another embodiment, the invention provides a method of inhibiting hepatitis C virus replication in a cell, comprising contacting said cell with a compound of the invention.

In yet another embodiment, the invention provides a packaged HCV-associated disorder treatment, comprising an HCV-modulating compound of the invention, packaged with instructions for using an effective amount of the HCV-modulating compound to treat an HCV-associated disorder.

In certain embodiments, the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

In another embodiment, the invention provides a method of treating HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma,

cryoglobulinaemia, non-Hodgkin's lymphoma, and/or a suppressed innate intracellular immune response in subject in

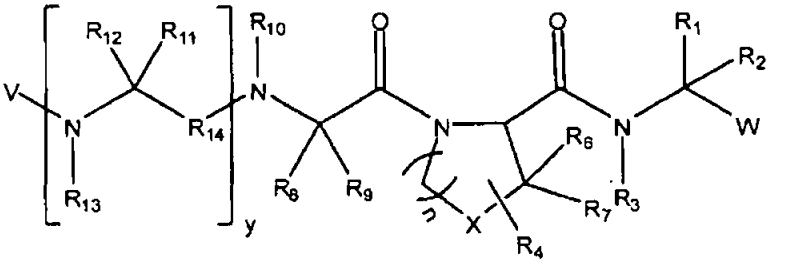
need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of the invention.

In one embodiment, the HCV to be treated is selected of any HCV genotype. In another embodiment, the HCV is selected from HCV genotype 1, 2 and/or 3.

***Detailed Description of the Invention***

This invention is directed to compounds, *e.g.*, peptide compounds, and intermediates thereto, as well as pharmaceutical compositions containing the compounds for use in treatment of HCV infection. This invention is also directed to the compounds of the invention or compositions thereof as protease inhibitors, particularly as serine protease inhibitors, and more particularly as HCV NS3 protease inhibitors. The compounds are particularly useful in interfering with the life cycle of the hepatitis C virus and in treating or preventing an HCV infection or physiological conditions associated therewith. The present invention is also directed to methods of combination therapy for inhibiting HCV replication in cells, or for treating or preventing an HCV infection in patients using the compounds of the invention or pharmaceutical compositions, or kits thereof.

In one aspect, the compounds of the invention are of Formula I:



I

and pharmaceutically acceptable salts and stereoisomers thereof;

wherein

y is 0 or 1;

n is 0, 1 or 2;

$R^{14}$ is C(O) or $SO_2$;

$R^1$, $R^2$, W, $R^{13}$ and V are each, independently, selected from hydrogen or from the group consisting of alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, mono- and di-alkylcarboxamide, arylalkyloxy and heterocyclylamino; each of which may be further independently substituted one or more times with $X^1$ and $X^2$ (or more preferably, each of which may be further substituted with 1, 2, 3, 4, or 5 residues independently selected from $X^1$ and $X^2$); wherein $X^1$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, aryloxy, arylthio, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaralkyl; wherein $X^1$ can be independently substituted with one or more $X^2$ moieties (or more preferably with 1, 2, 3, 4, or 5 $X^2$ moieties) which can be the same or different and are independently selected; wherein $X^2$ is hydroxy, oxo, alkyl, cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, thio, alkylthio, amino, mono- and di-alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyl, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each $X^2$ residue selected to be alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties (or more preferably with 1, 2, 3, 4, or 5 moieties) which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroaralkyl;

W is also selected from the group consisting of C(O)-C(O)H, C(=N-O-$R_{24}$)-C(O)-amine, C(O)-C(O)-amine, C(O)$NR_{24}S(O)_pR_{24}$, C(O)$NR_{24}S(O)_pN(R_{24})_2$ and C(O)-$[C(O)]_a$-heterocycle, wherein the heterocycle may be independently substituted one or more times (or preferably between one and five times) with aryl, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, and $C_{3-6}$-cycloalkyl, wherein a is 0 or 1, wherein each $R_{24}$ is independently selected from hydrogen or from the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, each of which may be independently substituted one or more

times (or preferably between one and five times) with a halogen atom or $C_{1-4}$-alkyl;

V is also selected from the group consisting of $-Q^1-Q^2$, wherein $Q^1$ is absent, C(O), N(H), N($C_{1-4}$-alkyl), C=N(CN), C=N($SO_2CH_3$), C=N-COH-$C_{1-4}$-alkyl, or C=N-COH, and $Q^2$ is hydrogen or is selected from the group consisting of $C_{1-4}$-alkyl, O-$C_{1-4}$-alkyl, $NH_2$, N(H)-$C_{1-4}$-alkyl, N($C_{1-4}$-alkyl)$_2$, $SO_2$-aryl, $SO_2$-$C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl-$C_{0-4}$-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, or $C_{3-6}$-cycloalkyl;

or $R^1$ and $R^2$ may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times (or preferably between one and five times);

$R^3$ is selected from the group consisting of hydrogen, $C_{1-4}$-alkyl and $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl;

X is O, S, N, $NR^5$, $CR^5$ or $CR^5R^{5a}$;

$R^4$ is selected from hydrogen or from the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or $C_{1-4}$-alkyl;

$R^5$ is selected from hydrogen or oxo or from the group consisting of hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heterocycle-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl , $C_{3-8}$-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

$R^{5a}$ is selected from the group consisting of hydrogen, hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl and heteroaryl-$C_{0-4}$-alkyl,

or $R^4$ and $R^5$ may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

or $R^5$ and $R^6$ may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

or $R^5$ and $R^{5a}$ may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide, or two of said 0-4 substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide;

$R^6$, $R^7$, $R^8$, $R^9$, $R^{10}$, $R^{11}$ and $R^{12}$ are each, independently, selected from the group consisting of hydrogen, $C_{1-4}$-alkyl and $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl;

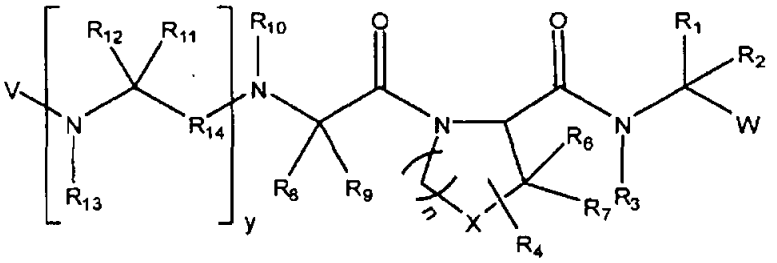
or $R^6$ and $R^7$ may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, mono- and di-$C_{1-4}$-alkylamino, mono- and di-$C_{1-4}$-alkyl-carboxamide, $C_{1-4}$-

alkoxycarbonyl, and phenyl;

or $R^3$ and W may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times (or preferably between one and five times); and

or when y is 0, $R^{10}$ and V may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times (or preferably between one and five times).

In another aspect, the compounds of the invention are of Formula III:



III

and pharmaceutically acceptable salts and stereoisomers thereof;

wherein

y is 0 or 1;

n is 0, 1 or 2;

$R^{14}$ is C(O) or $SO_2$;

$R^1$, $R^2$, W, $R^{13}$ and V are each, independently, selected from hydrogen or from the group consisting of alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, mono- and di-alkylcarboxamide, aralkyloxy and heterocyclylamino; each of which may be further independently substituted one or more times with $X^1$ and $X^2$ (or more preferably, each of which may be further substituted with 1, 2, 3, 4, or 5 residues independently selected from $X^1$ and $X^2$); wherein $X^1$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, aryloxy, arylthio, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaralkyl; wherein $X^1$ can be independently substituted with one or more $X^2$ moieties (or more preferably with 1, 2, 3,

4, or 5 $X^2$ moieties) which can be the same or different and are independently selected; wherein $X^2$ is hydroxy, oxo, alkyl, cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, thio, alkylthio, amino, mono- and di-alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyl, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each $X^2$ residue selected to be alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties (or more preferably with 1, 2, 3, 4, or 5 moieties) which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroaralkyl;

W is also selected from the group consisting of C(O)OH, $C(O)OR_{24}$, C(O)-amine, $P(O)(OR_{24})_2$, C(O)-C(O)OH, $C(=N\text{-}O\text{-}R_{24})$-C(O)-amine, $C(O)NHS(O)_2R_{24}$, $C(O)NHS(O)_2N(R_{24})_2$, C(O)-C(O)-amine, $CONHSO_2$-amine and C(O)-$[C(O)]_a$-heterocycle, wherein the heterocycle may be substituted or unsubstituted, wherein a is 0 or 1, wherein each $R_{24}$ is independently selected from the group consisting of hydrogen, halogen, hydroxyl, formyl, carboxylate, amide, amino, substituted or unsubstituted-$C_{1-4}$-alkyl, substituted or unsubstituted-$C_{1-4}$-alkoxy, substituted or unsubstituted-$C_{1-4}$-alkanoyl, substituted or unsubstituted-$C_{1-4}$-alkoxycarbonyl, substituted or unsubstituted-$C_{1-4}$-alkanoyloxy, substituted or unsubstituted mono- and di-$C_{1-4}$-alkylamino, substituted or unsubstituted-$C_{3-6}$cycloalkyl-$C_{0-4}$alkyl, substituted or unsubstituted aryl-$C_{0-4}$alkyl, and substituted or unsubstituted heterocycle-$C_{0-4}$alkyl;

V is also selected from the group consisting of $-Q^1$-$Q^2$, wherein $Q^1$ is absent, C(O), N(H), N($C_{1-4}$-alkyl), C=N(CN), $C=N(SO_2CH_3)$, C=N-COH-$C_{1-4}$-alkyl, or C=N-COH, and $Q^2$ is hydrogen or is selected from the group consisting of $C_{1-4}$-alkyl, O-$C_{1-4}$-alkyl, $NH_2$, N(H)-$C_{1-4}$-alkyl, N($C_{1-4}$-alkyl)$_2$, $SO_2$-aryl, $SO_2$-$C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl-$C_{0-4}$-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, or $C_{3-6}$-cycloalkyl;

or $R^1$ and $R^2$ may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further

substituted one or more times (or preferably between one and five times);

$R^3$ is selected from the group consisting of hydrogen, $C_{1-4}$-alkyl and $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl;

X is $CR^5R^{5a}$;

$R^4$ represents 0-4 substituents, each of which is independently selected from hydrogen or from the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or $C_{1-4}$-alkyl;

$R^5$ is selected from hydrogen or oxo or the group consisting of hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heterocycle-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl , $C_{3-8}$-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

$R^{5a}$ is selected from the group consisting of hydrogen, hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl and heteroaryl-$C_{0-4}$-alkyl,

or $R^4$ and $R^5$ may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

or $R^5$ and $R^{5a}$ may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide, or two of said 0-4 substitutents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-

alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide;

$R^6$ and $R^7$ are each, independently, selected from the group consisting of hydroxy, amino, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, and mono- and di-$C_{1-4}$alkylamino, and $C_{3-6}$cycloalkyl$C_{0-4}$alkyl;

$R^8$, $R^9$, $R^{10}$, $R^{11}$ and $R^{12}$ are each, independently, selected from the group consisting of hydrogen, $C_{1-4}$-alkyl and $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl;

or $R^6$ and $R^7$ may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, mono- and di-$C_{1-4}$-alkylamino, mono- and di-$C_{1-4}$-alkyl-carboxamide, $C_{1-4}$-alkoxycarbonyl, and phenyl;

wherein at least one of $R^5$ and $R^{5a}$ or $R^6$ and $R^7$, taken in combination, form a spirocyclic ring having at least one spirocyclic ring substituent;

or $R^3$ and W may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times (or preferably between one and five times); and

or when y is 0, $R^{10}$ and V may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times (or preferably between one and five times).

In one embodiment of fomula I, y is 0 or 1;

n is 0 or 1;

$R^{14}$ is C(O) or $SO_2$

$R^1$ is selected from the group consisting of H and $C_{1-4}$-alkyl;

$R^2$ is selected from the group consisting of $C_{1-4}$-alkyl, $C(O)C_{1-4}$-alkyl, $C(O)OC_{1-4}$-alkyl, and $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl;

or $R^1$ and $R^2$ together form a cyclopropane ring;

W is also selected from the group consisting of C(O)-C(O)H, $C(=N\text{-}O\text{-}R_{24})$-C(O)-amine, C(O)-C(O)-amine and $C(O)\text{-}[C(O)]_a$-heterocycle, wherein the heterocycle may be independently substituted one or more times (or preferably between one and five times) with aryl, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, and $C_{3-6}$-cycloalkyl, wherein a is 0 or 1, wherein each $R_{24}$ is independently selected from hydrogen or from the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or $C_{1-4}$-alkyl;

$R^3$ is selected from the group consisting of H and $C_{1-4}$-alkyl;

X is O, $NR^5$ or $CR^5R^{5a}$;

$R^4$ is selected from hydrogen or from the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or $C_{1-4}$-alkyl;

$R^5$ is selected from hydrogen or oxo or the group consisting of hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heterocycle-$C_{0-4}$-alkyl and heteroaryl-$C_{0-4}$-alkyl, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

$R^{5a}$ is selected from the group consisting of hydrogen, hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl and heteroaryl-$C_{0-4}$-alkyl,

or $R^4$ and $R^5$ may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be

substituted with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

or $R^5$ and $R^{5a}$ may together form a spirocarbocyclic saturated ring having between 3 and 6 carbon ring atoms which is optionally substituted by 0-2 substituents selected from halogen, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{1-6}$-alkoxy, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, phenyl-$C_{0-4}$-alkyl, naphthyl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, or two substituents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or $C_{1-4}$-alkyl groups;

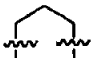
$R^8$, $R^{10}$ and $R^{11}$ are each, independently, selected from the group consisting of H and $C_{1-4}$-alkyl;

$R^6$, $R^7$ and $R^{13}$ is H;

$R^9$ and $R^{12}$ are each, independently, selected from the group consisting of hydrogen, $C_{1-4}$-alkyl and $C_{3-6}$-cycloalkyl; and

V is also selected from the group consisting of $-Q^1$-$Q^2$, wherein $Q^1$ is absent, C(O), N(H), N($C_{1-4}$-alkyl), C=N(CN), C=N($SO_2CH_3$), C=N-COH-$C_{1-4}$-alkyl, or C=N-COH, and $Q^2$ is hydrogen or is selected from the group consisting of $C_{1-4}$-alkyl, O-$C_{1-4}$-alkyl, $NH_2$, N(H)-$C_{1-4}$-alkyl, N($C_{1-4}$-alkyl)$_2$, $SO_2$-aryl, $SO_2$-$C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl-$C_{0-4}$-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, or $C_{3-6}$-cycloalkyl;

or $R^3$ and W can together form a 6-membered ring of the formula II:



II

wherein formula II may be further substituted;

or when y is 0, $R^{10}$ and V can form a cyclopropyl ring that may be further substituted by an amide group.

In another embodiment of Formula I or Formula III, $R^{14}$ is C(O).

In yet another embodiment of Formula I or Formula III, y is 0, and $R^{10}$ and V form a cyclopropyl ring that is substituted with C(O)N(H)-pyrazine.

In still another embodiment of Formula I, wherein $R^4$, $R^6$ and $R^7$ are hydrogen, and $R^5$ is aryl-$C_{0-3}$-alkyl, -O-heteroaryl, or heteroaryl-$C_{0-3}$-alkyl, wherein aryl and heteroaryl may be independently substituted one or more times (or preferably between

one and five times) with a halogen atom, aryl, trihalomethyl, $C_{3-6}$-cycloalkyl or $C_{1-4}$-alkyl.

In one embodiment of Formula I, n is 1, and $R^4$ and $R^5$ together form the following fused ring systems:

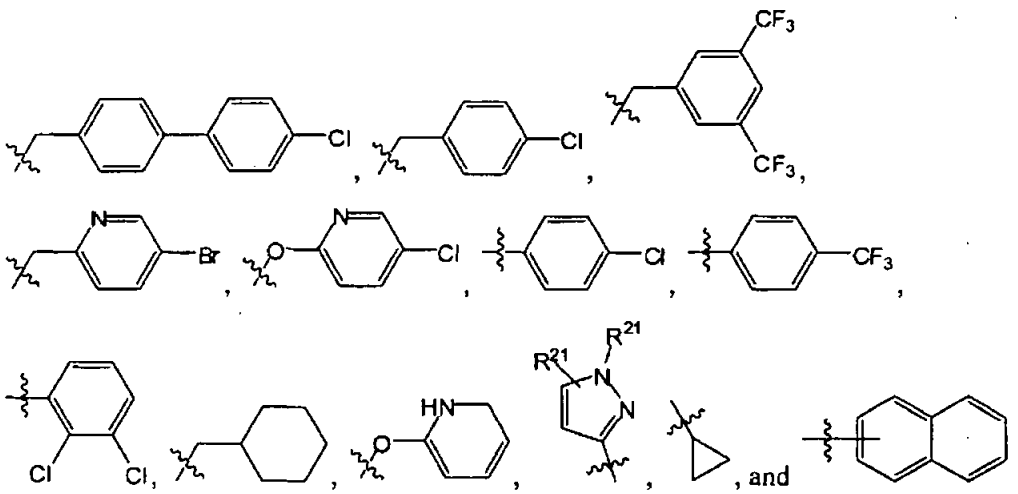


wherein $R^{18}$ is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and $C_{1-4}$-alkyl.

In another embodiment of Formula I, $R^5$ is selected from the group consisting of piperidine, phenyl, -O-pyridinyl and $CH_2$-pyridinyl, wherein the phenyl and pyridinyl groups may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or $C_{1-4}$-alkyl.

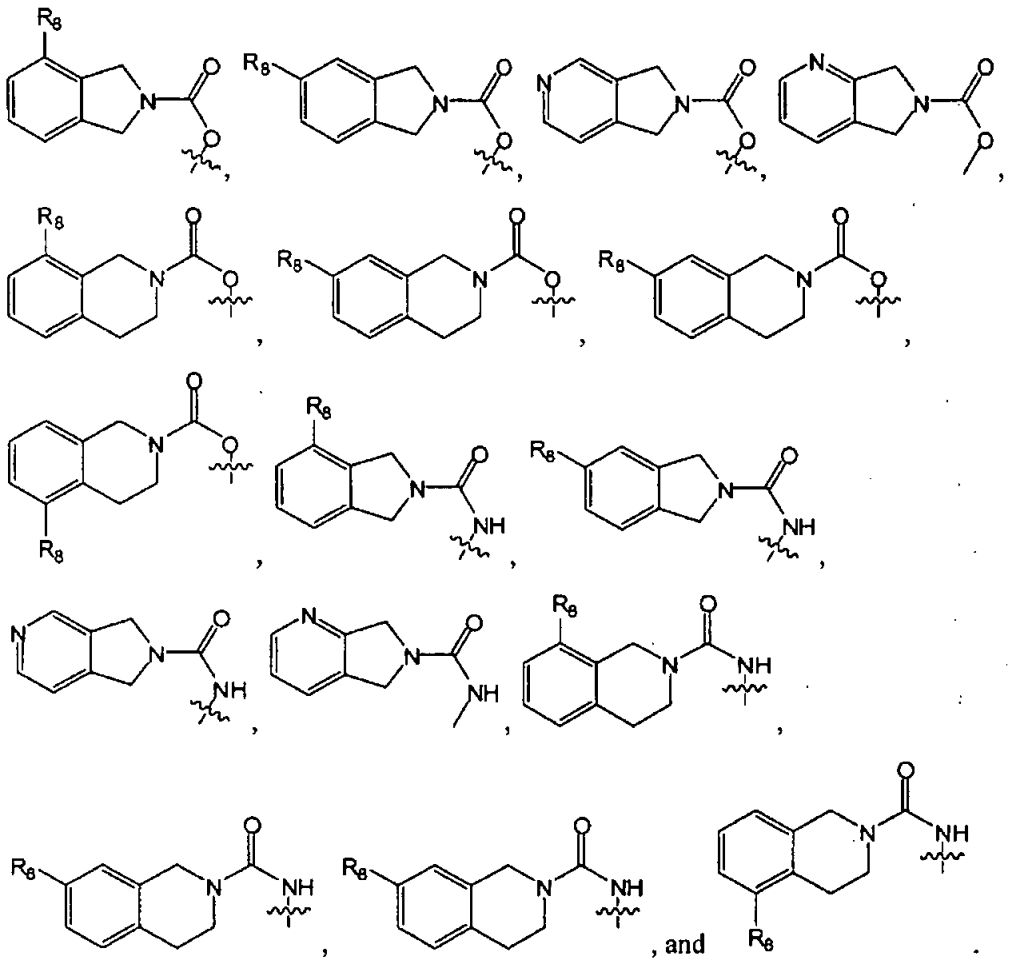
In yet another embodiment of Formula I, $R^5$ is 5-chloro-pyridin-2-yl.

In still another embodiment of Formula I, $R^5$ is selected from the group consisting of

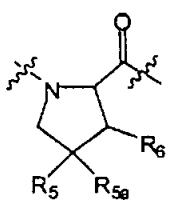


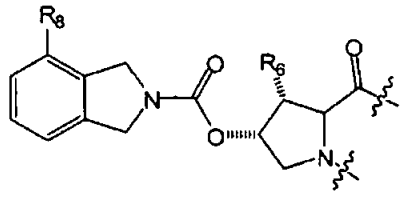
wherein $R^{21}$ is independently selected from the group consisting of $C_{1-4}$-alkyl and aryl.

Yet other compounds of Formula I or Formula III include those compounds in which X is $CR_{5a}$, $R_{5a}$ is hydrogen or methyl, and $R_5$ is a residue selected from the group consisting of:



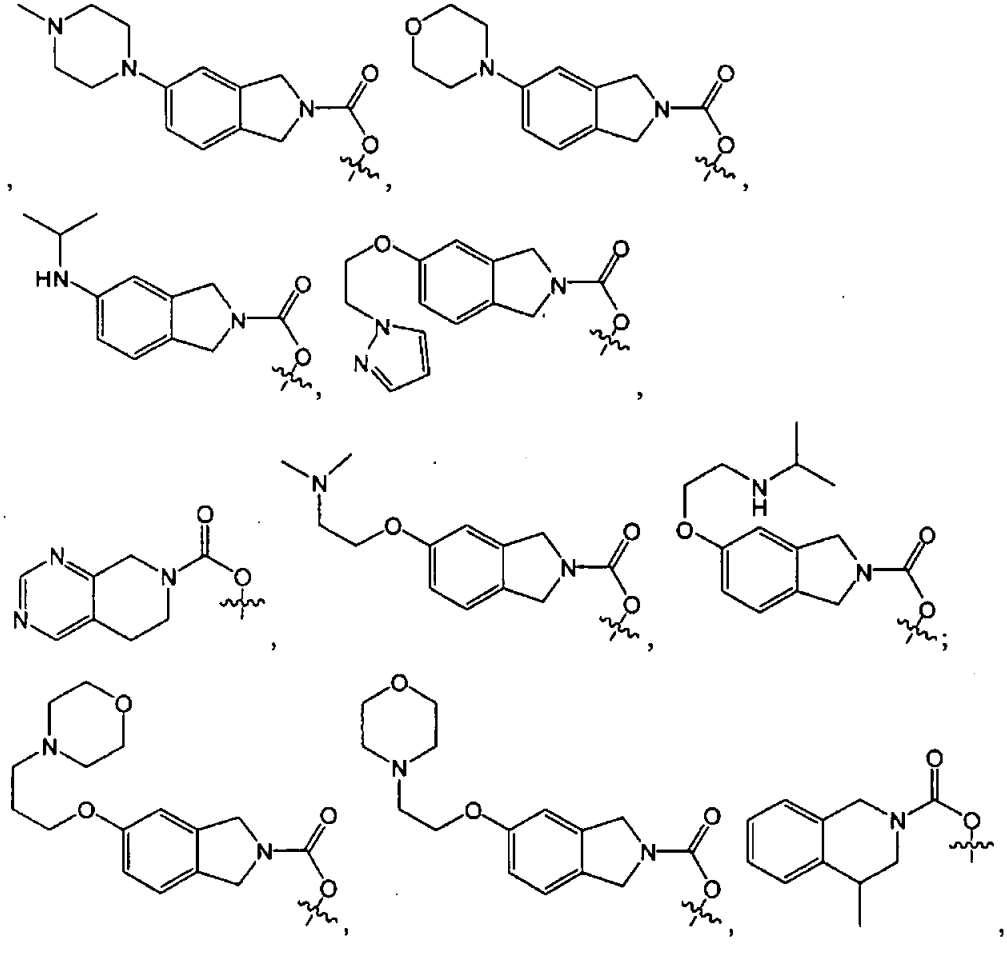
wherein $R_8$ is selected from hydrogen, methyl, ethyl, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-fluoromethoxy, fluoro, and chloro.

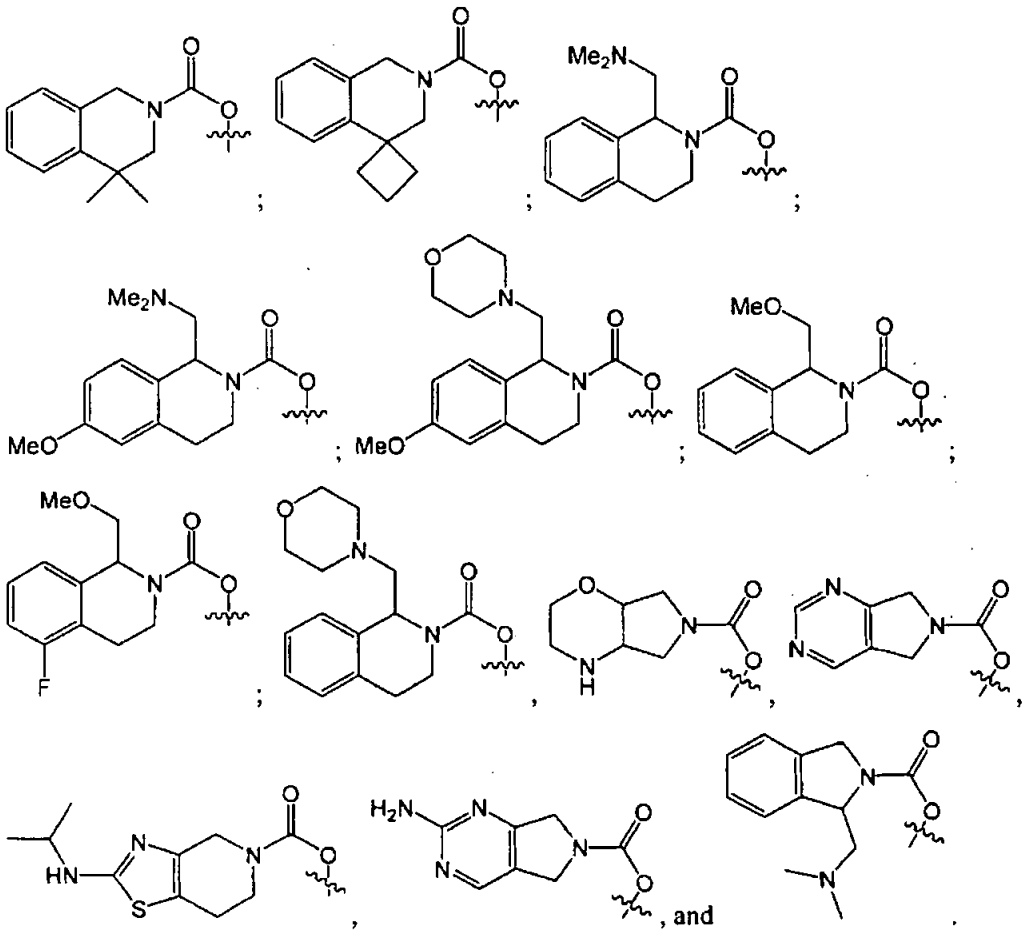
In still other compounds of Formula I or Formula III include those compounds in which the residue  is a residue of the formula:



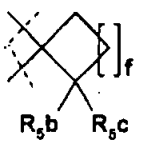
wherein wherein $R_6$ is hydrogen, methyl, ethyl, and mono-, di-, and tri-fluoromethyl; $R_8$ is selected from $R_8$ is selected from hydrogen, methyl, ethyl, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-fluoromethoxy, fluoro, and chloro.

Still other compounds of Formula I or Formula III include those compounds in which X is $CR_{5a}$, $R_{5a}$ is hydrogen or methyl, and $R_5$ is a residue selected from the group consisting of:





In still other embodiments, compounds of Formula I include those compounds in which $CR^5R^{5a}$, when taken in combination, form a spirocyclic 3 to 6 member carbocyclic ring. Certain spirocyclic rings include groups of the formula:



wherein

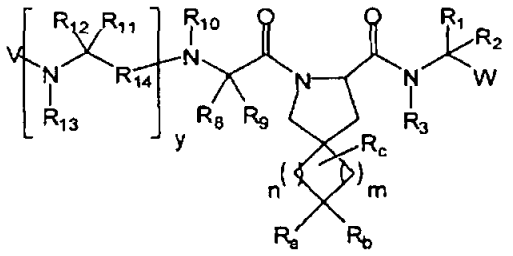
f is 0, 1, 2, 3, 4 or 5;

$R_{5b}$ and $R_{5c}$ are independently selected from hydrogen halogen, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{1-6}$-alkoxy, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, phenyl-$C_{0-4}$-alkyl, naphthyl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, or two substituents taken together form a fused or spirocyclic

3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or $C_{1-4}$-alkyl groups.

In still other embodiments, compounds of Formula I include those compounds in which X is $CR^5R^{5a}$, $R^4$ is hydrogen, and $R^5$ and $R^{5a}$ taken in combination form a 3 to 6 member spirocyclic carbocycle substituted with 0-2 substituents selected from halogen, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{1-6}$-alkoxy, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, phenyl-$C_{0-4}$-alkyl, naphthyl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, or two substituents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or $C_{1-4}$-alkyl groups.

Certain compounds of Formula I include those compounds of the formula:



wherein

m and n are 0 or 1 such that a sum of m and n equals 1 or 2;

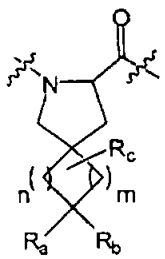
$R_a$ is hydrogen, $C_{1-4}$alkyl, or phenyl;

$R_b$ is hydrogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy-$C_{0-4}$alkyl, mono- and di-$C_{1-4}$alkylamino$C_{0-4}$alkyl, mono- and di-$C_{1-4}$alkyl carboxamide, $C_{1-4}$alkanoyl, $C_{1-4}$alkoxycarbonyl, or phenyl

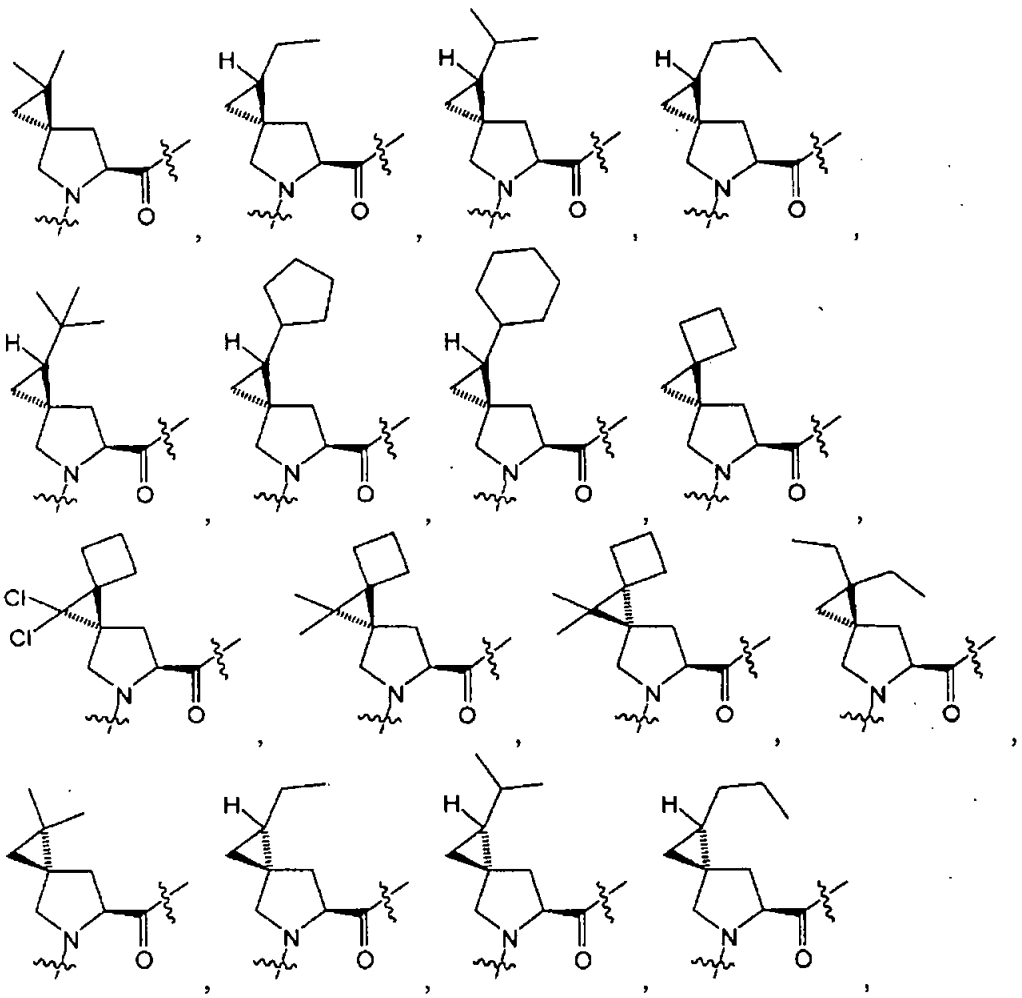
or $R_a$ and $R_b$ taken together form a fused or spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, and phenyl; and

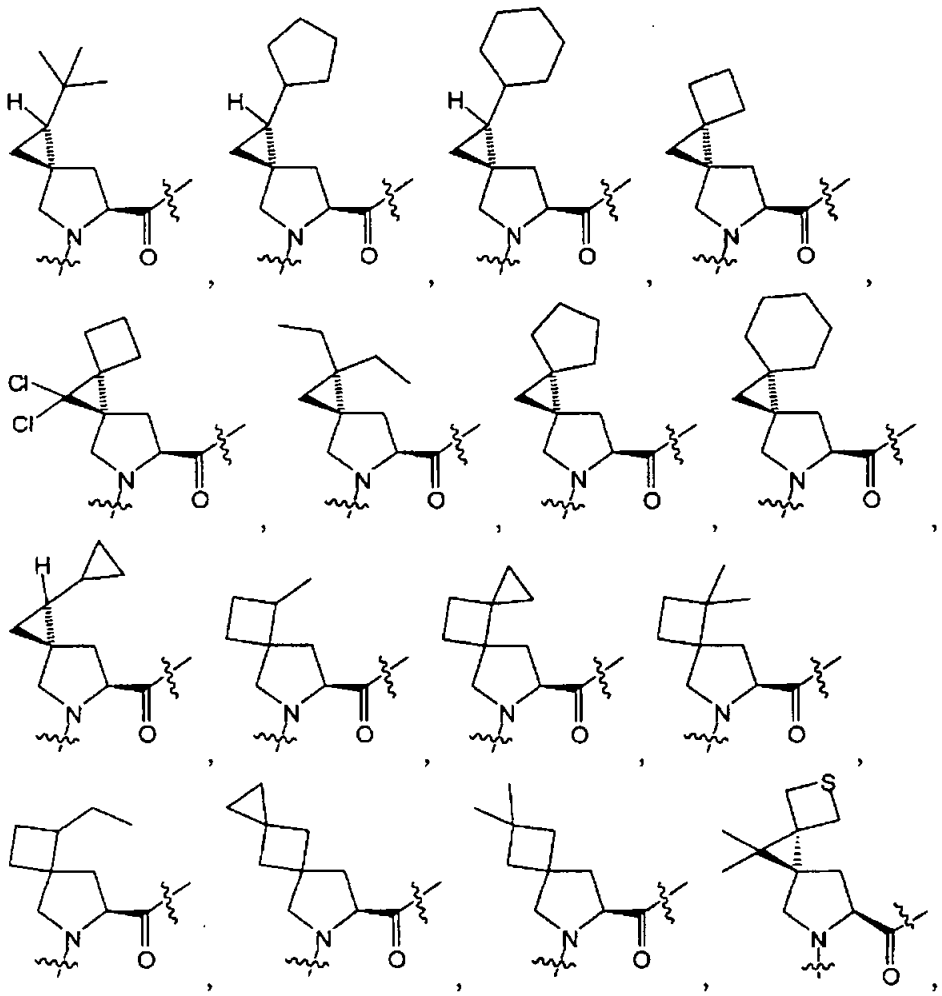
$R_c$ represents 0 to 4 substituents which are independently selected at each occurrence of $R_c$ from the group consisting of halogen, $C_{1-4}$alkyl, and phenyl, or two *geminal* $R_c$ substituents, taken in combination form a 3 to 6 member spirocyclic ring.

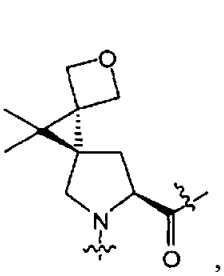
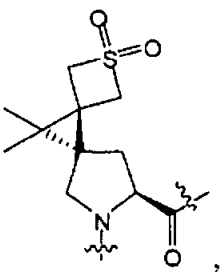
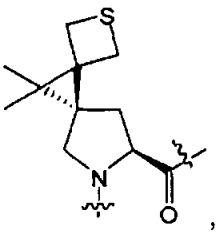
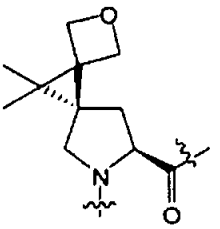
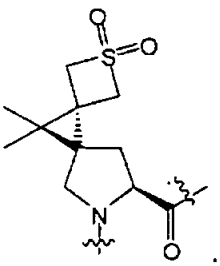
In certain other embodiments, compounds of Formula I include those compounds in which the divalent residue:



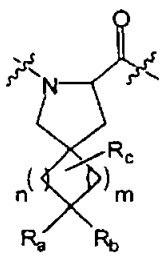
is selected from the group consisting of:



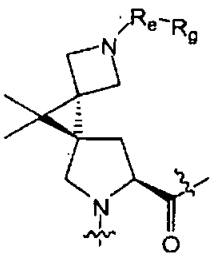
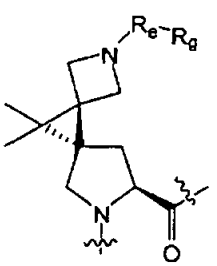






and


In certain other embodiments, compounds of Formula I include those compounds in which the divalent residue:



is selected from the group consisting of:

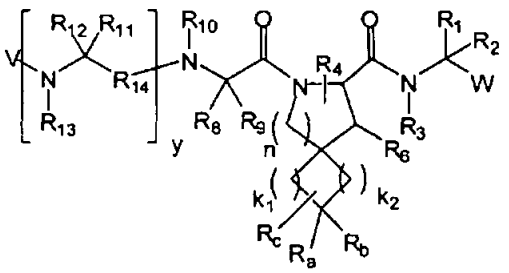

and


wherein $R_e$ is absent, C(O), or $S(O)_2$; and $R_g$ is selected hydrogen or selected from the group consisting of $C_{1-6}$alkyl, aryl$C_{0-4}$alkyl, heteroaryl$C_{0-4}$alkyl, heterocyclyl$C_{0-4}$alkyl, and $C_{3-7}$cycloalkyl$C_{0-4}$alkyl, each of which is substituted with 0 to 4 independently selected substituents selected from the group consisting of cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl,

$C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide.

In certain embodiments, compounds of Formula III include those compounds in which $R^5$ and $R^{5a}$, taken in combination, form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which spirocyclic ring is substituted with a spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, and wherein each of the spirocyclic rings has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide.

In another embodiment, compounds of Formula III include compounds of the formula:



wherein

$k_1$ and $k_2$ are 0 or 1 such that a sum of $k_1$ and $k_2$ equals 1 or 2;

$R_a$ and $R_b$ taken together form a spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, and phenyl;

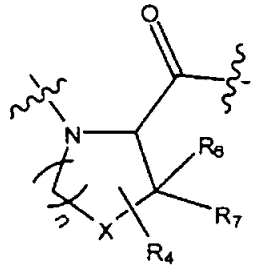
$R_c$ represents 0 to 2 substituents which are independently selected at each occurrence of

$R_c$ from the group consisting of halogen, $C_{1-4}$alkyl, and phenyl, or two *geminal* $R_c$ substituents, taken in combination form a 3 to 6 member spirocyclic ring;

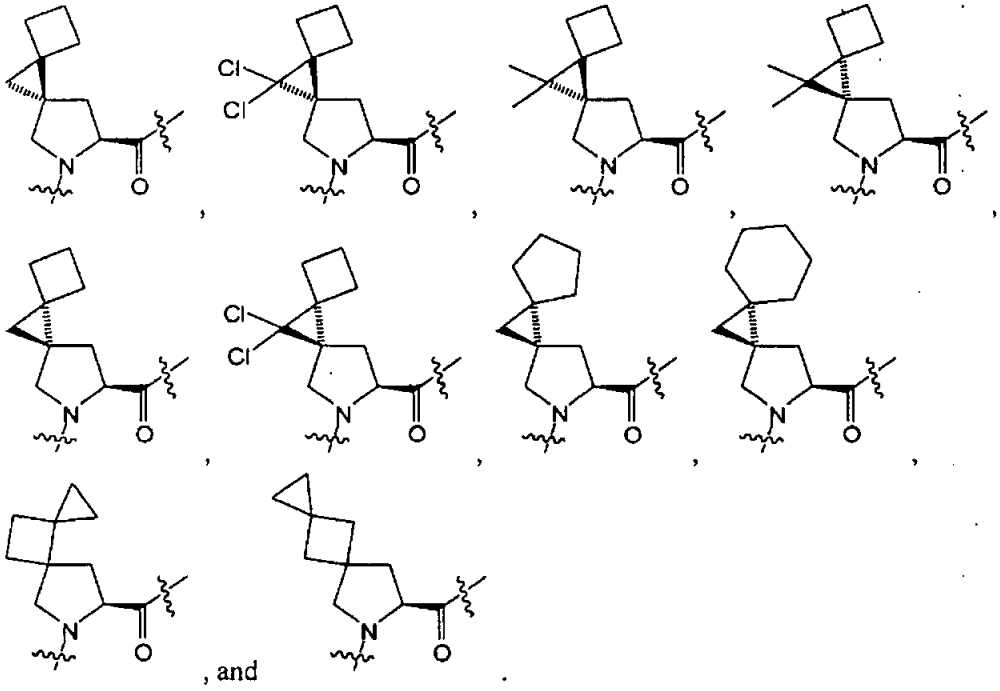
$R_4$ represents 0, 1, or 2 substituents each of which is independently selected from H and $C_{1-4}$-alkyl; and

$R_6$ is hydrogen or $C_{1-4}$alkyl.

In still another aspect, compounds of Formula III include those compounds in which the divalent residue:



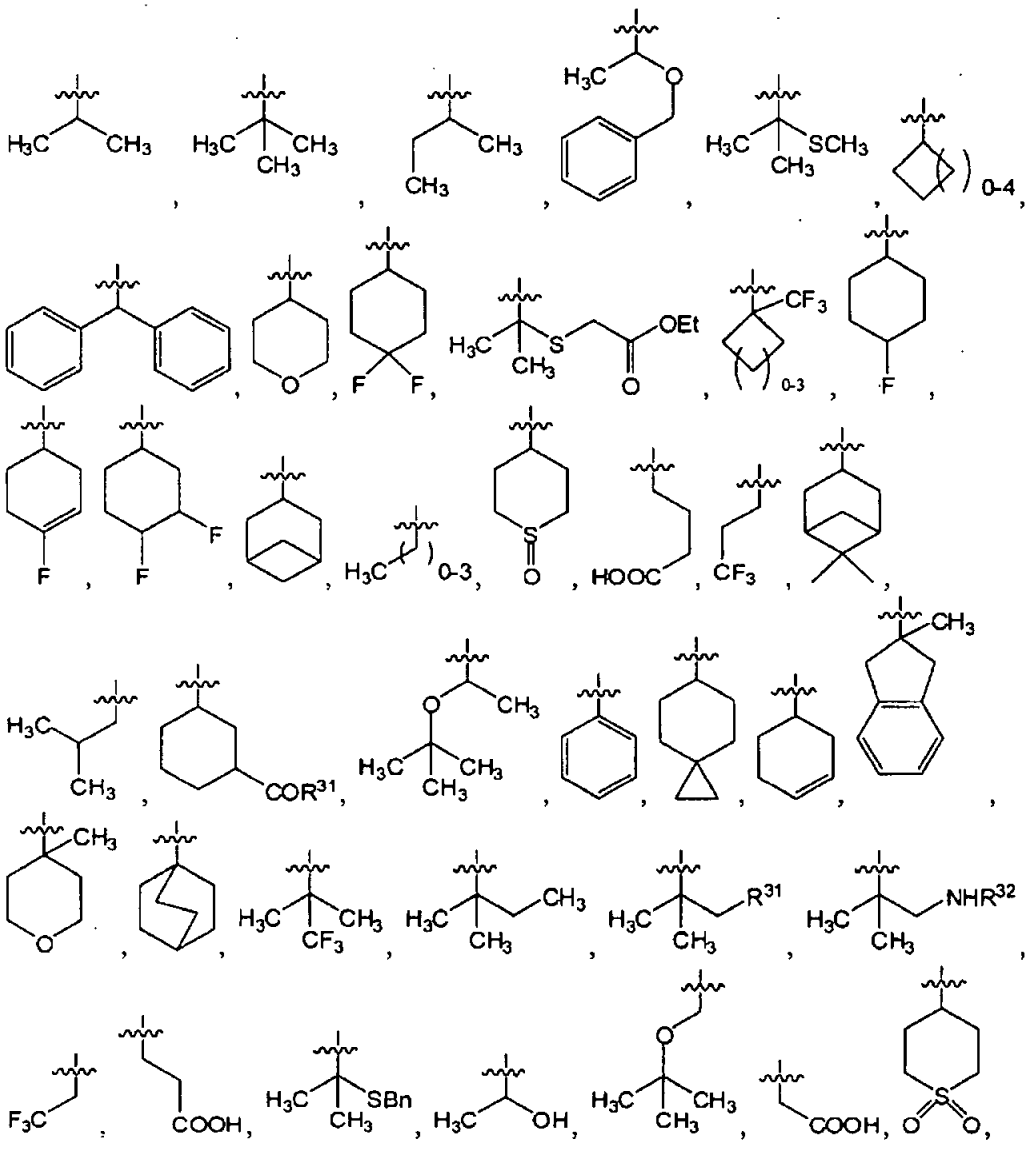
is selected from the group consisting of:

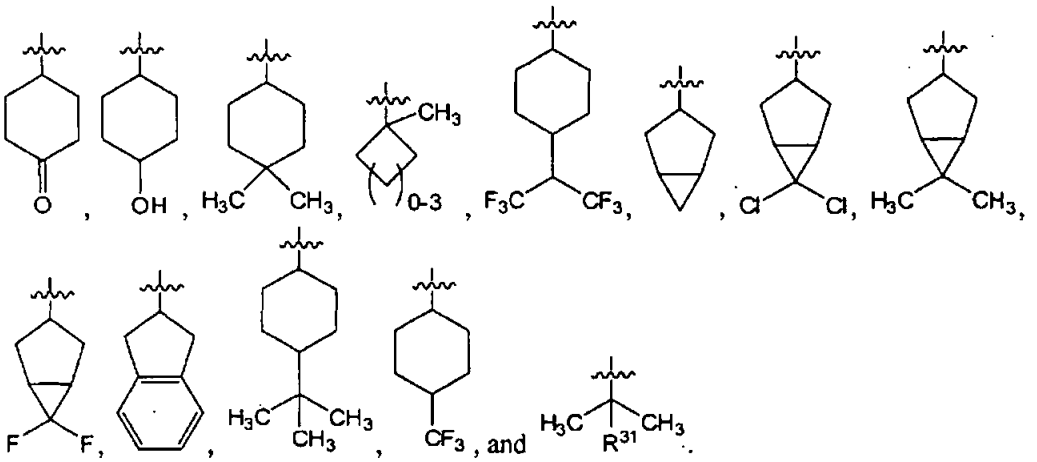


, and

In yet other embodiments, compounds having the structure of Formula I or

Formula III have substituents at $R^6$, $R^9$, $R^{11}$, and $R^{12}$ which are each, independently, selected from the group consisting of:

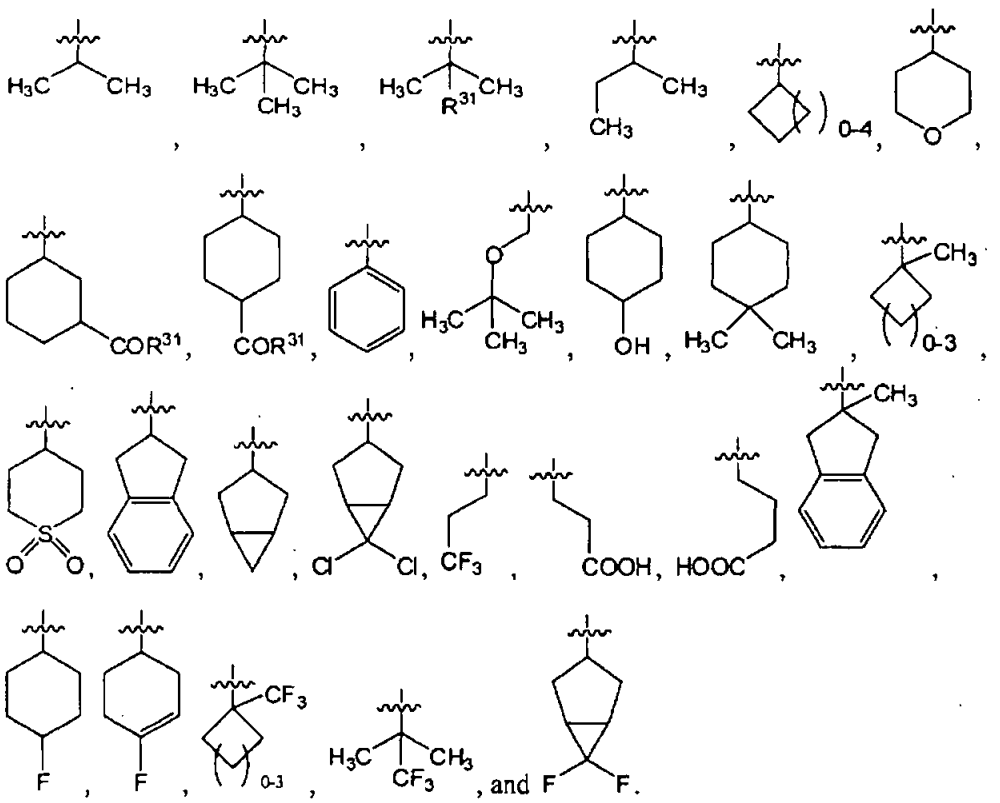




wherein $R^{31}$ is hydroxy or $C_{1-6}$alkoxy; and

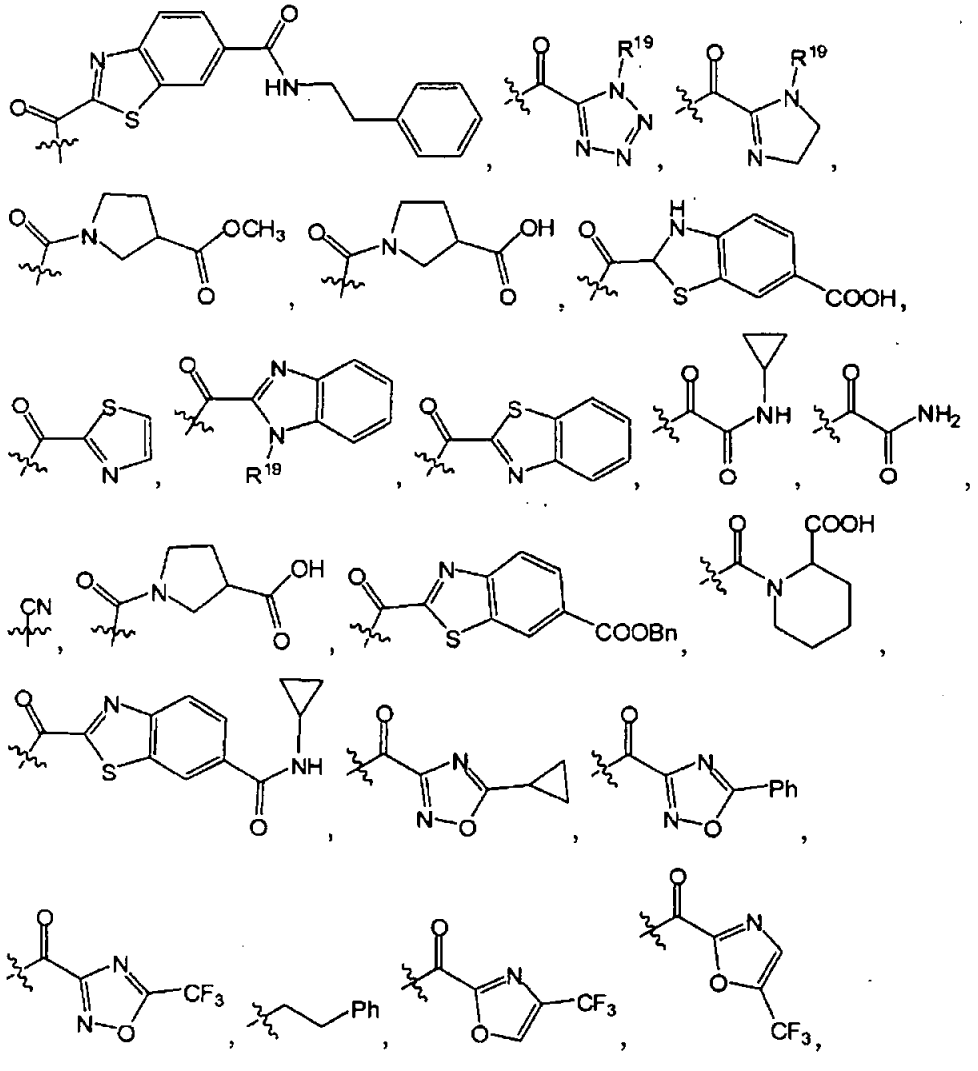
$R^{32}$ is hydrogen, acetyl, C(O)O$^t$Bu, or C(O)N(H)$^t$Bu.

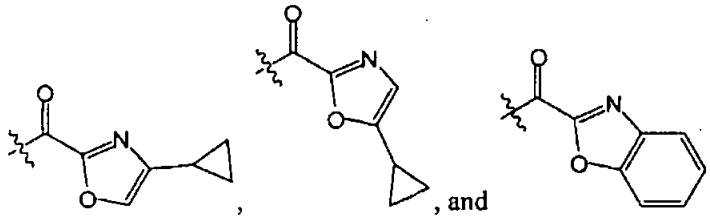
In certain other embodiments, compounds having the structure of Formula I or Formula III, are substituted at $R^3$ with a substituent selected from the group consisting of:



In one embodiment of Formula I or Formula III, W is selected from the group consisting of C(O)-C(O)$NH_2$, C(O)-C(O)N(H)-cyclopropyl, C(O)-benzothiazole, C(O)-benzoimidazole, C(O)-oxazole, C(O)-imidazole, and C(O)-oxadiazole, wherein the benzothiazole, benzoimidazole, oxazole and oxadiazole groups may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, $C_{3-6}$-cycloalkyl or $C_{1-4}$-alkyl.

In another embodiment of Formula I or Formula III, W is selected from the group consisting of





wherein $R^{19}$ is selected from the group consisting of hydrogen, aryl, trihalomethyl, and $C_{1-4}$-alkyl.

In yet another embodiment of Formula I or Formula III, $R^2$ is selected from the group consisting of propyl and $(CH_2)_2$-cyclobutyl.

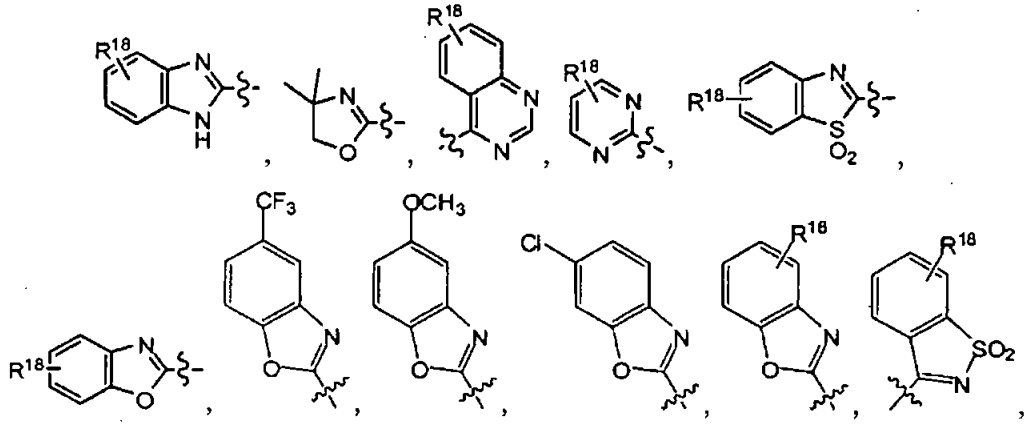
In still another embodiment of Formula I or Formula III, $R^{11}$ is H and $R^{12}$ is $C_{3-6}$-cycloalkyl.

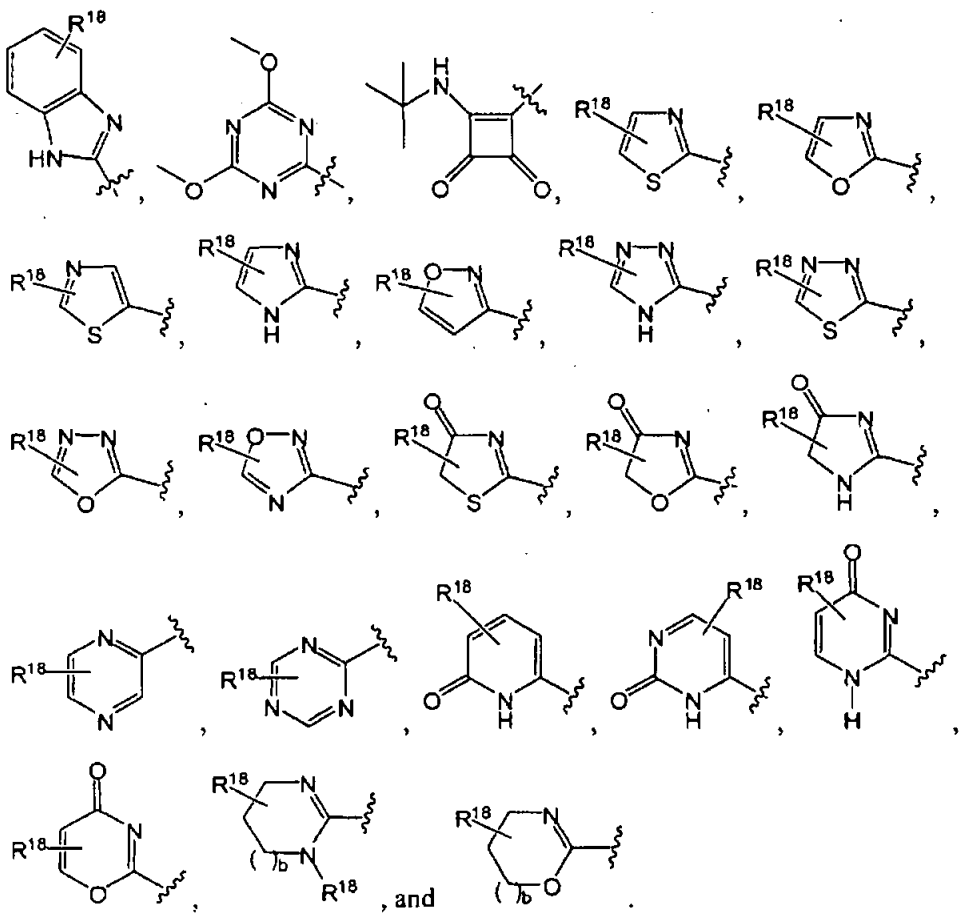
In one embodiment of Formula I or Formula III, $R^{12}$ is cyclohexyl.

In another embodiment of Formula I or Formula III, V is selected from the group consisting of C(O)-N(H)-*t*-butyl.

In yet another embodiment of Formula I or Formula III, V is $C(O)-R^{20}$, wherein $R^{20}$ is selected from the group consisting of $C_{3-6}$-cycloalkyl, phenyl, pyrazine, benzoxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, $CF_3$, $C_{1-4}$-alkyl or $C_{3-6}$-cycloalkyl.

In still another embodiment of Formula I or Formula III, V is $R^{20}$ or $C(O)-R^{20}$, wherein $R^{20}$ is selected from the group consisting of

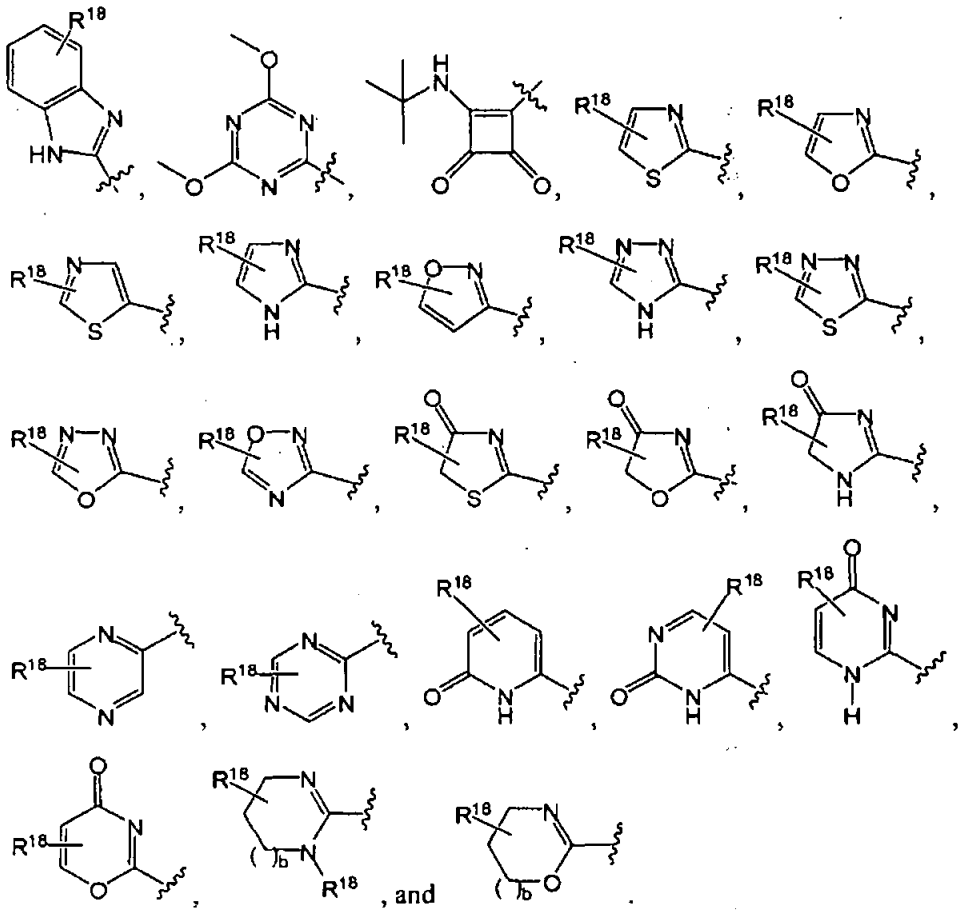




wherein b is 0, 1, or 2; and $R_{18}$ is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and $C_{1-4}$-alkyl.

In another embodiment of Formula I or Formula III, V is selected from the group consisting of $C_{3-6}$-cycloalkyl, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, $CF_3$, $C_{1-4}$-alkyl or $C_{3-6}$-cycloalkyl.

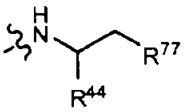
In certain embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula $-C(O)-R^{20}$, wherein $R^{20}$ is a residue of the formula (i):

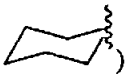


wherein b is 0, 1, or 2; and $R_{18}$ is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and $C_{1-4}$-alkyl.

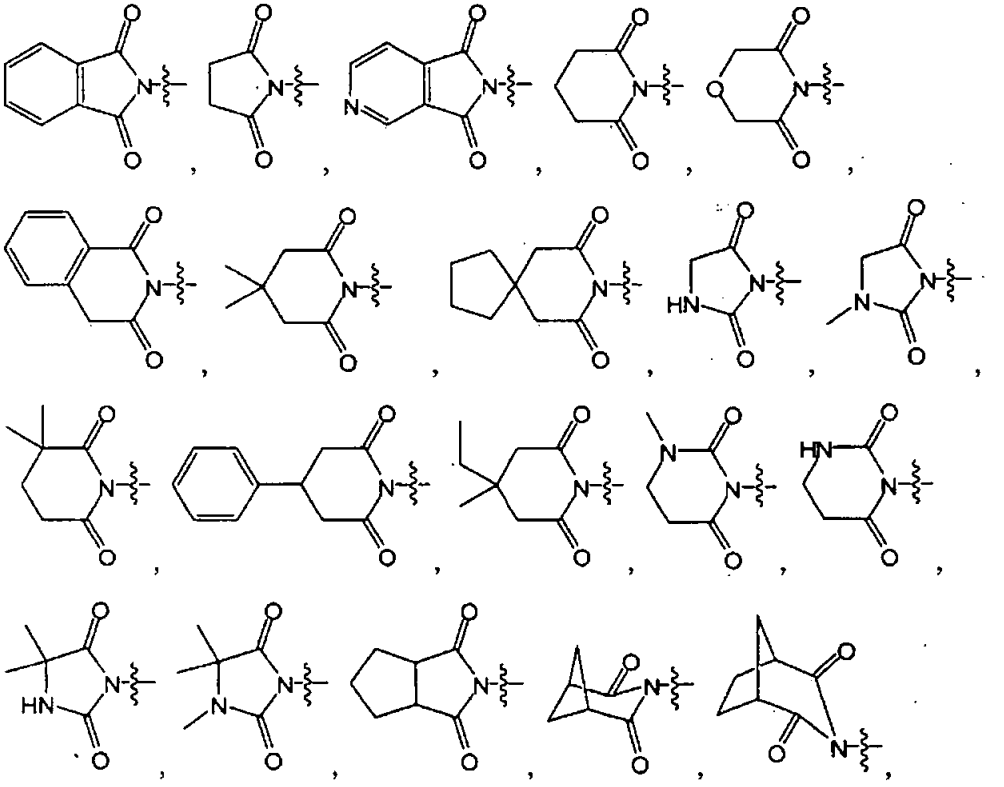
In another embodiment of Formula I or Formula III, V is selected from the group consisting of $C_{3-6}$-cycloalkyl, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, $CF_3$, $C_{1-4}$-alkyl or $C_{3-6}$-cycloalkyl.

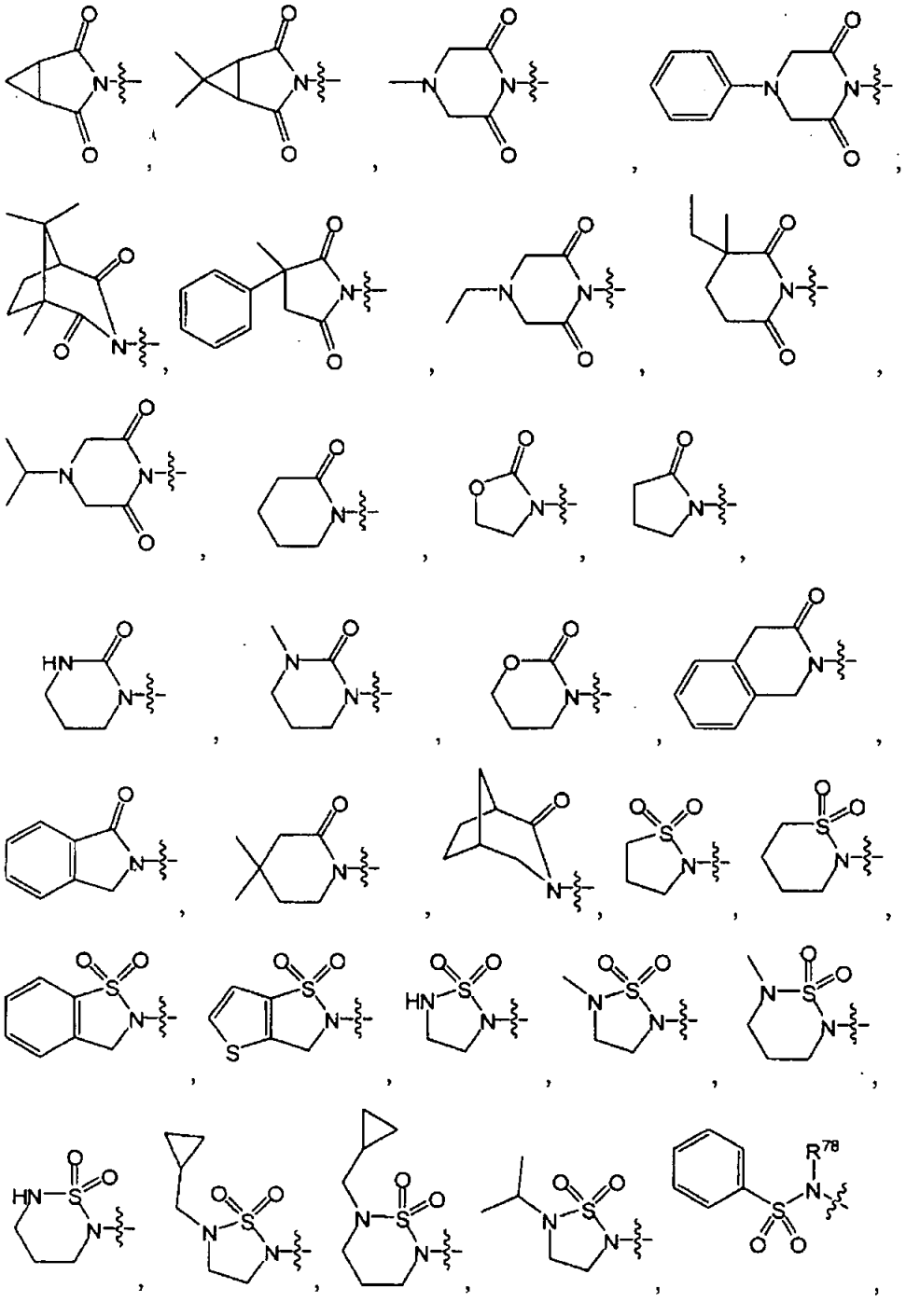
In certain embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula $-C(O)-R^{20}$, wherein $R^{20}$ is a residue of the formula (i):

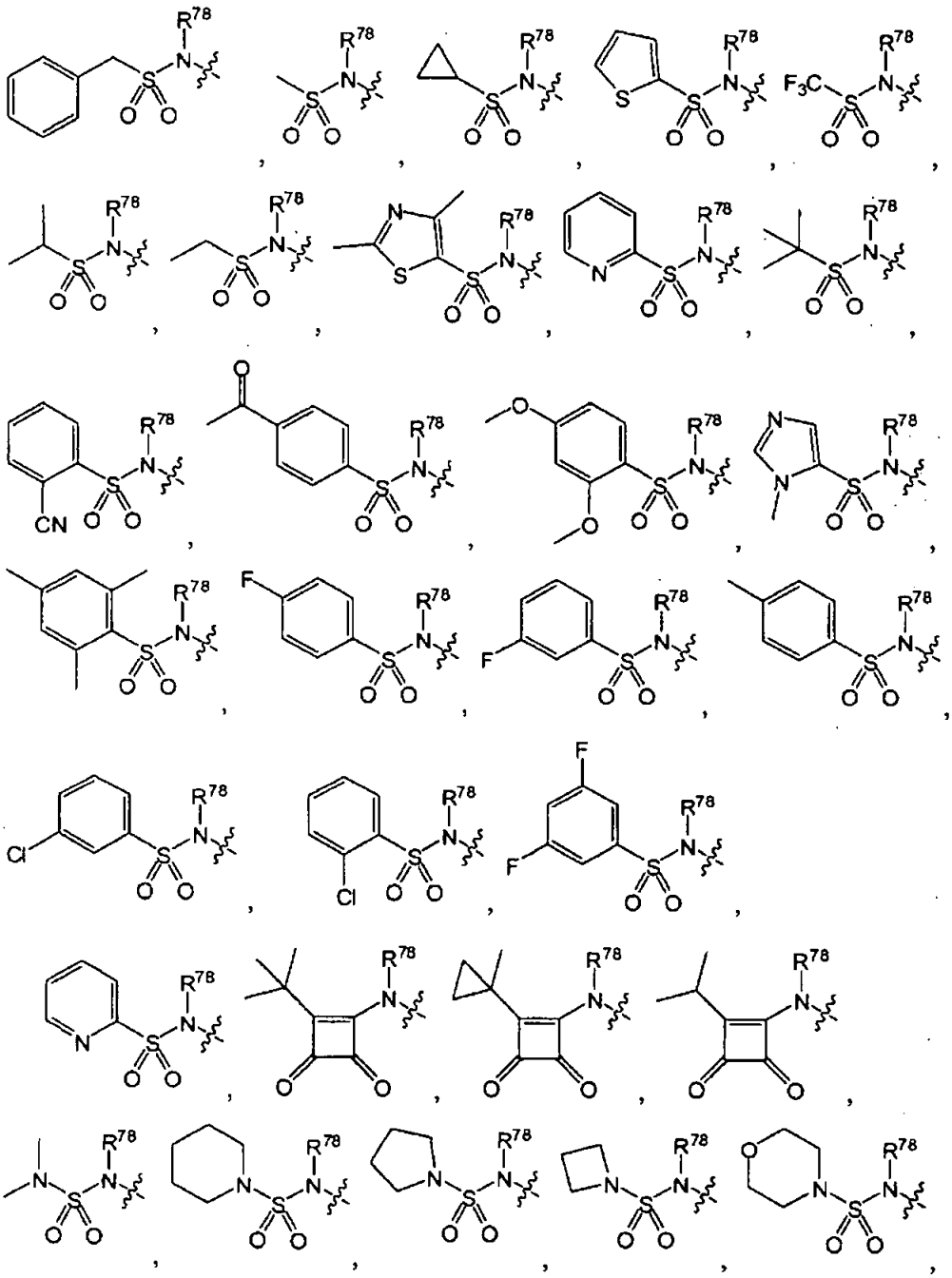


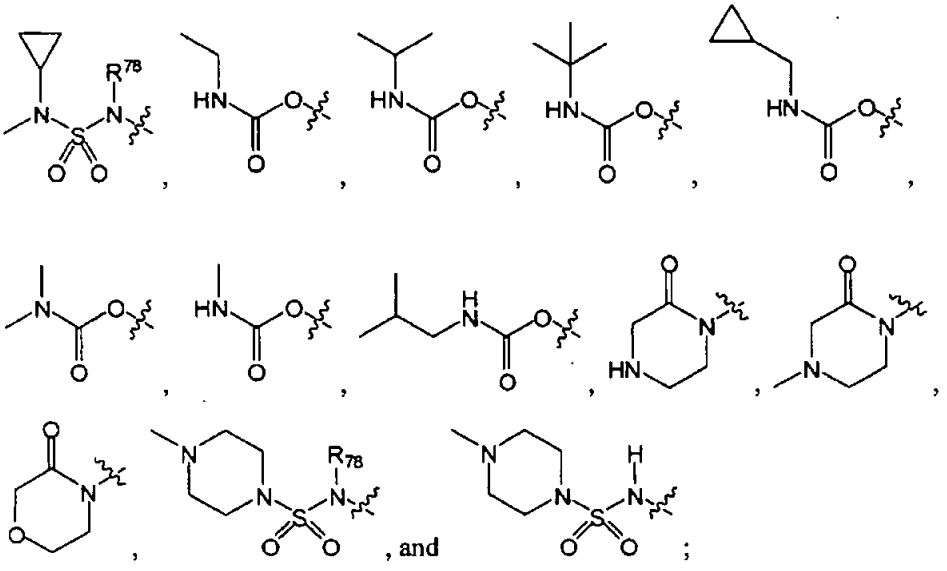
wherein $R^{44}$ is selected from the group consisting of: *tert*-butyl, isopropyl, cyclohexyl, spirocyclohexyl (e.g.,  ) and 1-methylcyclohexyl;

and $R^{77}$ is selected from the group consisting of:



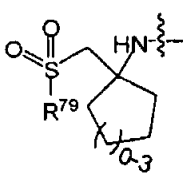






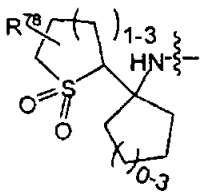
Where $R^{78}$ is selected from methyl, ethyl, isopropyl, tert-butyl and phenyl.

In yet other embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula –C(O)-V', wherein V' is a residue of the formula (ii):



wherein $R^{79}$ is selected form the group consisting of methyl, ethyl, isopropyl, tert-butyl, sec-butyl, 4-methyl-butyl, 1,1-dimethylpropyl, 1,1-dimethylbutyl, phenyl, benzyl, cyclopentyl, cyclohexyl, furylmethyl, and pyridyl (e.g., 2-pyridyl, 3-pyridyl, or 4-pyridyl).

In certain other embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula –C(O)-V', wherein V' is a residue of the formula (iii):

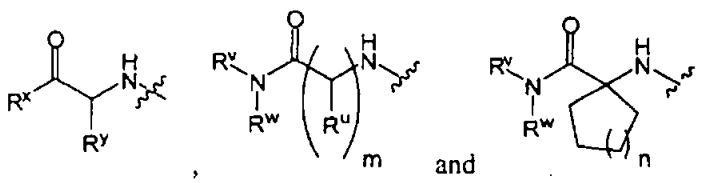


(iii)

wherein $R^{78}$ represents 0-3 groups independently selected from $C_{1-6}$alkyl and $C_{3-6}$cycloalkyl.

In certain embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula –C(O)-V′, wherein V′ is a residue of the formula (iv):

(iv)



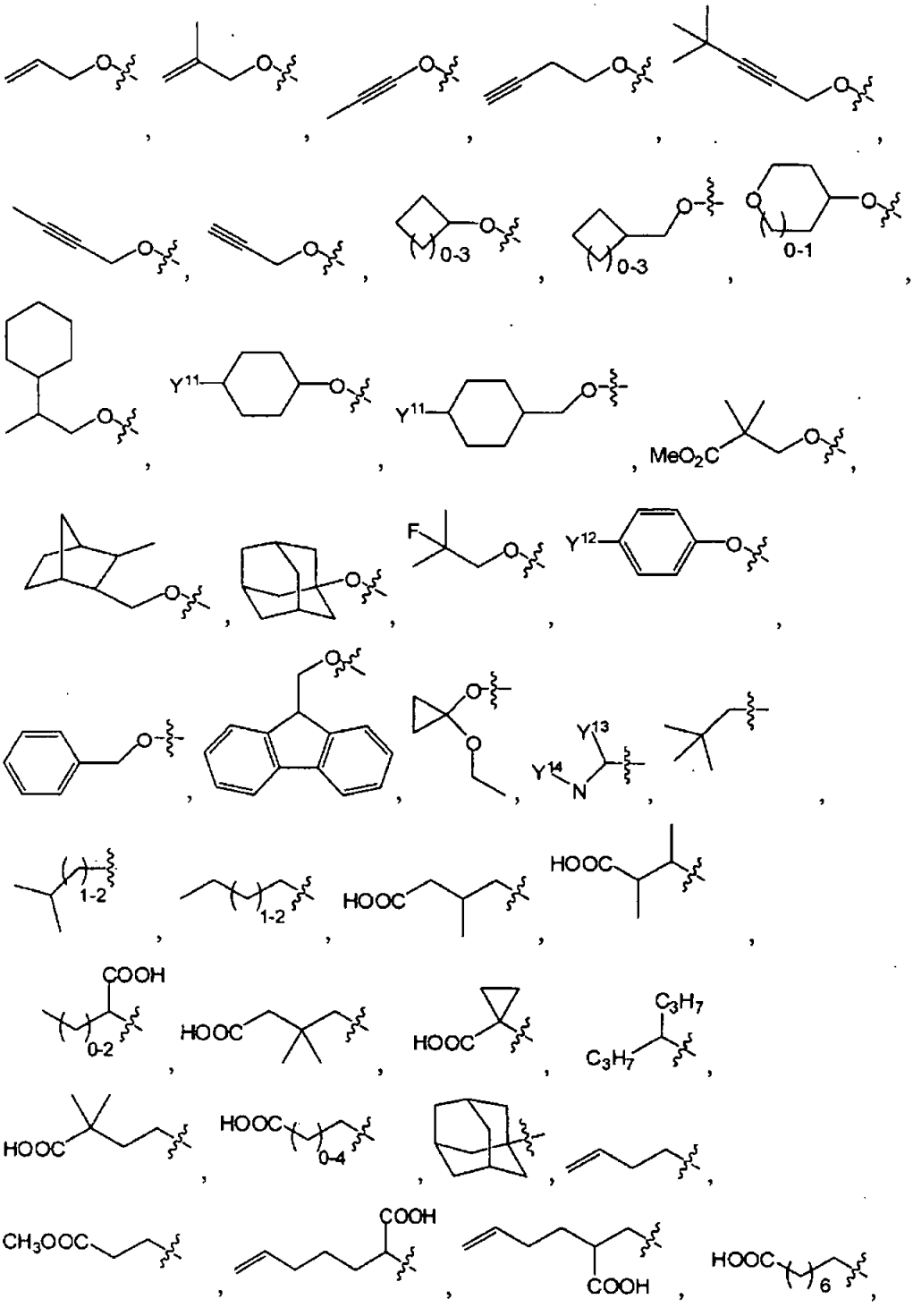
wherein m is 1 or 2; n is 0, 1, 2, or 3;

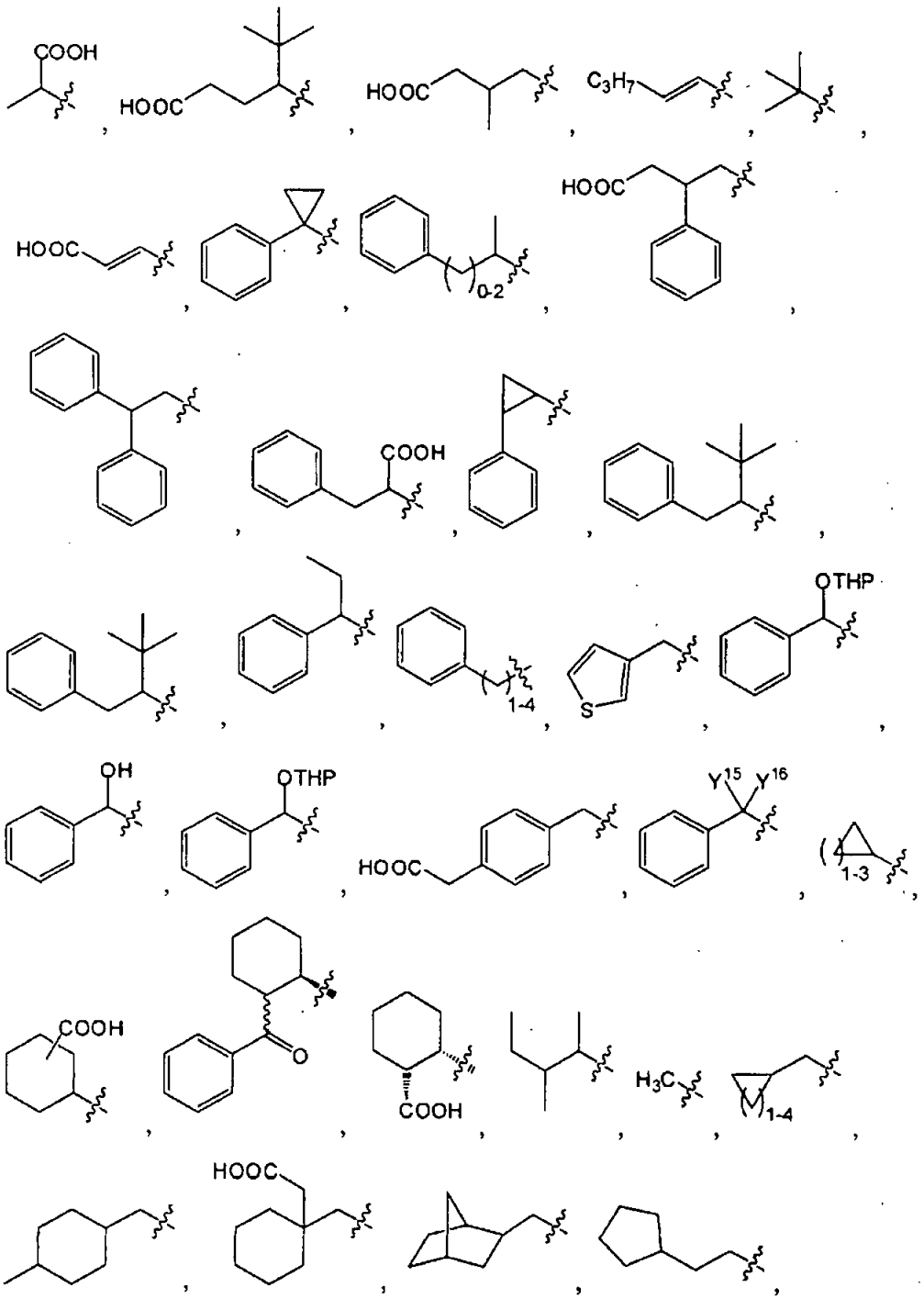
$R^u$, $R^v$, and $R^w$, are independently selected at each occurrence from the group consisting of hydrogen, $C_{1-6}$alkyl, aryl$C_{0-4}$alkyl, heteroaryl$C_{0-4}$alkyl, heterocyclyl$C_{0-4}$alkyl, and cycloalkyl$C_{0-4}$alkyl; or

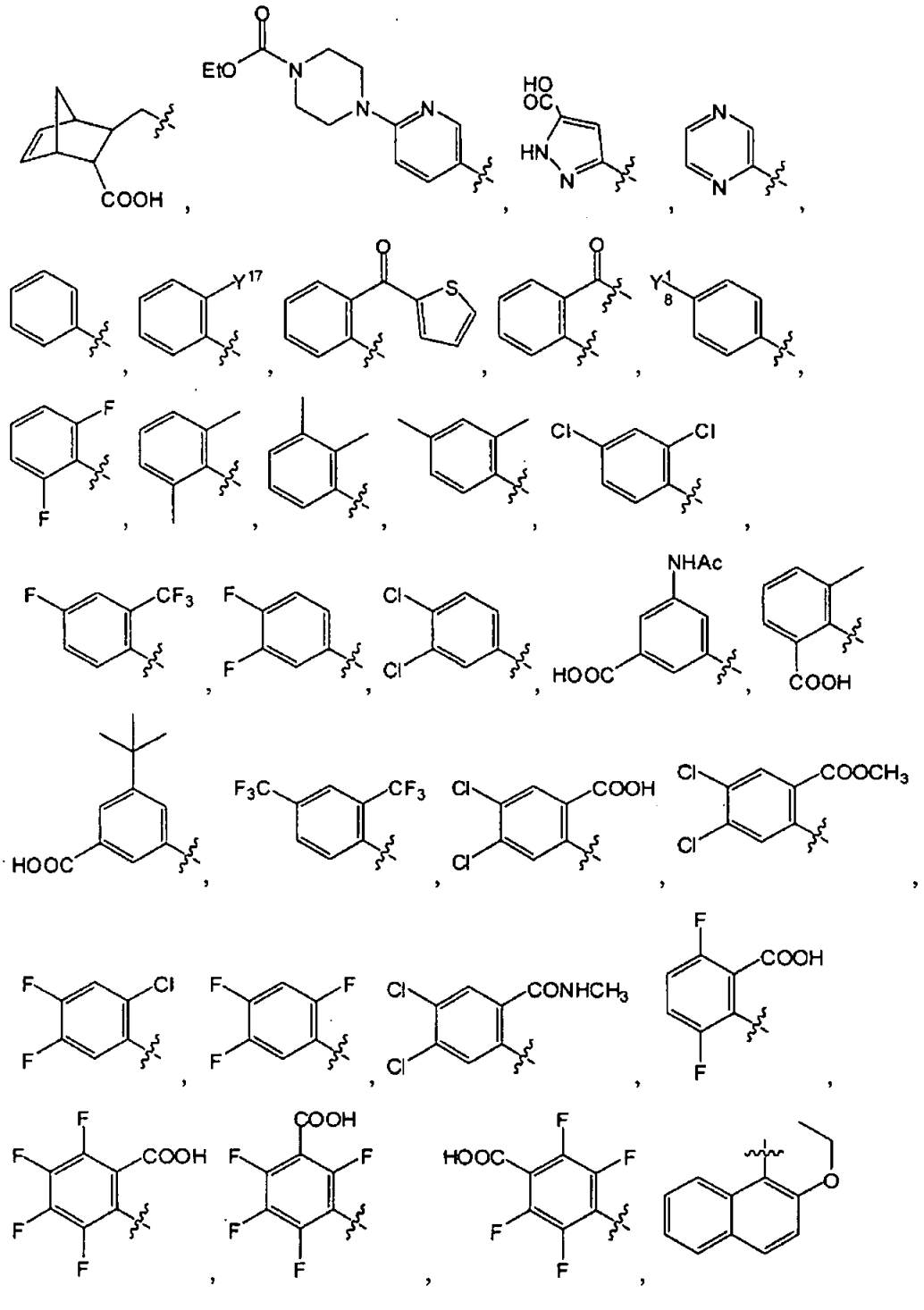
$R^v$ and $R^w$, taken in combination, form a ring having between 3 and 7 ring atoms and having 0, 1, 2 ring heteroatoms which is substituted with 0-2 alkyl groups and 0-1 spirocyclic groups.

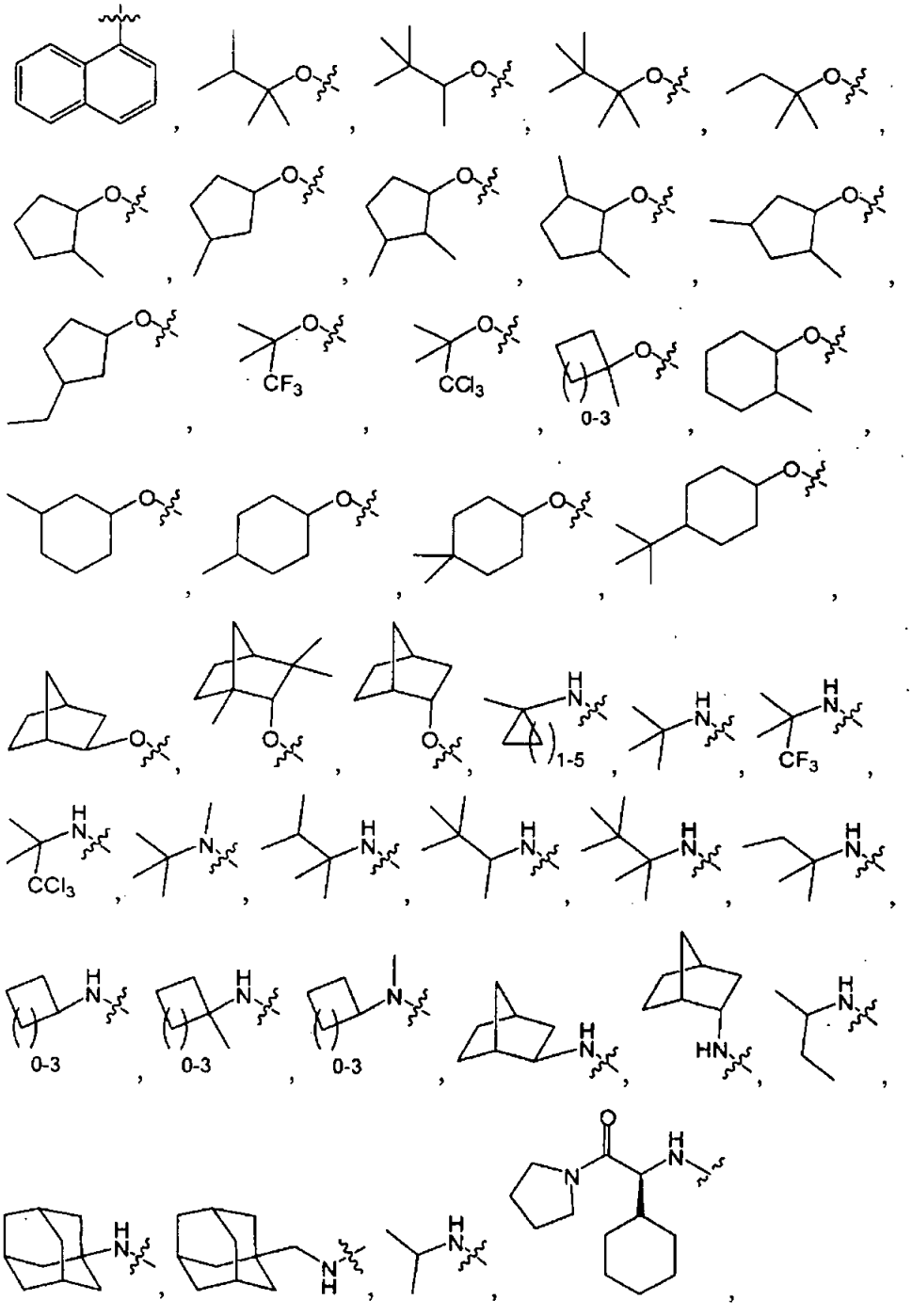
$R^x$ and $R^y$ are each independently selected from the group consisting of phenyl, $C_{1-6}$alkyl, and $C_{3-6}$cycloalkyl, or $R^x$ and $R^y$ are each independently selected from the group consisting of phenyl, cyclopropyl, isopropyl, tert-butyl, and cyclohexyl.

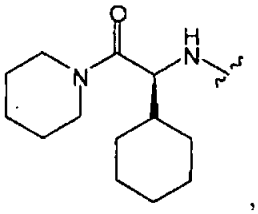
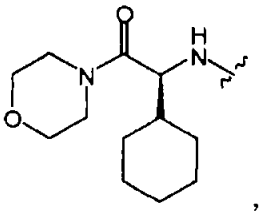
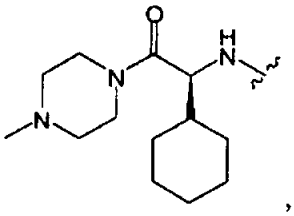
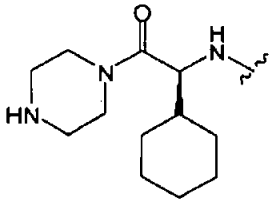
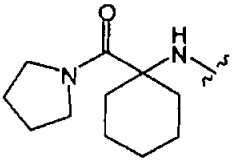
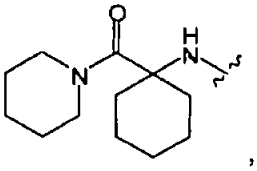
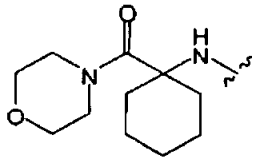
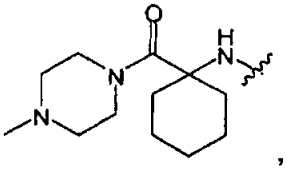
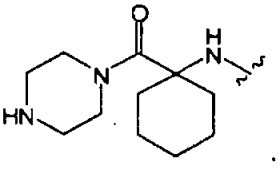
In certain embodiments, compounds of Formula I or Formula III comprise a V group selected from residues having the formula –C(O)-V′, wherein V′ is a residue selected from the group consisting of tert-butoxy, 2,2-dimethylpropoxy, sec-butoxy, 1,2-dimethylpropoxy, 3-pentoxy, isopropoxy, $C_{1-9}$alkoxy, 2,2,2-trichloroethoxy,


0-3
0-3
0-1
Y11
Y11
MeO2C
F
Y12
Y13
Y14
N
1-2
1-2
HOOC
HOOC
COOH
0-2
HOOC
HOOC
C3H7
C3H7
HOOC
HOOC
0-4
CH3OOC
COOH
COOH
HOOC
6


COOH
HOOC
HOOC
$C_3H_7$
HOOC
0-2
HOOC
COOH
1-4
S
OTHP
OH
OTHP
HOOC
$Y^{15}$ $Y^{16}$
1-3
COOH
O
COOH
$H_3C$
1-4
HOOC




CF3
CCl3
0-3
1-5
CF3
CCl3
0-3
0-3
0-3
HN

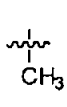
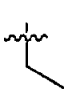
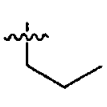
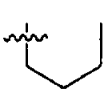
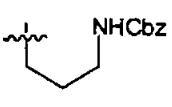
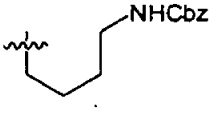
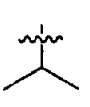
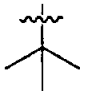
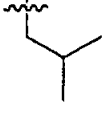
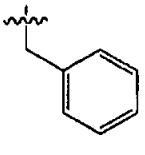
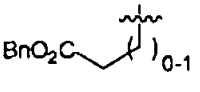
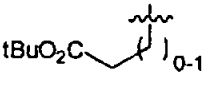
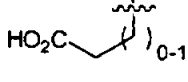
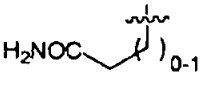









, and

wherein

$Y^{11}$ is selected from the group consisting of hydrogen, -C(O)OH, -C(O)OEt, -OMe, -Ph, -OPh, -NHMe, -NHAc, -NHPh, $-CH(Me)_2$, 1-triazolyl, 1-imidazolyl, and $-NHCH_2COOH$;

$Y^{12}$ is selected from the group consisting of hydrogen, -C(O)OH, -C(O)OMe, -OMe, F, Cl, and Br;

$Y^{13}$ is selected from the group consisting of the following moieties:















, and

$Y^{14}$ is $S(O)_2Me$, -C(O)Me, -Boc, -iBoc, Cbz, or –Alloc;

$Y^{15}$ and $Y^{16}$ can be the same or different and are independently selected from the group consisting of alkyl, aryl, heteroalkyl, and heteroaryl;

$Y^{17}$ is $–CF_3$, $-NO_2$, $-C(O)NH_2$, -OH, $-C(O)OCH_3$, $-OCH_3$, $-OC_6H_5$, $-C_6H_5$, $-C(O)C_6H_5$, $-NH_2$, or –C(O)OH; and

$Y^{18}$ is $–C(O)OCH_3$, $-NO_2$, $-N(CH_3)_2$, F, $-OCH_3$, $-C(H)_2C(O)OH$, -C(O)OH, $-S(O)_2NH_2$, or $–N(H)C(O)CH_3$

In one embodiment, any of the $C_{3-6}$-cycloalkyl groups may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl.

In another embodiment of formula I, $R^4$ is H and $R^5$ is aryl-$C_{0-3}$-alkyl, -O-heterocycle, or heterocycle-$C_{0-3}$-alkyl, wherein aryl and heterocycle may be independently substituted one or more times (or preferably between one and five times) with a halogen atom, aryl, trihalomethyl, $C_{3-6}$-cycloalkyl or $C_{1-4}$-alkyl.

In yet another embodiment of Formula I or Formula III, W is selected from the group consisting of $C(O)$-$C(O)N(R^{23})_2$, wherein $R^{23}$ is independently selected from hydrogen or from the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl, aryl and heterocycle, each of which may be independently substituted one or more times (or preferably between one and five times) with a halogen atom or $C_{1-4}$-alkyl.

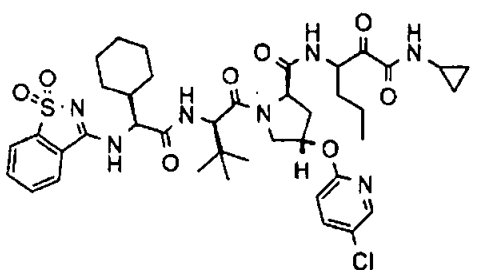
In still another embodiment of Formula I or Formula III, W is C(O)-C(O)-cyclopropyl

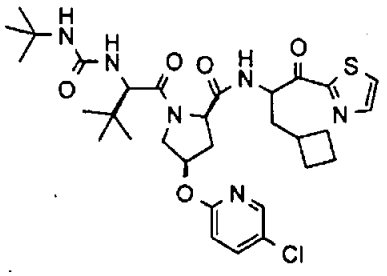
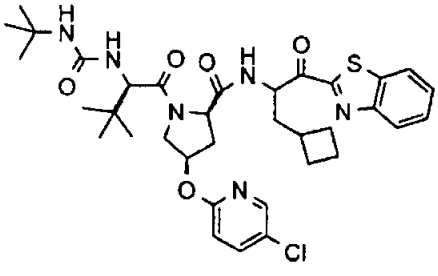
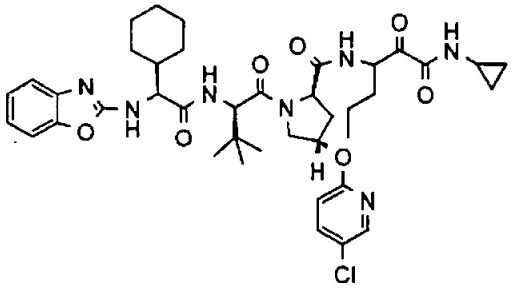
In one embodiment of Formula I or Formula III, any of the heterocycle groups are independently selected from the group consisting of acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline, benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl,

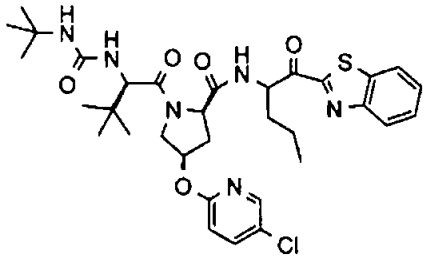
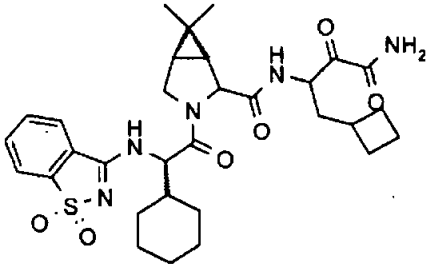
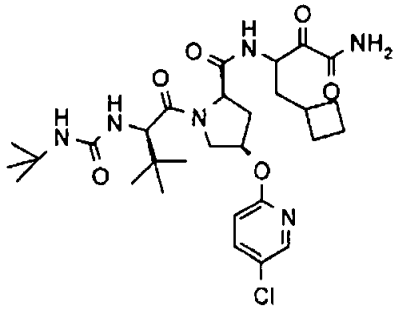
pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof, each of which may be independently further substituted one or more times (or preferably between one and five times) with a halogen atom, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, or $C_{3-6}$-cycloalkyl.

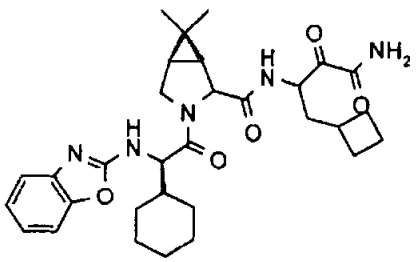
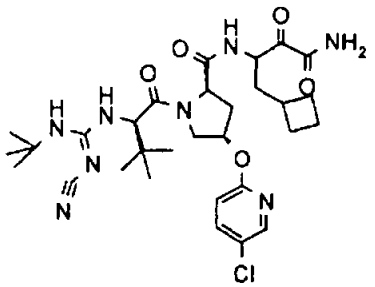
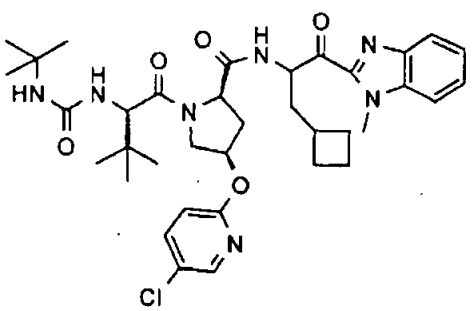
Preferred embodiments of the compounds of the invention (including pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof) are shown below in Table A and Table B, and are also considered to be "compounds of the invention."

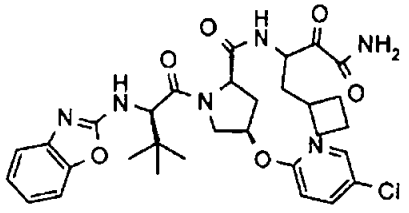
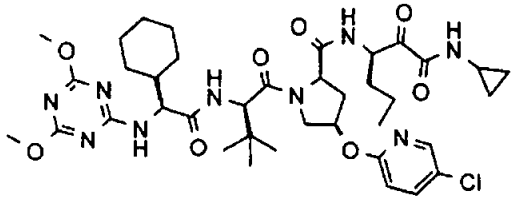
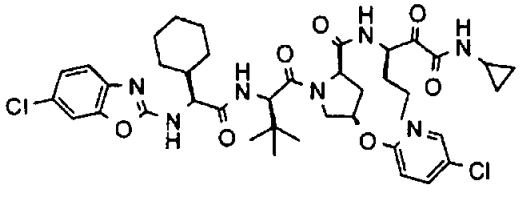
**TABLE A**

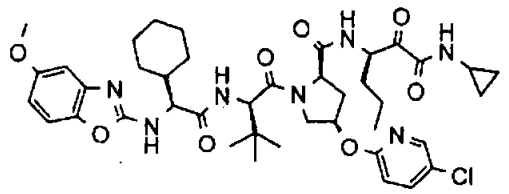
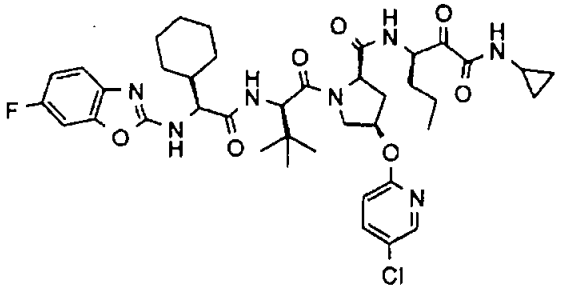
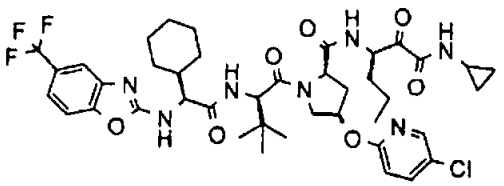
| Structure | Compound No. |
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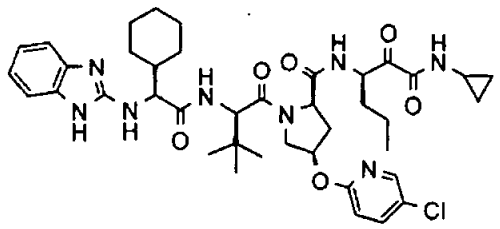
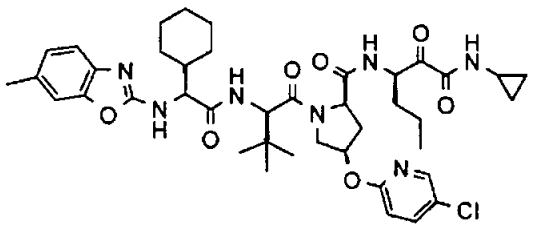
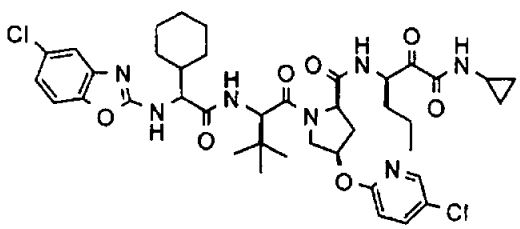
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|  | A-4 |

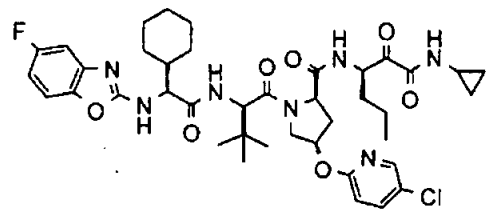
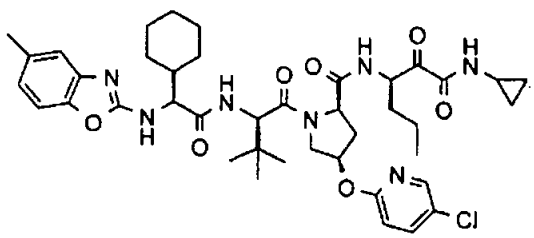
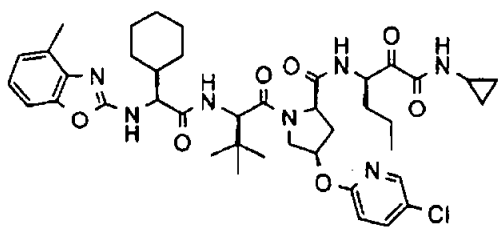
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|  | A-7 |

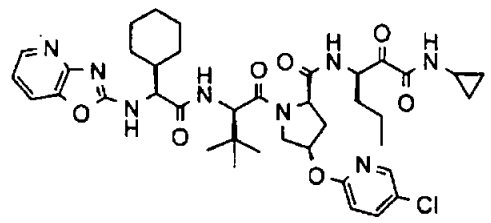
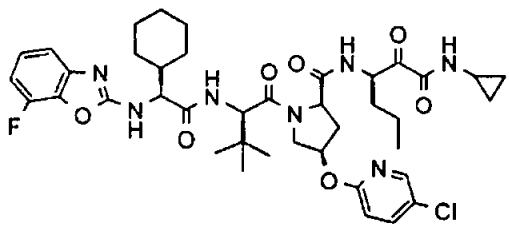
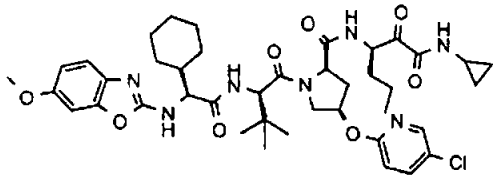
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|  | A-12 |
|  | A-13 |

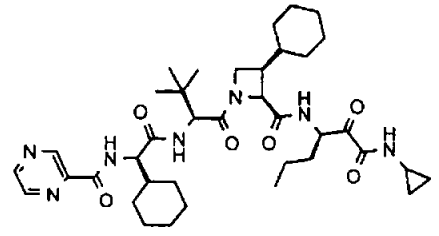
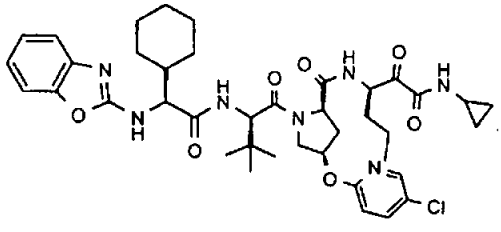
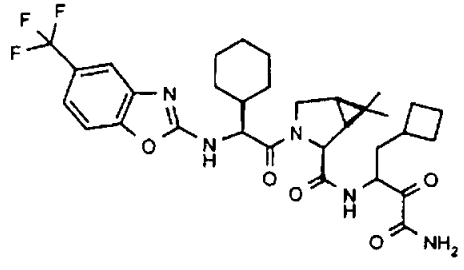
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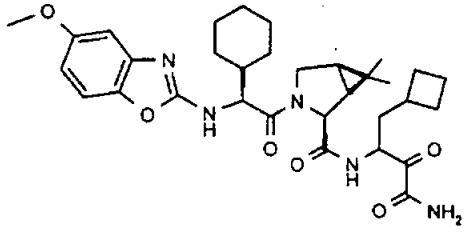
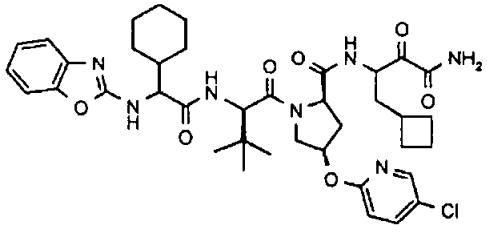
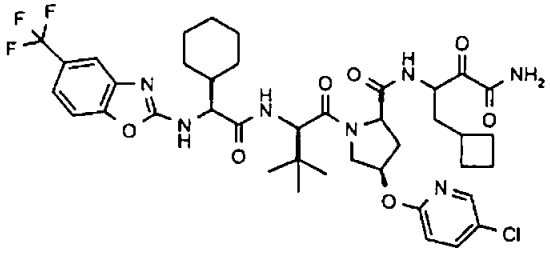
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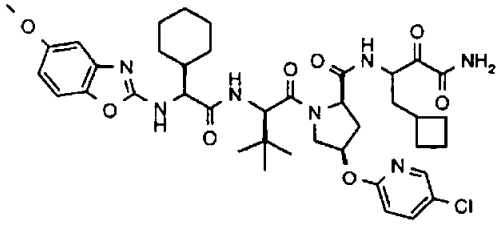
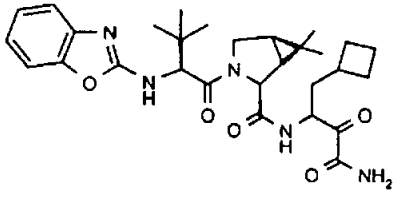
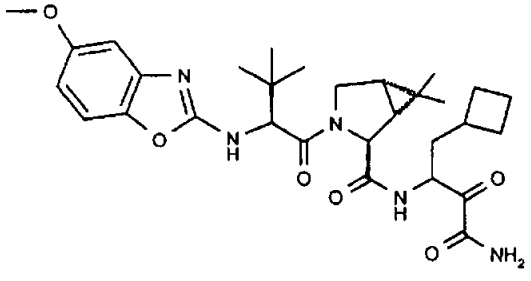
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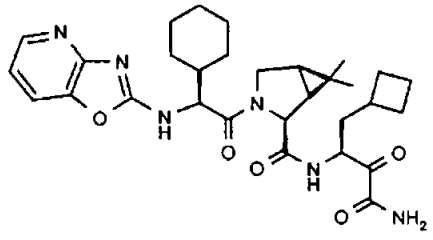
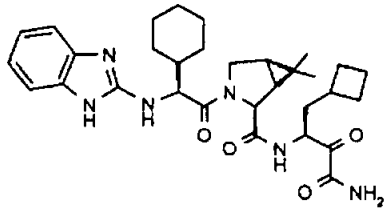
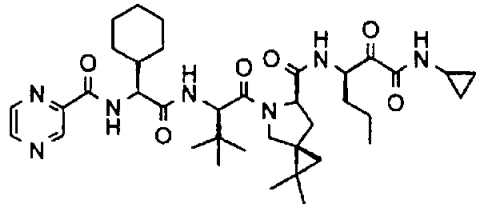
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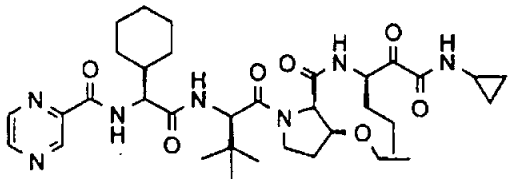
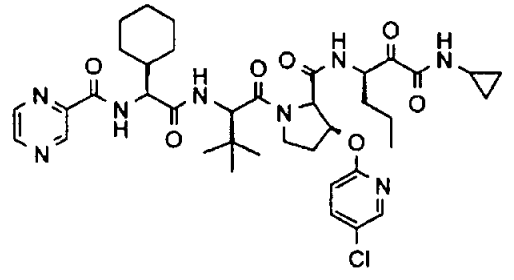
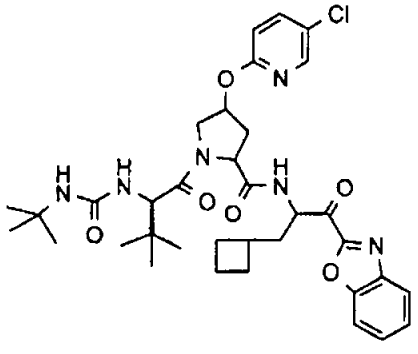
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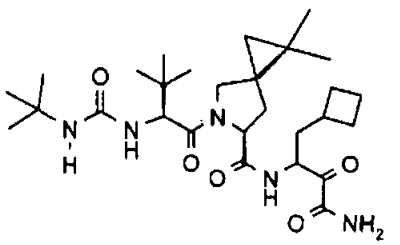
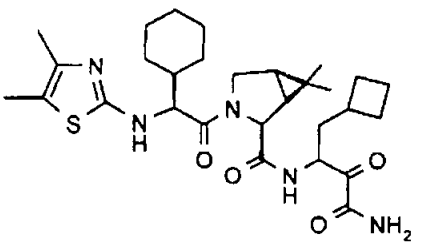
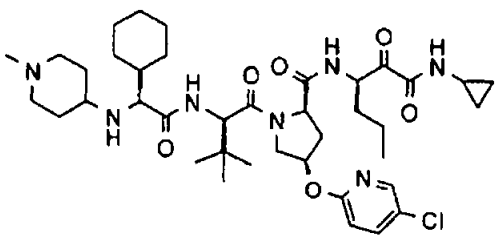
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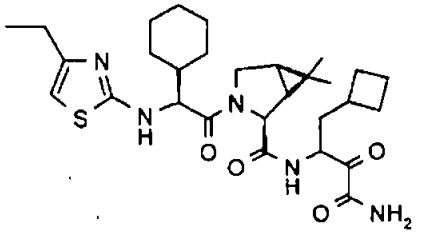
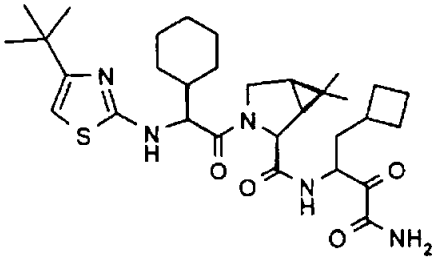
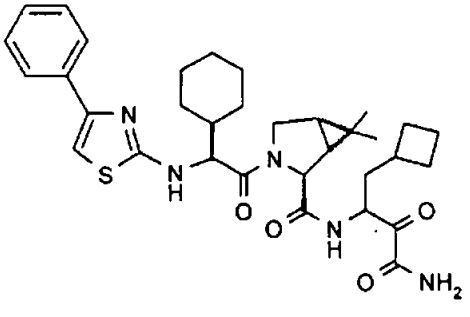
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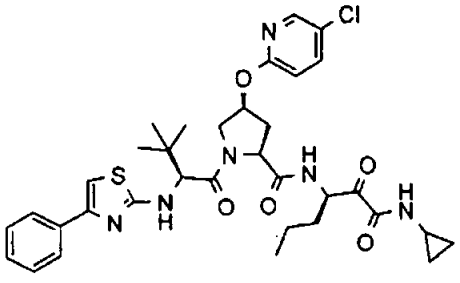
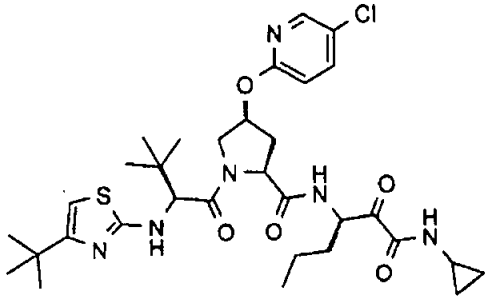
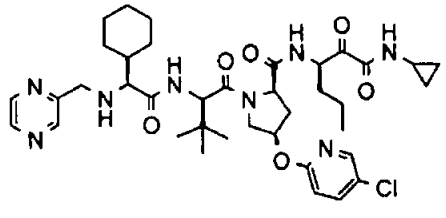
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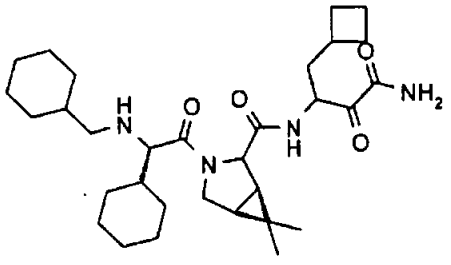
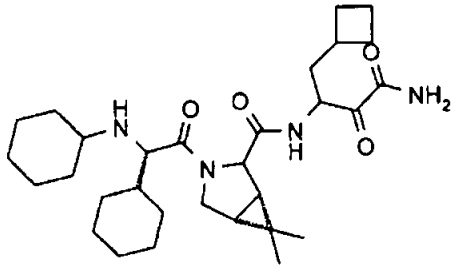
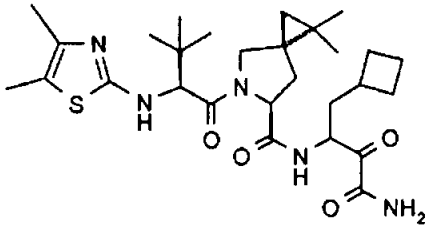
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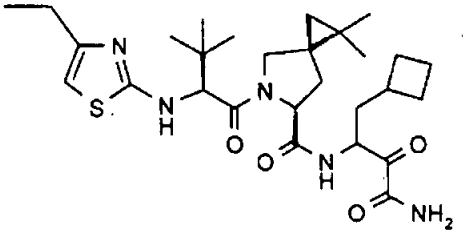
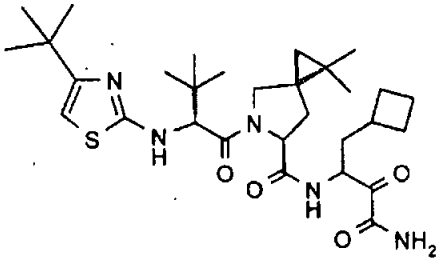
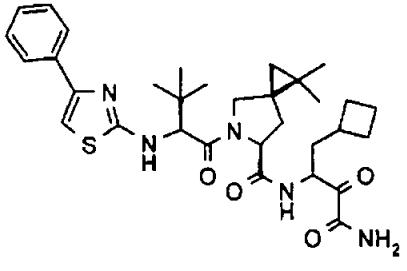
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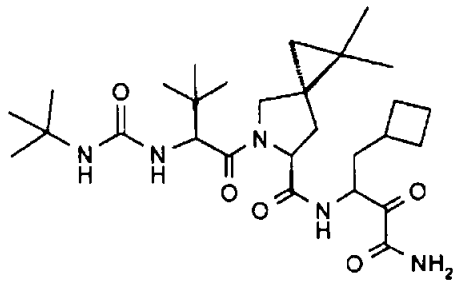
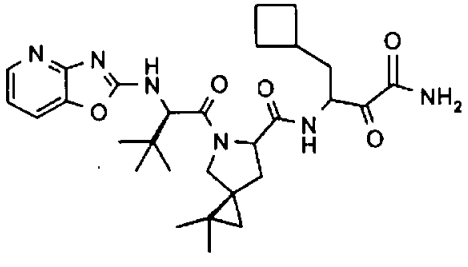
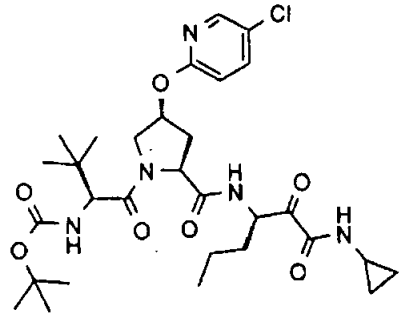
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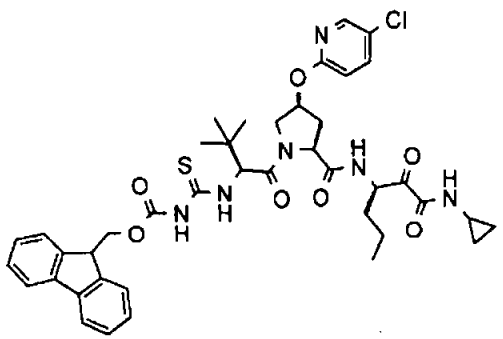
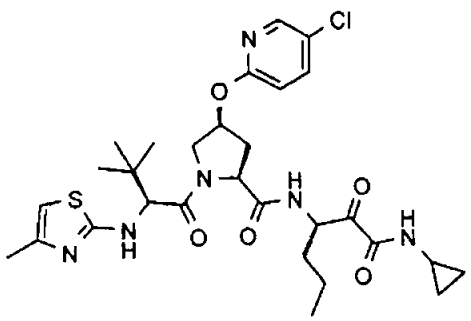
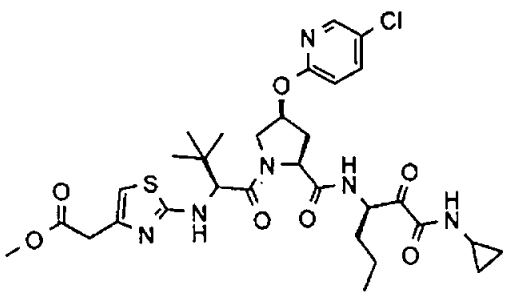
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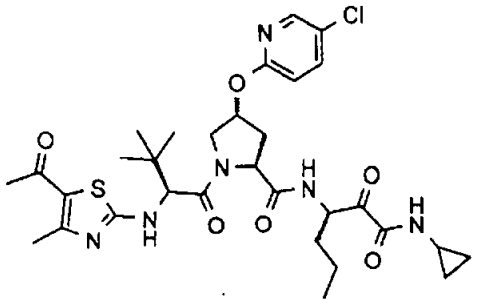
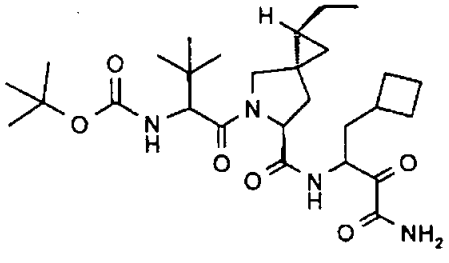
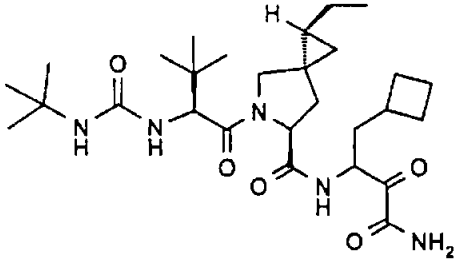
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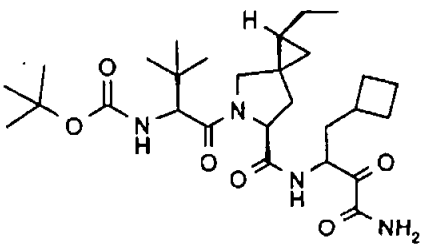
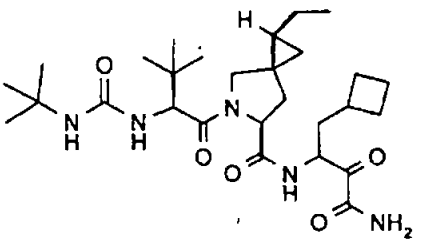
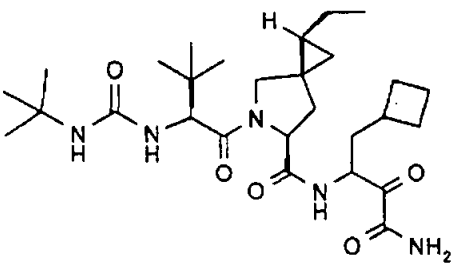
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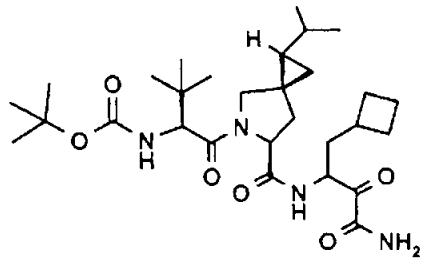
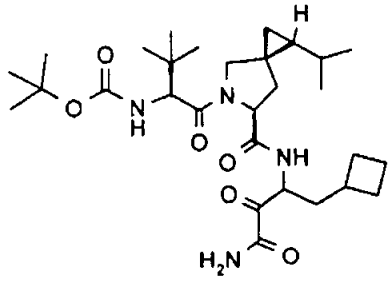
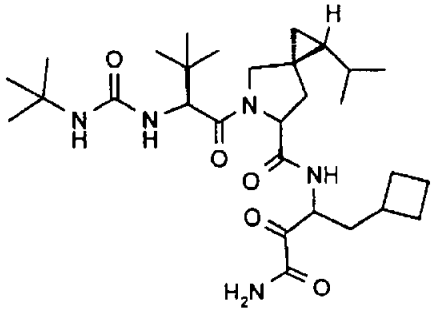
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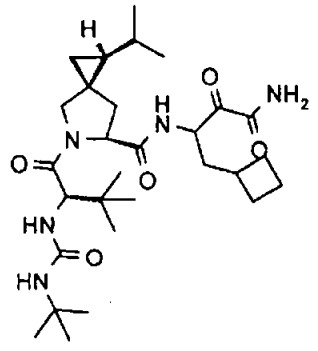
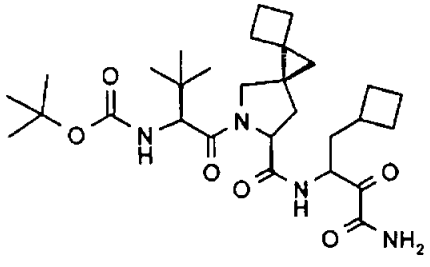
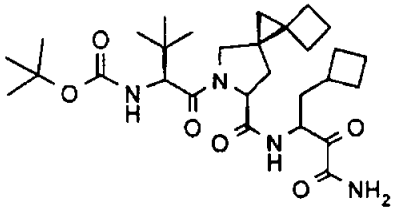
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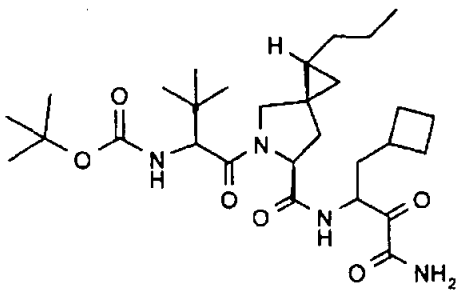
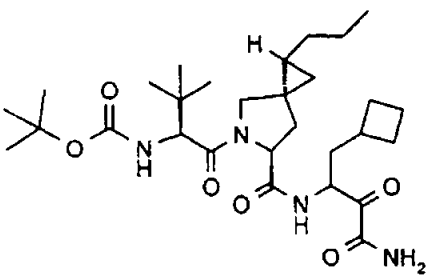
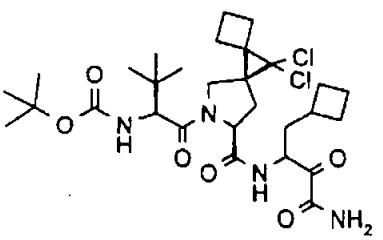
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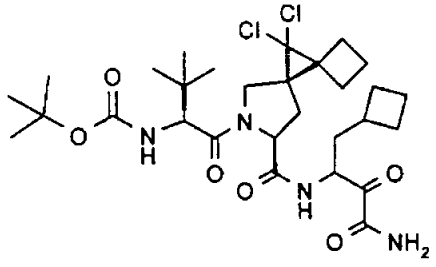
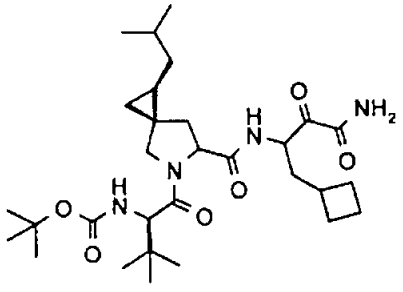
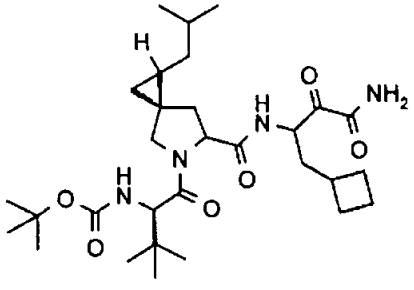
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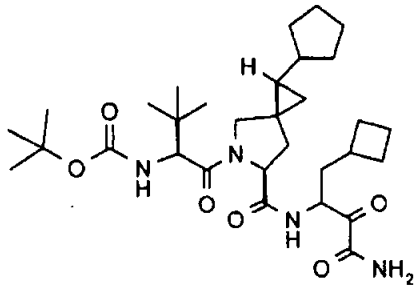
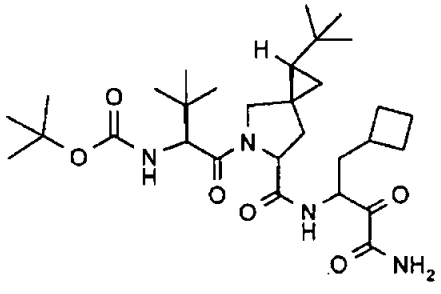
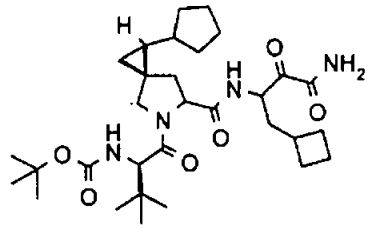
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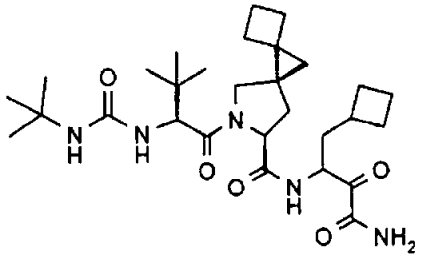
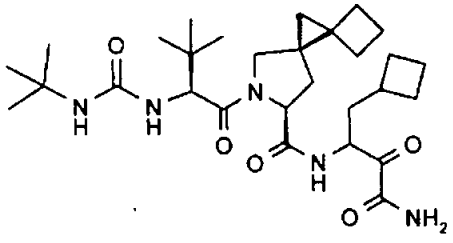
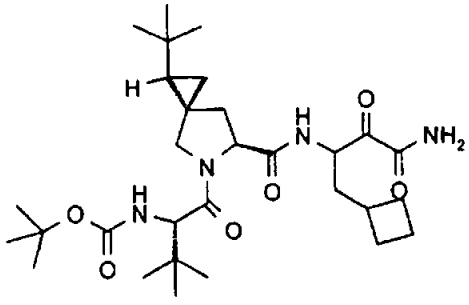
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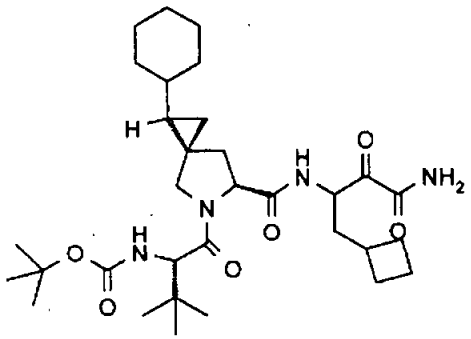
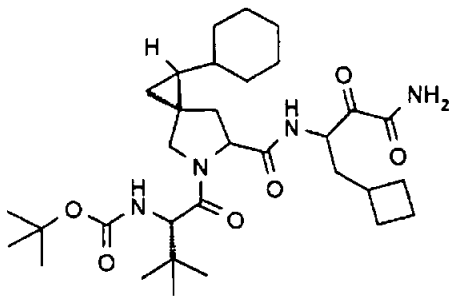
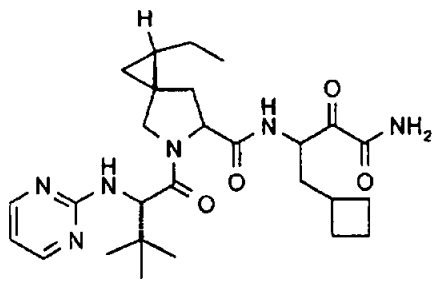
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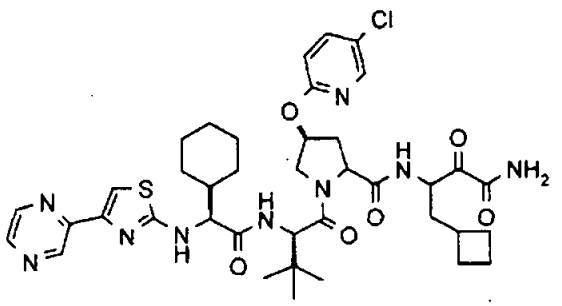
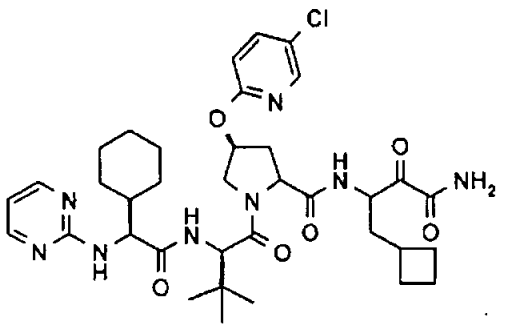
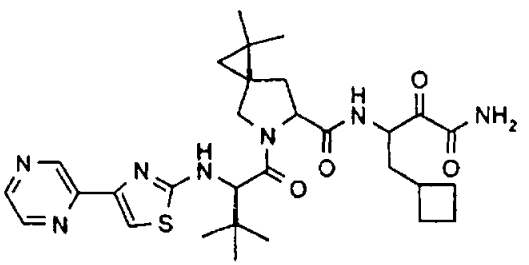
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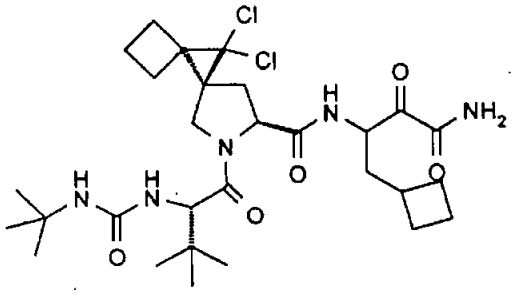
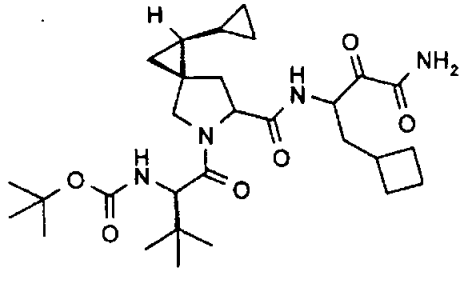
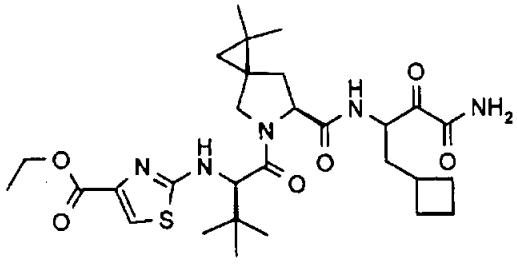
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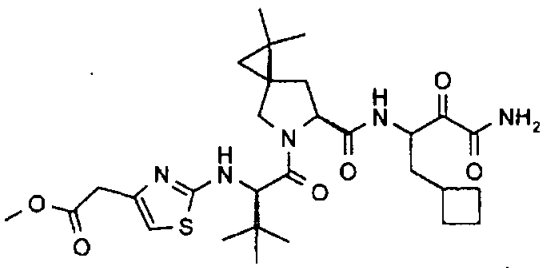
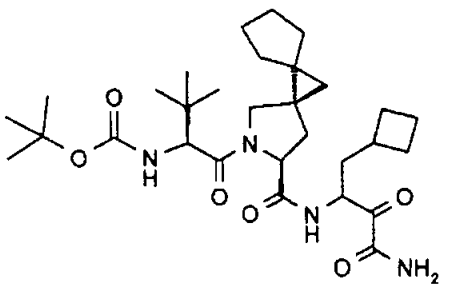
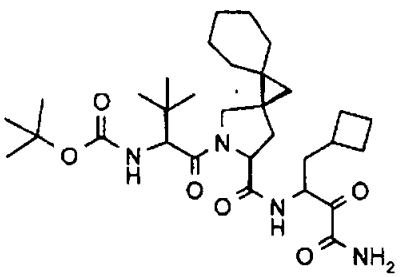
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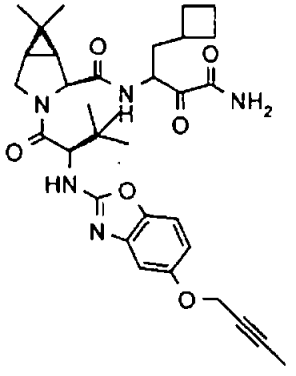
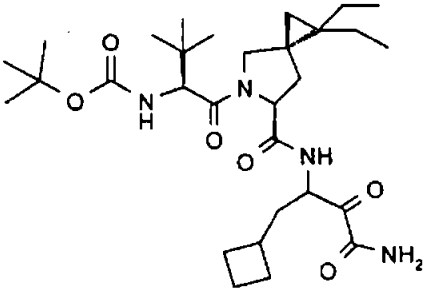
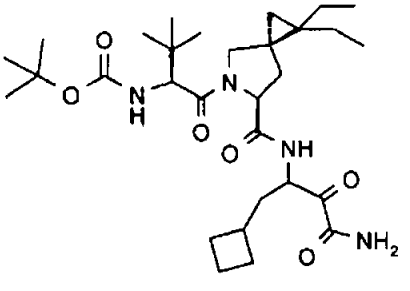
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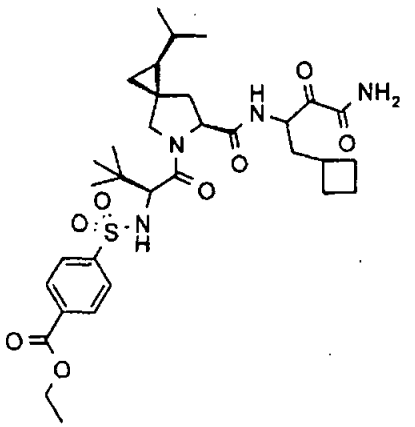
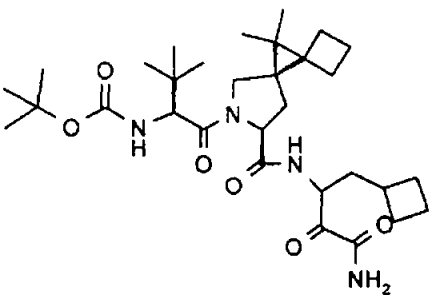
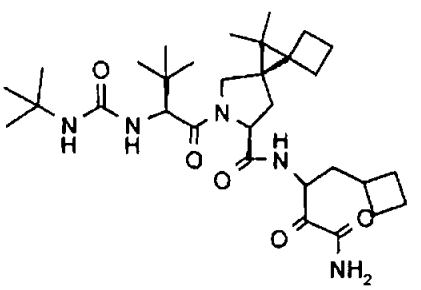
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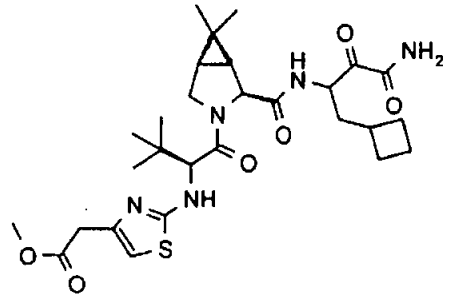
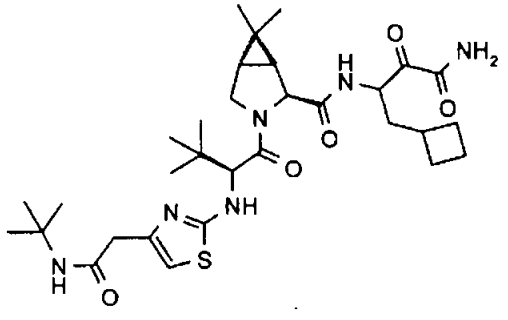
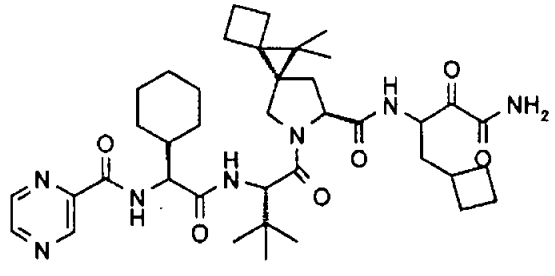
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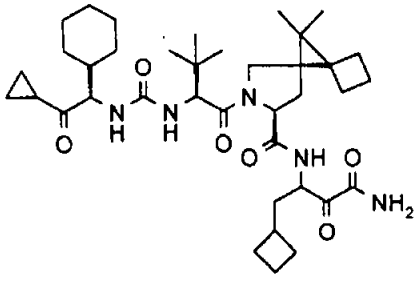
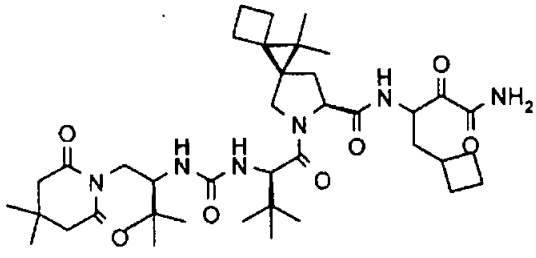
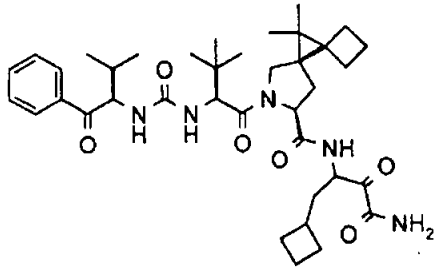
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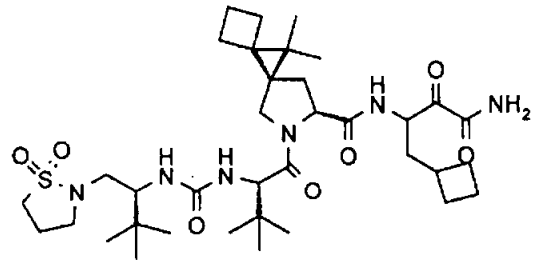
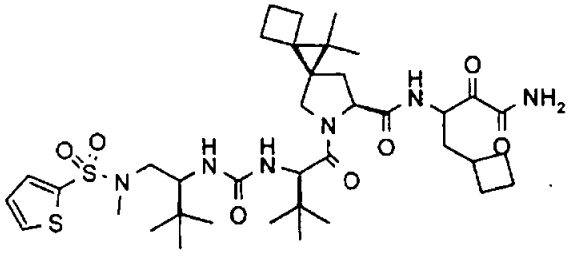
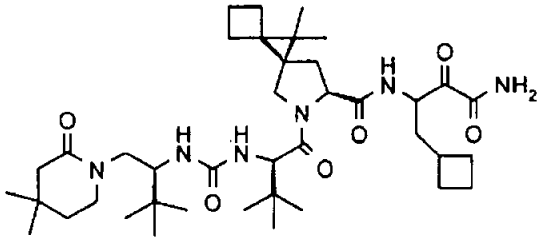
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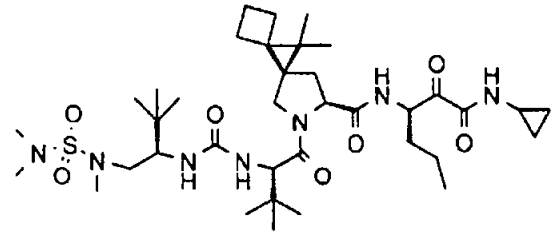
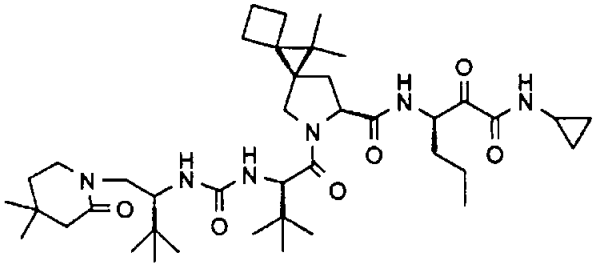
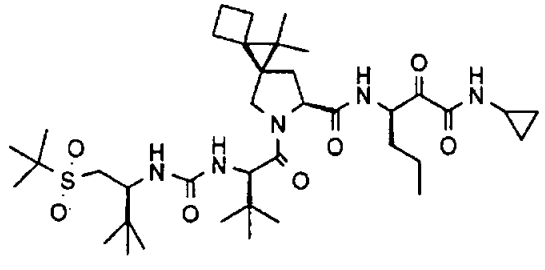
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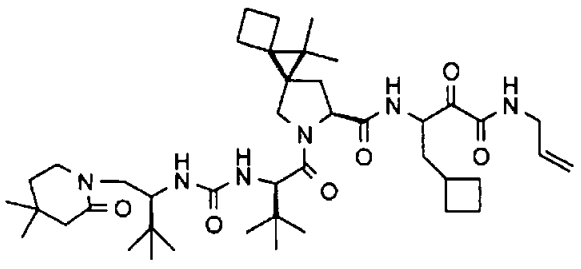
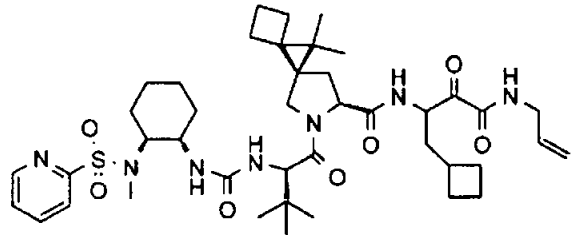
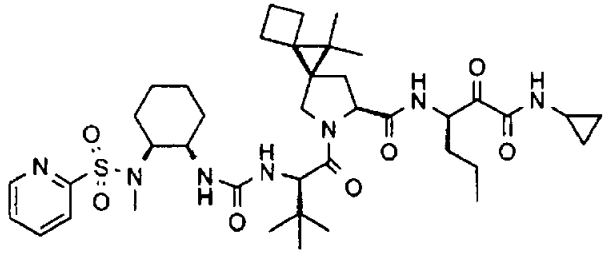
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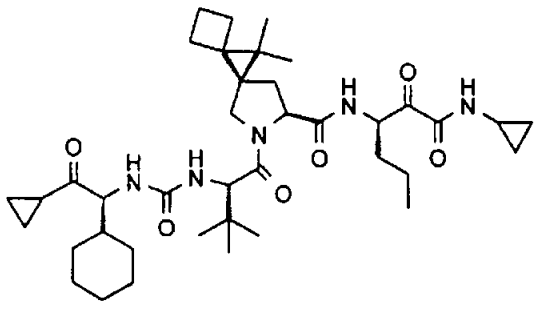
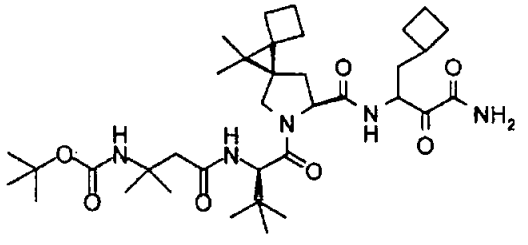
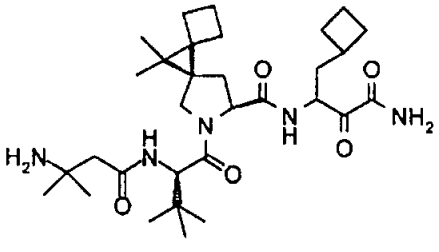
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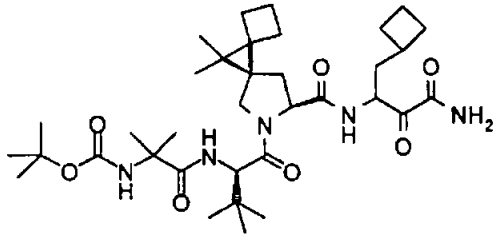
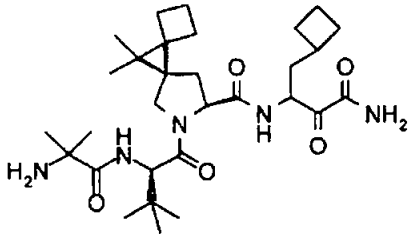
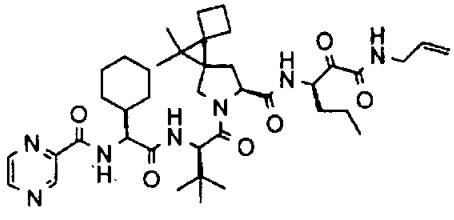
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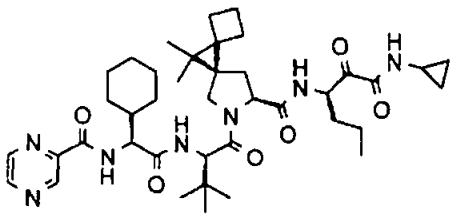
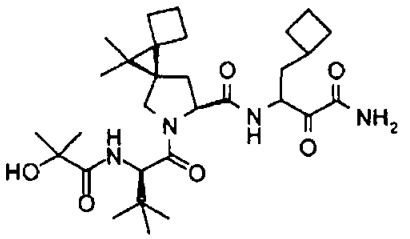
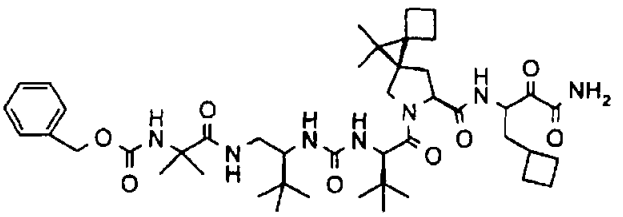
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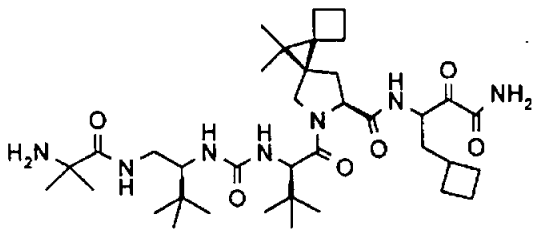
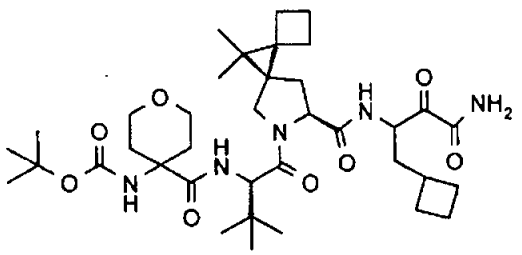
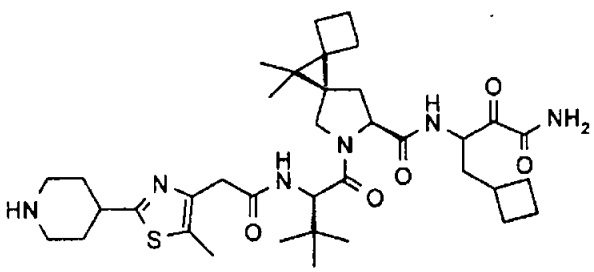
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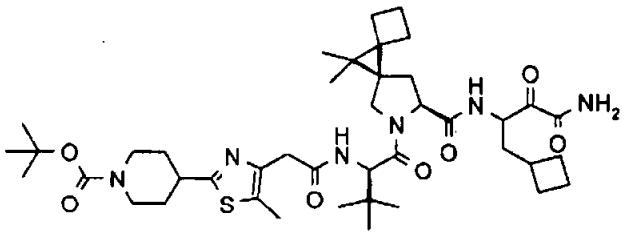
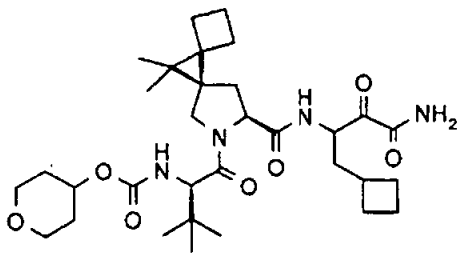
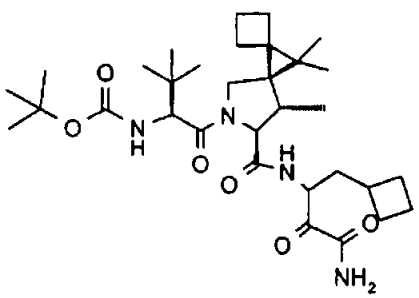
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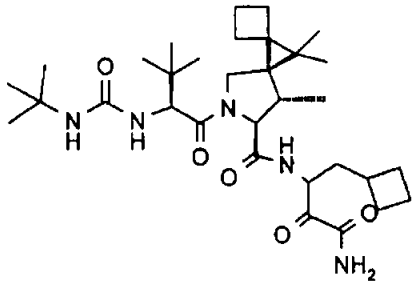
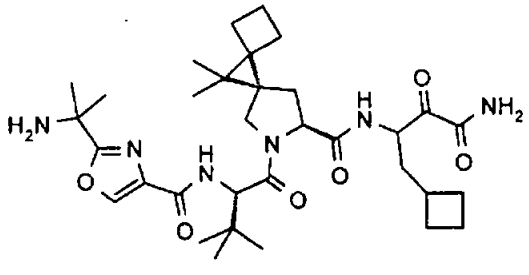
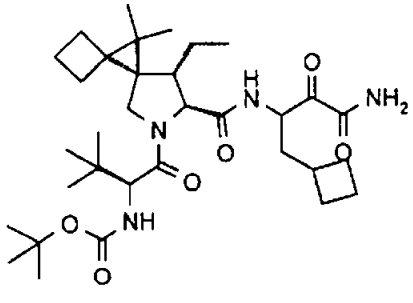
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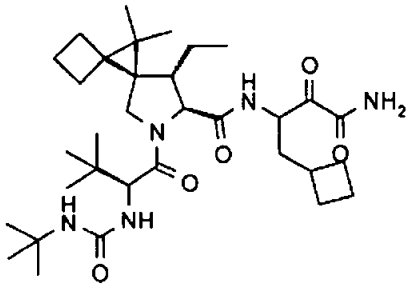
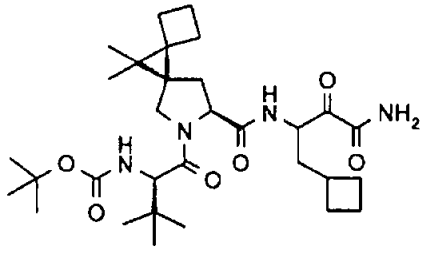
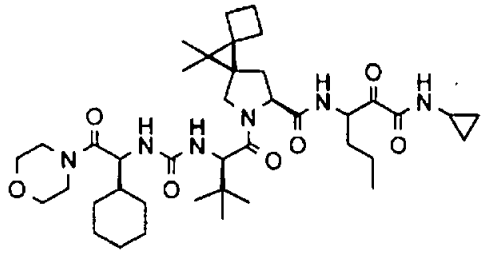
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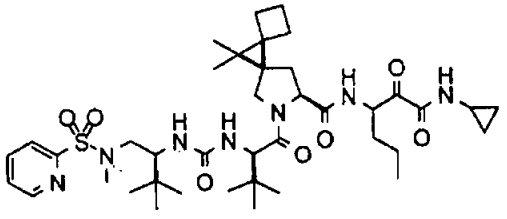
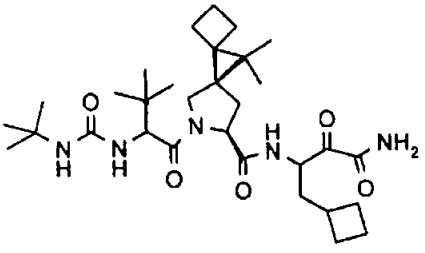
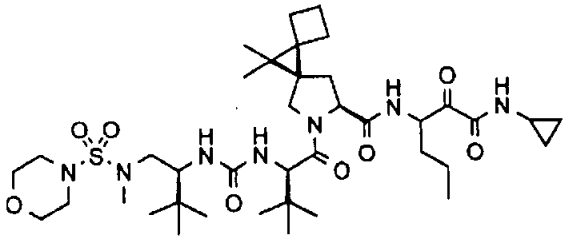
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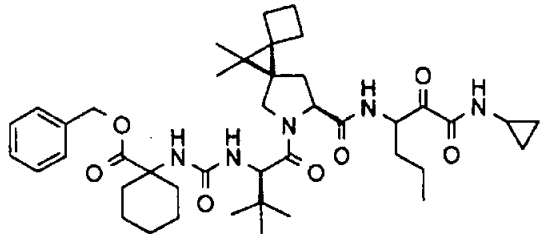
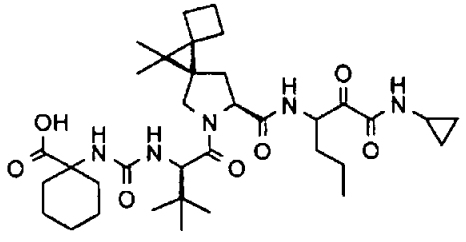
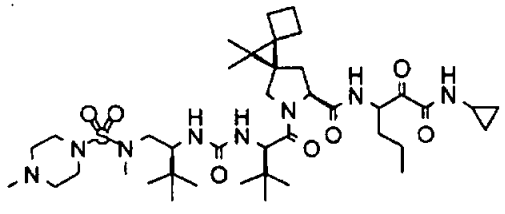
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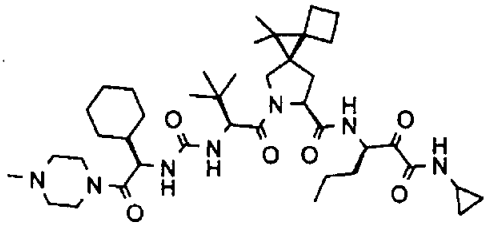
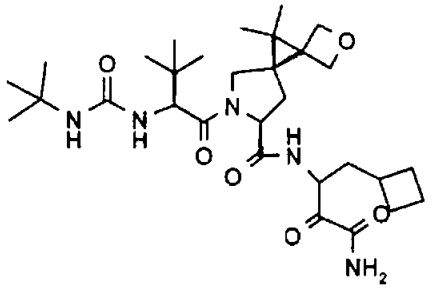
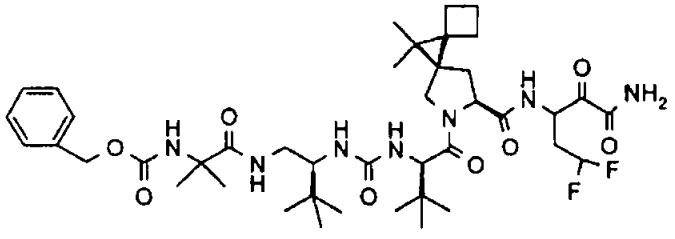
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|  | A-140 |
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|  | A-142 |

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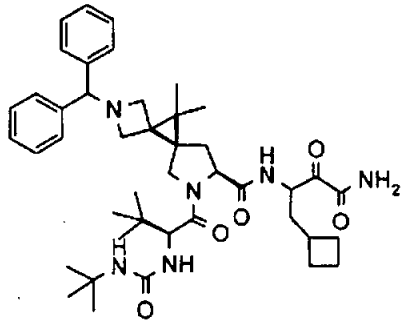
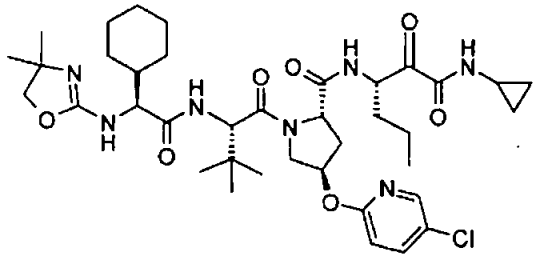
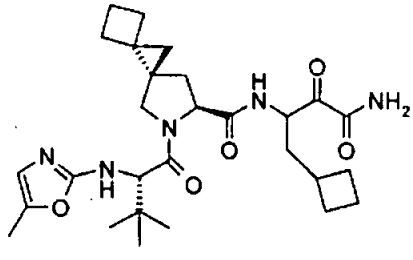
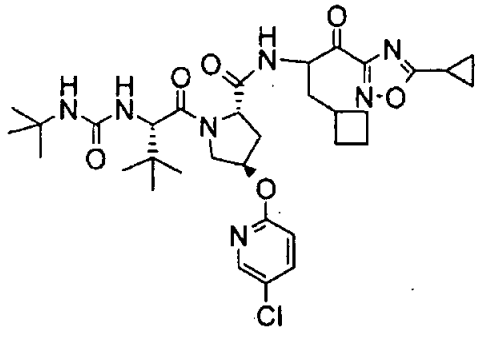
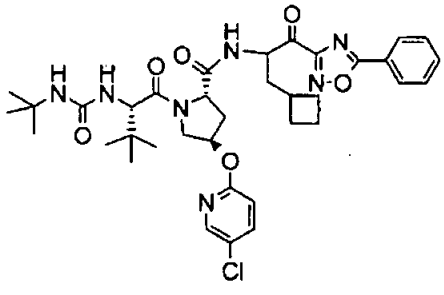
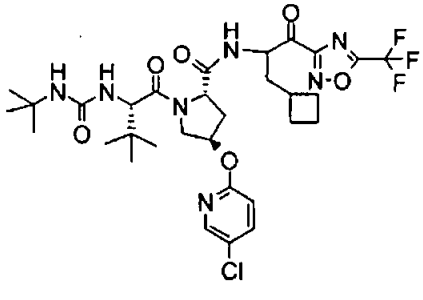
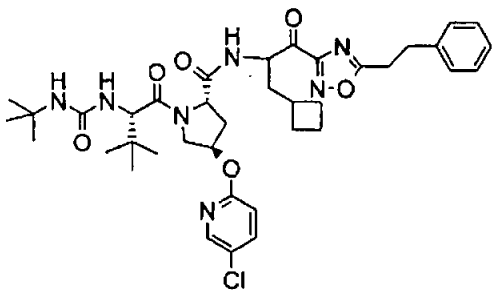
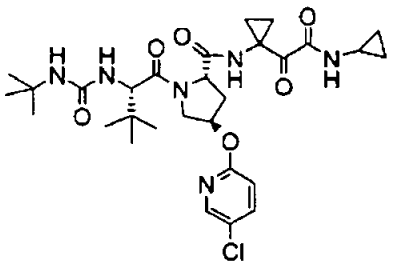
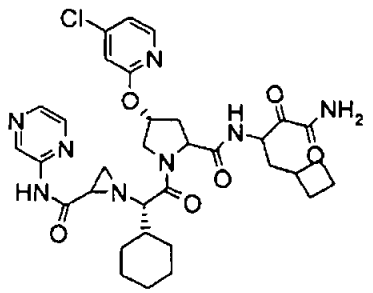
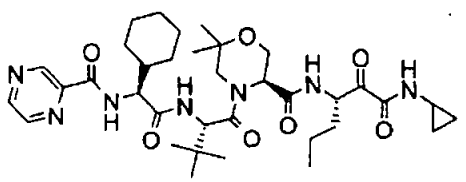
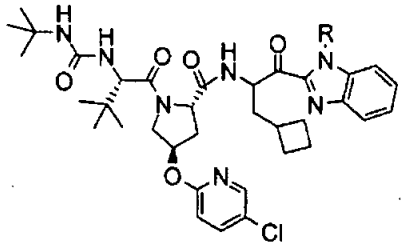
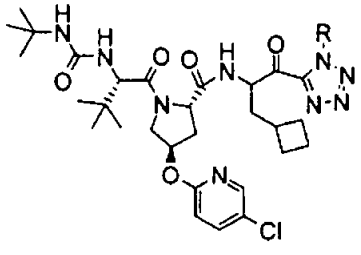
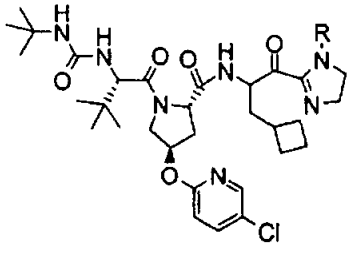
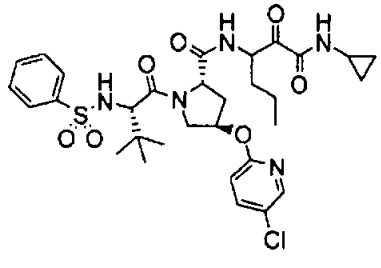
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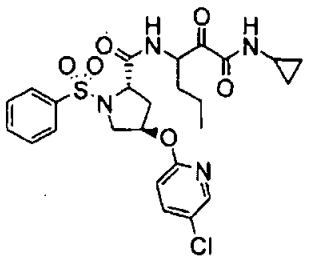
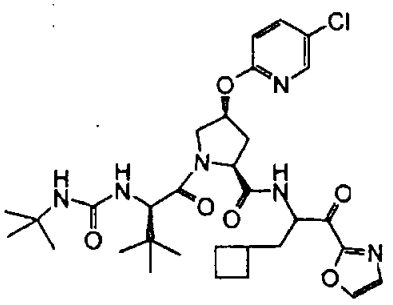
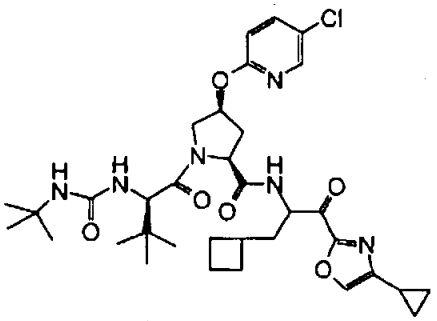
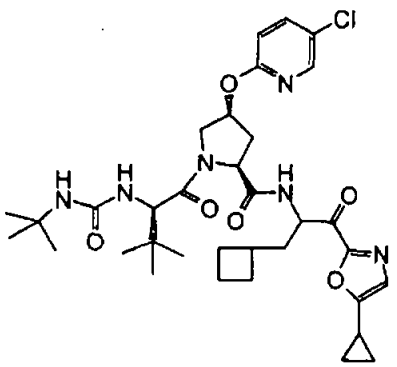
**TABLE B**

| Structure | Compound No. |
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|  | B-3 |

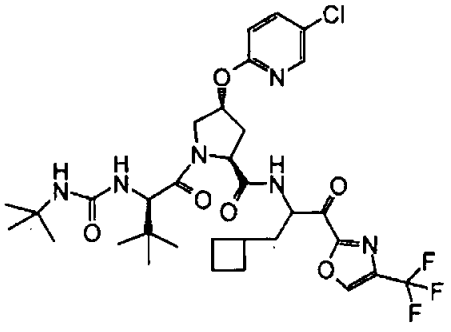
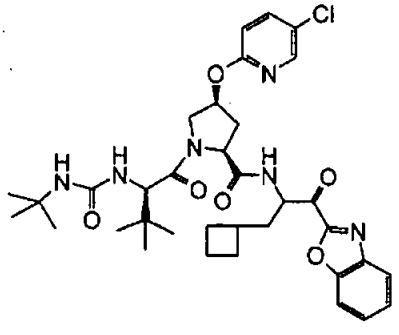
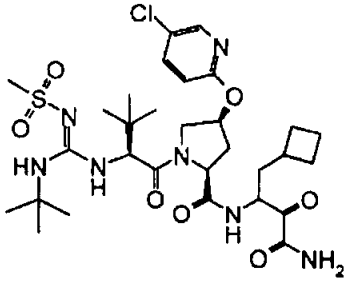
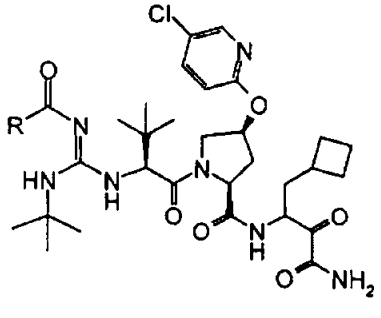
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|  | **B-7** |

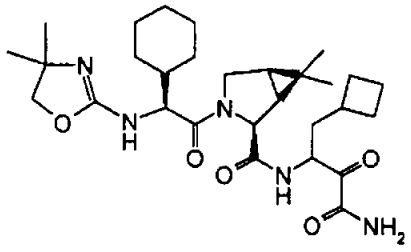
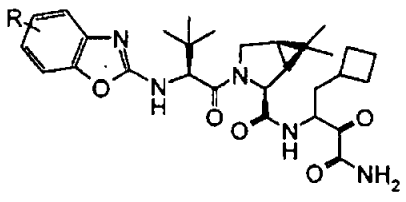
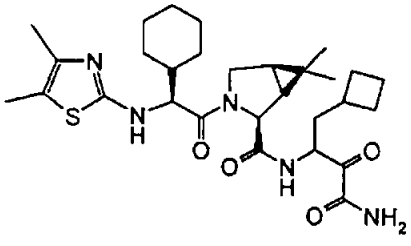
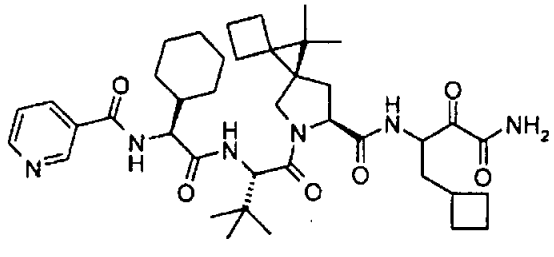
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|  | **B-11** |

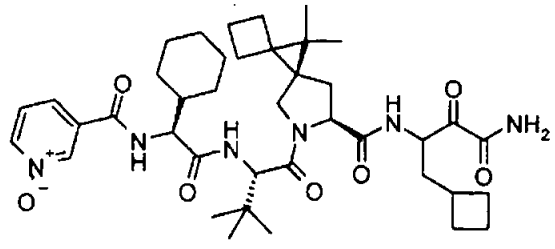
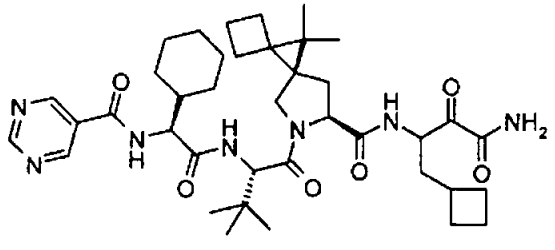
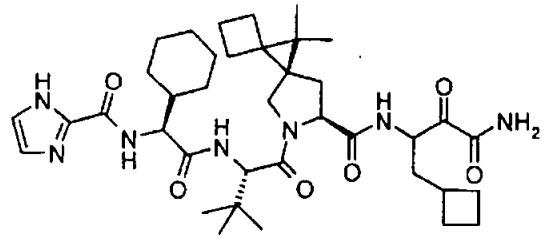
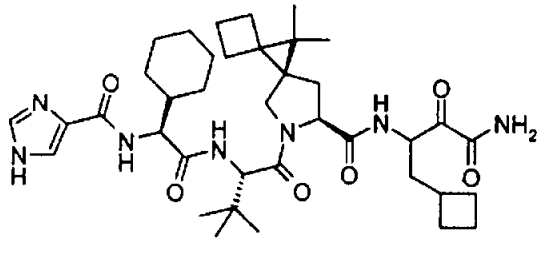
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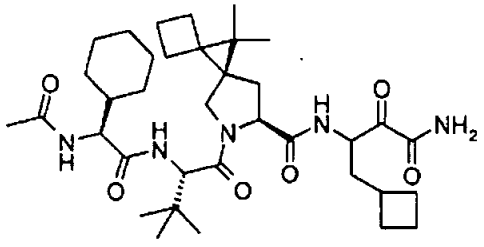
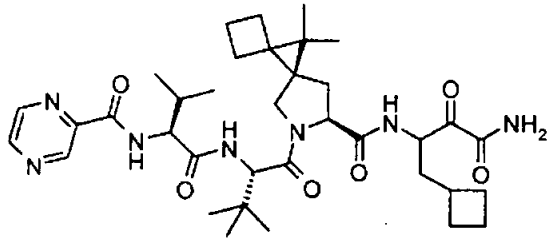
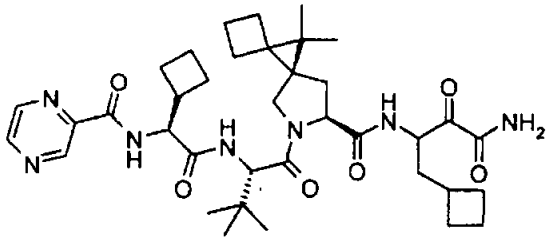
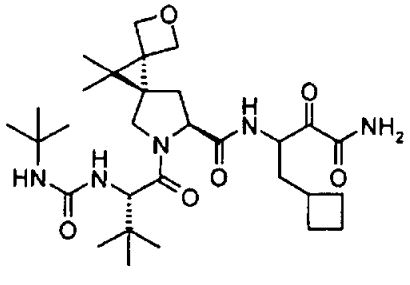
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|  | **B-15** |

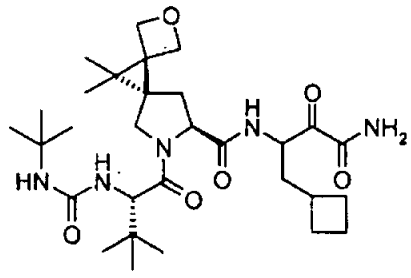
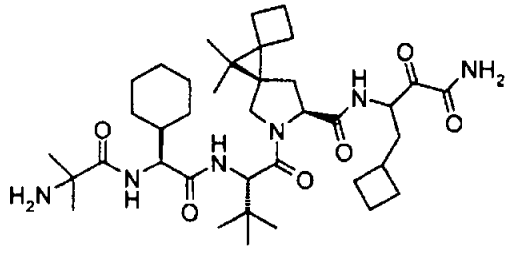
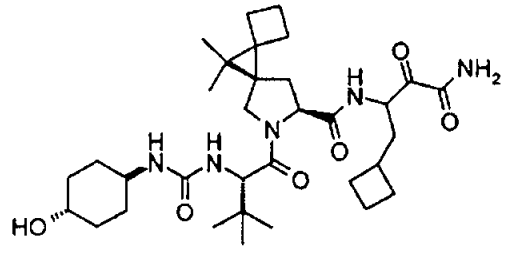
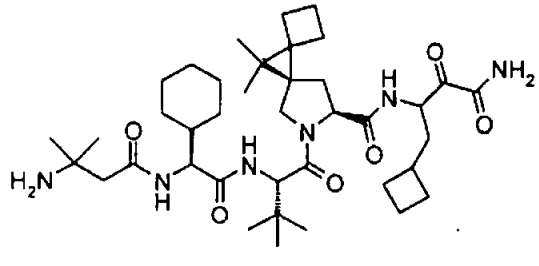
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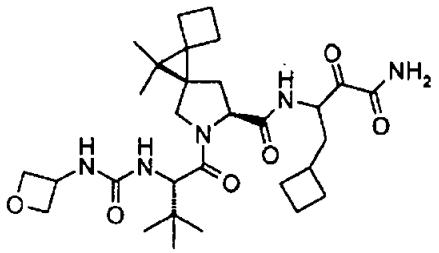
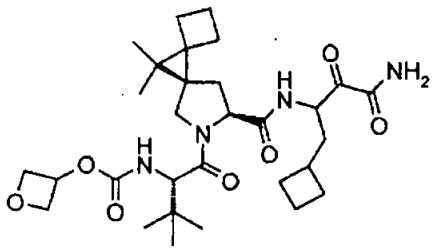
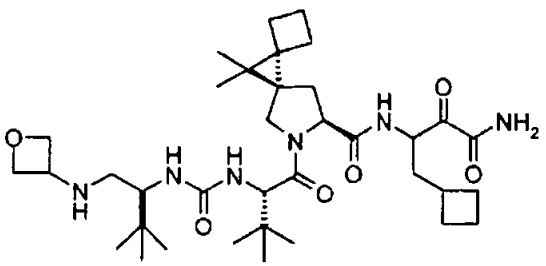
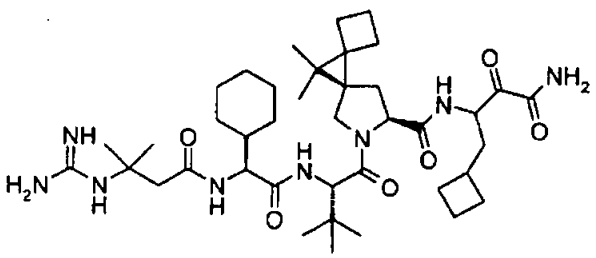
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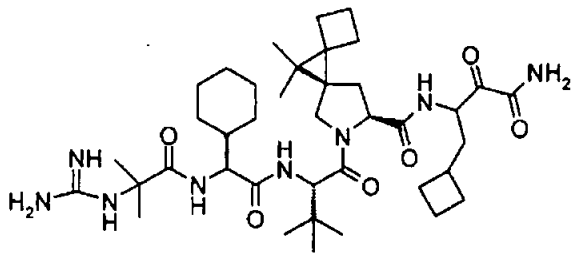
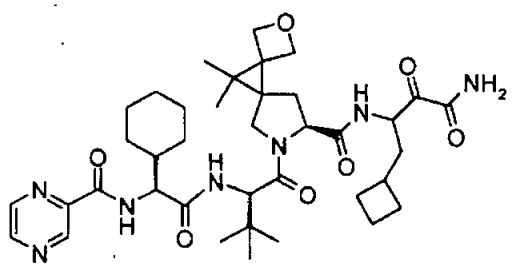
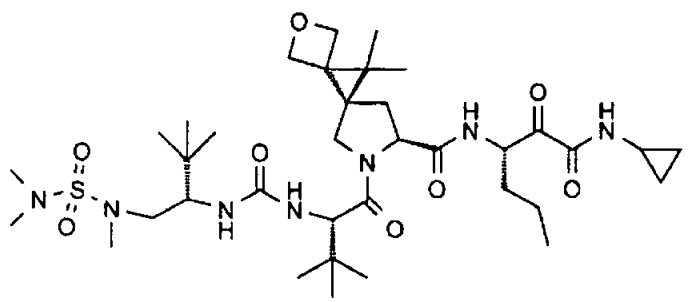
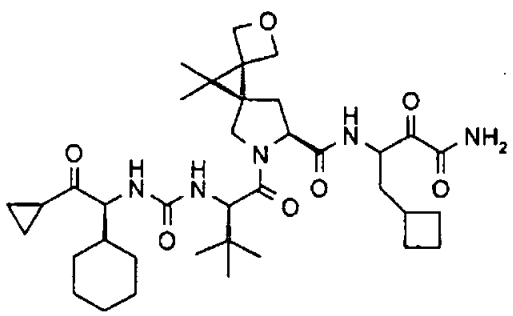
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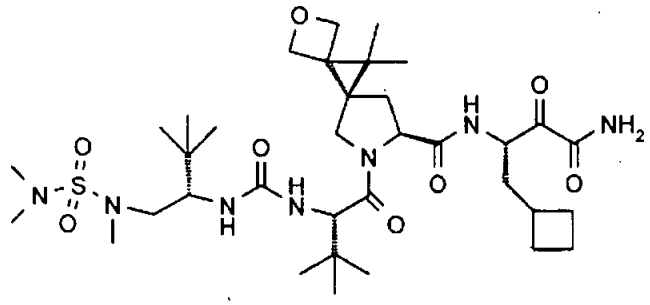
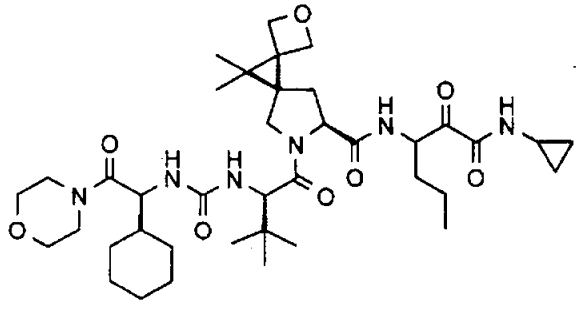
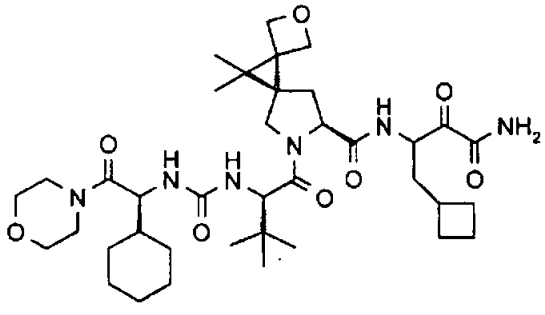
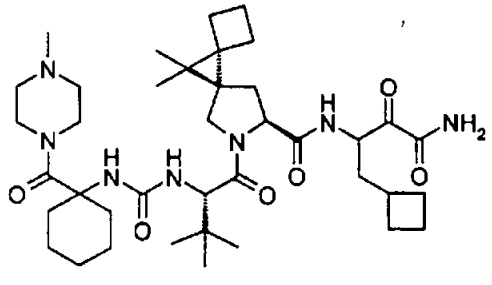
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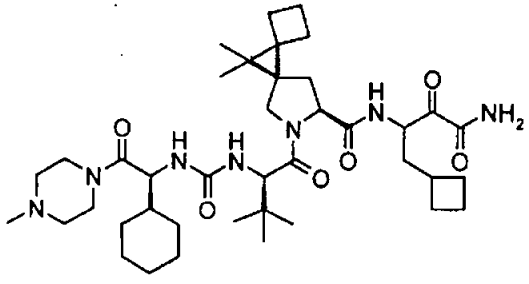
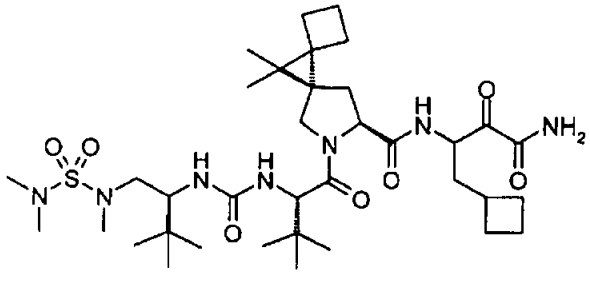
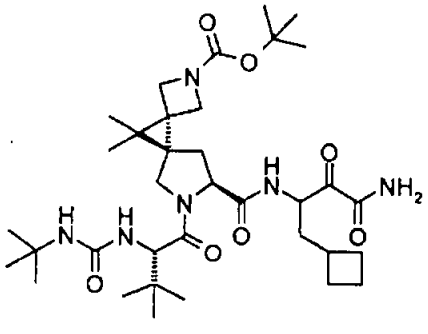
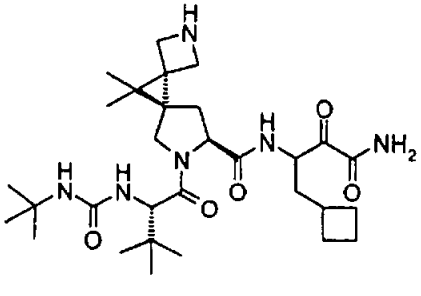
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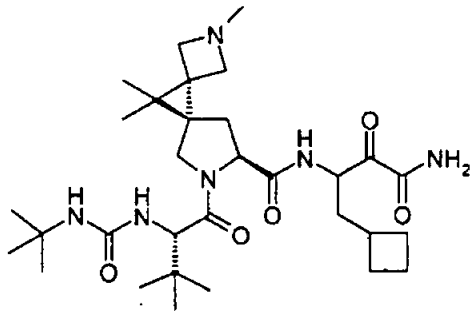
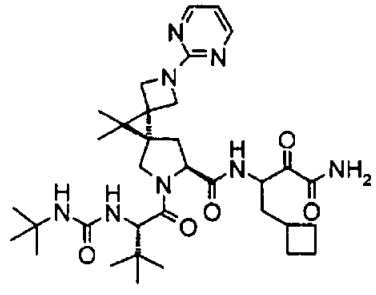
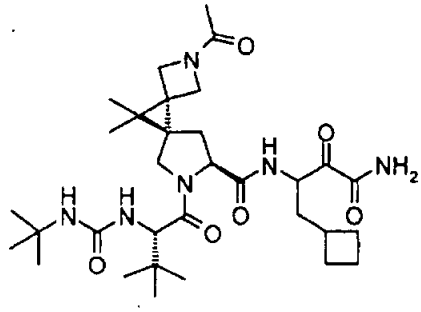
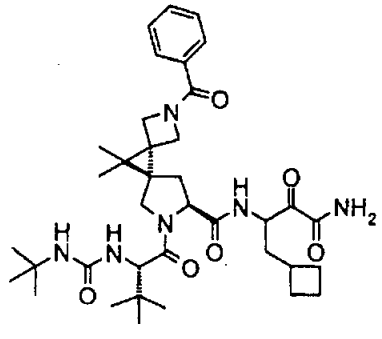
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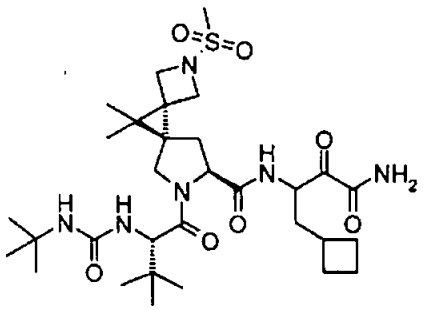
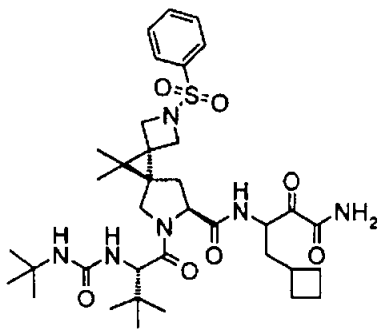
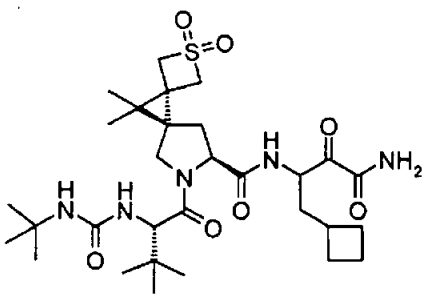
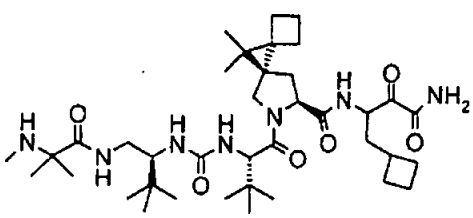
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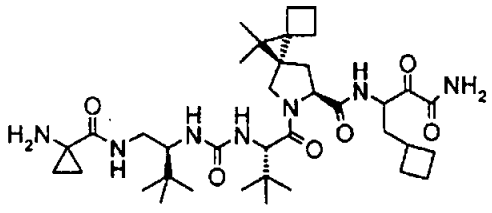
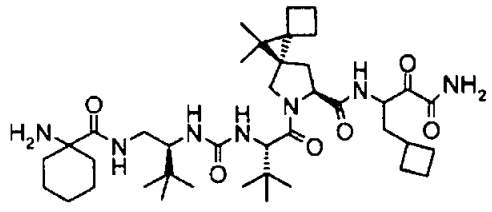
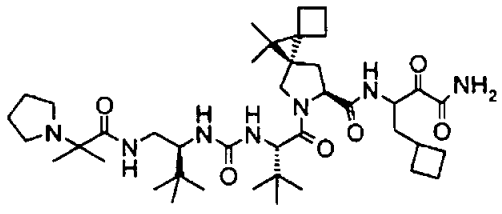
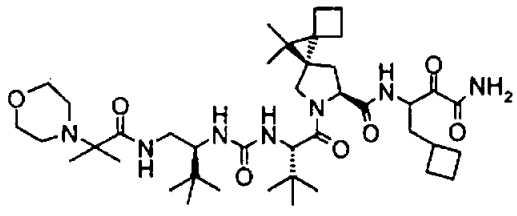
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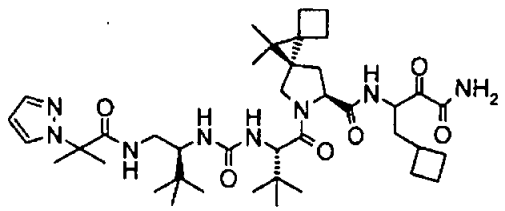
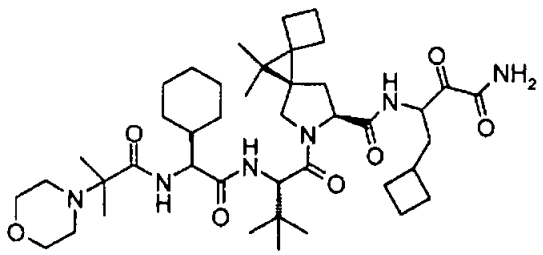
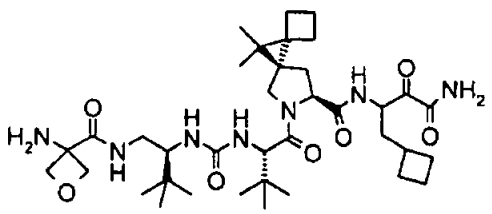
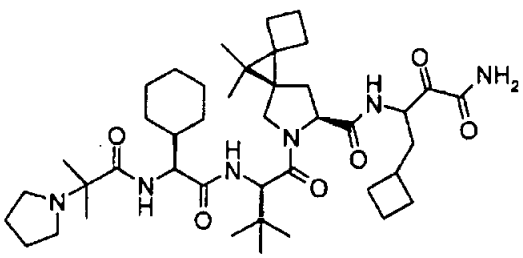
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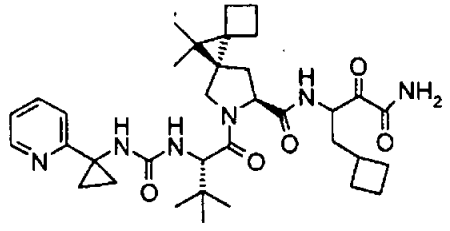
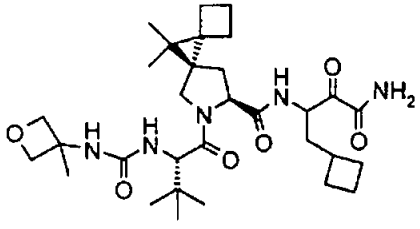
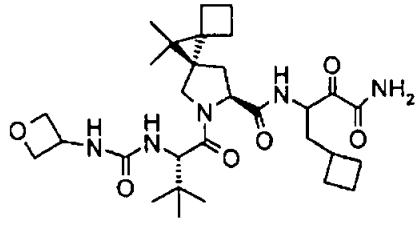
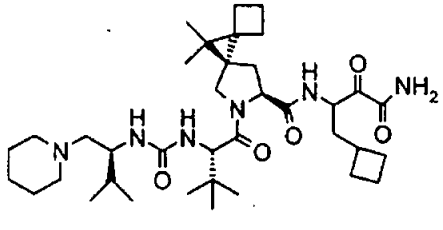
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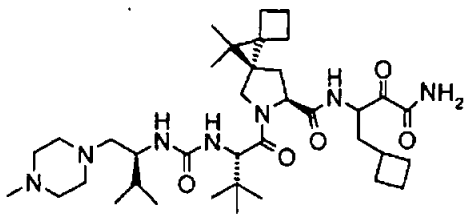
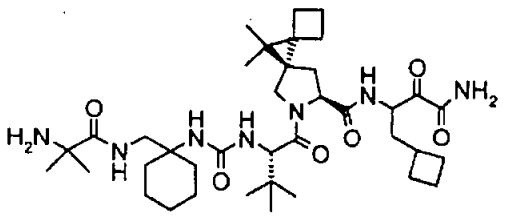
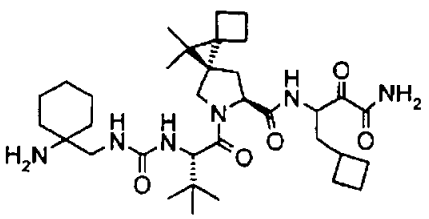
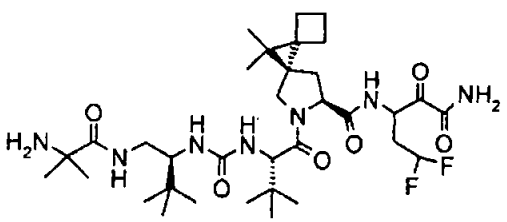
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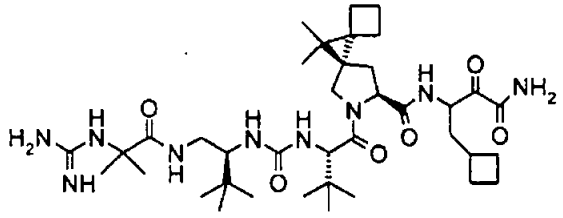
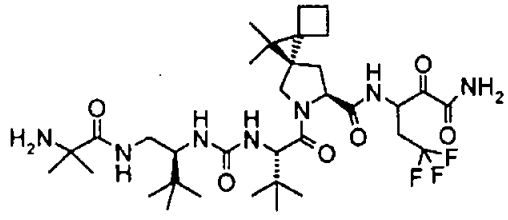
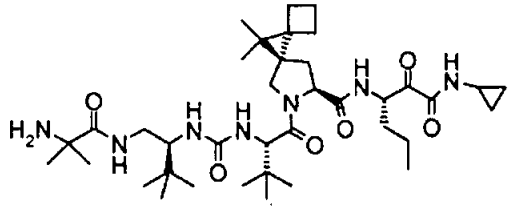
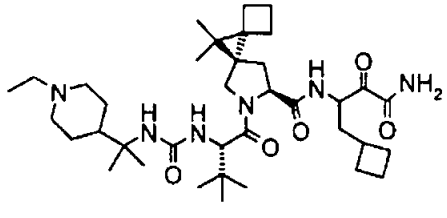
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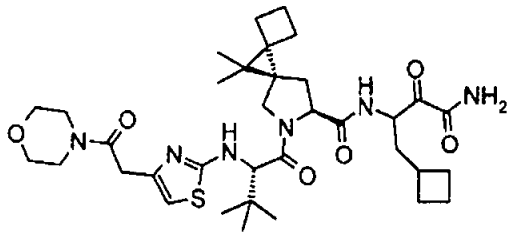
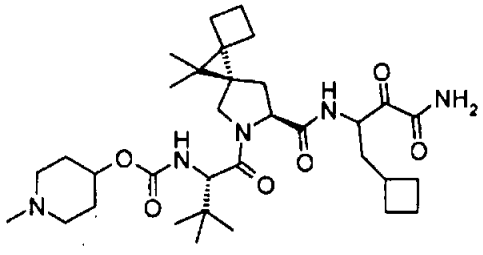
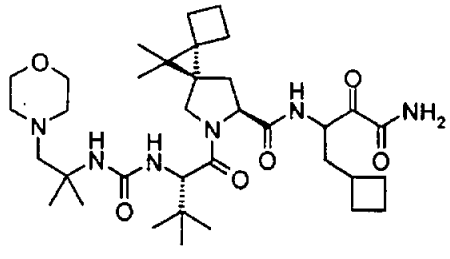
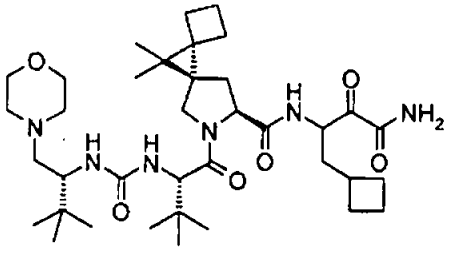
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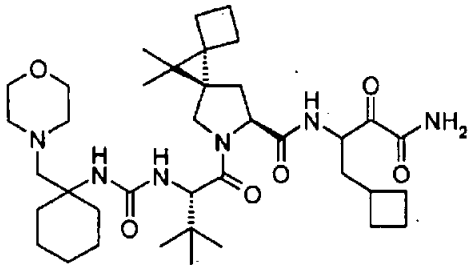
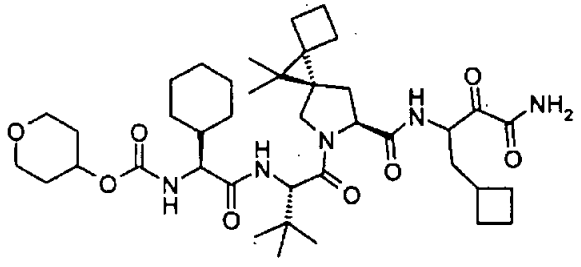
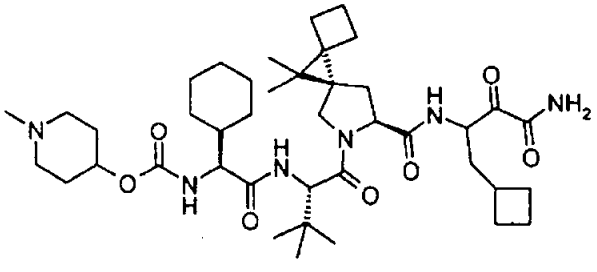
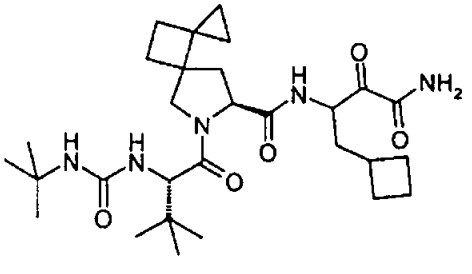
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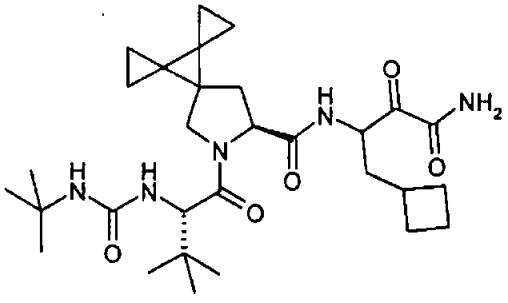
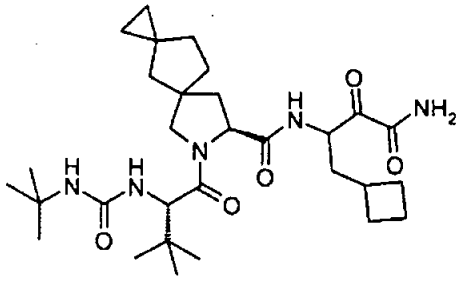
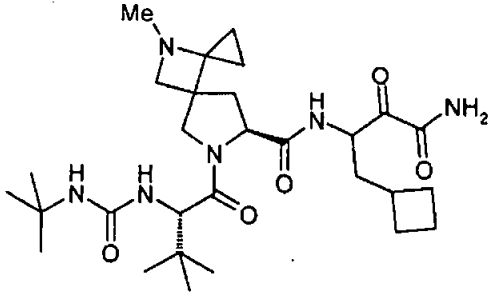
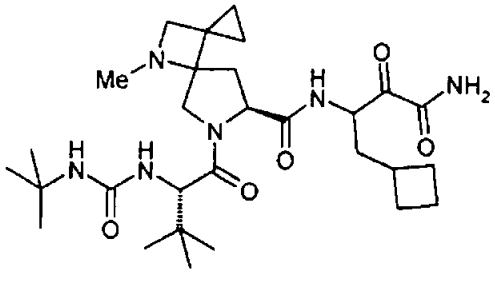
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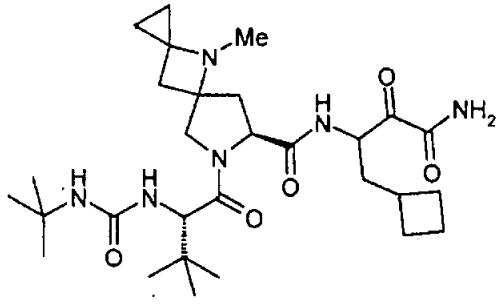
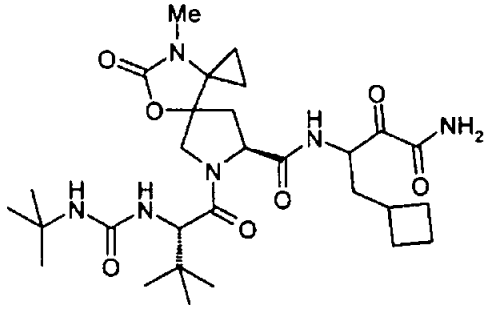
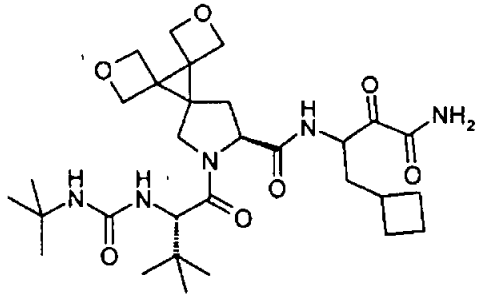
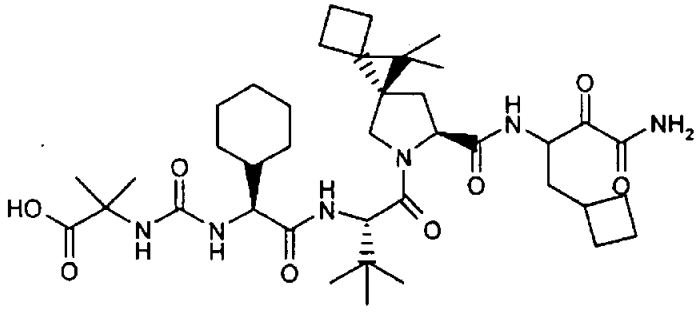
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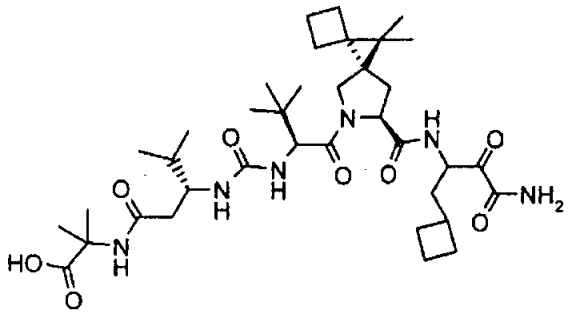
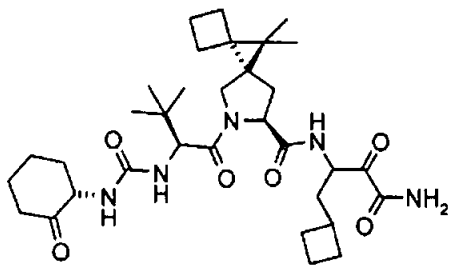
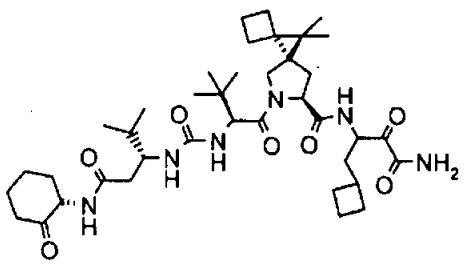
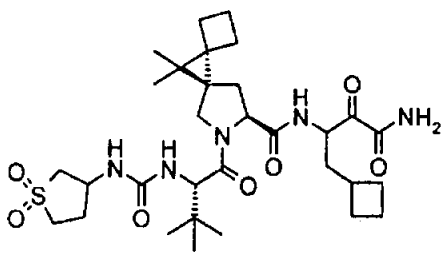
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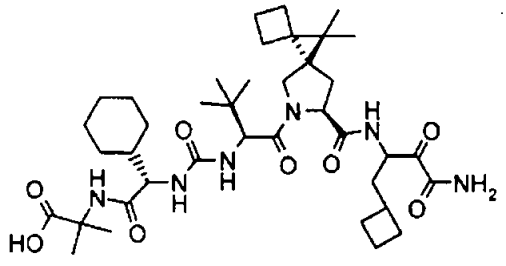
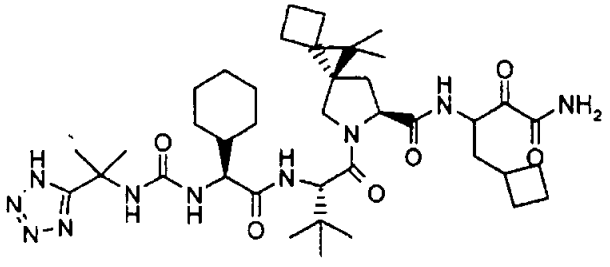
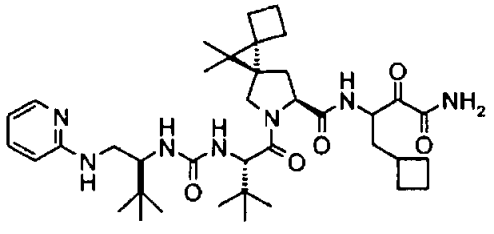
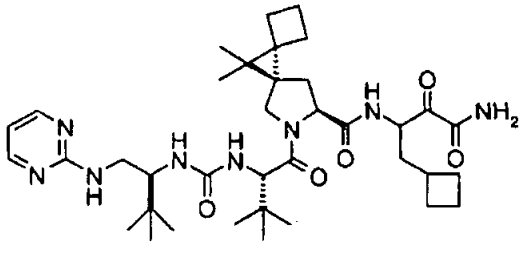
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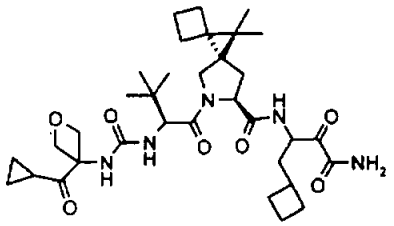
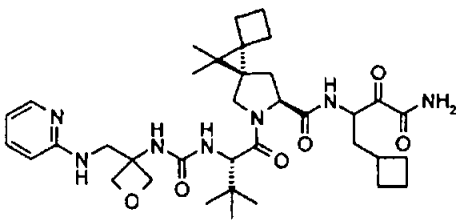
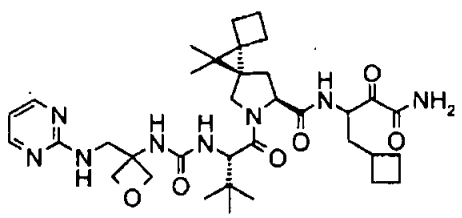
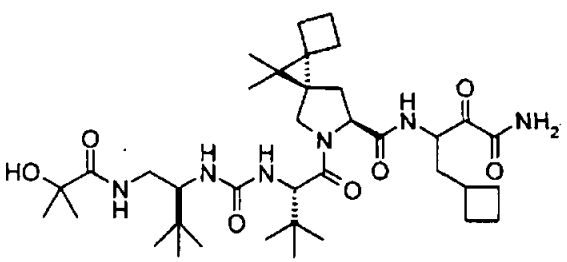
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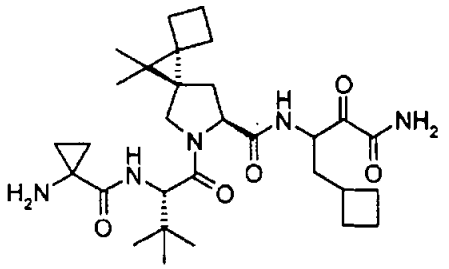
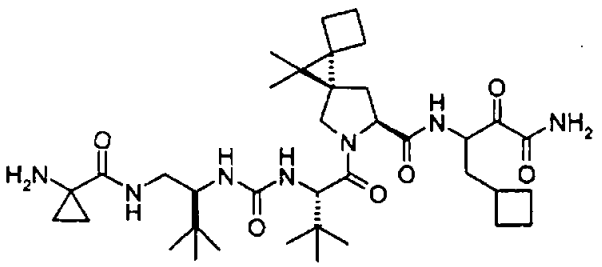
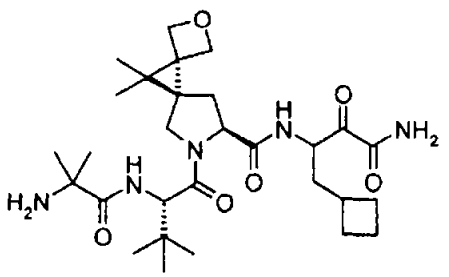
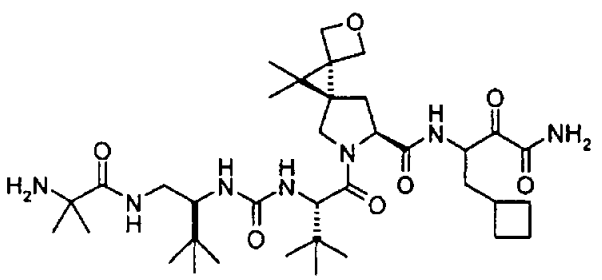
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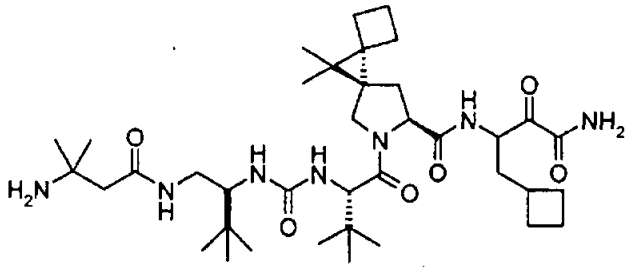
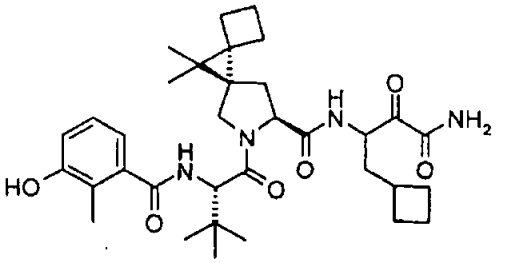
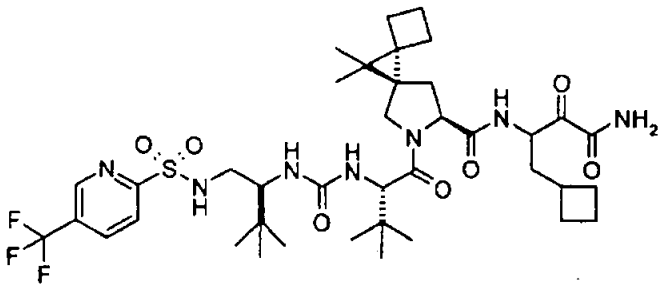
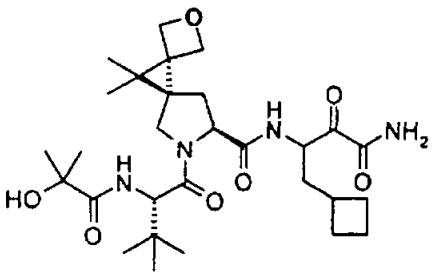
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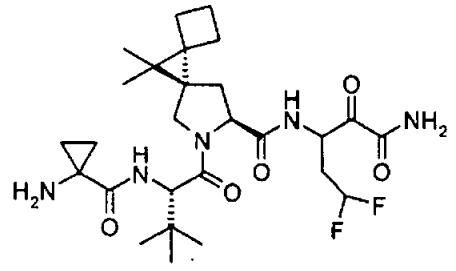
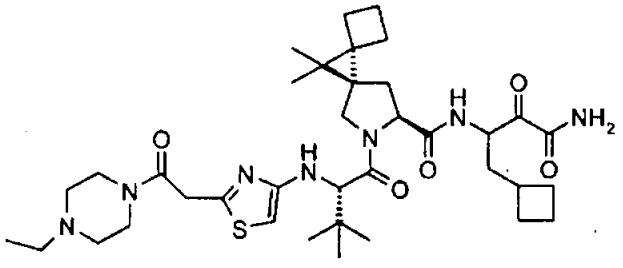
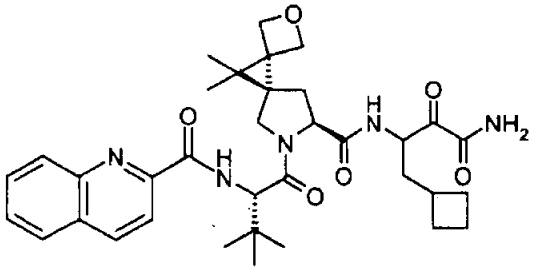
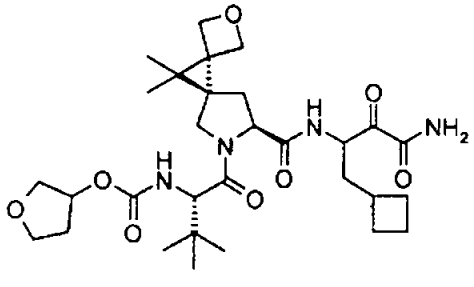
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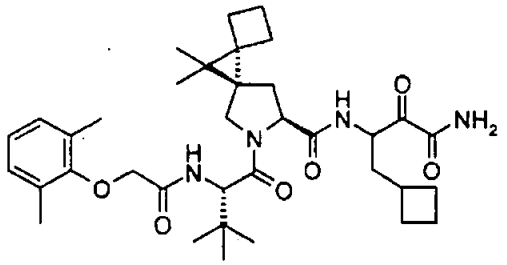
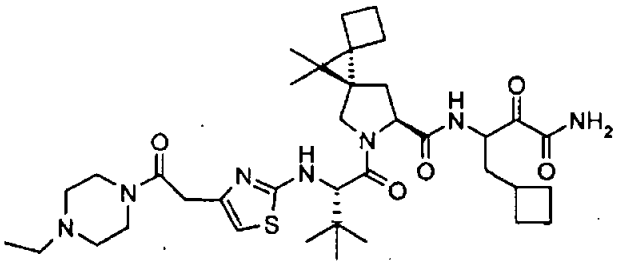
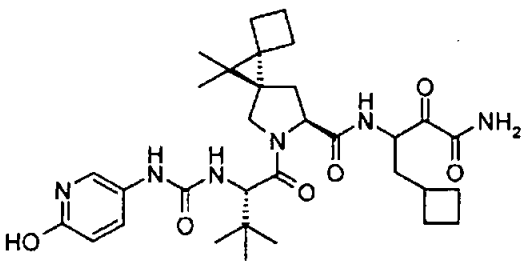
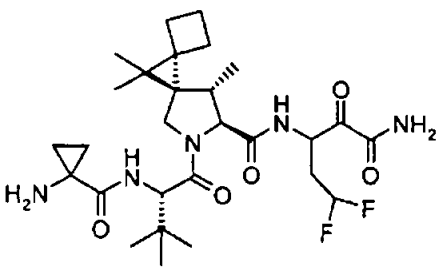
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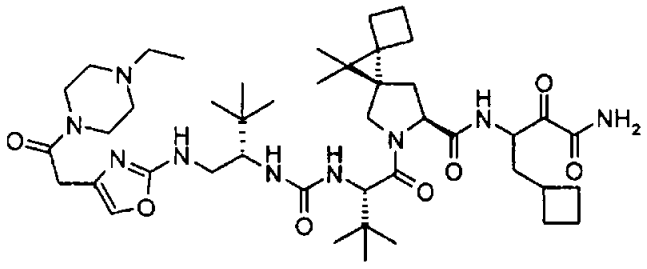
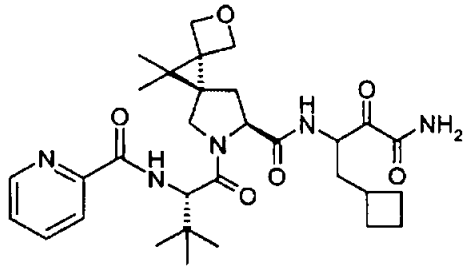
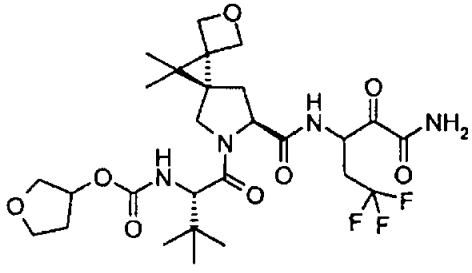
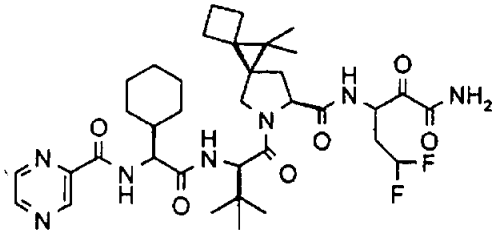
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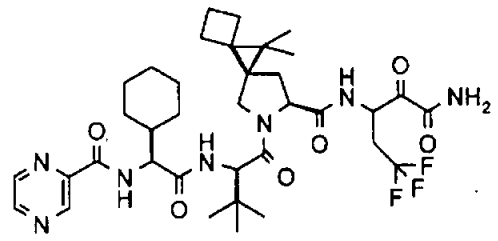
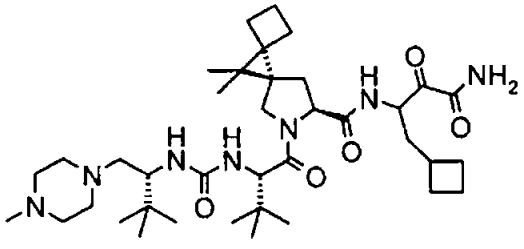
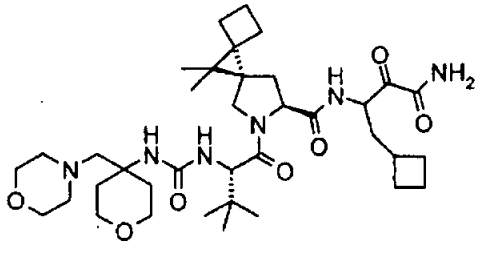
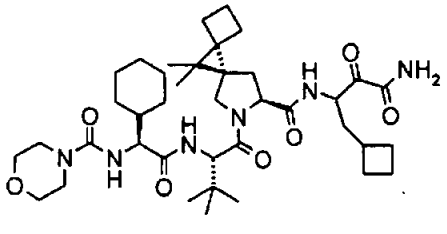
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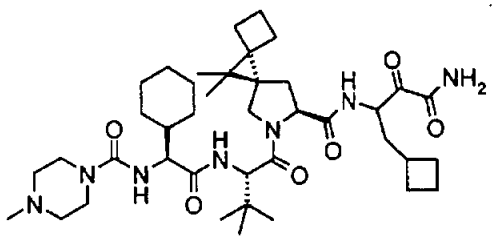
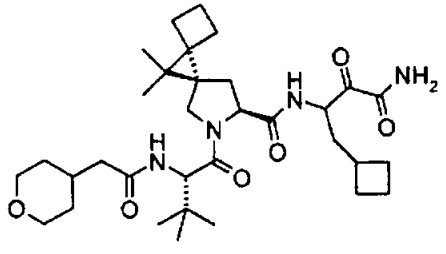
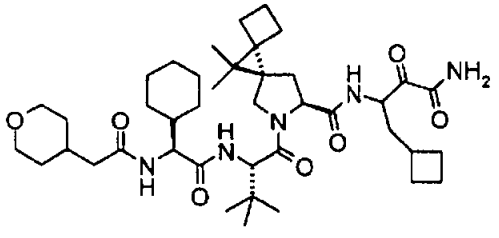
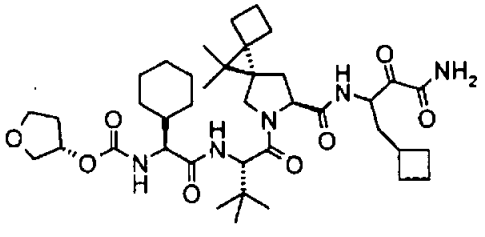
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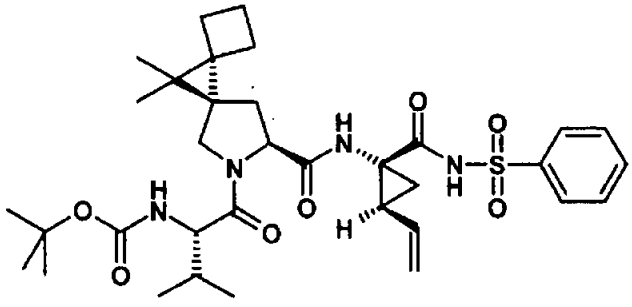
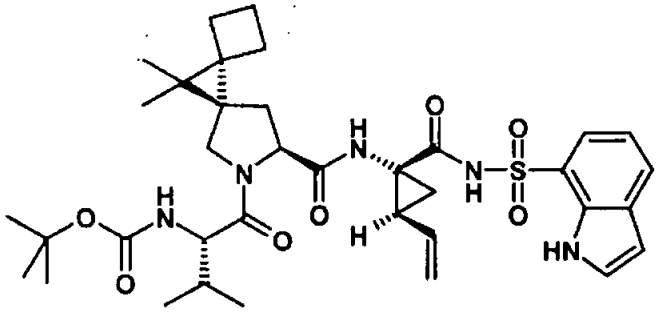
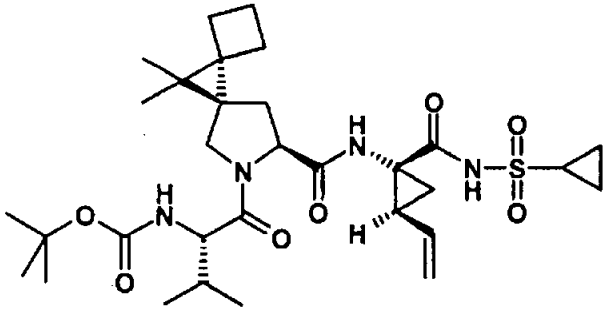
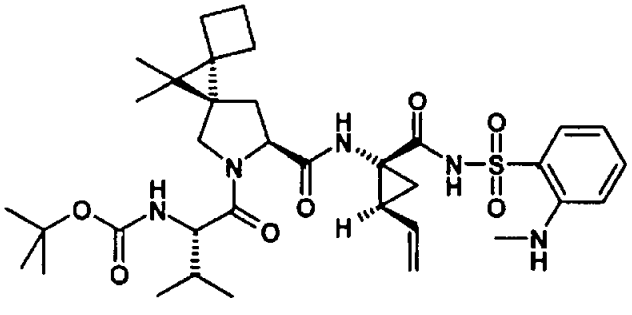
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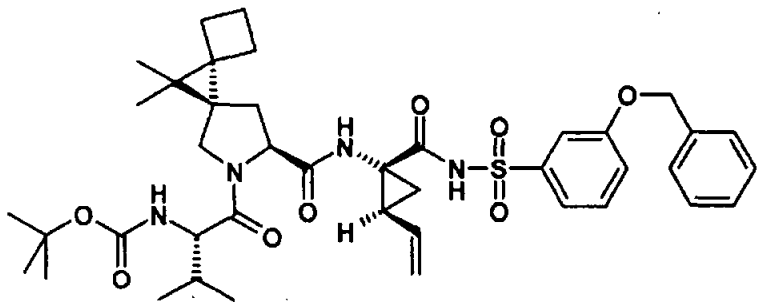
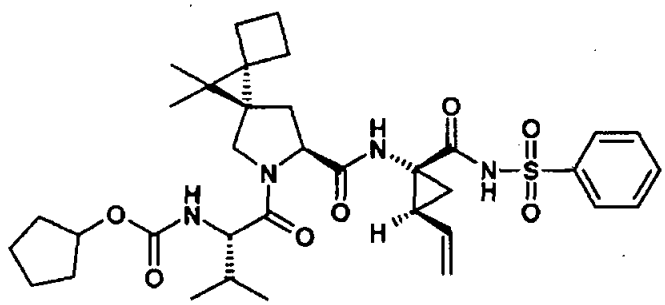
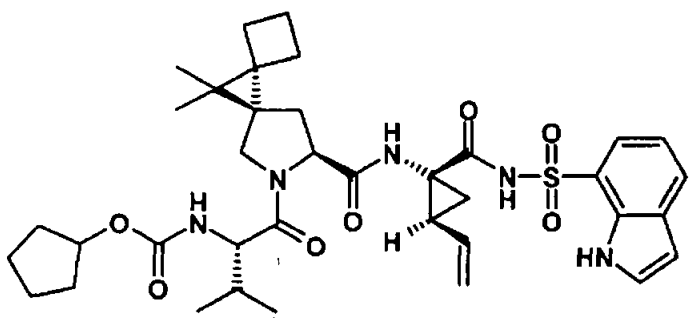
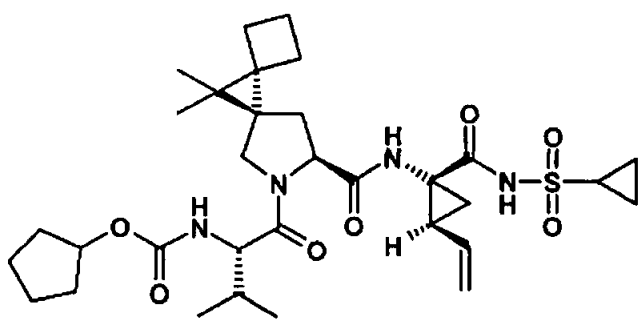
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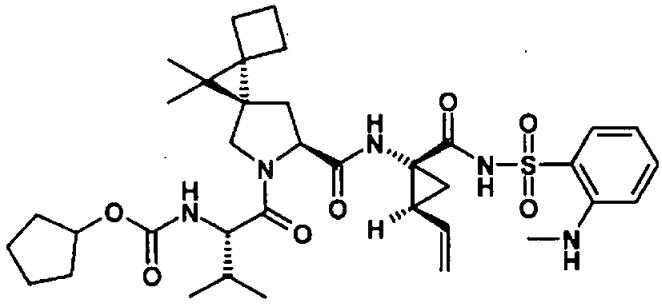
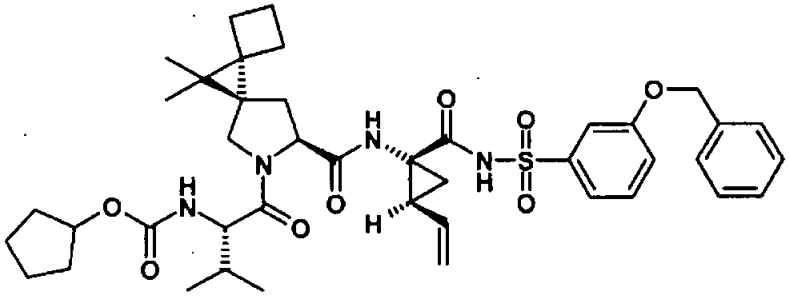
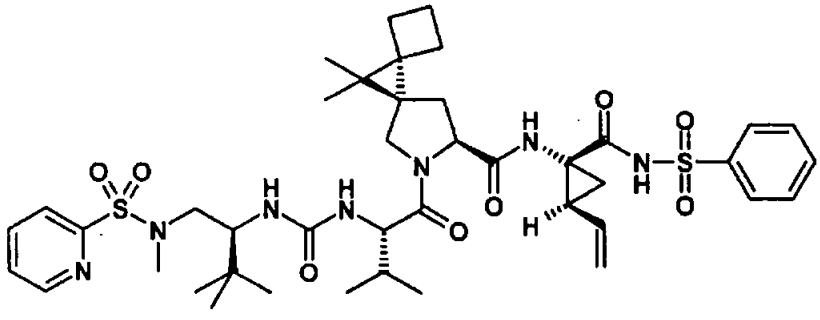
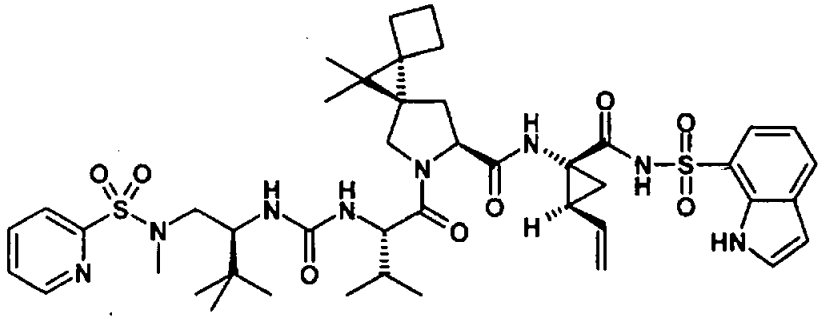
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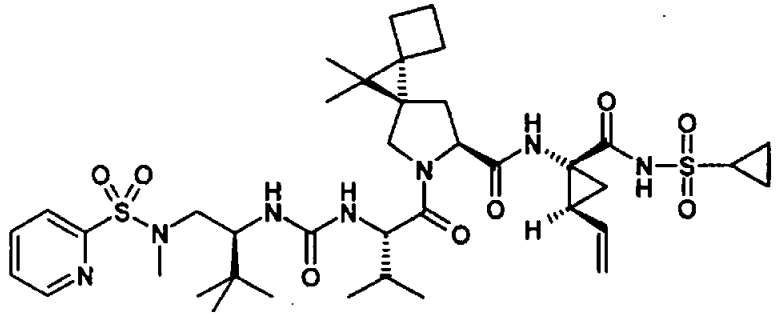
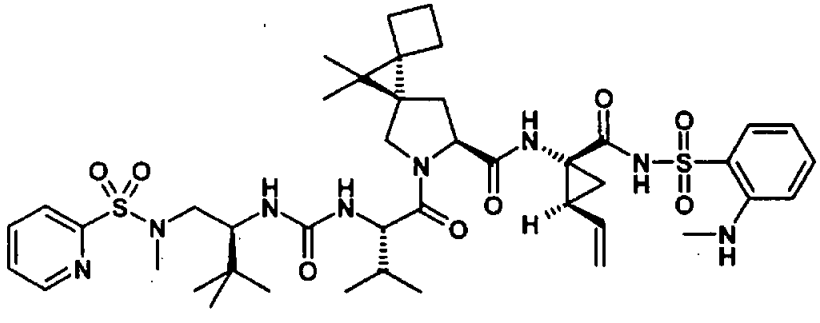
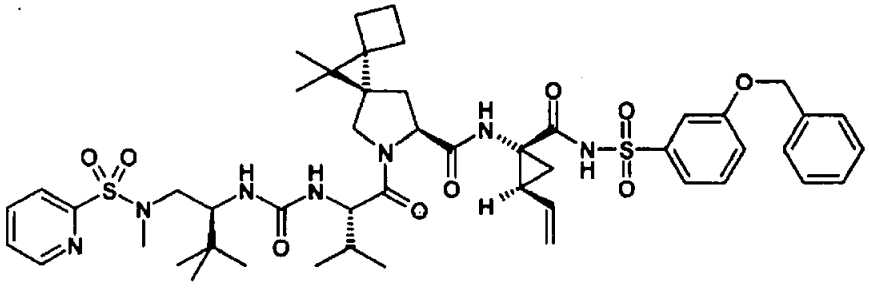
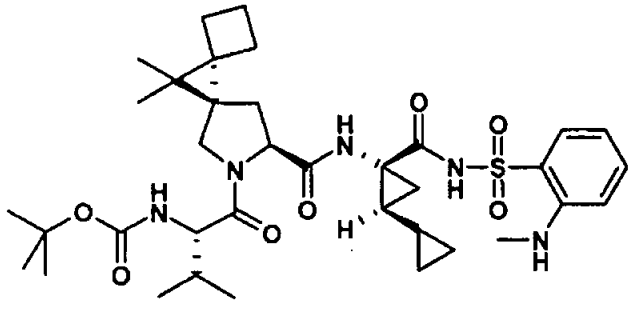
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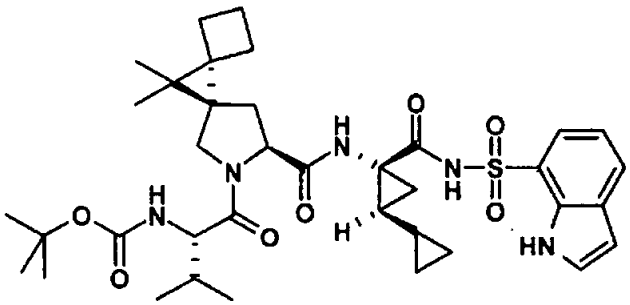
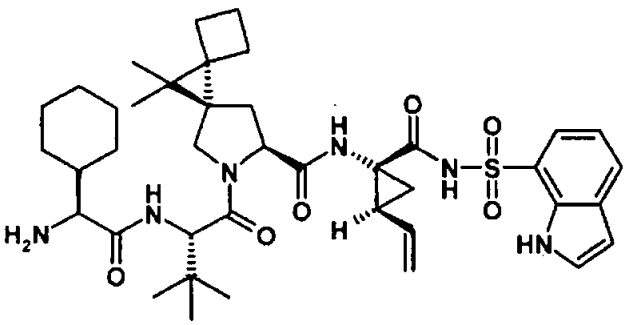
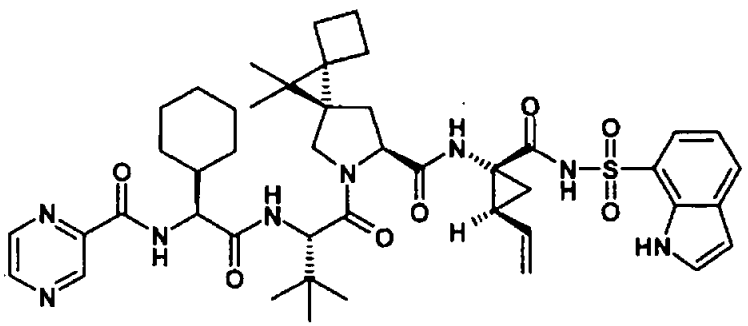
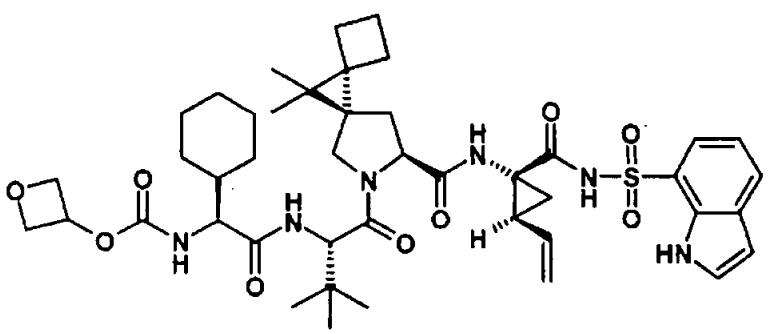
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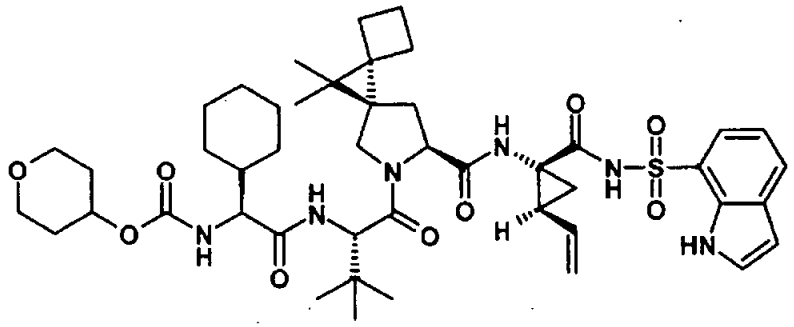
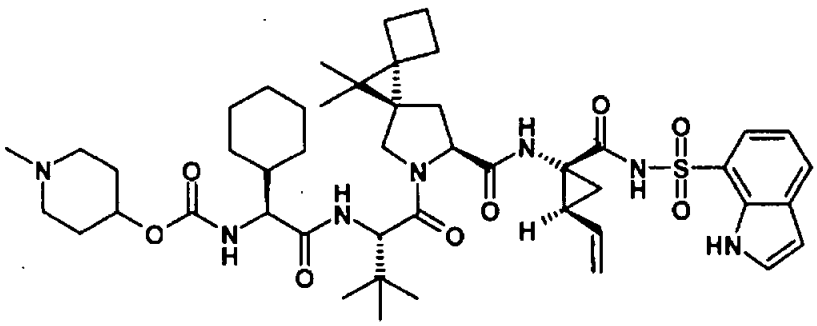
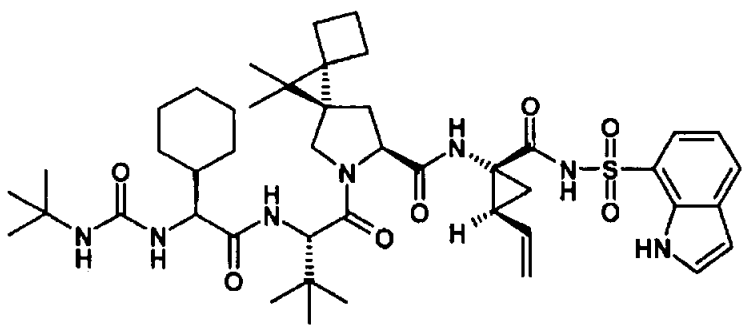
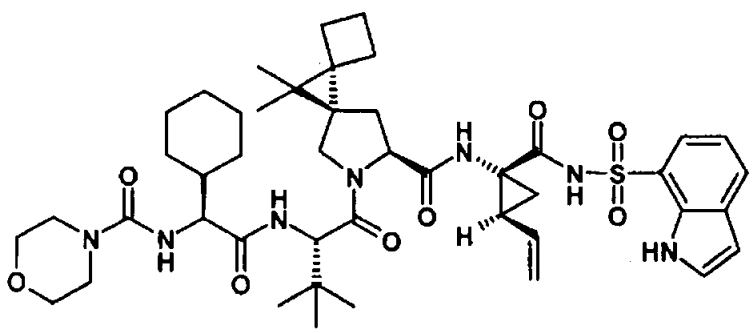
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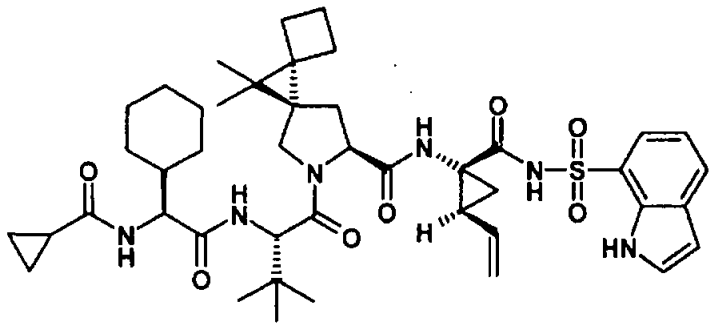
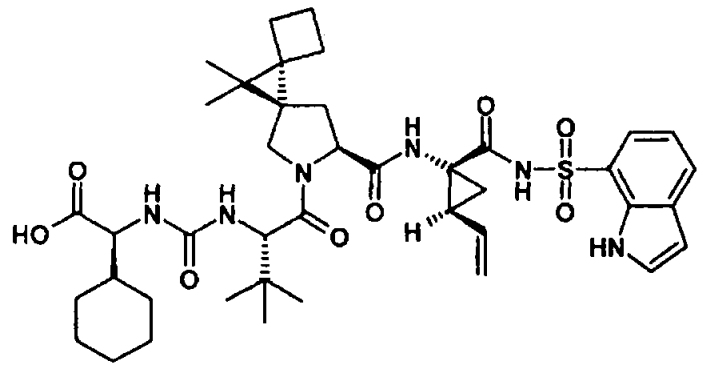
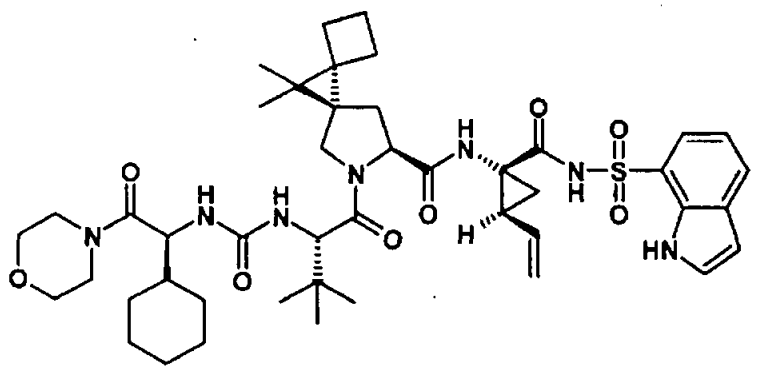
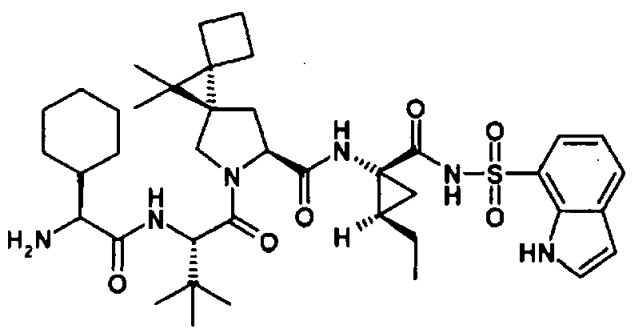
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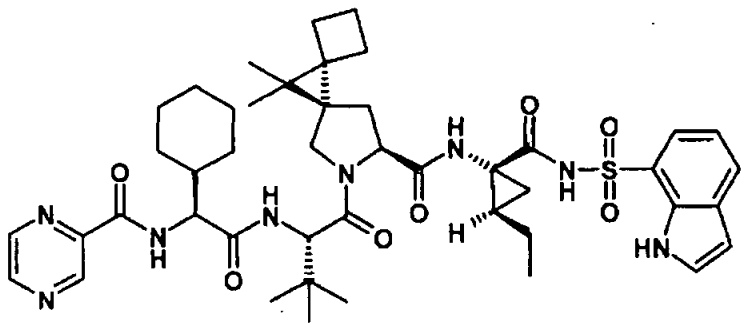
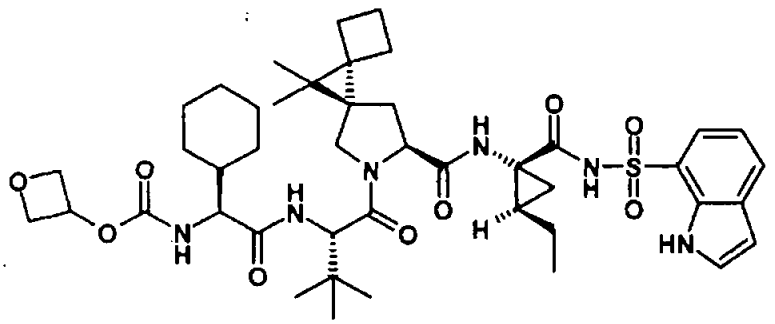
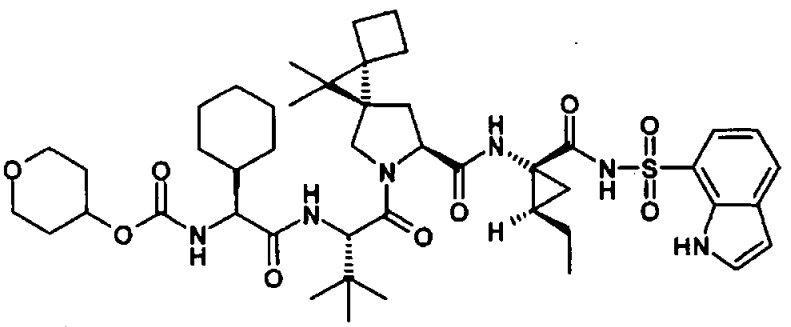
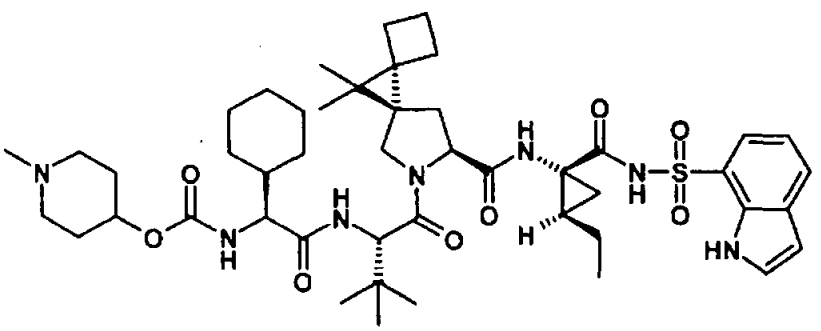
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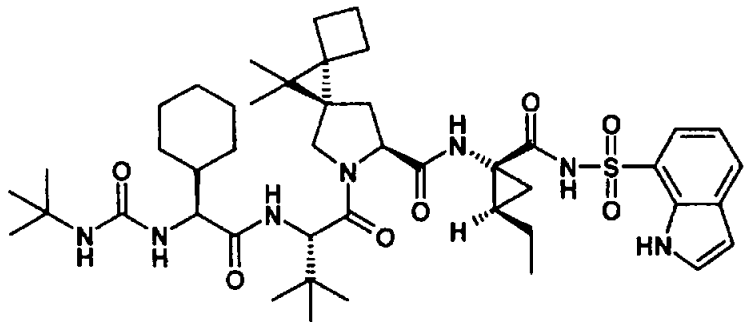
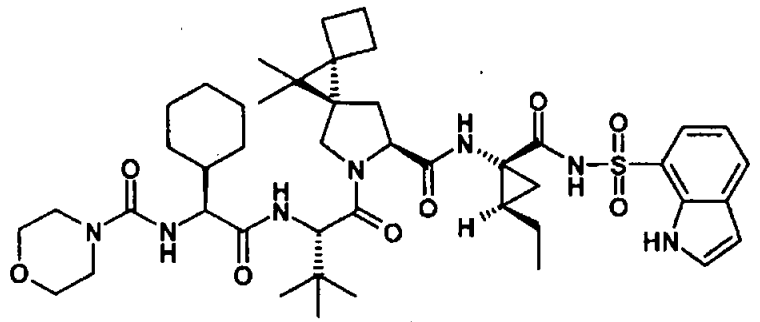
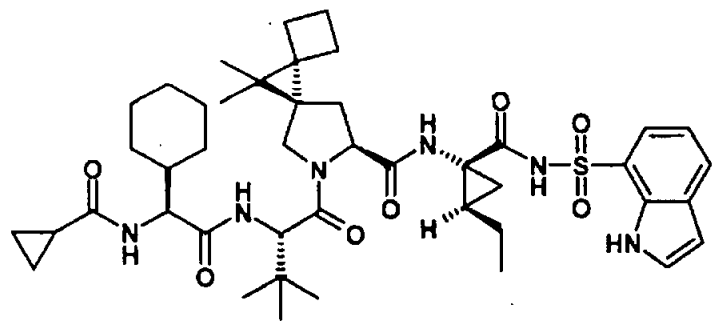
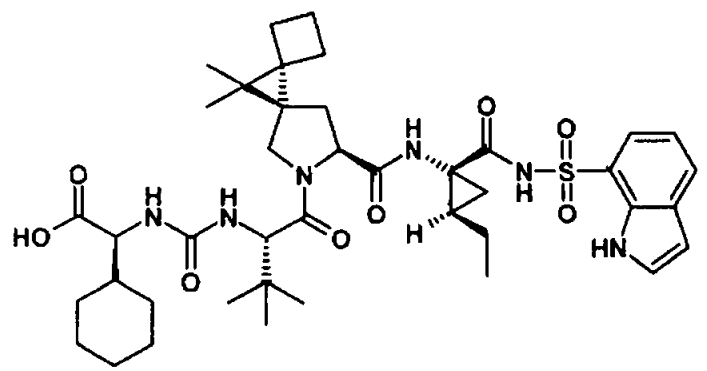
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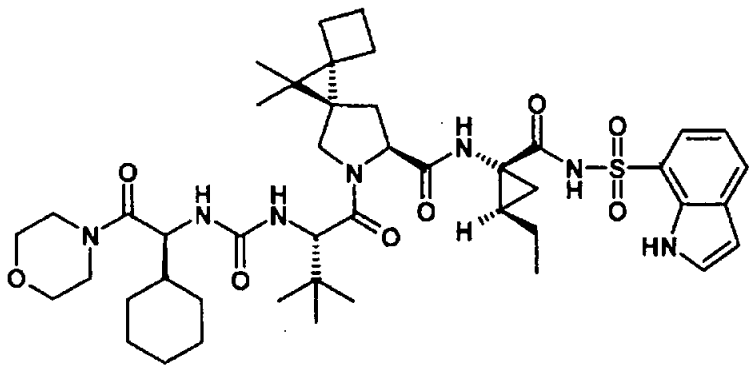
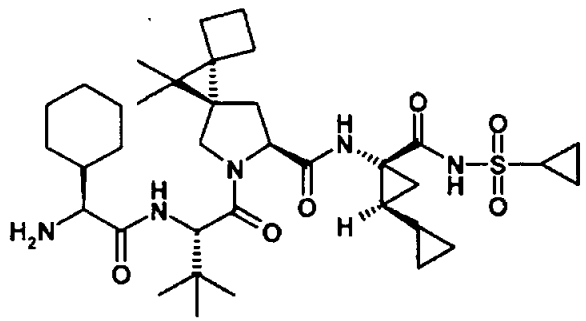
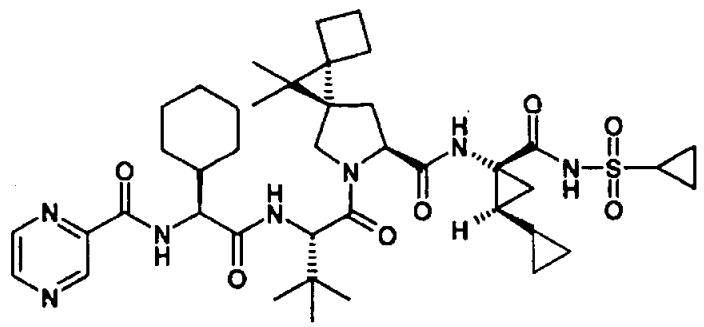
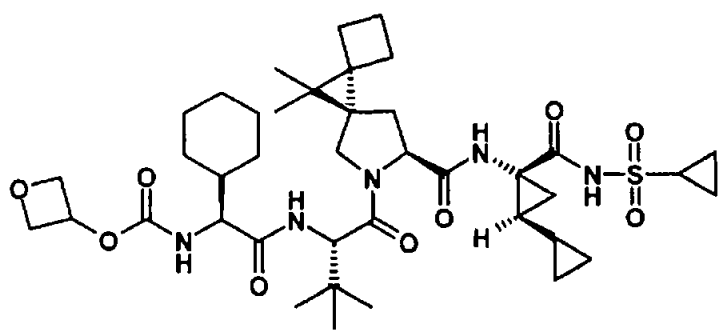
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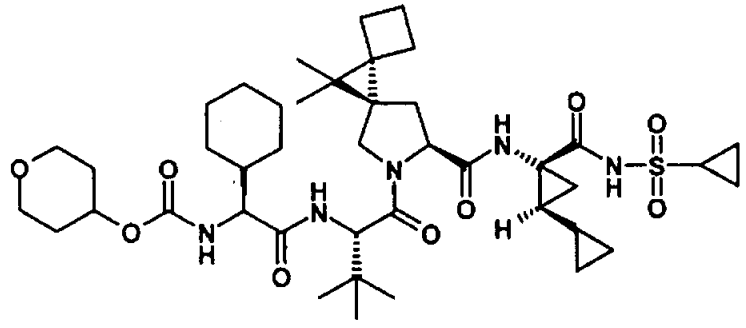
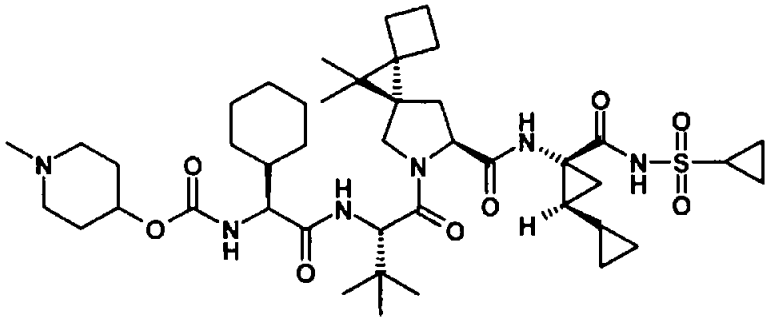
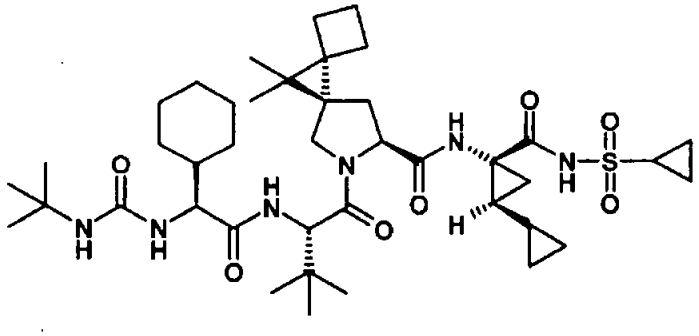
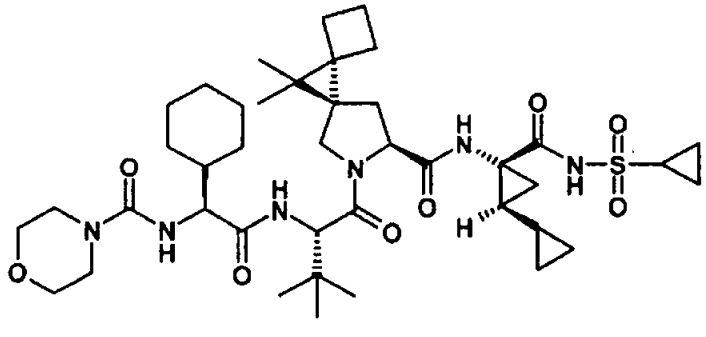
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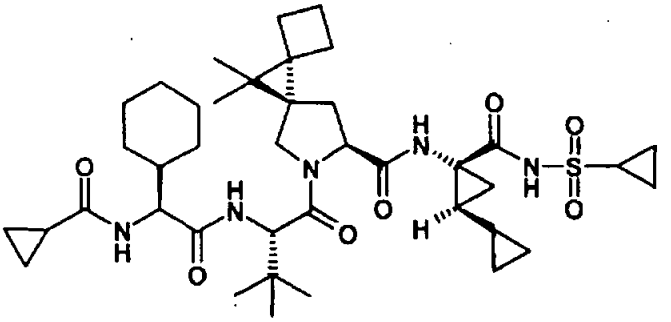
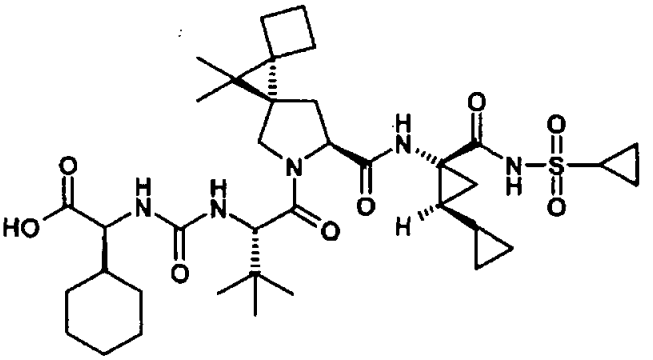
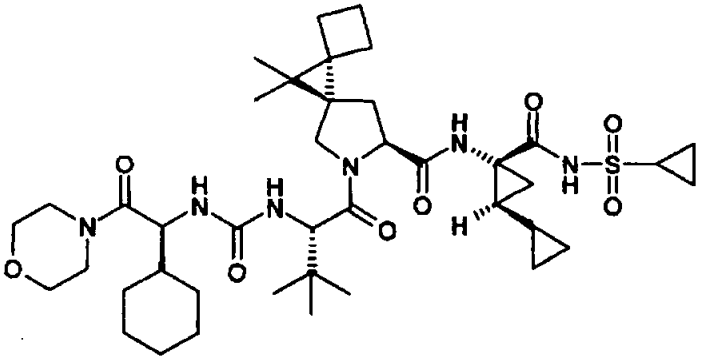
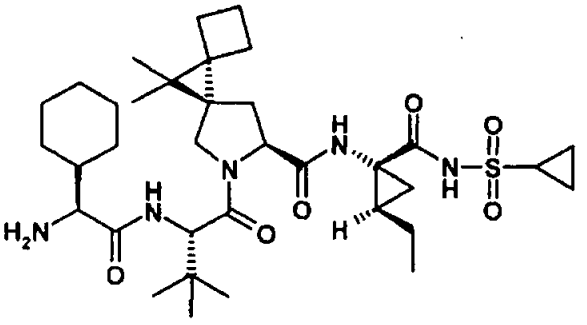
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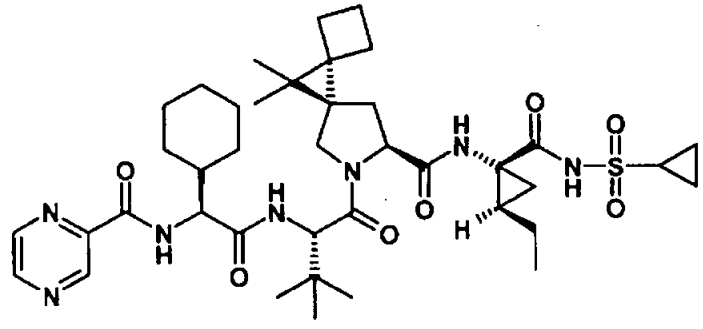
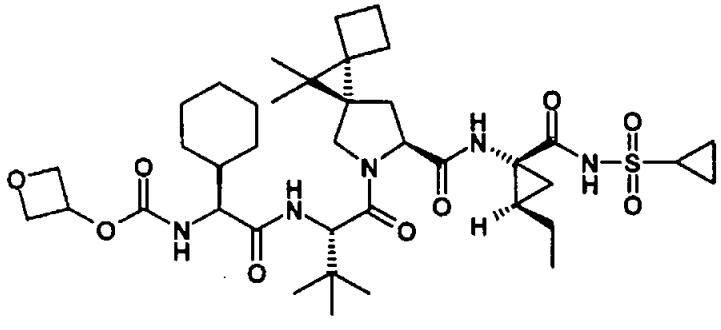
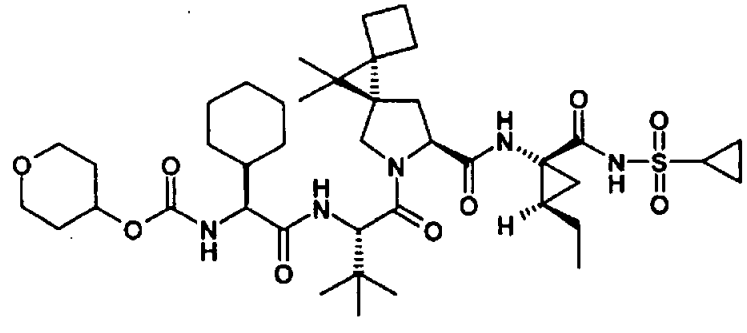
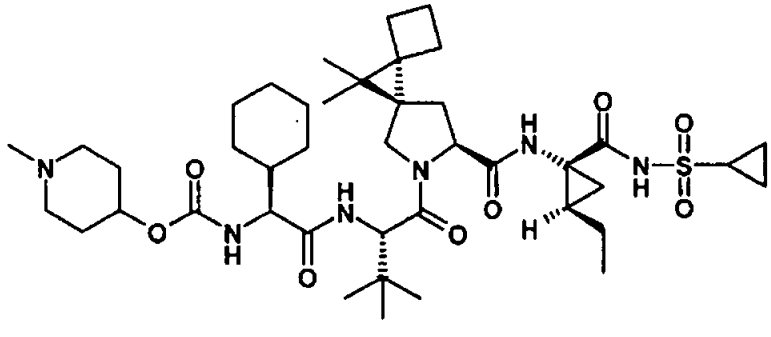
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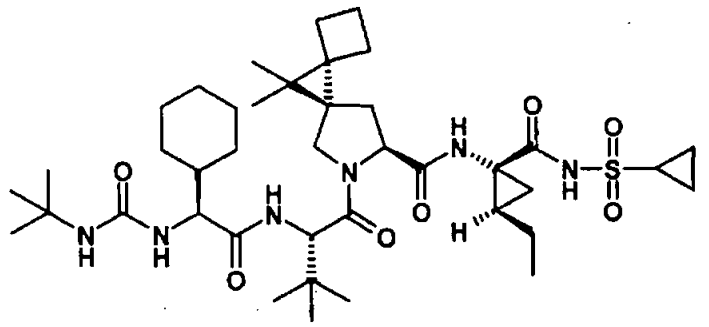
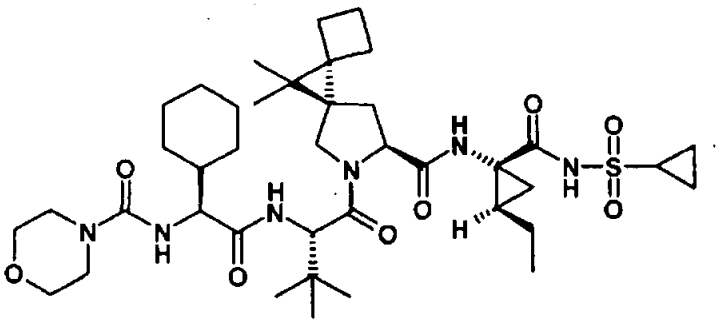
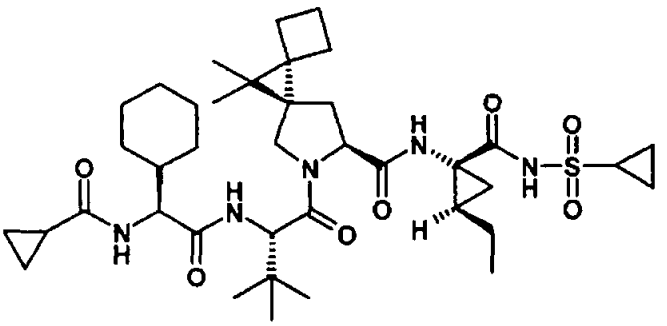
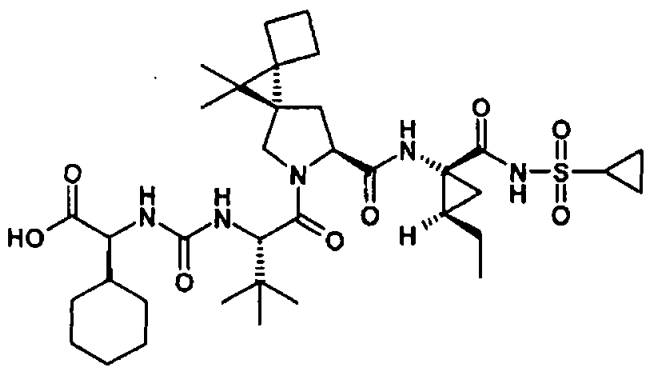
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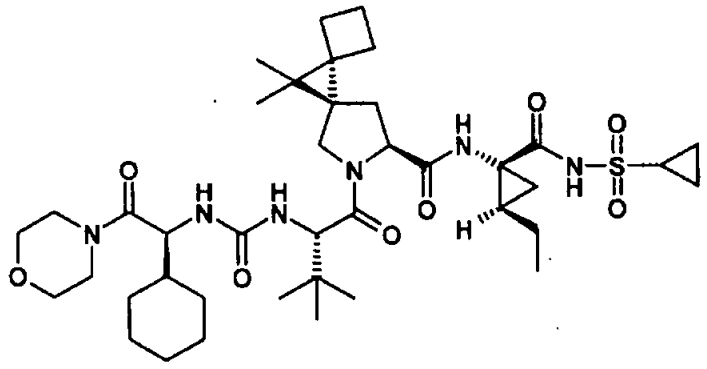
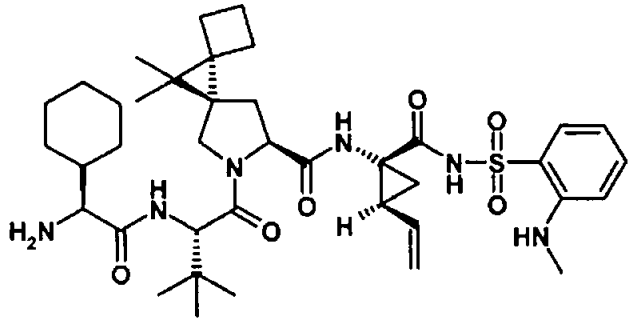
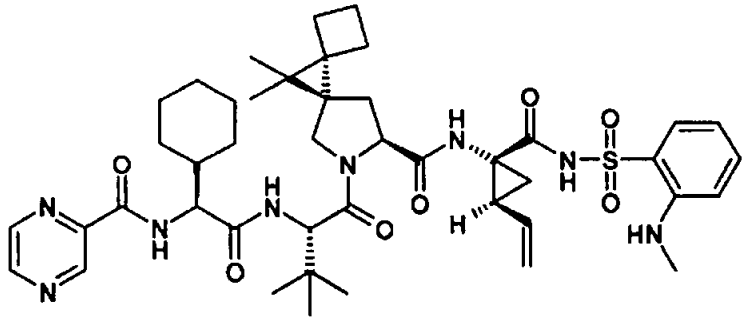
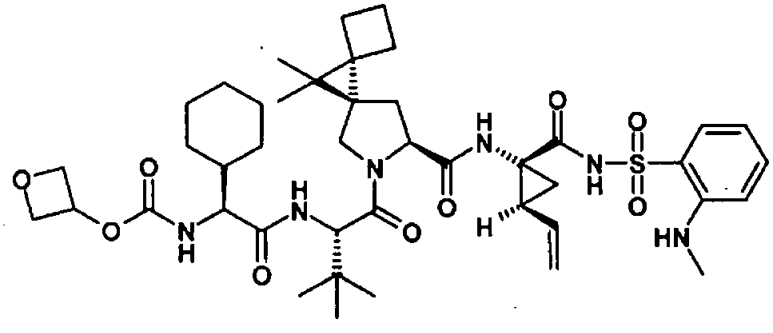
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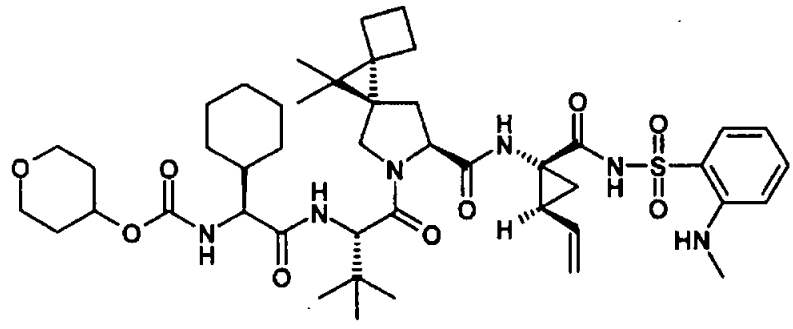
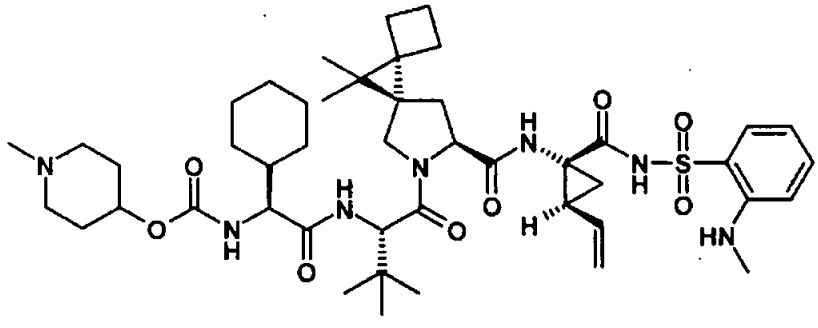
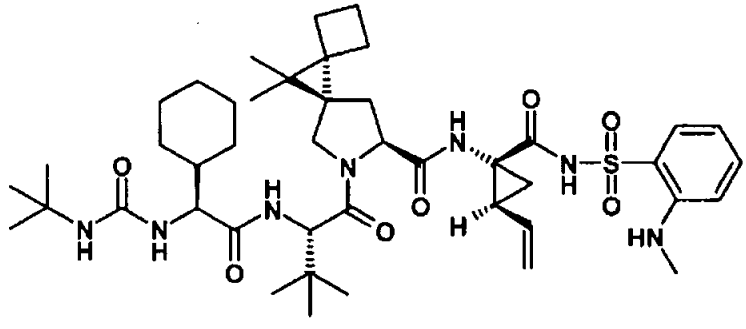
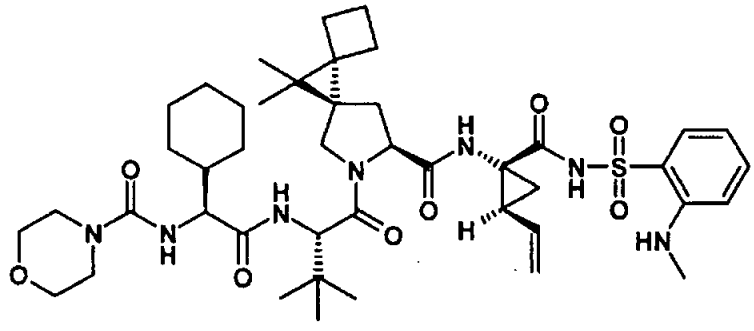
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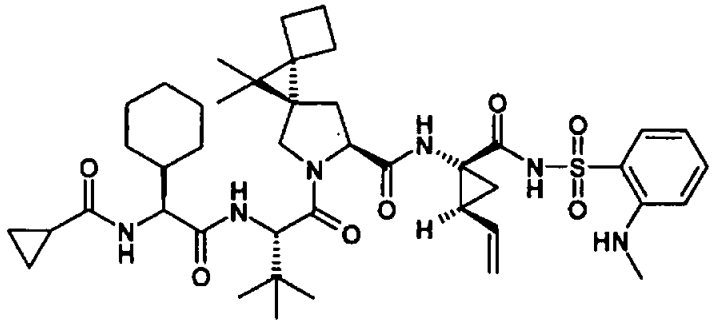
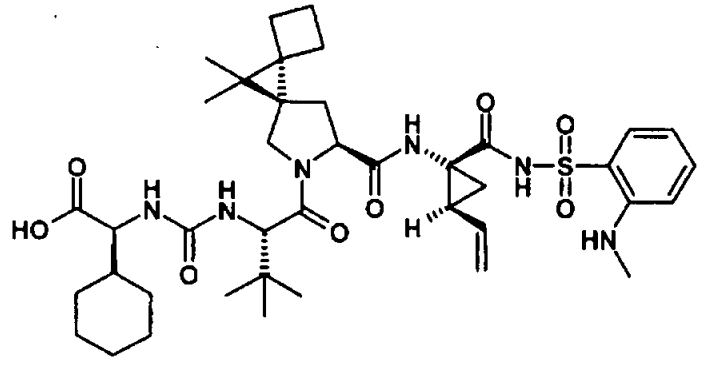
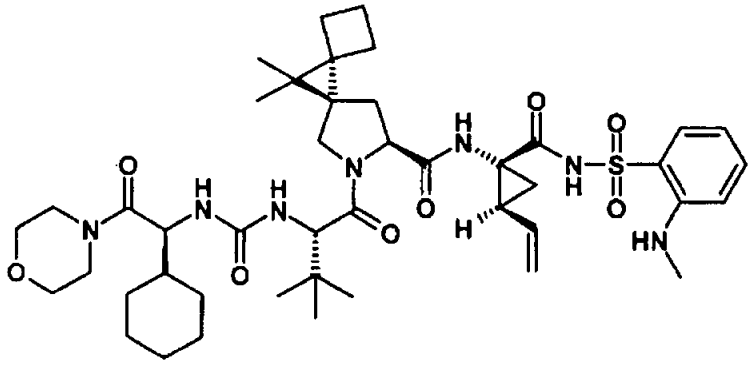
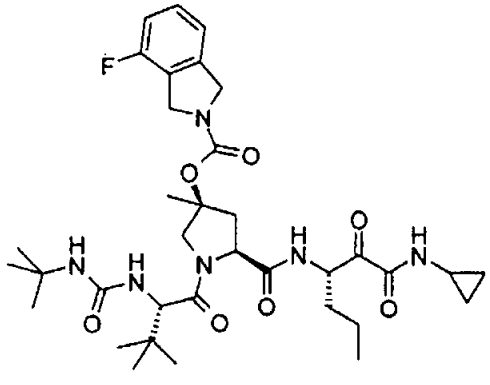
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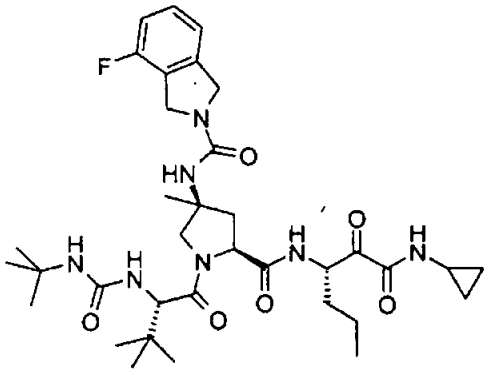
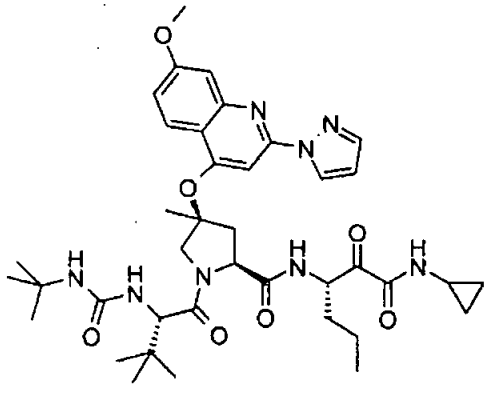
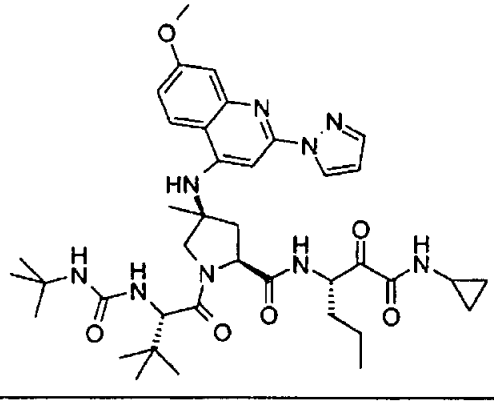
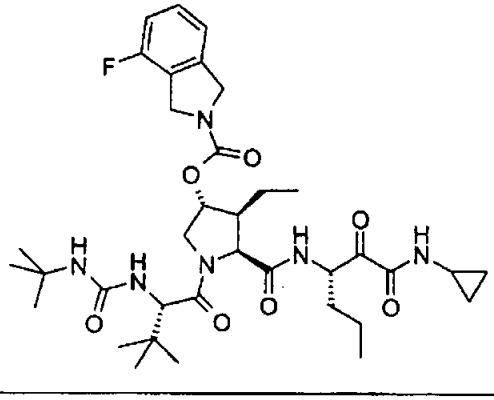
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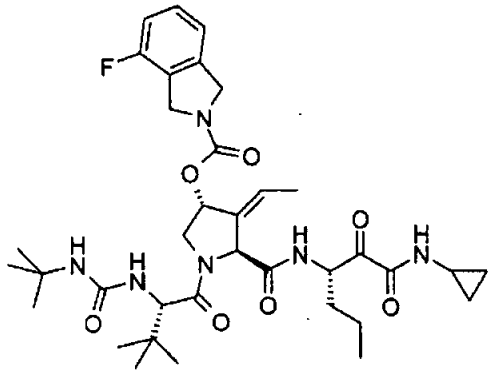
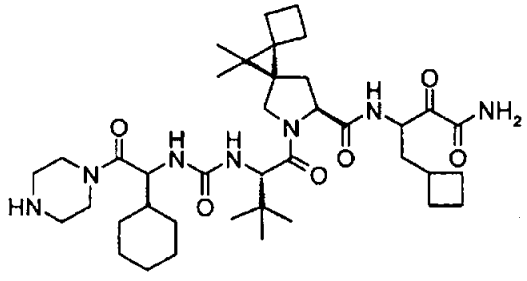
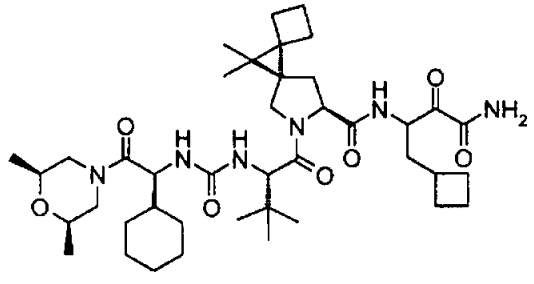
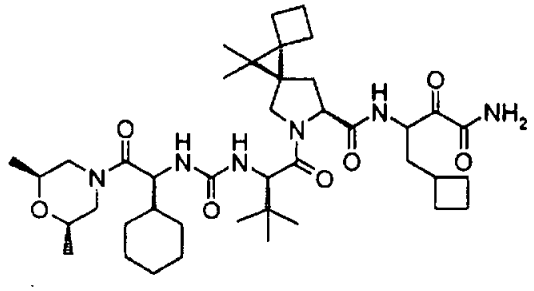
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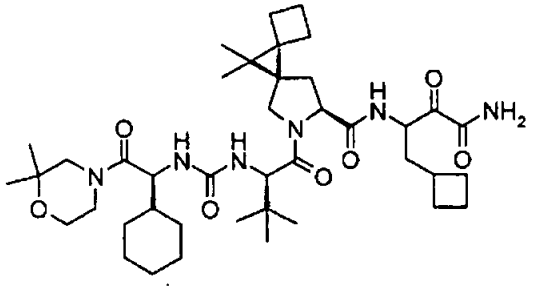
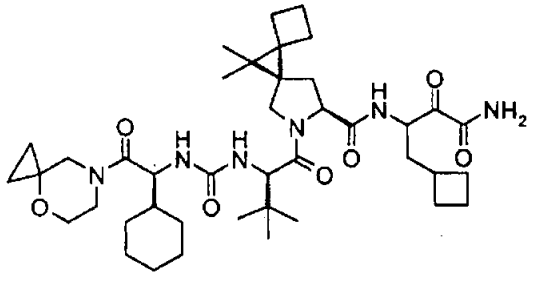
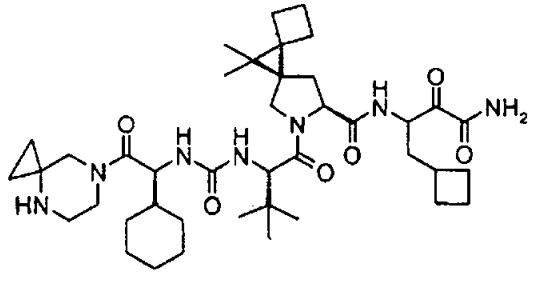
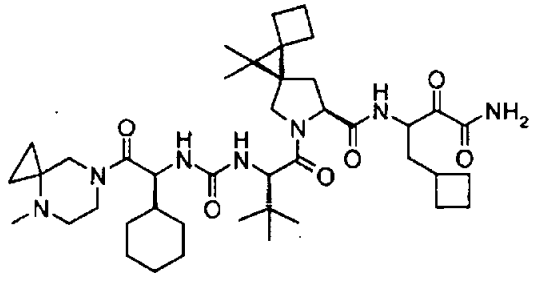
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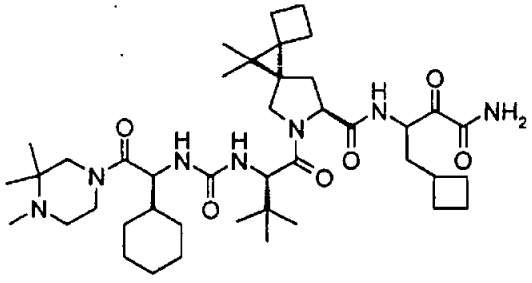
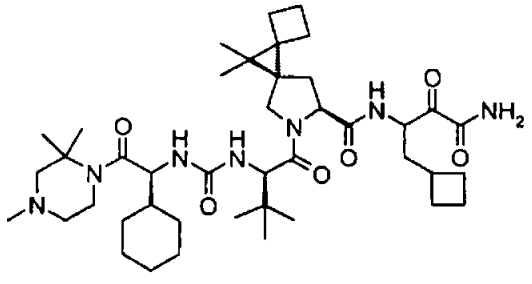
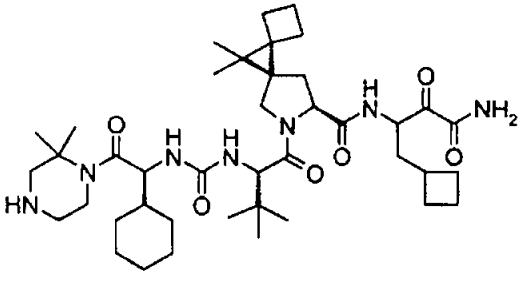
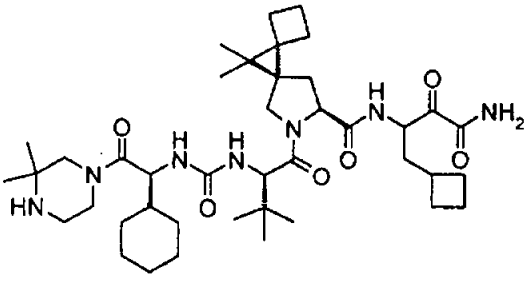
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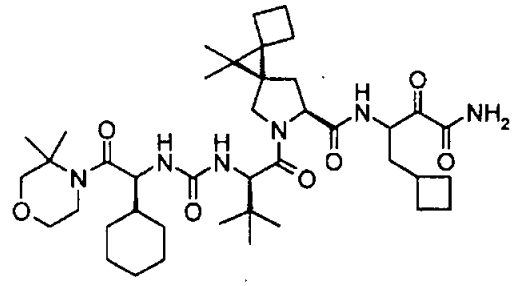
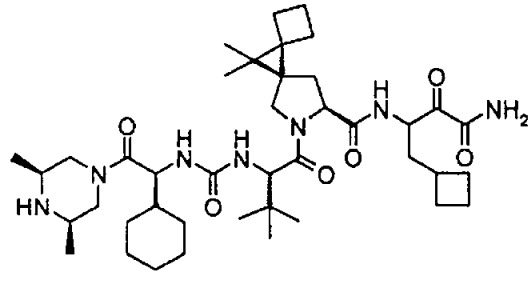
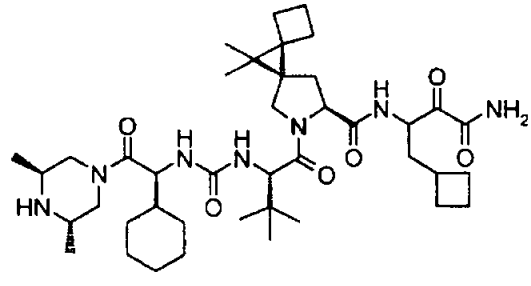
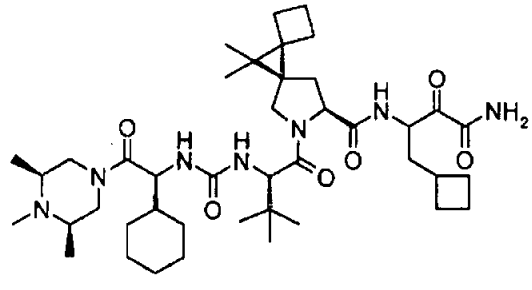
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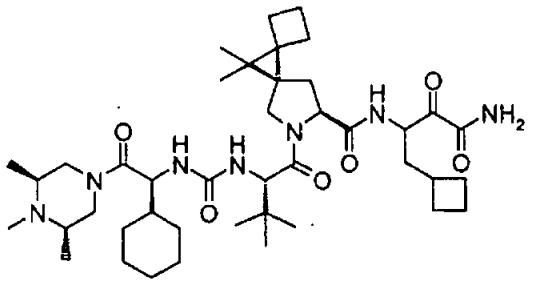
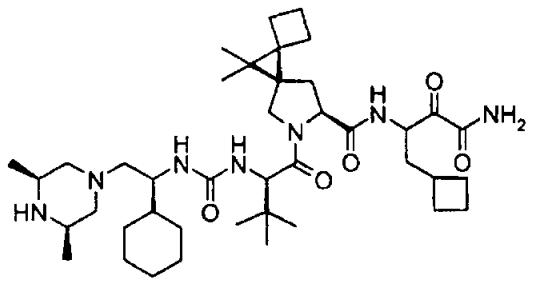
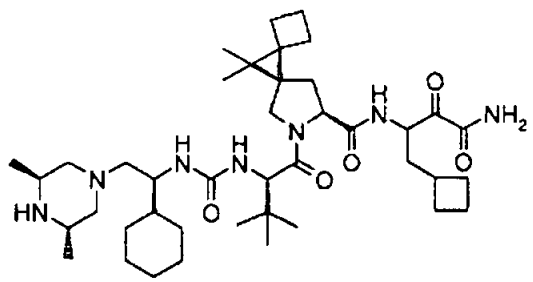
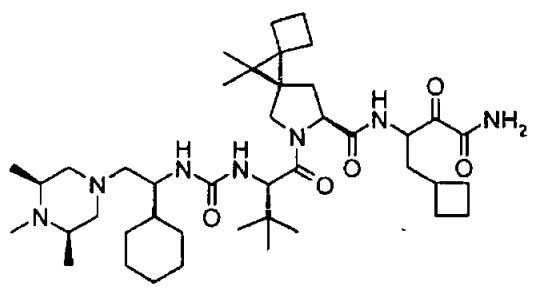
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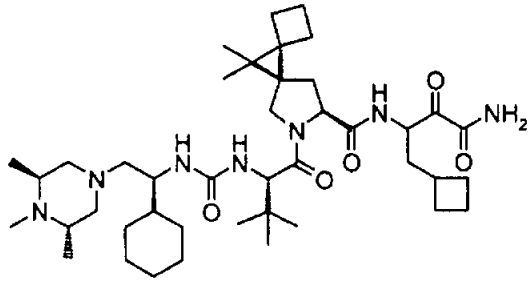
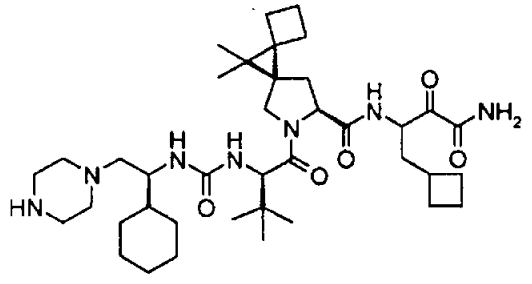
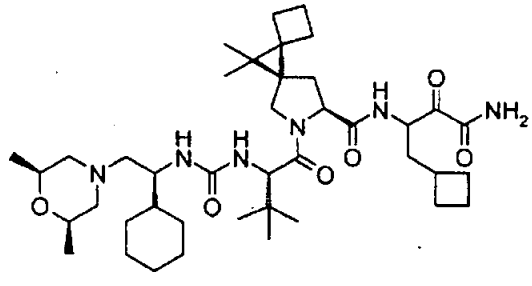
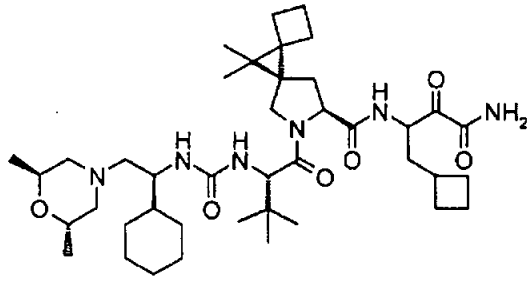
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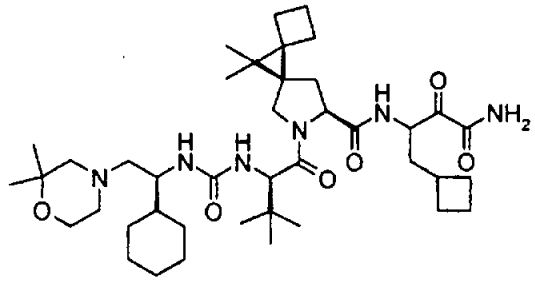
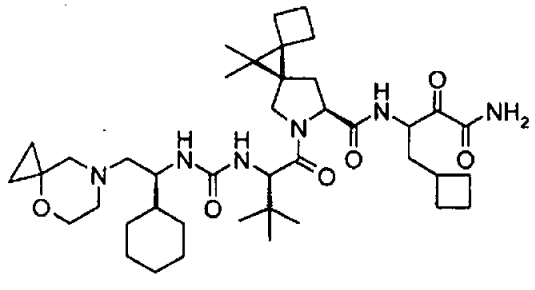
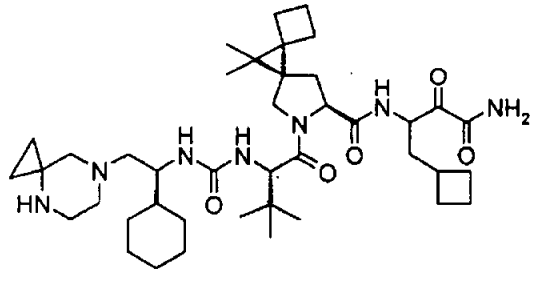
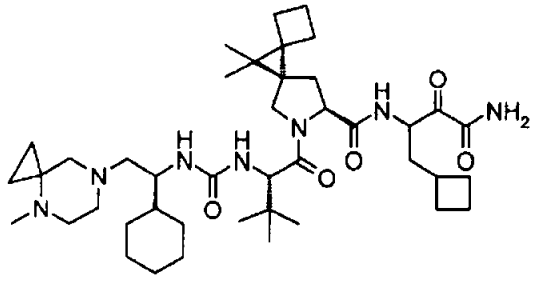
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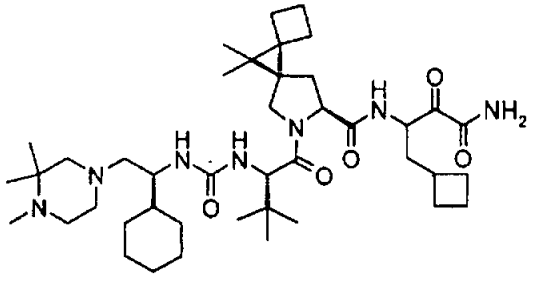
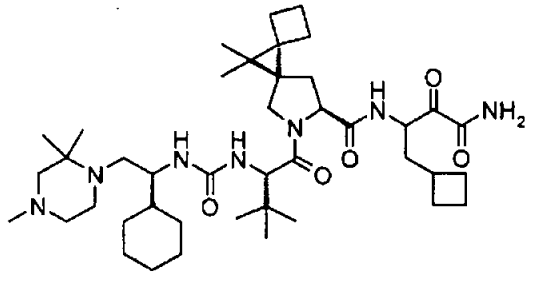
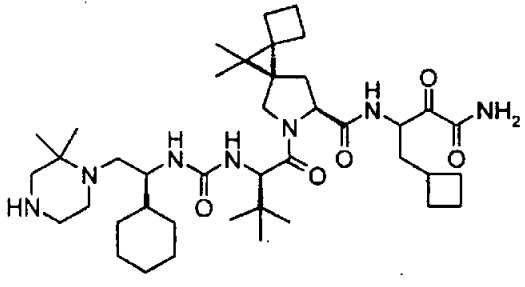
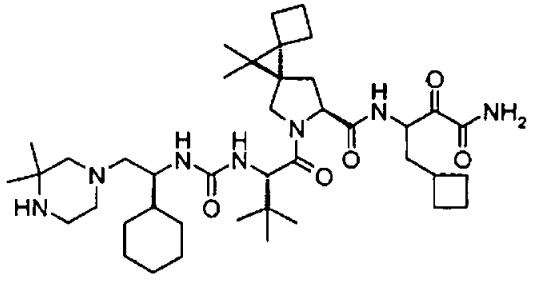
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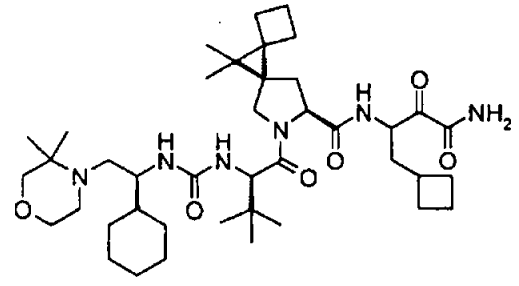
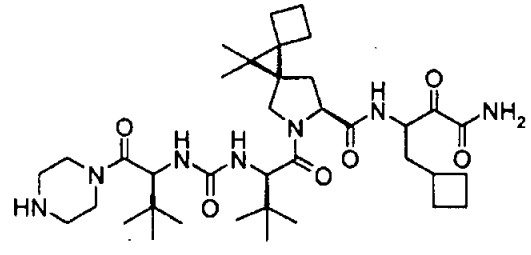
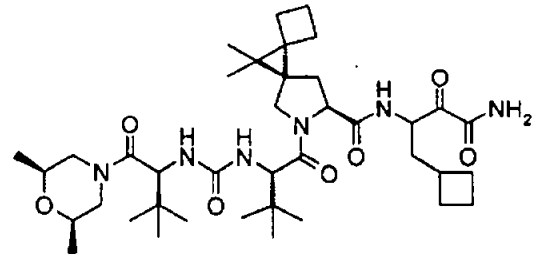
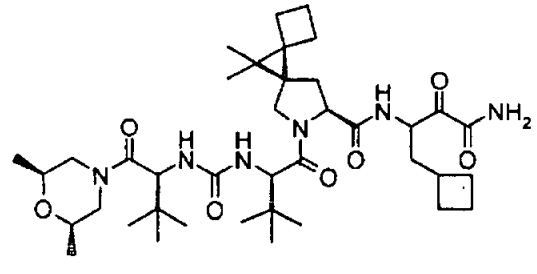
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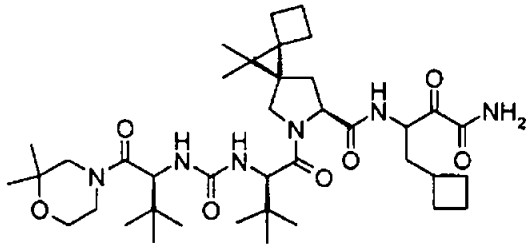
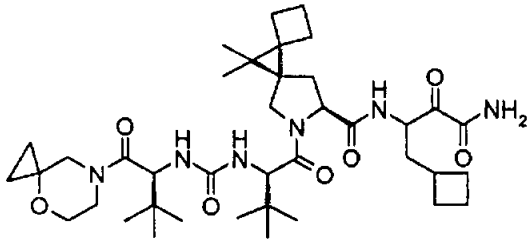
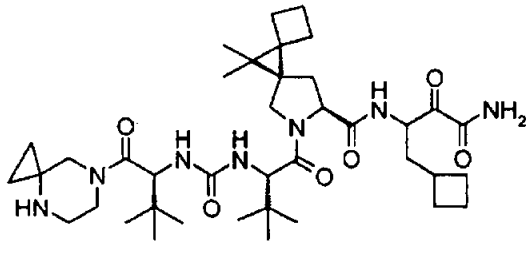
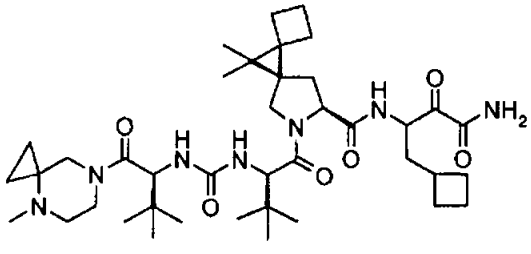
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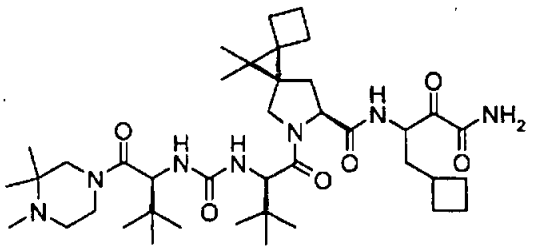
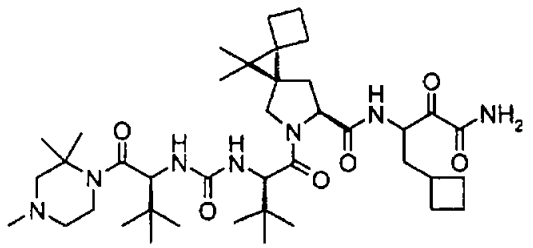
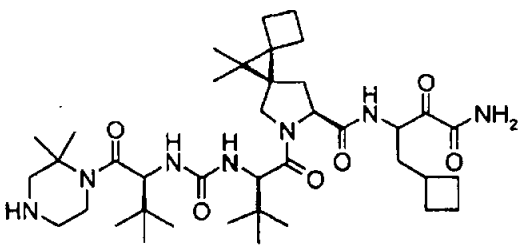
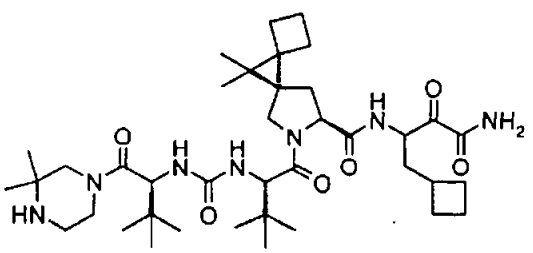
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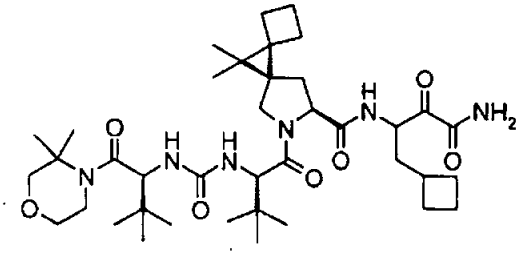
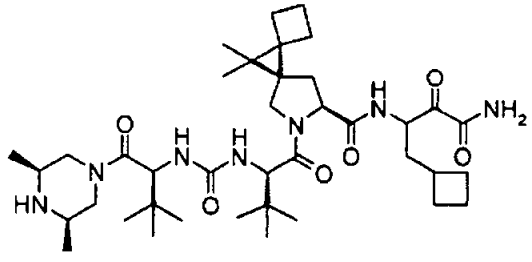
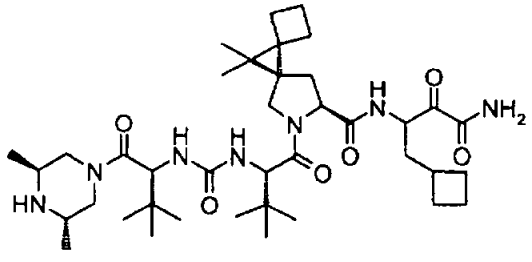
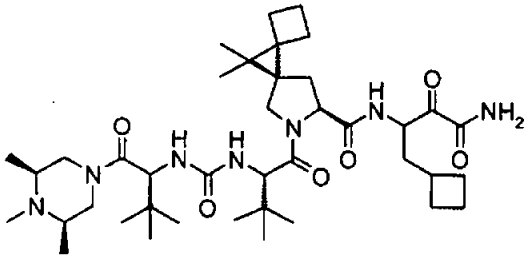
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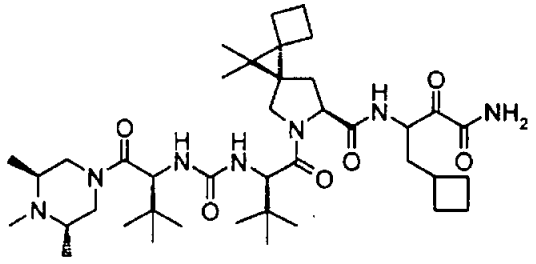
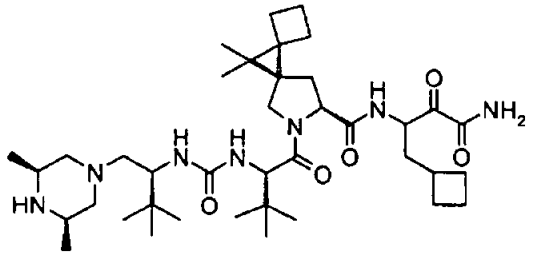
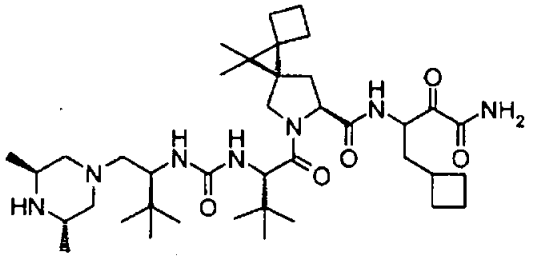
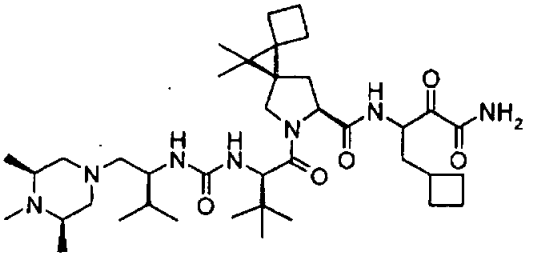
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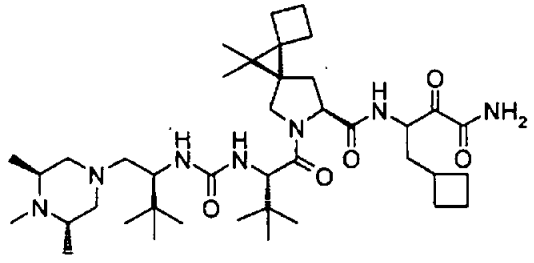
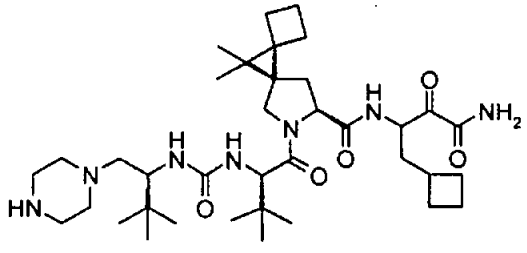
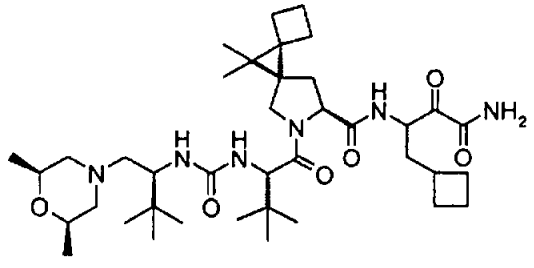
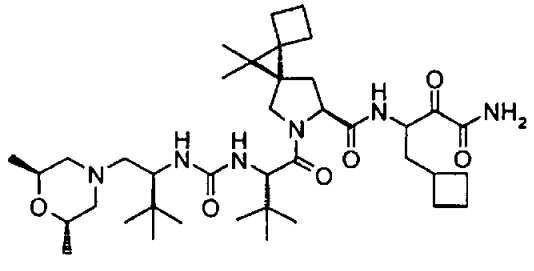
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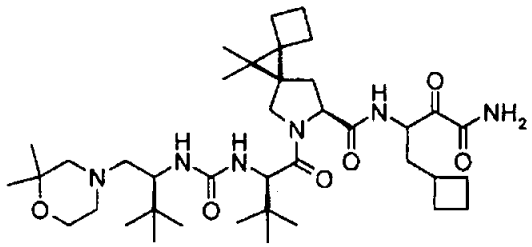
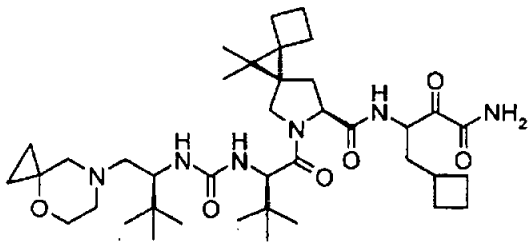
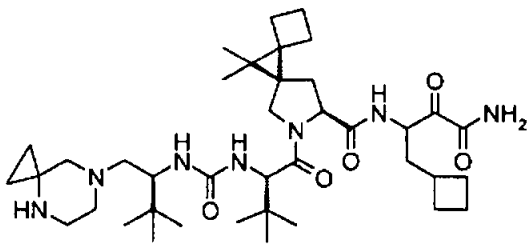
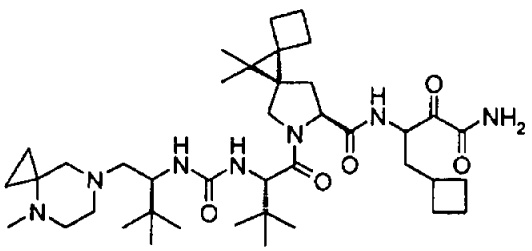
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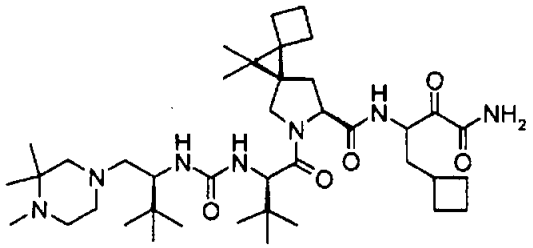
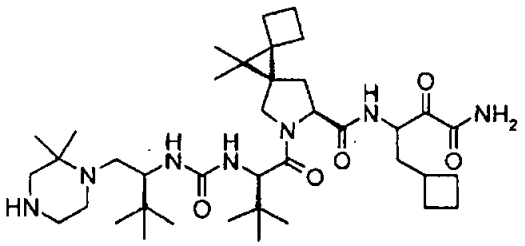
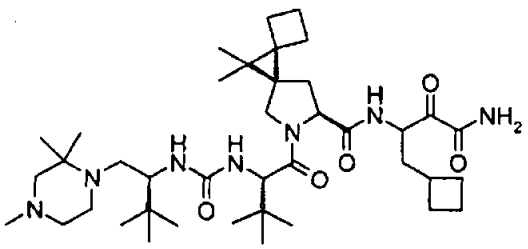
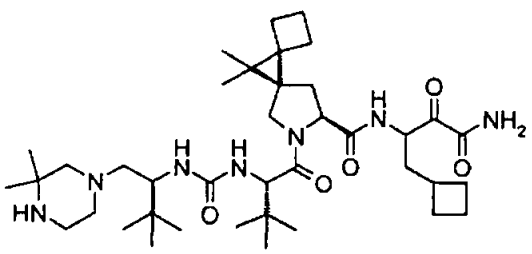
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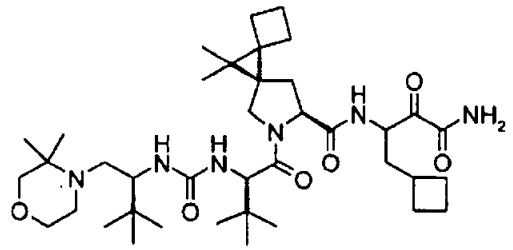
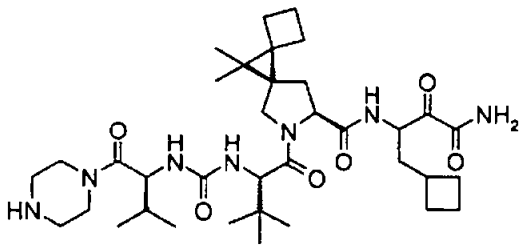
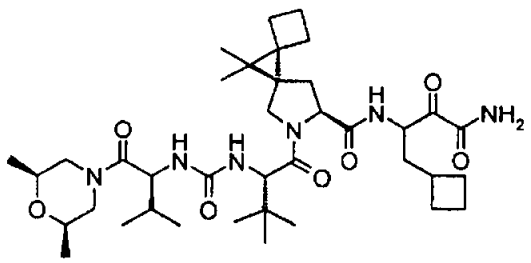
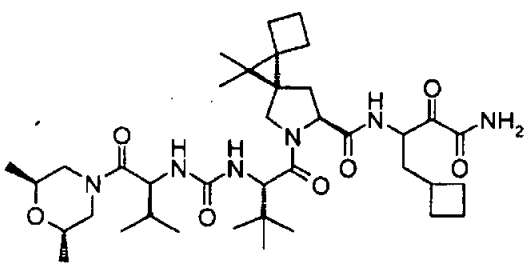
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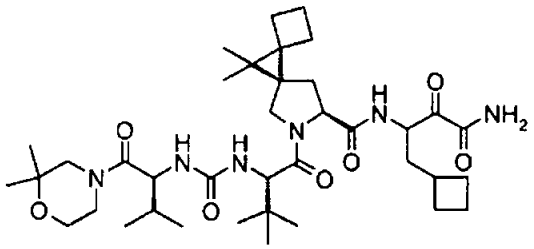
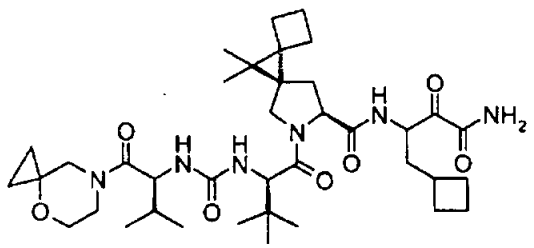
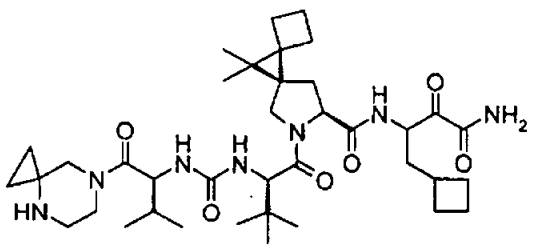
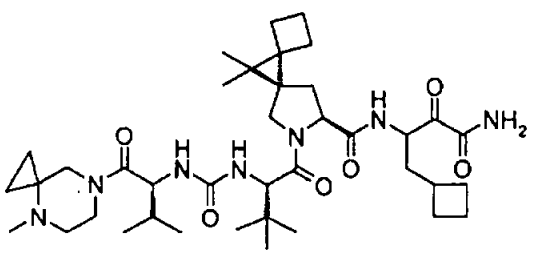
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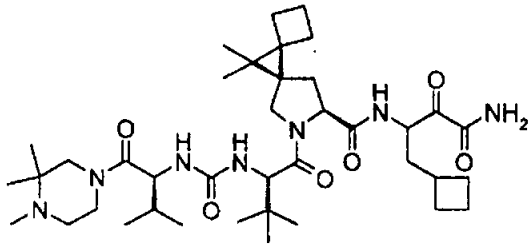
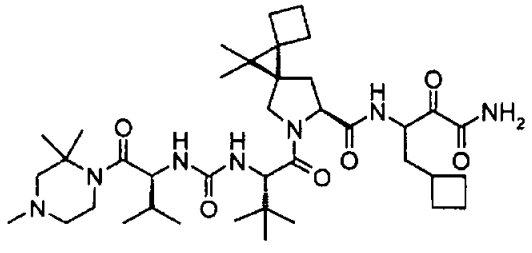
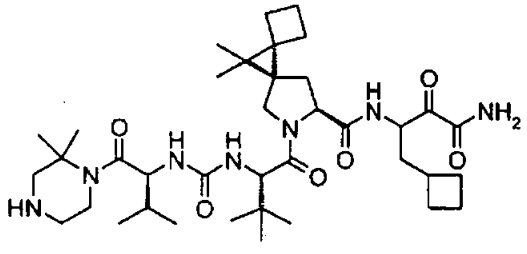
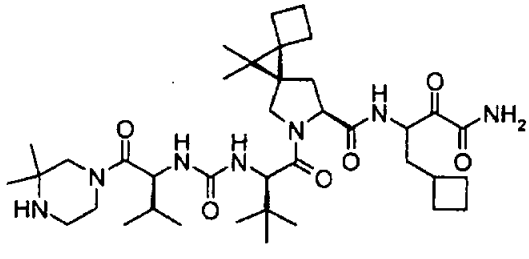
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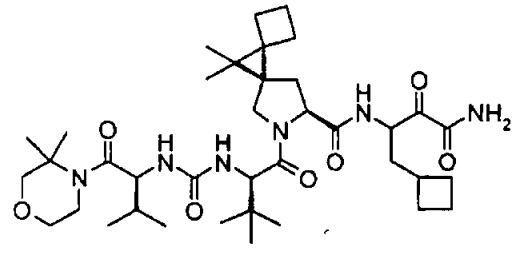
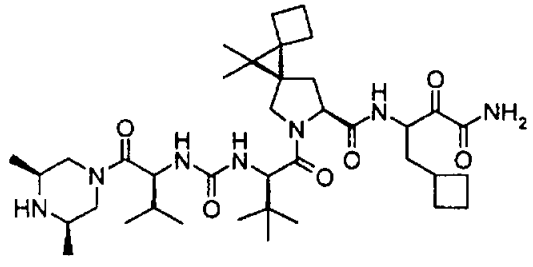
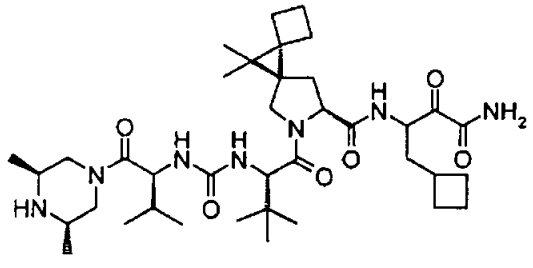
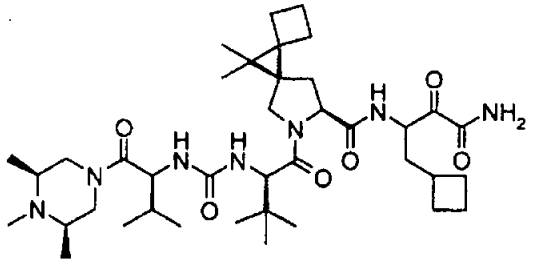
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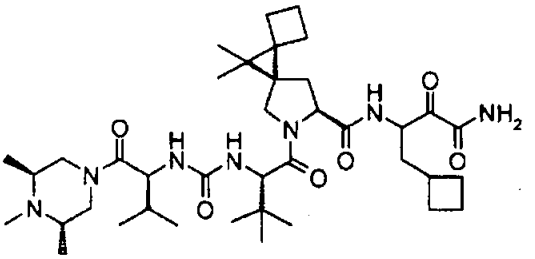
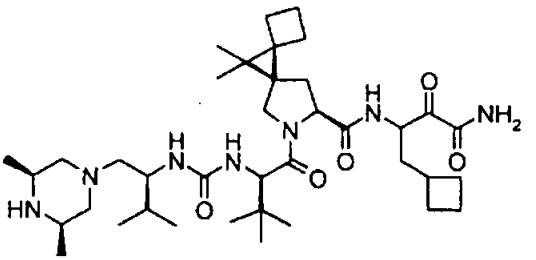
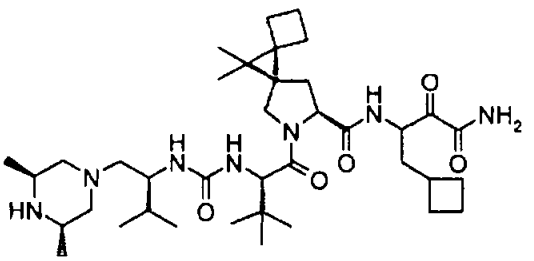
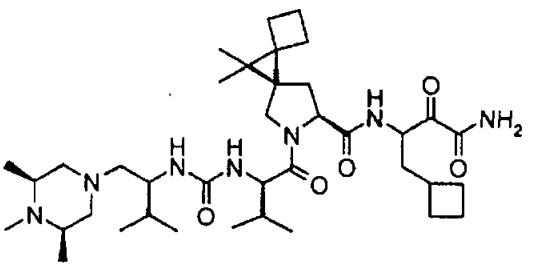
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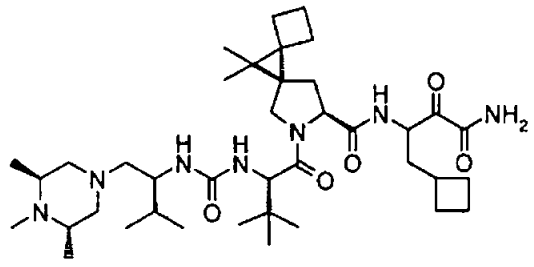
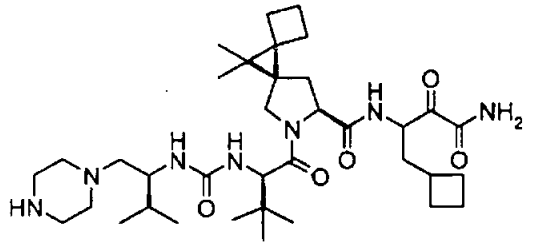
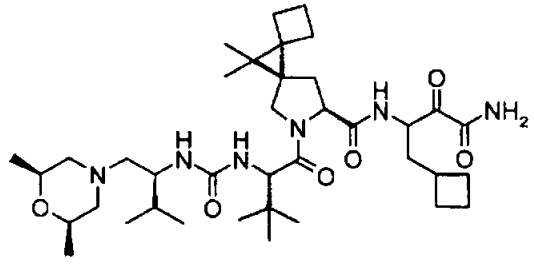
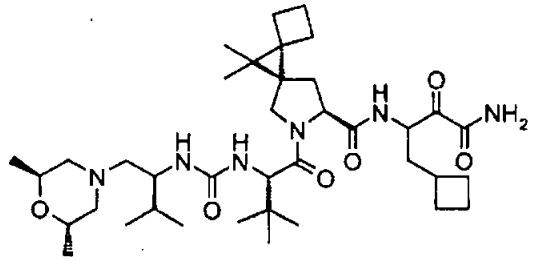
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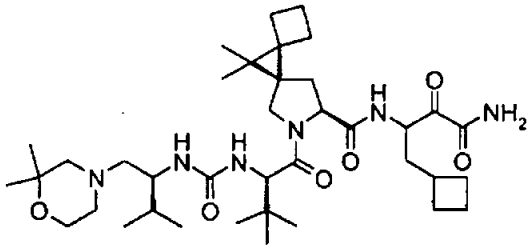
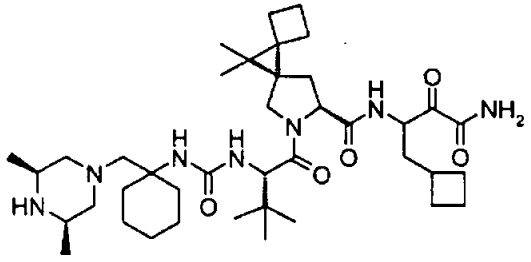
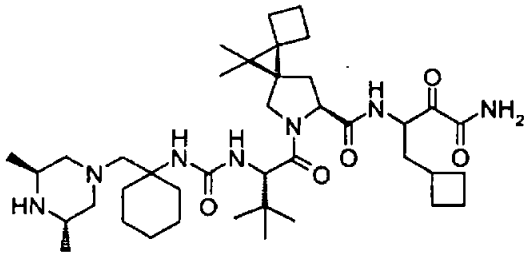
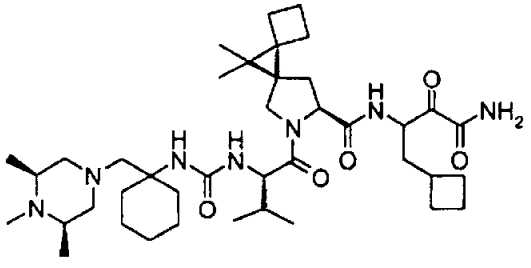
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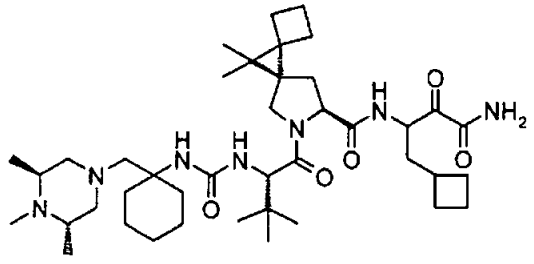
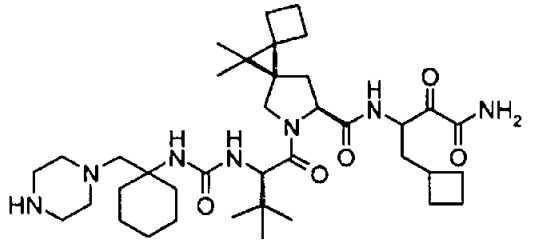
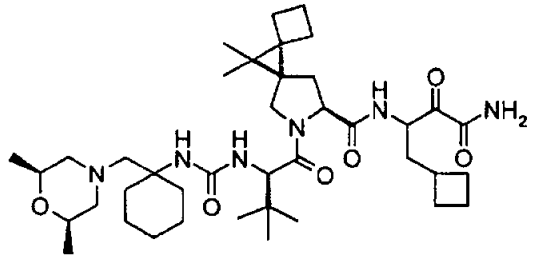
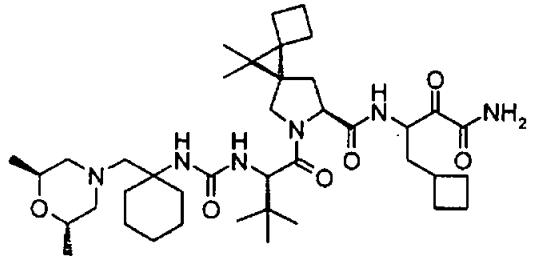
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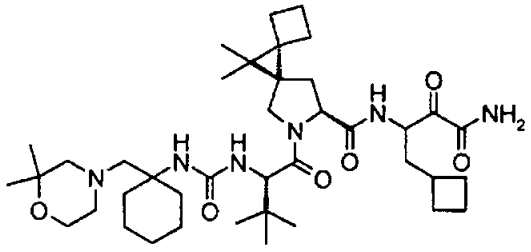
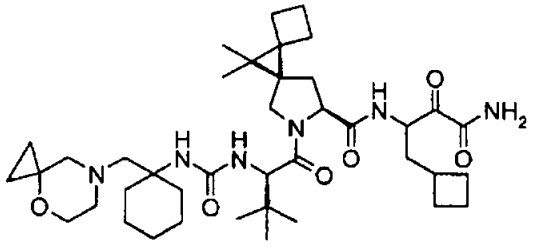
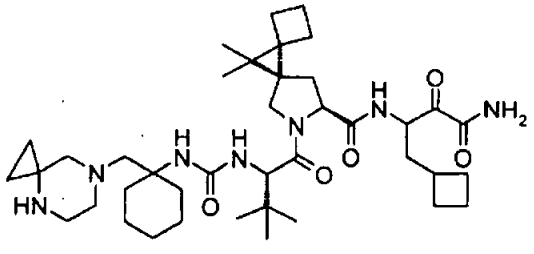
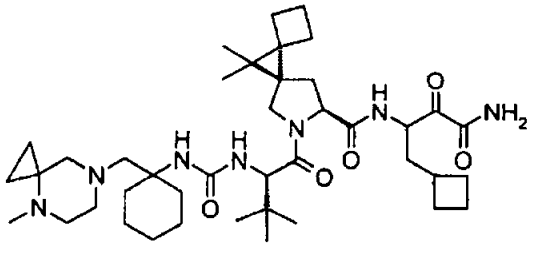
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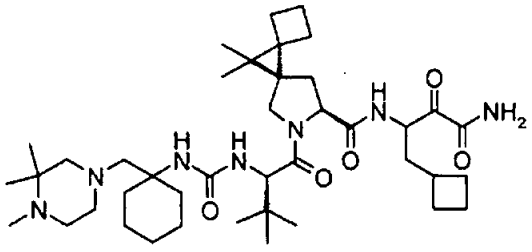
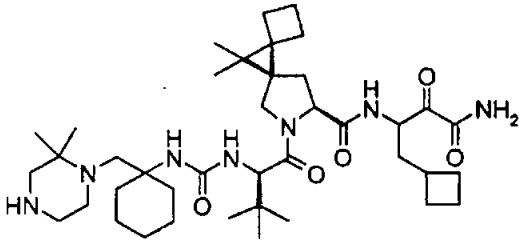
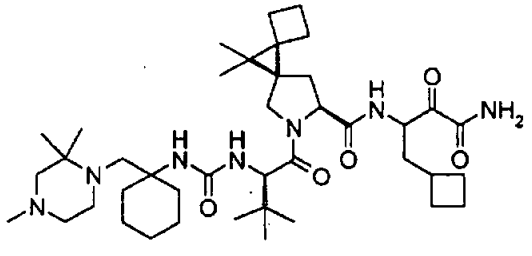
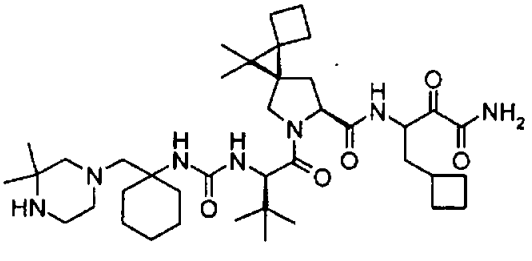
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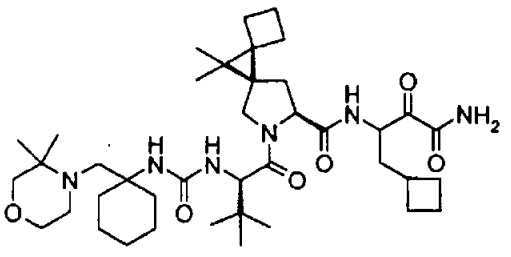
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Using the HCV NS3-4A protease and Luciferase-HCV replicon assays described in the exemplification section below, the compounds of the invention (including compounds of Table A depicted above) are found to show $IC_{50}$ values for HCV inhibition in the range from 10 to more than 100 μM, or 0.5 to 30 μM, including, for example, the range from 0.5 to10 μM or less.

In certain embodiments, a compound of the present invention is further characterized as a modulator of HCV, including a mammalian HCV, and especially including a human HCV. In a preferred embodiment, the compound of the invention is an HCV inhibitor.

In certain embodiments, the compound of the invention is not VX-950 or Sch 503034 (see, *e.g.*, Curr. Med. Chem., 2005, 12, 2317-2342; and Antimicrob Agents Chemother. 2006 Mar;50(3):1013-20, both of which are incorporated herein by reference in their entirety).

In other embodiments, the compounds of the invention are not the species described in International Patent Application Nos. WO 2005/058821, WO/2005/021584, WO/01/18369, WO/03/062265, WO/02/18369, WO/2003/087092 and U.S. Pat. App. No. 2002/0032175.

The terms "HCV-associated state" or "HCV-associated disorder" include disorders and states (*e.g.*, a disease state) that are associated with the activity of HCV, *e.g.*, infection of HCV in a subject. HCV-associated states include HCV-infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

HCV-associated states are often associated with the NS3 serine protease of HCV, which is responsible for several steps in the processing of the HCV polyprotein into smaller functional proteins. NS3 protease forms a heterodimeric complex with the NS4A protein, an essential cofactor that enhances enzymatic activity, and is believed to help anchor HCV to the endoplasmic reticulum. NS3 first autocatalyzes hydrolysis of the NS3-NS4A juncture, and then cleaves the HCV polyprotein intermolecularly at the NS4A-NS4B, NS4B-NS5A and

NS5A-NS5B intersections. This process is associated with replication of HCV in a subject. Inhibiting or modulating the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins will inhibit or modulate replication of HCV in a subject, thereby preventing or treating the HCV-associated state. In a particular embodiment, the HCV-associated state is associated with the activity of the NS3 protease. In another particular embodiment, the HCV-associated state is associated with the activity of NS3-NS4A heterodimeric complex.

In one embodiment, the compounds of the invention are NS3/NS4A protease inhibitors. In another embodiment, the compounds of the invention are NS2/NS3 protease inhibitors.

Without being bound by theory, it is believed that the disruption of the above protein-protein interactions by the compounds of the invention will interfere with viral polyprotein processing by the NS3 protease and thus viral replication.

HCV-associated disorders also include HCV-dependent diseases. HCV-dependent diseases include, *e.g.*, any disease or disorder that depend on or related to activity or misregulation of at least one strain of HCV.

The present invention includes treatment of HCV-associated disorders as described above, but the invention is not intended to be limited to the manner by which the compound performs its intended function of treatment of a disease. The present invention includes treatment of diseases described herein in any manner that allows treatment to occur, *e.g.*, HCV infection.

In a related embodiment, the compounds of the invention can be useful for treating diseases related to HIV, as well as HIV infection and AIDS (Acquired Immune Deficiency Syndrome).

In certain embodiments, the invention provides a pharmaceutical composition of any of the compounds of the present invention. In a related embodiment, the invention provides a pharmaceutical composition of any of the compounds of the present invention and a pharmaceutically acceptable carrier or excipient of any of these compounds. In certain embodiments, the invention includes the compounds as novel chemical entities.

In one embodiment, the invention includes a packaged HCV-associated disorder treatment. The packaged treatment includes a compound of the invention packaged with instructions for using an effective amount of the compound of the invention for an intended use.

The compounds of the present invention are suitable as active agents in pharmaceutical compositions that are efficacious particularly for treating HCV-associated

disorders. The pharmaceutical composition in various embodiments has a pharmaceutically effective amount of the present active agent along with other pharmaceutically acceptable excipients, carriers, fillers, diluents and the like. The phrase, "pharmaceutically effective amount" as used herein indicates an amount necessary to administer to a host, or to a cell, issue, or organ of a host, to achieve a therapeutic result, especially an anti-HCV effect, *e.g.*, inhibition of proliferation of the HCV virus, or of any other HCV-associated disease.

In one embodiment, the diseases to be treated by compounds of the invention include, for example, HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

In other embodiments, the present invention provides a method for inhibiting the activity of HCV. The method includes contacting a cell with any of the compounds of the present invention. In a related embodiment, the method further provides that the compound is present in an amount effective to selectively inhibit the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins. In another related embodiment, the method provides that the compound is present in an amount effective to diminish the HCV RNA load in a subject.

In other embodiments, the present invention provides a use of any of the compounds of the invention for manufacture of a medicament to treat HCV infection in a subject.

In other embodiments, the invention provides a method of manufacture of a medicament, including formulating any of the compounds of the present invention for treatment of a subject.

*Definitions*

The term "treat," "treated," "treating" or "treatment" includes the diminishment or alleviation of at least one symptom associated or caused by the state, disorder or disease being treated. In certain embodiments, the treatment comprises the induction of an HCV-inhibited state, followed by the activation of the HCV-modulating compound, which would in turn diminish or alleviate at least one symptom associated or caused by the HCV-associated state, disorder or disease being treated. For example, treatment can be diminishment of one or several symptoms of a disorder or complete eradication of a disorder.

The term "subject" is intended to include organisms, *e.g.*, prokaryotes and eukaryotes, which are capable of suffering from or afflicted with an HCV-associated disorder. Examples of subjects include mammals, *e.g.*, humans, dogs, cows, horses, pigs, sheep, goats, cats, mice,

rabbits, rats, and transgenic non-human animals. In certain embodiments, the subject is a human, *e.g.*, a human suffering from, at risk of suffering from, or potentially capable of suffering from an HCV-associated disorder, and for diseases or conditions described herein, *e.g.*, HCV infection. In another embodiment, the subject is a cell.

The language "HCV-modulating compound," "modulator of HCV" or "HCV inhibitor" refers to compounds that modulate, *e.g.*, inhibit, or otherwise alter, the activity of HCV. Similarly, an "NS3/NS4A protease inhibitor," or an "NS2/NS3 protease inhibitor" refers to a compound that modulates, *e.g.*, inhibits, or otherwise alters, the interaction of these proteases with one another. Examples of HCV-modulating compounds include compounds of Formula I or Formula III, as well as Table A and Table B (including pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof).

Additionally, the method includes administering to a subject an effective amount of an HCV-modulating compound of the invention, *e.g.*, HCV-modulating compounds of Formula I or Formula III, as well as Table A and Table B (including pharmaceutically acceptable salts thereof, as well as enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates thereof).

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, *etc.*), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, *etc.*), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. Furthermore, the expression "$C_x$-$C_y$-alkyl", wherein x is 1-5 and y is 2-10 indicates a particular alkyl group (straight- or branched-chain) of a particular range of carbons. For example, the expression $C_1$-$C_4$-alkyl includes, but is not limited to, methyl, ethyl, propyl, butyl, isopropyl, tert-butyl, isobutyl and sec-butyl. Moreover, the term $C_{3-6}$-cycloalkyl includes, but is not limited to, cyclopropyl, cyclopentyl, and cyclohexyl. As discussed below, these alkyl groups, as well as cycloalkyl groups, may be further substituted. "$C_0$-$C_n$alkyl" refers to a single covalent bond ($C_0$) or an alkyl group having from 1 to n carbon atoms; for example "$C_0$-$C_4$alkyl" refers to a single covalent bond or a $C_1$-$C_4$alkyl group; "$C_0$-$C_8$alkyl" refers to a single covalent bond or a $C_1$-$C_8$alkyl group. In some instances, a substituent of an alkyl group is specifically indicated. For example, "$C_1$-$C_4$hydroxyalkyl" refers to a $C_1$-$C_4$alkyl group that has at least one hydroxy substituent.

"Alkylene" refers to a divalent alkyl group, as defined above. $C_0$-$C_4$alkylene is a single covalent bond or an alkylene group having from 1 to 4 carbon atoms; and $C_0$-$C_6$alkylene is a single covalent bond or an alkylene group having from 1 to 6 carbon atoms.

A "cycloalkyl" is a group that comprises one or more saturated and/or partially saturated rings in which all ring members are carbon, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of the foregoing, such as cyclohexenyl. Cycloalkyl groups do not comprise an aromatic ring or a heterocyclic ring. Certain cycloalkyl groups are $C_3$-$C_8$cycloalkyl, in which the group contains a single ring with from 3 to 8 ring members. A "($C_3$-$C_8$cycloalkyl)$C_0$-$C_4$alkyl" is a $C_3$-$C_8$cycloalkyl group linked via a single covalent bond or a $C_1$-$C_4$alkylene group.

Moreover, alkyl (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, *etc.*) include both "unsubstituted alkyl" and "substituted alkyl", the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone, which allow the molecule to perform its intended function.

The term "substituted" is intended to describe moieties having substituents replacing a hydrogen on one or more atoms, *e.g.* C, O or N, of a molecule. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, morpholino, phenol, benzyl, phenyl, piperazine, cyclopentane, cyclohexane, pyridine, 5H-tetrazole, triazole, piperidine, or an aromatic or heteroaromatic moiety.

Further examples of substituents of the invention, which are not intended to be limiting, include moieties selected from straight or branched alkyl (preferably $C_1$-$C_5$), cycloalkyl (preferably $C_3$-$C_8$), alkoxy (preferably $C_1$-$C_6$), thioalkyl (preferably $C_1$-$C_6$), alkenyl (preferably $C_2$-$C_6$), alkynyl (preferably $C_2$-$C_6$), heterocyclic, carbocyclic, aryl (*e.g.*, phenyl), aryloxy (*e.g.*, phenoxy), aralkyl (*e.g.*, benzyl), aryloxyalkyl (*e.g.*, phenyloxyalkyl), arylacetamidoyl, alkylaryl, heteroaralkyl, alkylcarbonyl and arylcarbonyl or other such acyl group, heteroarylcarbonyl, or heteroaryl group,

$(CR'R")_{0-3}NR'R"$ (*e.g.*, $-NH_2$), $(CR'R")_{0-3}CN$ (*e.g.*, -CN), $-NO_2$, halogen (*e.g.*, -F, -Cl, -Br, or -I), $(CR'R")_{0-3}C(halogen)_3$ (*e.g.*, $-CF_3$), $(CR'R")_{0-3}CH(halogen)_2$, $(CR'R")_{0-3}CH_2(halogen)$, $(CR'R")_{0-3}CONR'R"$, $(CR'R")_{0-3}(CNH)NR'R"$, $(CR'R")_{0-3}S(O)_{1-2}NR'R"$, $(CR'R")_{0-3}CHO$, $(CR'R")_{0-3}O(CR'R")_{0-3}H$, $(CR'R")_{0-3}S(O)_{0-3}R'$ (*e.g.*, $-SO_3H$, $-OSO_3H$), $(CR'R")_{0-3}O(CR'R")_{0-3}H$ (*e.g.*, $-CH_2OCH_3$ and $-OCH_3$), $(CR'R")_{0-3}S(CR'R")_{0-3}H$ (*e.g.*, -SH and $-SCH_3$), $(CR'R")_{0-3}OH$ (*e.g.*, -OH), $(CR'R")_{0-3}COR'$, $(CR'R")_{0-3}$(substituted or unsubstituted phenyl), $(CR'R")_{0-3}(C_3-C_8$ cycloalkyl), $(CR'R")_{0-3}CO_2R'$ (*e.g.*, $-CO_2H$), or $(CR'R")_{0-3}OR'$ group, or the side chain of any naturally occurring amino acid; wherein R' and R" are each independently hydrogen, a $C_1-C_5$ alkyl, $C_2-C_5$ alkenyl, $C_2-C_5$ alkynyl, or aryl group. Such substituents can include, for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, oxime, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, or an aromatic or heteroaromatic moiety. In certain embodiments, a carbonyl moiety (C=O) may be further derivatized with an oxime moiety, *e.g.*, an aldehyde moiety may be derivatized as its oxime (-C=N-OH) analog. It will be understood by those skilled in the art that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate. Cycloalkyls can be further substituted, *e.g.*, with the substituents described above. An "aralkyl" moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (*i.e.*, benzyl)).

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one double bond.

For example, the term "alkenyl" includes straight-chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups that include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, $C_2-C_6$ for

straight chain, $C_3$-$C_6$ for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term $C_2$-$C_6$ includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls", the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

For example, the term "alkynyl" includes straight-chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, *etc.*), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups that include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, $C_2$-$C_6$ for straight chain, $C_3$-$C_6$ for branched chain). The term $C_2$-$C_6$ includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls", the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino,

sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "amine" or "amino" should be understood as being broadly applied to both a molecule, or a moiety or functional group, as generally understood in the art, and may be primary, secondary, or tertiary. The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon, hydrogen or heteroatom. The terms include, for example, but are not limited to, "alkylamino," "arylamino," "diarylamino," "alkylarylamino," "alkylaminoaryl," "arylaminoalkyl," "alkaminoalkyl," "amide," "amido," and "aminocarbonyl." The term "alkyl amino" comprises groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group.

The term "amide," "amido" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarbonyl" or "alkylaminocarbonyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carbonyl group. It includes arylaminocarbonyl and arylcarbonylamino groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarbonyl," "alkenylaminocarbonyl," "alkynylaminocarbonyl," "arylaminocarbonyl," "alkylcarbonylamino," "alkenylcarbonylamino," "alkynylcarbonylamino," and "arylcarbonylamino" are included in term "amide." Amides also include urea groups (aminocarbonylamino) and carbamates (oxycarbonylamino).

The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, phenyl, pyrrole, furan, thiophene, thiazole, isothiaozole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, and pyrimidine, and the like. Furthermore, the term "aryl" includes multicyclic aryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl,

quinoline, isoquinoline, anthryl, phenanthryl, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles", "heterocycles," "heteroaryls" or "heteroaromatics." The aromatic ring can be substituted at one or more ring positions with such substituents as described above, as for example, alkyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (*e.g.*, tetralin).

Certain aryl groups recited herein are $C_6$-$C_{10}$aryl$C_0$-$C_8$alkyl groups (*i.e.*, groups in which a 6- to 10-membered carbocyclic group comprising at least one aromatic ring is linked via a single covalent bond or a $C_1$-$C_8$alkylene group). Such groups include, for example, phenyl and indanyl, as well as groups in which either of the foregoing is linked via $C_1$-$C_8$alkylene, preferably via $C_1$-$C_4$alkylene. Phenyl groups linked via a single covalent bond or $C_1$-$C_6$alkylene group are designated phenyl$C_0$-$C_6$alkyl (*e.g.*, benzyl, 1-phenyl-ethyl, 1-phenyl-propyl and 2-phenyl-ethyl).

The term heteroaryl, as used herein, represents a stable monocyclic or bicyclic ring of up to 7 atoms in each ring, wherein at least one ring is aromatic and contains from 1 to 4 heteroatoms selected from the group consisting of O, N and S. Heteroaryl groups within the scope of this definition include but are not limited to: acridinyl, carbazolyl, cinnolinyl, quinoxalinyl, pyrrazolyl, indolyl, benzotriazolyl, furanyl, thienyl, benzothienyl, benzofuranyl, quinolinyl, isoquinolinyl, oxazolyl, isoxazolyl, indolyl, pyrazinyl, pyridazinyl, pyridinyl, pyrimidinyl, pyrrolyl, tetrahydroquinoline. As with the definition of heterocycle below, "heteroaryl" is also understood to include the N-oxide derivative of any nitrogen-containing heteroaryl. In cases where the heteroaryl substituent is bicyclic and one ring is non-aromatic or contains no heteroatoms, it is understood that attachment is via the aromatic ring or via the heteroatom containing ring, respectively.

The term "heterocycle" or "heterocyclyl" as used herein is intended to mean a 5- to 10-membered aromatic or nonaromatic heterocycle containing from 1 to 4 heteroatoms selected from the group consisting of O, N and S, and includes bicyclic groups. "Heterocyclyl" therefore includes the above mentioned heteroaryls, as well as dihydro and tetrathydro analogs thereof. Further examples of "heterocyclyl" include, but are not limited to the following: benzoimidazolyl, benzofuranyl, benzofurazanyl, benzopyrazolyl, benzotriazolyl, benzothiophenyl, benzoxazolyl, carbazolyl, carbolinyl, cinnolinyl, furanyl, imidazolyl, indolinyl, indolyl, indolazinyl, indazolyl, isobenzofuranyl, isoindolyl, isoquinolyl, isothiazolyl, isoxazolyl, naphthpyridinyl, oxadiazolyl, oxazolyl, oxazoline, isoxazoline, oxetanyl, pyranyl, pyrazinyl, pyrazolyl, pyridazinyl, pyridopyridinyl, pyridazinyl, pyridyl, pyrimidyl, pyrrolyl, quinazolinyl, quinolyl, quinoxalinyl, tetrahydropyranyl, tetrazolyl, tetrazolopyridyl, thiadiazolyl, thiazolyl, thienyl, triazolyl, azetidinyl, 1,4-dioxanyl, hexahydroazepinyl, piperazinyl, piperidinyl, pyridin-2-onyl, pyrrolidinyl, morpholinyl, thiomorpholinyl, dihydrobenzoimidazolyl, dihydrobenzofuranyl, dihydrobenzothiophenyl, dihydrobenzoxazolyl, dihydrofuranyl, dihydroimidazolyl, dihydroindolyl, dihydroisooxazolyl, dihydroisothiazolyl, dihydrooxadiazolyl, dihydrooxazolyl, dihydropyrazinyl, dihydropyrazolyl, dihydropyridinyl, dihydropyrimidinyl, dihydropyrrolyl, dihydroquinolinyl, dihydrotetrazolyl, dihydrothiadiazolyl, dihydrothiazolyl, dihydrothienyl, dihydrotriazolyl, dihydroazetidinyl, methylenedioxybenzoyl, tetrahydrofuranyl, and tetrahydrothienyl, and N-oxides thereof. Attachment of a heterocyclyl substituent can occur via a carbon atom or via a heteroatom.

A "heterocycle$C_0$-$C_8$alkyl" is a heterocyclic group linked via a single covalent bond or $C_1$-$C_8$alkylene group. A (4- to 7-membered heterocycle)$C_0$-$C_8$alkyl is a heterocyclic group (*e.g.*, monocyclic or bicyclic) having from 4 to 7 ring members linked via a single covalent bond or an alkylene group having from 1 to 8 carbon atoms. A "(6-membered heteroaryl)$C_0$-$C_6$alkyl" refers to a heteroaryl group linked via a direct bond or $C_1$-$C_6$alkyl group.

The term "acyl" includes compounds and moieties which contain the acyl radical ($CH_3CO$-) or a carbonyl group. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino,

arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups and may include cyclic groups such as cyclopentoxy. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, *etc.*

The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom, and tautomeric forms thereof. Examples of moieties that contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, *etc.* The term "carboxy moiety" or "carbonyl moiety" refers to groups such as "alkylcarbonyl" groups wherein an alkyl group is covalently bound to a carbonyl group, "alkenylcarbonyl" groups wherein an alkenyl group is covalently bound to a carbonyl group, "alkynylcarbonyl" groups wherein an alkynyl group is covalently bound to a carbonyl group, "arylcarbonyl" groups wherein an aryl group is covalently attached to the carbonyl group. Furthermore, the term also refers to groups wherein one or more heteroatoms are covalently bonded to the carbonyl moiety. For example, the term includes moieties such as, for example, aminocarbonyl moieties, (wherein a nitrogen atom is bound to

the carbon of the carbonyl group, *e.g.*, an amide), aminocarbonyloxy moieties, wherein an oxygen and a nitrogen atom are both bond to the carbon of the carbonyl group (*e.g.*, also referred to as a "carbamate"). Furthermore, aminocarbonylamino groups (*e.g.*, ureas) are also include as well as other combinations of carbonyl groups bound to heteroatoms (*e.g.*, nitrogen, oxygen, sulfur, *etc.* as well as carbon atoms). Furthermore, the heteroatom can be further substituted with one or more alkyl, alkenyl, alkynyl, aryl, aralkyl, acyl, *etc.* moieties.

The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom. The term "thiocarbonyl moiety" includes moieties that are analogous to carbonyl moieties. For example, "thiocarbonyl" moieties include aminothiocarbonyl, wherein an amino group is bound to the carbon atom of the thiocarbonyl group, furthermore other thiocarbonyl moieties include, oxythiocarbonyls (oxygen bound to the carbon atom), aminothiocarbonylamino groups, *etc.*

The term "ether" includes compounds or moieties that contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom that is covalently bonded to another alkyl group.

The term "ester" includes compounds and moieties that contain a carbon or a heteroatom bound to an oxygen atom that is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, *etc.* The alkyl, alkenyl, or alkynyl groups are as defined above.

The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom that is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

The term "hydroxy" or "hydroxyl" includes groups with an –OH or –O$^-$.

The term "halogen" includes fluorine, bromine, chlorine, iodine, *etc.* The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The terms "polycyclyl" or "polycyclic radical" include moieties with two or more rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which

two or more carbons are common to two adjoining rings, *e.g.*, the rings are "fused rings". Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, alkylaminoacarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

Additionally, the phrase "any combination thereof" implies that any number of the listed functional groups and molecules may be combined to create a larger molecular architecture. For example, the terms "phenyl," "carbonyl" (or "=O"), "-O-," "–OH," and $C_{1-6}$ (*i.e.*, $-CH_3$ and $-CH_2CH_2CH_2-$) can be combined to form a 3-methoxy-4-propoxybenzoic acid substituent. It is to be understood that when combining functional groups and molecules to create a larger molecular architecture, hydrogens can be removed or added, as required to satisfy the valence of each atom.

It is to be understood that all of the compounds of the invention described above will further include bonds between adjacent atoms and/or hydrogens as required to satisfy the valence of each atom. That is, bonds and/or hydrogen atoms are added to provide the following number of total bonds to each of the following types of atoms: carbon: four bonds; nitrogen: three bonds; oxygen: two bonds; and sulfur: two bonds.

Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more suitable groups (which may be the same or different). Optional substitution is also indicated by the phrase "substituted with from 0 to X substituents," where X is the maximum number of possible substituents. Certain optionally substituted groups are substituted with from 0 to 2, 3 or 4 independently selected substituents (*i.e.*, are unsubstituted or substituted with up to the recited maximum number of substitutents).

It will be noted that the structures of some of the compounds of this invention include

asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (*e.g.*, all enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates) are included within the scope of this invention. Such isomers can be obtained in substantially pure form by classical separation techniques and by stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof. Compounds described herein may be obtained through art recognized synthesis strategies.

It will also be noted that the substituents of some of the compounds of this invention include isomeric cyclic structures. It is to be understood accordingly that constitutional isomers of particular substituents are included within the scope of this invention, unless indicated otherwise. For example, the term "tetrazole" includes tetrazole, 2*H*-tetrazole, 3*H*-tetrazole, 4*H*-tetrazole and 5*H*-tetrazole.

*Use in HCV-associated disorders*

The compounds of the present invention have valuable pharmacological properties and are useful in the treatment of diseases. In certain embodiments, compounds of the invention are useful in the treatment of HCV-associated disorders, *e.g.*, as drugs to treat HCV infection.

The term "use" includes any one or more of the following embodiments of the invention, respectively: the use in the treatment of HCV-associated disorders; the use for the manufacture of pharmaceutical compositions for use in the treatment of these diseases, *e.g.*, in the manufacture of a medicament; methods of use of compounds of the invention in the treatment of these diseases; pharmaceutical preparations having compounds of the invention for the treatment of these diseases; and compounds of the invention for use in the treatment of these diseases; as appropriate and expedient, if not stated otherwise. In particular, diseases to be treated and are thus preferred for use of a compound of the present invention are selected from HCV-associated disorders, including those corresponding to HCV-infection, as well as those diseases that depend on the activity of one or more of the NS3, NS4A, NS4B, NS5A and NS5B proteins, or a NS3-NS4A, NS4A-NS4B, NS4B-NS5A or NS5A-NS5B complex. The term "use" further includes embodiments of compositions herein which bind to an HCV protein sufficiently to serve as tracers or labels, so that when coupled to a fluor or tag, or made radioactive, can be used as a research reagent or as a diagnostic or an imaging agent.

In certain embodiments, a compound of the present invention is used for treating HCV-associated diseases, and use of the compound of the present invention as an inhibitor of

any one or more HCVs. It is envisioned that a use can be a treatment of inhibiting one or more strains of HCV.

*Assays*

The inhibition of HCV activity may be measured as using a number of assays available in the art. An example of such an assay can be found in Anal Biochem. 1996 240(1): 60-7; which is incorporated by reference in its entirety. Assays for measurement of HCV activity are also described in the experimental section below.

*Pharmaceutical Compositions*

The language "effective amount" of the compound is that amount necessary or sufficient to treat or prevent an HCV-associated disorder, *e.g.* prevent the various morphological and somatic symptoms of an HCV-associated disorder, and/or a disease or condition described herein. In an example, an effective amount of the HCV -modulating compound is the amount sufficient to treat HCV infection in a subject. In another example, an effective amount of the HCV-modulating compound is the amount sufficient to treat HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response in a subject. The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular compound of the invention. For example, the choice of the compound of the invention can affect what constitutes an "effective amount." One of ordinary skill in the art would be able to study the factors contained herein and make the determination regarding the effective amount of the compounds of the invention without undue experimentation.

The regimen of administration can affect what constitutes an effective amount. The compound of the invention can be administered to the subject either prior to or after the onset of an HCV-associated state. Further, several divided dosages, as well as staggered dosages, can be administered daily or sequentially, or the dose can be continuously infused, or can be a bolus injection. Further, the dosages of the compound(s) of the invention can be proportionally increased or decreased as indicated by the exigencies of the therapeutic or prophylactic situation.

Compounds of the invention may be used in the treatment of states, disorders or diseases as described herein, or for the manufacture of pharmaceutical compositions for use in the treatment of these diseases. Methods of use of compounds of the present invention in the treatment of these diseases, or pharmaceutical preparations having compounds of the

present invention for the treatment of these diseases.

The language "pharmaceutical composition" includes preparations suitable for administration to mammals, *e.g.*, humans. When the compounds of the present invention are administered as pharmaceuticals to mammals, *e.g.*, humans, they can be given per se or as a pharmaceutical composition containing, for example, 0.1 to 99.5% (more preferably, 0.5 to 90%) of active ingredient in combination with a pharmaceutically acceptable carrier.

The phrase "pharmaceutically acceptable carrier" is art recognized and includes a pharmaceutically acceptable material, composition or vehicle, suitable for administering compounds of the present invention to mammals. The carriers include liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting the subject agent from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; and other non-toxic compatible substances employed in pharmaceutical formulations.

Wetting agents, emulsifiers and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, α-tocopherol, and the like; and metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations of the present invention include those suitable for oral, nasal, topical, transdermal, buccal, sublingual, rectal, vaginal and/or parenteral administration. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. The amount of active ingredient that can be combined with a carrier material to produce a single dosage form will generally be that amount of the compound that produces a therapeutic effect. Generally, out of one hundred per cent, this amount will range from about 1 per cent to about ninety-nine percent of active ingredient, preferably from about 5 per cent to about 70 per cent, most preferably from about 10 per cent to about 30 per cent.

Methods of preparing these formulations or compositions include the step of bringing into association a compound of the present invention with the carrier and, optionally, one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing into association a compound of the present invention with liquid carriers, or finely divided solid carriers, or both, and then, if necessary, shaping the product.

Formulations of the invention suitable for oral administration may be in the form of capsules, cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of a compound of the present invention as an active ingredient. A compound of the present invention may also be administered as a bolus, electuary or paste.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the

case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent.

The tablets, and other solid dosage forms of the pharmaceutical compositions of the present invention, such as dragees, capsules, pills and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions that can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions that can be used include polymeric substances and waxes. The active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration of the compounds of the invention include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluent commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Suspensions, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations of the pharmaceutical compositions of the invention for rectal or vaginal administration may be presented as a suppository, which may be prepared by mixing one or more compounds of the invention with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, and which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active compound.

Formulations of the present invention which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. The active compound may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that may be required.

The ointments, pastes, creams and gels may contain, in addition to an active compound of this invention, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof.

Powders and sprays can contain, in addition to a compound of this invention, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

Transdermal patches have the added advantage of providing controlled delivery of a compound of the present invention to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be

controlled by either providing a rate controlling membrane or dispersing the active compound in a polymer matrix or gel.

Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as being within the scope of this invention.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compounds of the invention in combination with one or more pharmaceutically acceptable sterile isotonic aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

Examples of suitable aqueous and nonaqueous carriers that may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material having poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally-administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the subject compounds in biodegradable polymers such as polylactide-polyglycolide. Depending on the

ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions that are compatible with body tissue.

The preparations of the present invention may be given orally, parenterally, topically, or rectally. They are of course given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, *etc.*, administration by injection, infusion or inhalation; topical by lotion or ointment; and rectal by suppositories. Oral administration is preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a compound, drug or other material other than directly into the central nervous system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

These compounds may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally and topically, as by powders, ointments or drops, including buccally and sublingually.

Regardless of the route of administration selected, the compounds of the present invention, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The selected dosage level will depend upon a variety of factors including the activity of the particular compound of the present invention employed, or the ester, salt or amide

thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compound employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors well known in the medical arts.

A physician or veterinarian having ordinary skill in the art can readily determine and prescribe the effective amount of the pharmaceutical composition required. For example, the physician or veterinarian could start doses of the compounds of the invention employed in the pharmaceutical composition at levels lower than that required in order to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved.

In general, a suitable daily dose of a compound of the invention will be that amount of the compound that is the lowest dose effective to produce a therapeutic effect. Such an effective dose will generally depend upon the factors described above. Generally, intravenous and subcutaneous doses of the compounds of this invention for a patient, when used for the indicated analgesic effects, will range from about 0.0001 to about 100 mg per kilogram of body weight per day, more preferably from about 0.01 to about 50 mg per kg per day, and still more preferably from about 1.0 to about 100 mg per kg per day. An effective amount is that amount treats an HCV-associated disorder.

If desired, the effective daily dose of the active compound may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

While it is possible for a compound of the present invention to be administered alone, it is preferable to administer the compound as a pharmaceutical composition.

*Synthetic Procedure*

Compounds of the present invention are prepared from commonly available compounds using procedures known to those skilled in the art, including any one or more of the following conditions without limitation:

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group," unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works, such as *e.g.*, Science of Synthesis: Houben-Weyl Methods of Molecular Transformation. Georg Thieme Verlag,

Stuttgart, Germany. 2005. 41627 pp. (URL: http://www.science-of-synthesis.com (Electronic Version, 48 Volumes)); J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of Organic Chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (*Amino acids, Peptides, Proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of Carbohydrates: Monosaccharides and Derivatives*), Georg Thieme Verlag, Stuttgart 1974. A characteristic of protecting groups is that they can be removed readily (*i.e.*, without the occurrence of undesired secondary reactions) for example by solvolysis, reduction, photolysis or alternatively under physiological conditions (*e.g.*, by enzymatic cleavage).

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.*, the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.*, by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.*, a free carboxy group and a free amino group, may be formed, *e.g.*, by the neutralisation of salts, such as acid addition salts, to the isoelectric point, *e.g.*, with weak bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for

example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by, *e.g.*, medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, *e.g.*, using chromatographic methods, distribution methods, (re-) crystallization, and the like.

General process conditions

The following applies in general to all processes mentioned throughout this disclosure.

The process steps to synthesize the compounds of the invention can be carried out under reaction conditions that are known per se, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, *e.g.*, in the $H^+$ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190°C, including, for example, from approximately -80°C to approximately 150°C, for example at from -80 to -60°C, at room temperature, at from -20 to 40°C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers, for example analogously to the methods described in Science of Synthesis: Houben-Weyl Methods of Molecular Transformation. Georg Thieme Verlag, Stuttgart, Germany. 2005.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofurane or dioxane, liquid

aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or N-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

Pro-drugs

The present invention also relates to pro-drugs of a compound of the present invention that are converted in vivo to the compounds of the present invention as described herein. Any reference to a compound of the present invention is therefore to be understood as referring also to the corresponding pro-drugs of the compound of the present invention, as appropriate and expedient.

Combinations

A compound of the present invention may also be used in combination with other agents, *e.g.*, an additional HCV-modulating compound that is or is not of the formula I, for treatment of and HCV-associated disorder in a subject.

By the term "combination", is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the present invention and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a

cooperative, *e.g.*, synergistic, effect, or any combination thereof.

For example, WO 2005/042020, incorporated herein by reference in its entirety, describes the combination of various HCV inhibitors with a cytochrome P450 ("CYP") inhibitor. Any CYP inhibitor that improves the pharmacokinetics of the relevant NS3/4A protease may be used in combination with the compounds of this invention. These CYP inhibitors include, but are not limited to, ritonavir (WO 94/14436, incorporated herein by reference in its entirety), ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, clomethiazole, cimetidine, itraconazole, fluconazole, miconazole, fluvoxamine, fluoxetine, nefazodone, sertraline, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdine, erythromycin, VX-944, and VX-497. Preferred CYP inhibitors include ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

Methods for measuring the ability of a compound to inhibit CYP activity are known (see, *e.g.*, US 6,037,157 and Yun, et al. Drug Metabolism & Disposition, vol. 21, pp. 403-407 (1993); incorporated herein by reference). For example, a compound to be evaluated may be incubated with 0.1, 0.5, and 1.0 mg protein/ml, or other appropriate concentration of human hepatic microsomes (e. g., commercially available, pooled characterized hepatic microsomes) for 0, 5, 10, 20, and 30 minutes, or other appropriate times, in the presence of an NADPH-generating system. Control incubations may be performed in the absence of hepatic microsomes for 0 and 30 minutes (triplicate). The samples may be analyzed for the presence of the compound. Incubation conditions that produce a linear rate of compound metabolism will be used a guide for further studies. Experiments known in the art can be used to determine the kinetics of the compound metabolism ($K_m$ and $V_{max}$). The rate of disappearance of compound may be determined and the data analyzed according to Michaelis-Menten kinetics by using Lineweaver-Burk, Eadie-Hofstee, or nonlinear regression analysis.

Inhibition of metabolism experiments may then be performed. For example, a compound (one concentration, $< K_m$) may be incubated with pooled human hepatic microsomes in the absence or presence of a CYP inhibitor (such as ritonavir) under the conditions determined above. As would be recognized, control incubations should contain the same concentration of organic solvent as the incubations with the CYP inhibitor. The concentrations of the compound in the samples may be quantitated, and the rate of disappearance of parent compound may be determined, with rates being expressed as a percentage of control activity.

Methods for evaluating the influence of co-administration of a compound of the invention and a CYP inhibitor in a subject are also known (see, *e.g.*, US2004/0028755; incorporated herein by reference). Any such methods could be used in connection with this invention to determine the pharmacokinetic impact of a combination. Subjects that would benefit from treatment according to this invention could then be selected.

Accordingly, one embodiment of this invention provides a method for administering an inhibitor of CYP3A4 and a compound of the invention. Another embodiment of this invention provides a method for administering an inhibitor of isozyme 3A4 ("CYP3A4"), isozyme 2C19 ("CYP2C19"), isozyme 2D6 ("CYP2D6"), isozyme 1A2 ("CYP1A2"), isozyme 2C9 ("CYP2C9"), or isozyme 2E1 ("CYP2E1"). In embodiments where the protease inhibitor is VX-950 (or a sterereoisomer thereof), the CYP inhibitor preferably inhibits CYP3A4.

As would be appreciated, CYP3A4 activity is broadly observed in humans. Accordingly, embodiments of this invention involving inhibition of isozyme 3A4 would be expected to be applicable to a broad range of patients.

Accordingly, this invention provides methods wherein the CYP inhibitor is administered together with the compound of the invention in the same dosage form or in separate dosage forms.

The compounds of the invention (e.g., compound of Formula I or subformulae thereof) may be administered as the sole ingredient or in combination or alteration with other antiviral agents, especially agents active against HCV. In combination therapy, effective dosages of two or more agents are administered together, whereas in alternation or sequential-step therapy, an effective dosage of each agent is administered serially or sequentially. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus. The dosages given will depend on absorption, inactivation and excretion rate of the drug as well as other factors. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions. The efficacy of a drug against the viral infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third antiviral compound that induces a different gene mutation than that caused by the principle

drug in a drug resistant virus. Alternatively, the pharmacokinetic, biodistribution or other parameters of the drug can be altered by such combination or alternation therapy.

Daily dosages required in practicing the method of the present invention will vary depending upon, for example, the compound of the invention employed , the host, the mode of administration, the severity of the condition to be treated. A preferred daily dosage range is about from 1 to 50 mg/kg per day as a single dose or in divided doses. Suitable daily dosages for patients are on the order of from e.g. 1 to 20 mg/kg p.o or i.v. Suitable unit dosage forms for oral administration comprise from ca. 0.25 to 10 mg/kg active ingredient, e.g. compound of Formula I or any subformulae thereof, together with one or more pharmaceutically acceptable diluents or carriers therefor. The amount of co-agent in the dosage form can vary greatly, e.g., 0.00001 to 1000mg/kg active ingredient.

Daily dosages with respect to the co-agent used will vary depending upon, for example, the compound employed, the host, the mode of administration and the severity of the condition to be treated. For example, lamivudine may be administered at a daily dosage of 100mg. The pegylated interferon may be administered parenterally one to three times per week, preferably once a week, at a total weekly dose ranging from 2 to 10 million IU, more preferable 5 to 10 million IU, most preferable 8 to 10 million IU. Because of the diverse types of co-agent that may be used, the amounts can vary greatly, e.g., .0001 to 5,000 mg/kg per day.

The current standard of care for treating hepatitis C is the combination of pegylated interferon alpha with ribavirin, of which the recommended doses are1.5 μg/kg/wk peginterferon alfa-2b or 180 μg/wk peginterferon alfa-2a, plus 1,000 to 1,200 mg daily of ribavirin for 48 weeks for genotype I patients, or 800 mg daily of ribavirin for 24 weeks for genotype 2/3 patients.

The compound of the invention (e.g., compound of Formula I or subformulae thereof) and co-agents of the invention may be administered by any conventional route, in particular enterally, e.g. orally, for example in the form of solutions for drinking, tablets or capsules or parenterally, for example in the form of injectable solutions or suspensions. Certain preferred pharmaceutical compositions may be e.g. those based on microemulsions as described in UK 2,222,770 A.

The compound of the invention (e.g., compound of Formula I or subformulae thereof) are administered together with other drugs (co-agents) e.g. a drug which has anti-viral activity, especially anti-Flaviviridae activity, most especially anti-HCV activity, e.g. an interferon, e.g. interferon-α-2a or interferon-α-2b, e.g. Intron$^{R}$ A, Roferon$^{R}$, Avonex$^{R}$, Rebif$^{R}$

or Betaferon$^{R}$, or an interferon conjugated to a water soluble polymer or to human albumin, e.g. albuferon, an anti-viral agent, e.g. ribavirin, lamivudine, the compounds disclosed in US patent no. 6,812,219 and WO 2004/002422 A2 (the disclosures of which are incorporated herein by reference in their entireties), an inhibitor of the HCV or other Flaviviridae virus encoded factors like the NS3/4A protease, helicase or RNA polymerase or a prodrug of such an inhibitor, an anti-fibrotic agent, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib, an immune modulating agent, e.g. mycophenolic acid, a salt or a prodrug thereof, e.g. sodium mycophenolate or mycophenolate mofetil, or a S1P receptor agonist, e.g. FTY720 or an analogue thereof optionally phosphorylated, e.g. as disclosed in EP627406A1, EP778263A1, EP1002792A1, WO02/18395, WO02/76995, WO 02/06268, JP2002316985, WO03/29184, WO03/29205, WO03/62252 and WO03/62248, the disclosures of which are incorporated herein by reference in their entireties.

Conjugates of interferon to a water-soluble polymer are meant to include especially conjugates to polyalkylene oxide homopolymers such as polyethylene glycol (PEG) or polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxide-based polymers, effectively non-antigenic materials such as dextran, polyvinyl pyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Such interferon-polymer conjugates are described in U.S. Pat. Nos. 4,766,106, 4,917,888, European Patent Application No. 0 236 987, European Patent Application No. 0 510 356 and International Application Publication No. WO 95/13090, the disclosures of which are incorporated herein by reference in their entireties. Since the polymeric modification sufficiently reduces antigenic responses, the foreign interferon need not be completely autologous. Interferon used to prepare polymer conjugates may be prepared from a mammalian extract, such as human, ruminant or bovine interferon, or recombinantly produced. Preferred are conjugates of interferon to polyethylene glycol, also known as pegylated interferons.

Especially preferred conjugates of interferon are pegylated alfa-interferons, for example pegylated interferon-α-2a, pegylated interferon-α-2b; pegylated consensus interferon or pegylated purified interferon- α product. Pegylated interferon- α -2a is described e.g. in European Patent 593,868 (incorporated herein by reference in its entirety) and commercially available e. g. under the tradename PEGASYS® (Hoffmann-La Roche). Pegylated interferon-α -2b is described, e.g. in European Patent 975,369 (incorporated herein by reference in its entirety) and commercially available e.g. under the tradename PEG-INTRON A® (Schering Plough). Pegylated consensus interferon is described in WO 96/11953 (incorporated herein

by reference in its entirety). The preferred pegylated α-interferons are pegylated interferon-α-2a and pegylated interferon-α-2b. Also preferred is pegylated consensus interferon.

Other preferred co-agents are fusion proteins of an interferon, for example fusion proteins of interferon- α -2a, interferon- α -2b; consensus interferon or purified interferon-α product, each of which is fused with another protein. Certain preferred fusion proteins comprise an interferon (e.g., interferon- α -2b) and an albumin as described in U.S. Patent 6,973,322 and international publications WO02/60071, WO05/003296 and WO05/077042 (Human Genome Sciences). A preferred interferon conjugated to a human albumin is Albuferon (Human Genome Sciences).

Cyclosporins which bind strongly to cyclophilin but are not immunosuppressive include those cyclosporins recited in U.S. Patents 5,767,069 and 5,981,479 and are incorporated herein by reference. MeIle$^4$-Cyclosporin is a preferred non-immunosuppressive cyclosporin. Certain other cyclosporin derivatives are described in WO2006039668 (Scynexis) and WO2006038088 (Debiopharm SA) and are incorporated herein by reference. A cyclosporin is considered to be non-immunosuppressive when it has an activity in the Mixed Lymphocyte Reaction (MLR) of no more than 5%, preferably no more than 2%, that of cyclosporin A. The Mixed Lymphocyte Reaction is described by T. Meo in "Immunological Methods", L. Lefkovits and B. Peris, Eds., Academic Press, N.Y. pp. 227 – 239 (1979). Spleen cells ($0.5 \times 10^6$) from Balb/c mice (female, 8 – 10 weeks) are co-incubated for 5 days with $0.5 \times 10^6$ irradiated (2000 rads) or mitomycin C treated spleen cells from CBA mice (female, 8 – 10 weeks). The irradiated allogeneic cells induce a proliferative response in the Balb c spleen cells which can be measured by labeled precursor incorporation into the DNA. Since the stimulator cells are irradiated (or mitomycin C treated) they do not respond to the Balb/c cells with proliferation but do retain their antigenicity. The $IC_{50}$ found for the test compound in the MLR is compared with that found for cyclosporin A in a parallel experiment. In addition, non-immunosuppressive cyclosporins lack the capacity of inhibiting CN and the downstream NF-AT pathway. [MeIle]$^4$-ciclosporin is a preferred non-immunosuppressive cyclophilin-binding cyclosporin for use according to the invention.

Ribavirin (1-β-D-ribofuranosyl-1-1,2,4-triazole-3-caroxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog sold under the trade name, Virazole (The Merck Index, 11$^{th}$ edition, Editor: Budavar, S, Merck & Co., Inc., Rahway, NJ, p1304,1989). United States Patent No. 3,798,209 and RE29,835 (incorporated herein by reference in their entireties) disclose and claim ribavirin. Ribavirin is structurally similar to

guanosine, and has *in vitro* activity against several DNA and RNA viruses including *Flaviviridae* (Gary L. Davis, Gastroenterology 118:S104-S114, 2000).

Ribavirin reduces serum amino transferase levels to normal in 40% of patients, but it does not lower serum levels of HCV-RNA (Gary L. Davis, Gastroenterology 118:S104-S114, 2000). Thus, ribavirin alone is not effective in reducing viral RNA levels. Additionally, ribavirin has significant toxicity and is known to induce anemia. Ribavirin is not approved for monotherapy against HCV; it is approved in combination with interferon alpha-2a or interferon alpha-2b for the treatment of HCV.

A further preferred combination is a combination of a compound of the invention (e.g., a compound of Formula I or any subformulae thereof) with a non-immunosuppressive cyclophilin-binding cyclosporine, with mycophenolic acid, a salt or a prodrug thereof, and/or with a S1P receptor agonist, e.g. FTY720.

Additional examples of compounds that can be used in combination or alternation treatments include:

(1) Interferons, including interferon alpha 2a or 2b and pegylated (PEG) interferon alpha 2a or 2b, for example:

(a) Intron-A®, interferon alfa-2b (Schering Corporation, Kenilworth, NJ);

(b) PEG-Intron®, peginteferon alfa-2b (Schering Corporation, Kenilworth, NJ);

(c) Roferon®, recombinant interferon alfa-2a (Hoffmann-La Roche, Nutley, NJ);

(d) Pegasys®, peginterferon alfa-2a (Hoffmann-La Roche, Nutley, NJ);

(e) Berefor®, interferon alfa 2 available (Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT);

(f) Sumiferon®, a purified blend of natural alpha interferons (Sumitomo, Japan)

(g) Wellferon®, lymphoblastoid interferon alpha n1 (GlaxoSmithKline);

(h) Infergen®, consensus alpha interferon (InterMune Pharmaceuticals, Inc., Brisbane, CA);

(i) Alferon®, a mixture of natural alpha interferons (Interferon Sciences, and Purdue Frederick Co., CT);

(j) Viraferon®;

(k) Consensus alpha interferon from Amgen, Inc., Newbury Park, CA,

Other forms of interferon include: interferon beta, gamma, tau and omega, such as Rebif ( Interferon beta 1a) by Serono, Omniferon (natural interferon) by Viragen, REBIF (interferon beta-1a) by Ares-Serono, Omega Interferon by BioMedicines; oral Interferon

Alpha by Amarillo Biosciences; an interferon conjugated to a water soluble polymer or to a human albumin, e.g., Albuferon (Human Genome Sciences), an antiviral agent, a consensus interferon, ovine or bovine interferon-tau

Conjugates of interferon to a water-soluble polymer are meant to include especially conjugates to polyalkylene oxide homopolymers such as polyethylene glocol (PEG) or polypropylene glycols, polyoxyethylenated polyols, copolymers thereof and block copolymers thereof. As an alternative to polyalkylene oxid-based polymers, effectively non-antigenic materials such as dextran, polyvinyl pyrrolidones, polyacrylamides, polyvinyl alcohols, carbohydrate-based polymers and the like can be used. Since the polymeric modification sufficiently reduces antigenic response, the foreign interferon need not be completely autologous. Interferon used to prepare polymer conjugates may be prepared from a mammalian extract, such as human, ruminant or bovine interferon, or recombinantly produced. Preferred are conjugates of interferon to polyethylene glycol, also known as pegylated interferons.

(2) Ribavirin, such as ribavirin (1-beta-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) from Valeant Pharmaceuticals, Inc., Costa Mesa, CA); Rebetol® from Schering Corporation, Kenilworth, NJ, and Copegus® from Hoffmann-La Roche, Nutley, NJ; and new ribavirin analogues in development such as Levovirin and Viramidine by Valeant,

(3) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo K. et al., *Antiviral Research*, 1996, 32, 9-18), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;

(4) Thiazolidines and benzanilides identified in Kakiuchi N. et al. *J. FEBS Letters* 421, 217-220; Takeshita N. et al. *Analytical Biochemistry, 1997, 247, 242-246;*

(5) A phenan-threnequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of Streptomyces sp., Sch 68631 (Chu M. et al., *Tetrahedron Letters*, 1996, 37, 7229-7232), and Sch 351633, isolated from the fungus *Penicillium griseofulvum,* which demonstrates activity in a scintillation proximity assay (Chu M. et al, *Bioorganic and Medicinal Chemistry Letters* 9, 1949-1952);

(6) Protease inhibitors.

Examples include substrate-based NS3 protease inhibitors (Attwood et al., *Antiviral peptide derivatives*, PCT WO 98/22496, 1998; Attwood et al., *Antiviral Chemistry and Chemotherapy* 1999, 10, 259-273; Attwood et al, *Preparation and use of amino acid derivatives as anti-viral agents*, German Patent Pub. DE 19914474; Tung et al. *Inhibitors of*

*serine proteases, particularly hepatitis C virus NS3 protease*; PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a boronic acid or phosphonate (Llinas-Brunet et al. *Hepatitis C inhibitor peptide analogues*, PCT WO 99/07734) are being investigated.

Non-substrate-based NS3 protease inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives (Sudo K. et al., *Biochemical and Biophysical Research Communications*, 1997, 238 643-647; Sudo K. et al. *Antiviral Chemistry and Chemotherapy*, 1998, 9, 186), including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a *para*-phenoxyphenyl group are also being investigated.

Sch 68631, a phenanthrenequinone, is an HCV protease inhibitor (Chu M et al., *Tetrahedron Letters* 37:7229-7232, 1996). In another example by the same authors, Sch 351633, isolated from the fungus *Penicillium grieofulvum*, was identified as a protease inhibitor (Chu M. et al., *Bioorganic and Medicinal Chemistry Letters* 9:1949-1952). Nanomolar potency against the HCV NS3 protease enzyme has been achieved by the design of selective inhibitors based on the macromolecule eglin c. Eglin c, isolated from leech, is a potent inhibitor of several serine proteases such as S. griseus proteases A and B, ∀-chymotrypsin, chymase and subtilisin. Qasim M.A. et al., *Biochemistry* 36:1598-1607, 1997.

U.S. patents disclosing protease inhibitors for the treatment of HCV include, for example, U.S. Patent No. 6,004,933 to Spruce et al (incorporated herein by reference in its entirety) which discloses a class of cysteine protease inhibitors for inhibiting HCV endopeptidase 2; U.S. Patent No. 5,990,276 to Zhang et al.(incorporated herein by reference in its entirety) which discloses synthetic inhibitors of hepatitis C virus NS3 protease; U.S. Patent No. 5,538,865 to Reyes et al.(incorporated herein by reference in its entirety). Peptides as NS3 serine protease inhibitors of HCV are disclosed in WO 02/008251 to Corvas International, Inc., and WO 02/08187 and WO 02/008256 to Schering Corporation (incorporated herein by reference in their entireties). HCV inhibitor tripeptides are disclosed in U.S. Patent Nos. 6,534,523, 6,410,531 and 6,420,380 to Boehringer Ingelheim and WO 02/060926 to Bristol Myers Squibb (incorporated herein by reference in their entireties). Diaryl peptides as NS3 serine protease inhibitors of HCV are disclosed in WO 02/48172 to Schering Corporation (incorporated herein by reference). Imidazoleidinones as NS3 serine protease inhibitors of HCV are disclosed in WO 02/18198 to Schering Corporation and WO 02/48157 to Bristol Myers Squibb (incorporated herein by reference in their entireties). WO

98/17679 to Vertex Pharmaceuticals and WO 02/48116 to Bristol Myers Squibb also disclose HCV protease inhibitors (incorporated herein by reference in their entireties).

HCV NS3-4A serine protease inhibitors including BILN 2061 by Boehringer Ingelheim, VX-950 by Vertex, SCH 6/7 by Schering-Plough, and other compounds currently in preclinical development;

Substrate-based NS3 protease inhibitors, including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an elecrophile such as a boronic acid or phosphonate; Non-substrate-based NS3 protease inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a para-phenoxyphenyl group; and Sch68631, a phenanthrenequinone, an HCV protease inhibitor.

Sch 351633, isolated from the fungus *Penicillium griseofulvum* was identified as a protease inhibitor. Eglin c, isolated from leech is a potent inhibitor of several serine proteases such as S. griseus proteases A and B, a-chymotrypsin, chymase and subtilisin.

US patent no. 6004933 (incorporated herein by reference in its entirety) discloses a class of cysteine protease inhibitors from inhibiting HCV endopeptidase 2; synthetic inhibitors of HCV NS3 protease (pat), HCV inhibitor tripeptides (pat), diaryl peptides such as NS3 serine protease inhibitors of HCV (pat), Imidazolidindiones as NS3 serine protease inhibitors of HCV (pat).

Thiazolidines and benzanilides (ref). Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate especially compound RD-16250 possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193

Phenan-threnequinone possessing activity against protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of *Streptomyces* sp, Sch68631 and Sch351633, isolated from the fungus *Penicillium griseofulvum*, which demonstrates activity in a scintillation proximity assay.

(7) Nucleoside or non-nucleoside inhibitors of HCV NS5B RNA-dependent RNA polymerase, such as 2'-C-methyl-3'-O-L-valine ester ribofuranosyl cytidine (Idenix) as disclosed in WO 2004/002422 A2 (incorporated herein by reference in its entirety), R803 (Rigel), JTK-003 (Japan Tabacco), HCV-086 (ViroPharma/Wyeth) and other compounds currently in preclinical development;

gliotoxin (ref) and the natural product cerulenin;

2'-fluoronucleosides;

other nucleoside analogues as disclosed in WO 02/057287 A2, WO 02/057425 A2, WO 01/90121, WO 01/92282, and US patent no. 6,812,219, the disclosures of which are incorporated herein by reference in their entirety.

Idenix Pharmaceuticals discloses the use of branched nucleosides in the treatment of flaviviruses (including HCV) and pestiviruses in International Publication Nos. WO 01/90121 and WO 01/92282 (incorporated herein by reference in their entireties). Specifically, a method for the treatment of hepatitis C infection (and flaviviruses and pestiviruses) in humans and other host animals is disclosed in the Idenix publications that includes administering an effective amount of a biologically active 1', 2', 3' or 4'-branced B-D or B-L nucleosides or a pharmaceutically acceptable salt or prodrug thereof, administered either alone or in combination with another antiviral agent, optionally in a pharmaceutically acceptable carrier. Certain preferred biologically active 1', 2', 3', or 4' branched B-D or B-L nucleosides, including Telbivudine, are described in U.S. Patents 6,395,716 and 6,875,751, each of which are incorporated herein by reference.

Other patent applications disclosing the use of certain nucleoside analogs to treat hepatitis C virus include: PCTCA00/01316 (WO 01/32153; filed November 3, 2000) and PCT/CA01/00197 (WO 01/60315; filed February 19, 2001) filed by BioChem Pharma, Inc., (now Shire Biochem, Inc.); PCT/US02/01531 (WO 02/057425; filed January 18, 2002) and PCT/US02/03086 (WO 02/057287; filed January 18, 2002) filed by Merck & Co., Inc., PCT/EP01/09633 (WO 02/18404; published August 21, 2001) filed by Roche, and PCT Publication Nos. WO 01/79246 (filed April 13, 2001), WO 02/32920 (filed October 18, 2001) and WO 02/48165 by Pharmasset, Ltd. (the disclosures of which are incorporated herein by reference in their entireties)

PCT Publication No. WO 99/43691 to Emory University (incorporated herein by reference in its entirety), entitled "2'-Fluoronucleosides" discloses the use of certain 2'-fluoronucleosides to treat HCV.

Eldrup et al. (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International Conference on Antiviral Research (April 27, 2003, Savannah, GA)) described the structure activity relationship of 2'-modified nucleosides for inhibition of HCV.

Bhat et al. (Oral Session V, Hepatitis C Virus, Flaviviridae, 2003 (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International conference on Antiviral Research (April 27, 2003, Savannah, GA); p A75) describes the synthesis and pharmacokinetic properties of nucleoside analogues as possible inhibitors of HCV RNA replication. The authors report that 2'-modified nucleosides demonstrate potent inhibitory activity in cell-based replicon assays.

Olsen et al. (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International Conference on Antiviral Research (April 27, 2003, Savannah, Ga)p A76) also described the effects of the 2'-modified nucleosides on HCV RNA replication.

(8) Nucleotide polymerase inhibitors and gliotoxin (Ferrari R. et al. *Journal of Virology*, 1999, 73, 1649-1654), and the natural product cerulenin (Lohmann V. et al. *Virology*, 1998, 249, 108-118);

(9) HCV NS3 helicase inhibitors, such as VP_50406 by ViroPhama and compounds from Vertex. Other helicase inhibitors (Diana G.D. et al., *Compounds, compositions and methods for treatment of hepatitis C*, U.S. Patent No. 5,633,358 (incorporated herein by reference in its entirety); Diana G.D. et al., *Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis C*, PCT WO 97/36554);

(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5' non-coding region (NCR) of the virus (Alt M. et al., *Hepatology*, 1995, 22, 707-717), or nucleotides 326-348 comprising the 3' end of the NCR and nucleotides 371-388 located in the core coding region of the HCV RNA (Alt M. et al., *Archives of Virology*, 1997, 142, 589-599; Galderisi U. et al., *Journal of Cellular Physiology*, 199, 181, 251-257); such as ISIS 14803 by Isis Pharm/Elan, antisense by Hybridon, antisense by AVI bioPharma,

(11) Inhibitors of IRES-dependent translation (Ikeda N et al., *Agent for the prevention and treatment of hepatitis C*, Japanese Patent Pub. JP-08268890; Kai Y et al. *Prevention and treatment of viral diseases*, Japanese Patent Pub. JP-10101591); such as ISIS 14803 by Isis Pharm/Elan, IRES inhibitor by Anadys, IRES inhibitors by Immusol, targeted RNA chemistry by PTC Therapeutics

(12) Ribozymes, such as nuclease-resistant ribozymes (Maccjak, D.J. et al., *Hepatology* 1999, 30, abstract 995) and those directed in U.S. Patent No. 6,043,077 to Barber et al., and U.S. Patent Nos. 5,869,253 and 5,610,054 to Draper et al.(incorporated herein by reference in their entireties) for example, HEPTAZYME by RPI

(13) siRNA directed against HCV genome

(14) HCV replication inhibitor of any other mechanisms such as by VP50406ViroPharama/Wyeth, inhibitors from Achillion, Arrow

(15) An inhibitor of other targets in the HCV life cycle including viral entry, assembly and maturation

(16) An immune modulating agent such as an IMPDH inhibitor, mycophenolic acid, a salt or a prodrug thereof sodium mycophenolate or mycophenolate mofetil, or Merimebodib

(VX-497); thymosin alpha-1 (Zadaxin, by SciClone); or a S1P receptor agonist, e.g. FTY720 or analogue thereof optionally phosphorylated.

(17) An anti-fibrotic agent, such as a N-phenyl-2-pyrimidine-amine derivative, imatinib (Gleevac), IP-501 by Indevus, and Interferon gamma 1b from InterMune

(18) Therapeutic vaccine by Intercell, Epimmune/Genecor, Merix, Tripep (Chron-VacC), immunotherapy (Therapore) by Avant, T cell therapy by CellExSys, monoclonal antibody XTL-002 by STL, ANA 246 and ANA 246 BY Anadys,

(19) Other miscellaneous compounds including 1-amino-alkylcyclohexanes (U.S. Patent No. 6,034,134 to Gold et al.), alkyl lipids (U.S. Pat. No. 5,922,757 to Chojkier et al.), vitamin E and other anti-oxidants (U.S. Patent. No. 5,922,757 to Chojkier et al.), amantadine, bile acids (U.S. Pat. No. 5,846,99964 to Ozeki et al.), N-(phosphonoacetl)-L-aspartic acid, )U.S. Pat. No. 5,830,905 to Diana et al.), benzenedicarboxamides (U.S. Pat. No. 5,633,388 to Diane et al.), polyadenylic acid derivatives (U.s. Pat. No. 5,496,546 to Wang et al.), 2'3'-dideoxyinosine (U.S. Pat. No. 5,026,687 to Yarchoan et al.), benzimidazoles (U.S. Pat. No. 5,891,874 to Colacino et al.), plant extracts (U.S. Pat. No. 5,837,257 to Tsai et al., U.S. Pat. No. 5,725,859 to Omer et al., and U.S. Pat. No. 6,056,961) and piperidines (U.S. Pat. No. 5,830,905 to Diana et al.); the disclosures of which are incorporated herein by reference in their entireties. Also,squalene, telbivudine, N-(phosphonoacetyl)-L-aspartic acid, benzenedicarboxamides, polyadenylic acid derivatives, glycosylation inhibitors, and nonspecific cytoprotective agents that block cell injury caused by the virus infection.

(20) Any other compound currently in preclinical or clinical development for the treatment of HCV, including Interleukin-10 (Schering-Plough), AMANTADINE (Symmetrel) by Endo Labs Solvay, caspase inhibitor IDN-6556 by Idun Pharma, HCV/MF59 by Chiron, CIVACIR (Hepatitis C Immune Globulin) by NABI, CEPLENE (histamine dichloride) by Maxim, IDN-6556 by Idun PHARM, T67, a beta-tubulin inhibitor, by Tularik, a therapeutic vaccine directed to E2 by Innogenetics, FK788 by Fujisawa Helathcare, IdB1016 (Siliphos, oral silybin-phosphatidyl choline phytosome), fusion inhibitor by Trimeris, Dication by Immtech, hemopurifier by Aethlon Medical, UT 231B by United Therapeutics.

(21) Purine nucleoside analog antagonists of TlR7 (toll-like receptors) developed by Anadys, e.g., Isotorabine (ANA245) and its prodrug (ANA975), which are described in European applications EP348446 and EP636372, International Publications WO03/045968, WO05/121162 and WO05/25583, and U.S. Patent 6/973322, each of which is incorporated by reference.

(21) Non-nucleoside inhibitors developed by Genelabs and described in International Publications WO2004/108687, WO2005/12288, and WO2006/076529, each of which is incorporated by reference.

(22) Other co-agents (*e.g.*, non-immunomodulatory or immunomodulatory compounds) that may be used in combination with a compound of this invention include, but are not limited to, those specified in WO 02/18369, which is incorporated herein by reference.

Methods of this invention may also involve administration of another component comprising an additional agent selected from an immunomodulatory agent; an antiviral agent; an inhibitor of HCV protease; an inhibitor of another target in the HCV life cycle; a CYP inhibitor; or combinations thereof.

Accordingly, in another embodiment, this invention provides a method comprising administering a compound of the invention and another anti-viral agent, preferably an anti-HCV agent. Such anti-viral agents include, but are not limited to, immunomodulatory agents, such as α, β, and δ interferons, pegylated derivatized interferon-a compounds, and thymosin; other anti-viral agents, such as ribavirin, amantadine, and telbivudine; other inhibitors of hepatitis C proteases (NS2-NS3 inhibitors and NS3-NS4A inhibitors); inhibitors of other targets in the HCV life cycle, including helicase, polymerase, and metalloprotease inhibitors; inhibitors of internal ribosome entry; broad-spectrum viral inhibitors, such as IMPDH inhibitors (*e.g.*, compounds of United States Patent 5,807, 876,6, 498,178, 6,344, 465,6, 054,472, WO 97/40028, WO 98/40381, WO 00/56331, and mycophenolic acid and derivatives thereof, and including, but not limited to VX-497, VX-148, and/or VX-944); or combinations of any of the above.

In accordance with the foregoing the present invention provides in a yet further aspect:

- A pharmaceutical combination comprising a) a first agent which is a compound of the invention, e.g. a compound of formula I or any subformulae thereof, and b) a co-agent, e.g. a second drug agent as defined above.
- A method as defined above comprising co-administration, e.g. concomitantly or in sequence, of a therapeutically effective amount of a compound of the invention, e.g. a compound of formula I or any subformulae thereof, and a co-agent, e.g. a second drug agent as defined above.

The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected therapeutic agents to a single

patient, and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. Fixed combinations are also within the scope of the present invention. The administration of a pharmaceutical combination of the invention results in a beneficial effect, e.g. a synergistic therapeutic effect, compared to a monotherapy applying only one of its pharmaceutically active ingredients.

Each component of a combination according to this invention may be administered separately, together, or in any combination thereof. As recognized by skilled practitioners, dosages of interferon are typically measured in IU (*e.g.*, about 4 million IU to about 12 million IU).

If an additional agent is selected from another CYP inhibitor, the method would, therefore, employ two or more CYP inhibitors. Each component may be administered in one or more dosage forms. Each dosage form may be administered to the patient in any order.

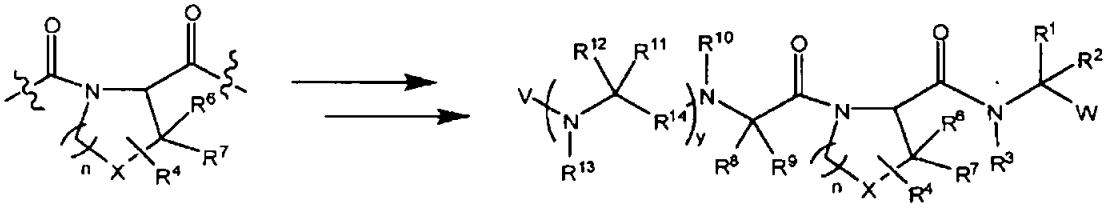
The compound of the invention and any additional agent may be formulated in separate dosage forms. Alternatively, to decrease the number of dosage forms administered to a patient, the compound of the invention and any additional agent may be formulated together in any combination. For example, the compound of the invention inhibitor may be formulated in one dosage form and the additional agent may be formulated together in another dosage form. Any separate dosage forms may be administered at the same time or different times.

Alternatively, a composition of this invention comprises an additional agent as described herein. Each component may be present in individual compositions, combination compositions, or in a single composition.

### *Exemplification of the Invention*

The invention is further illustrated by the following examples, which should not be construed as further limiting. The assays used throughout the Examples are accepted. Demonstration of efficacy in these assays is predictive of efficacy in subjects.

## GENERAL SYNTHESIS METHODS



All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents, and catalysts utilized to synthesis the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21). Further, the compounds of the present invention can be produced by organic synthesis methods known to one of ordinary skill in the art as shown in the following examples.

## LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| ACN | Acetonitrile |
| AcOEt / EtOAc | Ethyl acetate |
| AcOH | acetic acid |
| aq | aqueous |
| Ar | aryl |
| Bn | benzyl |
| Bu | butyl (nBu = n-butyl, tBu = tert-butyl) |
| CDI | Carbonyldiimidazole |
| $CH_3CN$ | Acetonitrile |
| DBU | 1,8-Diazabicyclo[5.4.0]-undec-7-ene |
| DCE | 1,2-Dichloroethane |
| DCM | Dichloromethane |
| DIPEA | N-Ethyldiisopropylamine |
| DMAP | Dimethylaminopyridine |
| DMF | N,N'-Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| EI | Electrospray ionisation |
| $Et_2O$ | Diethylether |
| $Et_3N$ | Triethylamine |
| Ether | Diethylether |
| EtOH | Ethanol |
| FC | Flash Chromatography |
| h | hour(s) |

| | |
|---|---|
| HATU | O-(7-Azabenzotriazole-1-yl)-N,N,N'N'-tetramethyluronium hexafluorophosphate |
| HBTU | O-(Benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate |
| HCl | Hydrochloric acid |
| HOBt | 1-Hydroxybenzotriazole |
| HPLC | High Performance Liquid Chromatography |
| $H_2O$ | Water |
| L | liter(s) |
| LC-MS | Liquid Chromatography Mass Spectrometry |
| Me | methyl |
| MeI | Iodomethane |
| MeOH | Methanol |
| mg | milligram |
| min | minute(s) |
| mL | milliliter |
| MS | Mass Spectrometry |
| Pd/C | palladium on charcoal |
| PG | protecting group |
| Ph | phenyl |
| Prep | Preparative |
| Rf | ratio of fronts |
| RP | reverse phase |
| Rt | Retention time |
| rt | Room temperature |
| $SiO_2$ | Silica gel |
| TBAF | Tetrabutylammonium fluoride |
| TEA | Triethylamine |
| TFA | Trifluoroacetic acid |
| THF | Tetrahydrofurane |
| TLC | Thin Layer Chromatography |

**HPLC methods:**

**Method A:**

HPLC

Instrument: Agilent system

column: waters symmetry C18, 3.5 μm , 2.1 x 50mm , flow 0.6 ml/min

solvent: $CH_3CN$ (0.1% $CF_3CO_2H$); $H_2O$ (0.1% $CF_3CO_2H$)

gradient: 0-3.5 min : 20-95% $CH_3CN$, 3.5-5 min : 95% $CH_3CN$, 5.5-5.55 min 95 % to 20% $CH_3CN$

**Method B:**

Agilent 1100 LC chromatographic system with Micromass ZMD MS detection. A binary gradient composed of A (water containing 5 % acetonitrile and 0.05% trifluoroacetic acid) and B (acetonitrile containing 0.045% trifluoroacetic acid) is used as a mobile phase on a Waters X Terra™ C-18 column (30 x 3 mm, 2.5 μm particle size) as a stationary phase. The following elution profile is applied: a linear gradient of 3.5 minutes at a flow rate of 0.6 ml/min from 5% of B to 95% of B, followed by an isocratic elution of 0.5 minutes at a flow rate of 0.7 ml/min of 95% of B, followed by an isocratic elution of 0.5 minutes at a flow rate of 0.8 ml/min of 95% of B, followed by a linear gradient of 0.2 minutes at a flow rate of 0.8 ml/min from 95% of B to 5% of B, followed by a isocratic elution of 0.2 minutes at a flow rate of 0.7 ml/min of 5% of B.

**Method C:**

HPLC

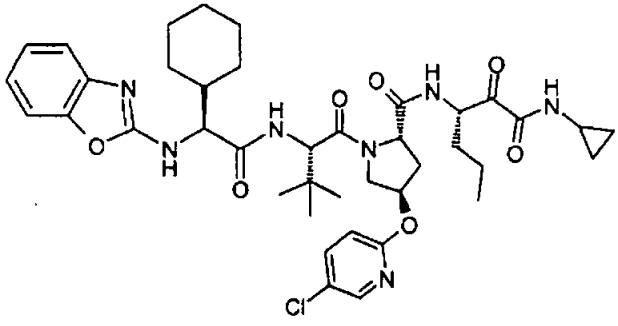
Instrument: Kontron, Kroma-System

Column: Macherey-Nagel, Lichrosphere 100-5 RP 18

Solvent: $CH_3CN$ (0.1% $CF_3CO_2H$); $H_2O$ (0.1% $CF_3CO_2H$)

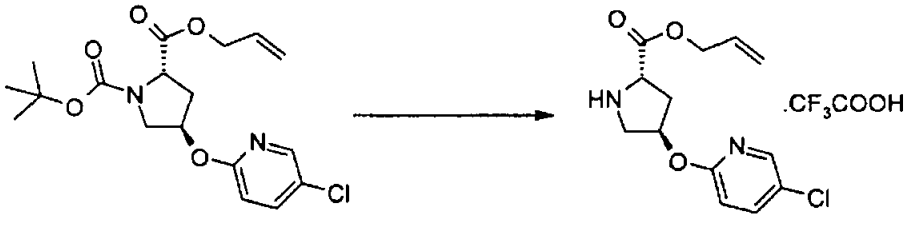
Gradient: 0-5 min: 10-100% $CH_3CN$; 5-7.5 min: 100% $CH_3CN$ (Flow 1.5mL/min)

**Example 1:**



1

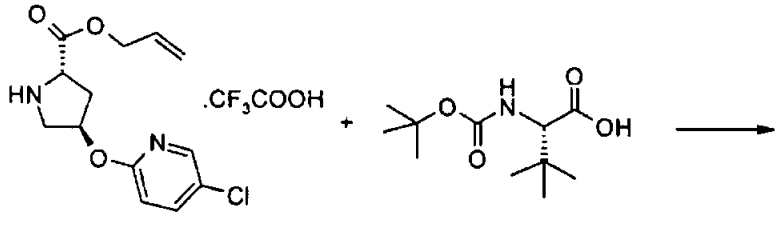
**Step 1-A:**



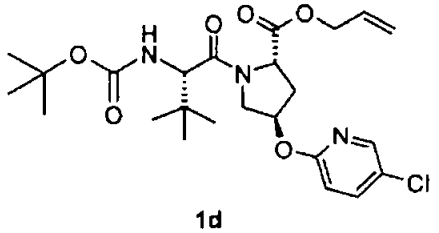
1a 1b

To a solution of **1a** (3.0 g, 7.84 mmol) in dichloromethane (20 mL) at room temperature is added TFA (20 mL ). The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo to give the desired product (4.5 g). Found m/z ES+ = 283 and ES- = 281.

**Step 1-B:**



1b 1c

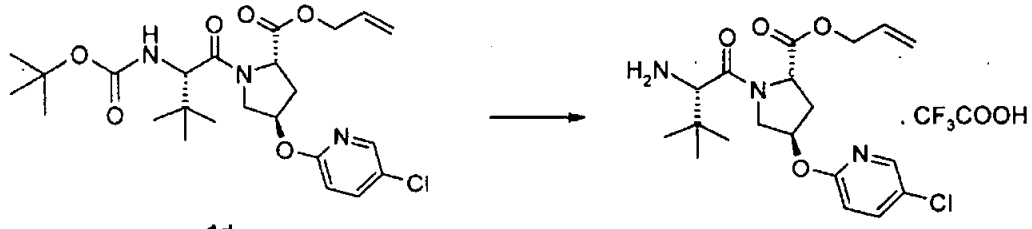


1d

A solution of **1c** (2.18 g, 9.45 mmol) in anhydrous dichloromethane (57 mL) and

anhydrous DMF (57 mL) is stirred at 0 °C is added HATU (1.4 eq, 5.0 g, 13.23 mmol). **1b** (1.2 eq, 4.50 g, 11.34 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 3.82 g, 37.8 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethyl acetate. The organic layer is washed with water, 1.0 N HCl aq. solution, aq. sat. $NaHCO_3$ solution, and brine. The organic layer is dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/hexane; 2:8 to 1:1) to afford **1d** (3.11 g). Found m/z ES+ = 496.

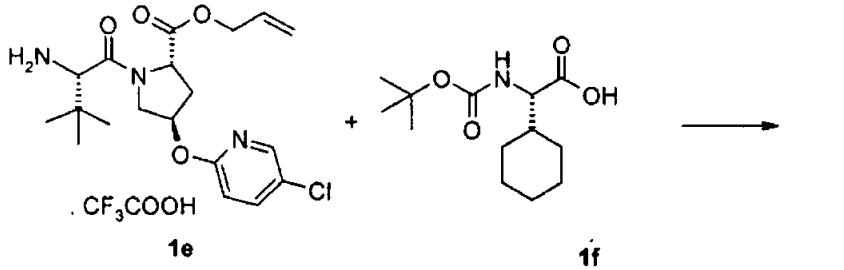
**Step 1-C:**



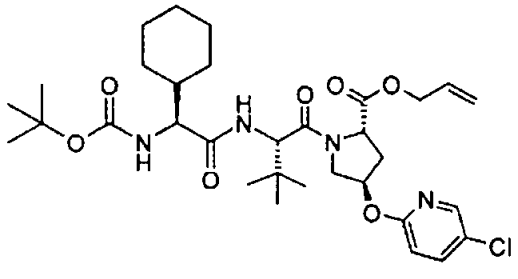
**1d** **1e**

To a solution of **1d** (3.1 g, 6.25 mmol) in dichloromethane (15 mL) at room temperature is added TFA (15 mL ). The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo to give 4.7 g of **1e**. Found m/z ES+ = 396.

**Step 1-D:**



**1e** **1f**

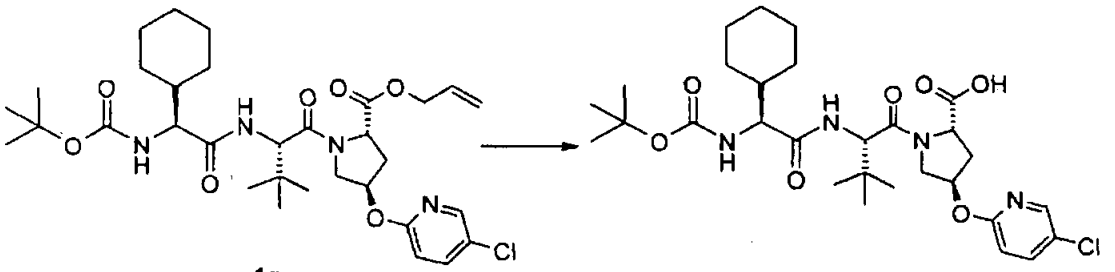


**1g**

A solution of Boc-L-2-cyclohexylglycine **1f** (2.0 g, 7.79 mmol) in anhydrous

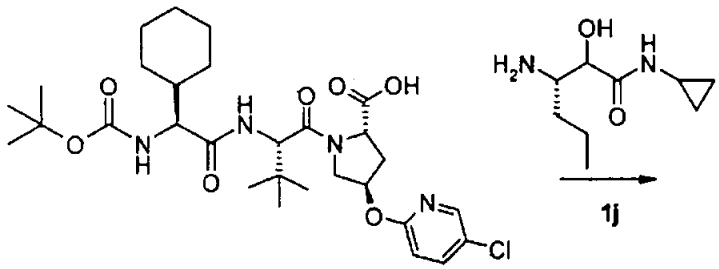
dichloromethane (40 mL) and anhydrous DMF (40 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 4.14 g, 10.90 mmol). **1e** (1.2 eq, 4.77 g, 9.35 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 3.15 g, 31.16 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is washed with water, aq. 1.0 N HCl solution, sat. aq. $NaHCO_3$ solution, and brine. The organic layer is dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/hexane; 2:8 to 1:1) to afford 3.0 g of **1g**. Found m/z ES+ = 635.

**Step 1-E:**




A solution of **1g** (3.0 g, 4.72 mmol) in 45 mL of a 1:1:1 mixture of THF/MeOH/water is added lithium hydroxide monohydrate (2 eq, 394 mg). The mixture is stirred for overnight. All the volatiles are evaporated in a vacuo and to the residue is added dichloromethane (100 mL). The pH of the aqueous layer is adjusted to pH 5 with dropwise addition of aq. 1.0 N HCl solution. The layers are separated and the aqueous layer is extracted with dichloromethane. The combined organic layers are dried ($Na_2SO_4$), filtered, and concentrated to afford 1.87 g of **1h** (1.87 g). Found m/z ES+ = 595 and ES- = 593

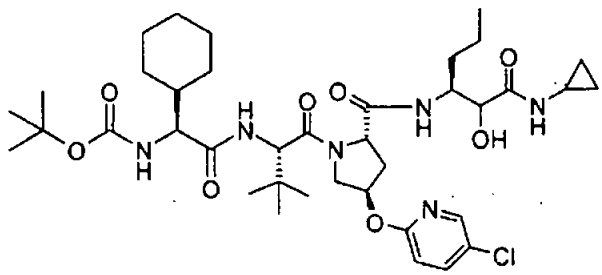
**Step 1-F:**



1i



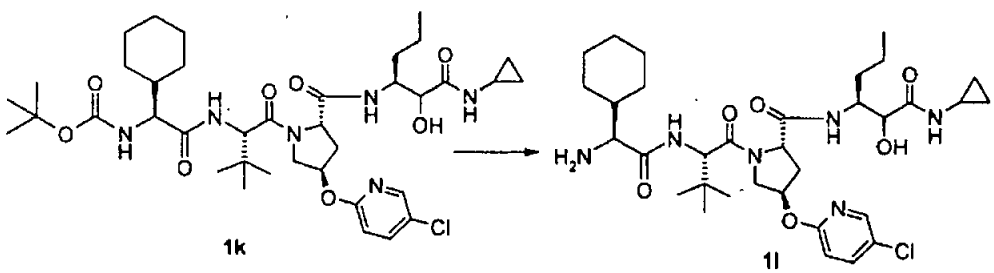
1j



1k

A solution of **1i** (2.80 g, 4.7 mmol) in anhydrous dichloromethane (24 mL) and anhydrous DMF (24 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 2.5 g, 6.58 mmol). The hydroxy ketoamide amine **1j** (1.2 eq, 1.05 g, 5.66 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 1.90 g, 18.80 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is washed with water, aq. 1.0 N HCl solution, sat. aq. $NaHCO_3$ solution, and brine. The organic layer is dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/hexane; 2:8 to 1:1) to afford 3.0 g of **1k**. Found m/z ES+ = 763 and ES- = 761.

**Step 1-G:**

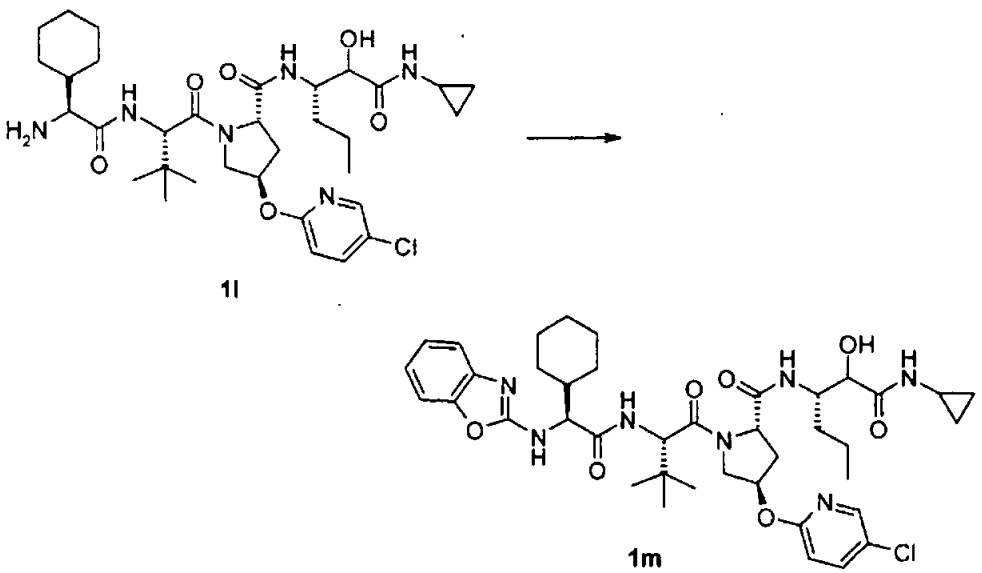


1k 1l

To a solution of **1k** (4.0 g, 5.24 mmol) in dichloromethane (26 mL) at room temperature is added TFA (26 mL ). The mixture is stirred for 3 hours after which the

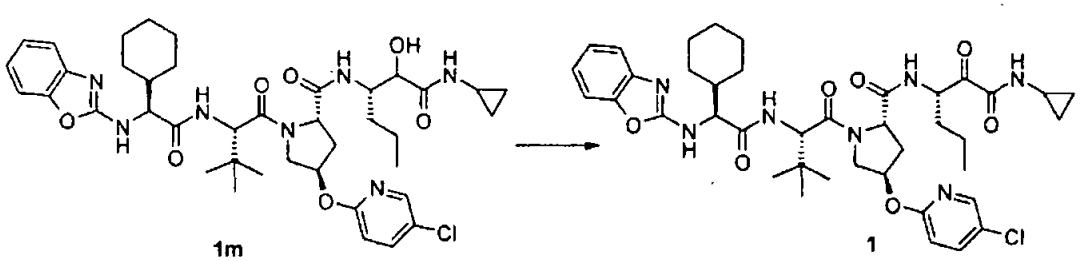
solvent is evaporated in vacuo and to the residue is added dichloromethane (100 mL). The pH is adjusted to 8 by dropwise addition of sat. aq. $NaHCO_3$ solution. The layers are separated. The organic layer is washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give 4.0 g of **1l** (4.0 g). Found m/z ES+ = 663 and ES- = 661.

**Step 1-H:**




To a solution of **1l** (350 mg, 0.53 mmol) in dioxane (1.0 mL) at room temperature added 2-chlorobenzaxazole (122 mg, 0.79 mmol ) and $NaHCO_3$ (89 mg, 1.1 mmol). The mixtures are stirred at 65 °C for 6 hours. The mixture then is loaded directly to silica gel column and eluted with hexane/EtOH (from 95/5 to 85/15) to give 360 mg of **1m**. Found m/z ES+ = 780 and ES- = 778.

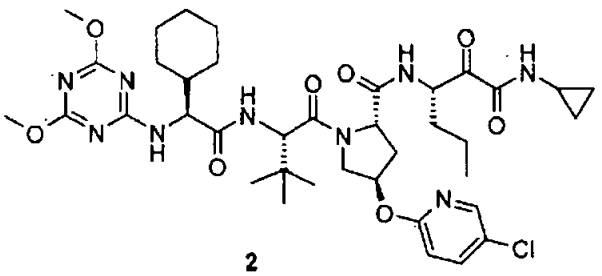
**Step 1-I:**




To a solution of **1m** (253 mg, 0.32 mmol) in $CH_2Cl_2$ (1.6 mL) at 0 °C is added DIPEA (1.3 mmol, 168 mg) followed by a solution of pyridine sulfoxide (0.65 mmol, 103 mg) in DMSO (1.6 mL). The solution is stirred at 0 °C for 10 min. To the solution is added

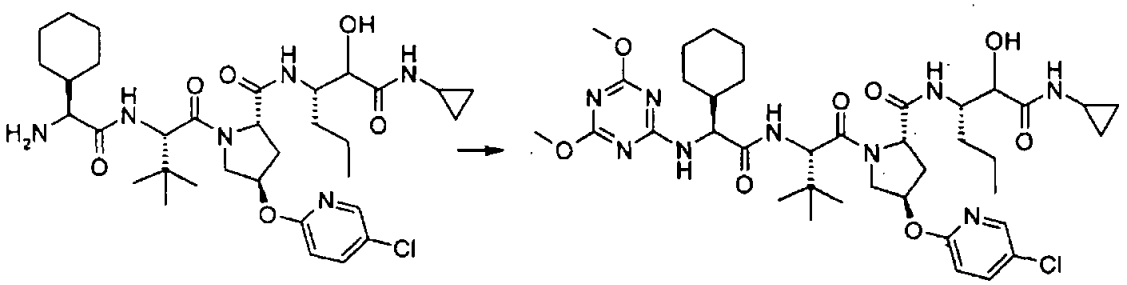
EtOAc and sat. aq. $NH_4Cl$ solution. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel column chromatography (hexane/Acetone, 1/1) to give 245 mg of **1**. Found m/z in ES+ 778, m/z in ES- = 776.

**Example 2:**



**2**

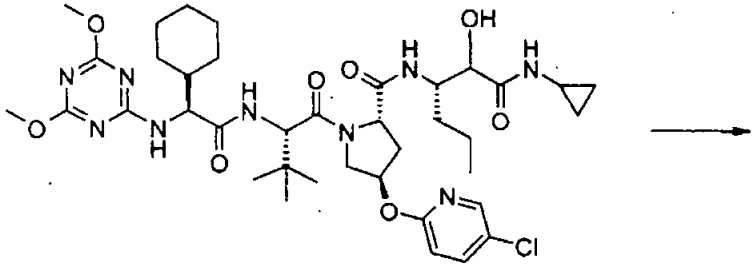
**Step 2-A:**



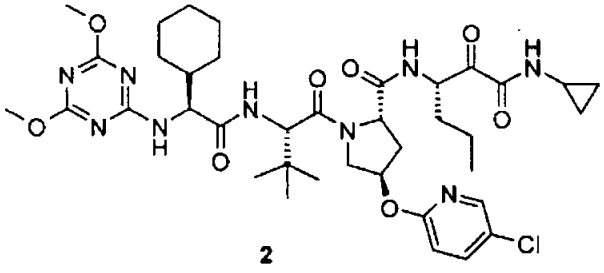
**1l** **2a**

To a solution of the amine **1l** (50 mg, 0.07 mmol) in dioxane (350 mL) at room temperature is added 2-chloro-4,6-dimethoxytriazine (20 mg, 0.11 mmol ) and $NaHCO_3$ (13 mg, 0.16 mmol). The mixtures are stirred at 80 °C for 2 hours. The reaction mixture is concentrated in a vacuo and to the residue is added ethyl acetate (30 mL). The organic layer is washed with aq. 1.0 N HCl solution, sat. aq. $NaHCO_3$ solution and brine. The organic solution is then dried over sodium sulfate and concentrated. Purification using preparative TLC (eluent: Acetone/hexane, 1:1) afford 48 mg of **2a**. Found m/z ES+ = 802 and ES- = 800.

**Step 2-B:**



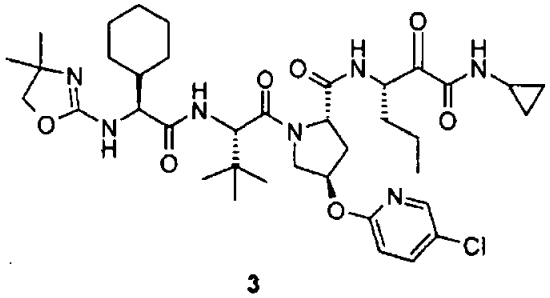
2a



2

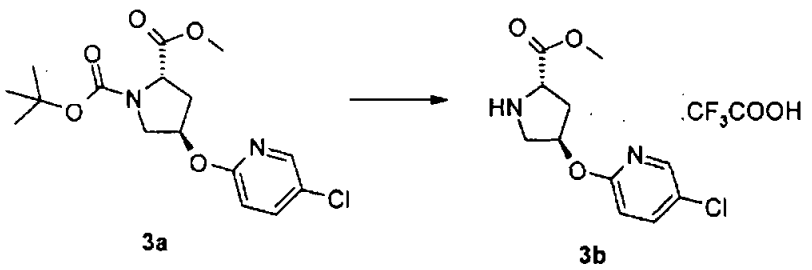
A solution o **2a** (48 mg, 0.06 mmol) in anhydrous dichloromethane (0.6 mL) is treated with DMP (2.0 eq, 51 mg). The reaction mixture is stirred at room temperature for 30 minutes. The mixture is added aq. 1.0 M sodium thiosulfate solution (2 mL) and the resulted mixtures are stirred for 5 minutes. Aq. sat. sodium bicarbonate solution (2 mL) is added and the stirring is continued for another 10 minutes. The phases are separated and the aqueous layer is extracted with dichloromethane. The combined organic layer are dried over sodium sulfate, filtered and concentrated. The residue is chromatographed using silica gel preparative TLC (Eluent: acetone/hexanes, 4:6) to afford 36 mg of **2**. Found m/z ES+ = 800.

**Example 3:**



3

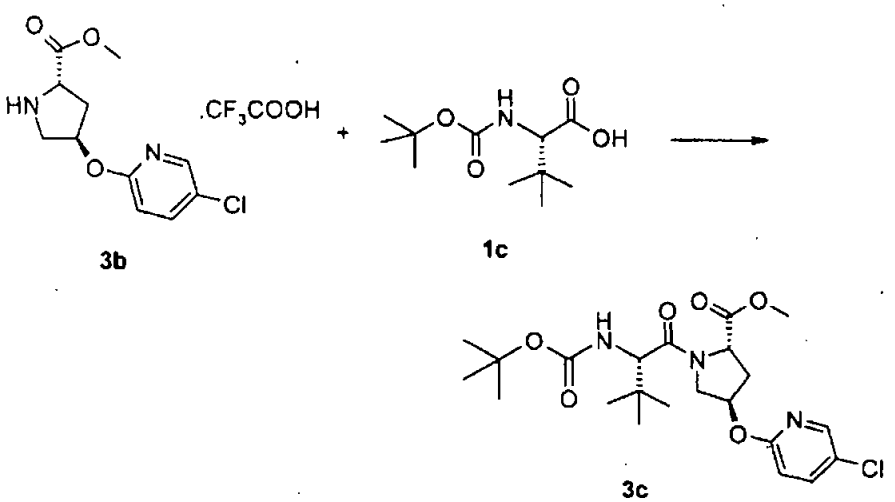
**Step 3-A:**



3a 3b

To a solution of **3a** (2.5 g, 7.0 mmol) in dichloromethane (6.0 mL) at room temperature is added TFA (6 mL ). The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo to give 4.0 g of **3b**. Found m/z ES+ = 257.

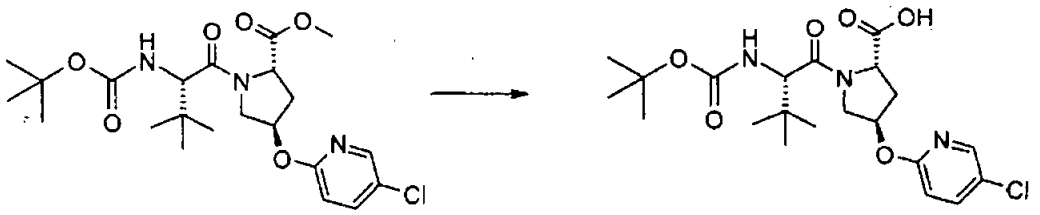
**Step 3-B:**



3b 1c 3c

A solution of **1c** (219 mg, 2.68 mmol) in anhydrous dichloromethane (13 mL) and anhydrous DMF (13 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 1.42 g, 3.75 mmol). **3b** (1.0 eq, 0.99 g, 2.67 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 1.08 g, 10.7 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is washed with water, aq. 1.0 N HCl solution, sat. aq. sodium bicarbonate solution, and brine. The organic layer is dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: EtOAc/Hexane, 1:1)) to afford 1.3 g of **3c**. Found m/z ES+ = 470.

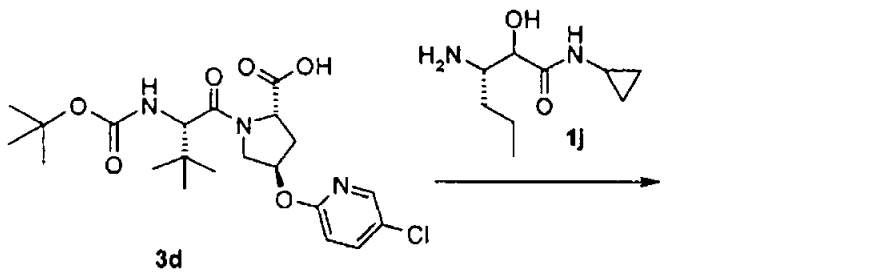
**Step 3-C:**



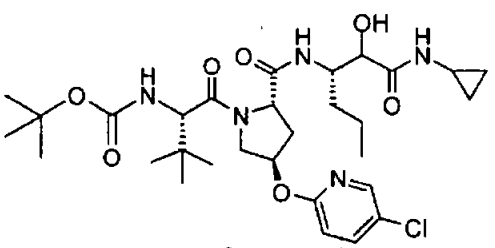
3c 3d

A solution of **3c** (1.2 g, 2.55 mmol) in 12 mL of a 1:1:1 mixture of THF/MeOH/water is added lithium hydroxide monohydrate (2.0 eq, 214 mg). The mixture is stirred overnight. All the volatiles are evaporated in a vacuo and to the residue is added dichloromethane. The pH of the aqueous layer is adjusted to 5 with dropwise addition of aq. 1.0 N HCl solution and layers are separated. The aqueous layer is extracted with dichloromethane. The combined organic layers are dried over sodium sulfate, filtered, and concentrated to afford 822 mg of **3d**. Found m/z ES+ = 456 and ES- = 454.

**Step 3-D:**



3d 1j

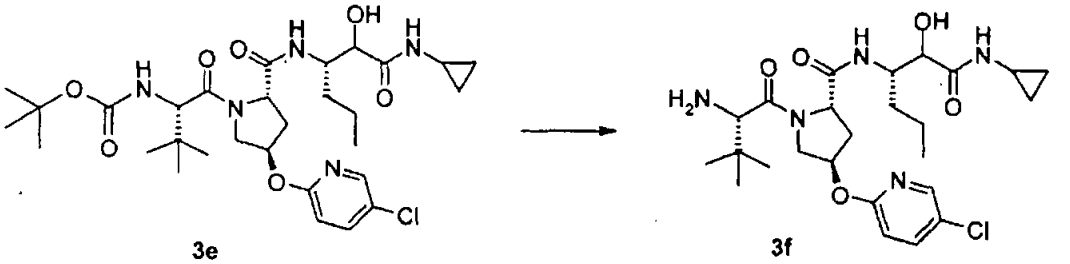


3e

A solution of **3d** (822 mg, 1.8 mmol) in anhydrous dichloromethane (4.5 mL) and anhydrous DMF (4.5 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 962 mg, 2.53 mmol). **1j** (1.0 eq, 335 mg, 1.8 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 731 mg, 7.23 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is washed with water, aq. 1.0 N HCl solution, sat. aq. sodium bicarbonate solution, and brine. The organic layer is dried over

$Na_2SO_4$, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (gradient: acetone/Hexanes, 3:7) to afford 800 mg of **3e**. Found m/z ES+ = 624.

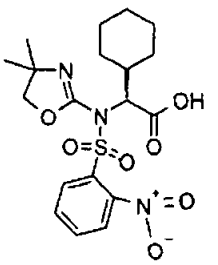
**Step 3-E:**



**3e** **3f**

To a solution of **3e** (800 mg, 1.28 mmol) in dichloromethane (3.5 mL) at room temperature is added triflouroacetic acid (3.5 mL ). The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo and to the residue is added dichloromethane. The pH is adjusted to 8 by dropwise addition of sat. aq. sodium bicarbonate solution. The layers are separated. The organic layer is washed with brine, dried over $Na_2SO_4$, and concentrated to give **3f**. Found m/z ES+ = 524.

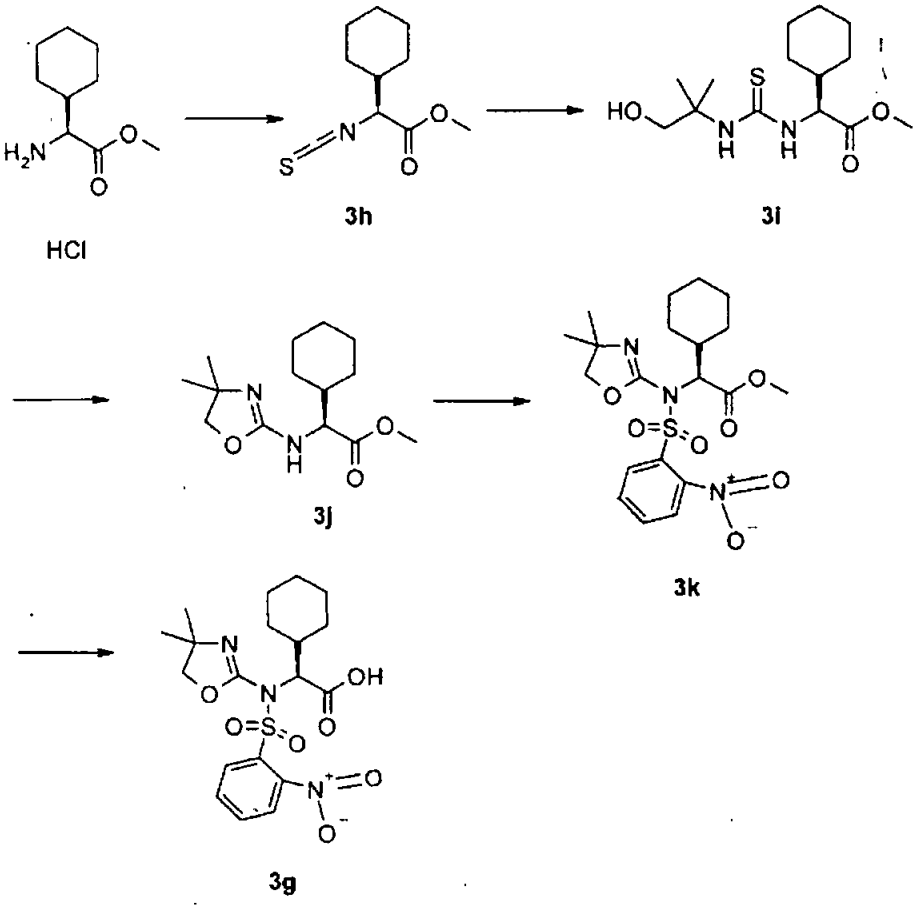
**Step 3-F:**



**3g**

2ª Parte 08-108182






To mixtures of H-cyclohexyl-gly-OMe•HCl (2.07 g, 10 mmol) in $CH_2Cl_2$ (100 mL) and saturated aqueous $NaHCO_3$ solution (100 mL) at room temperature added $CSCl_2$ (0.804 mL, 10 mmol). The mixture is stirred at room temperature for 30 minutes. The two phases are separated and the aqueous layer is extracted with $CH_2Cl_2$. The organic layers are combined, dried over $Na_2SO_4$ and concentrated to give 2.1 g of **3h**, which is continued to the next step with no further purification.

To a solution of 2-amino-2-methyl-1-propanol (178 mg, 2.0 mmol) in THF (2.0 mL) added **3h** (426 mg, 2.0 mmol). The solution is stirred at room temperature for 12 hours after which the solvent is evaporated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 2/1) to give 438 mg of **3i**. Found m/z in ES+ = 303, m/z in ES- = 301.

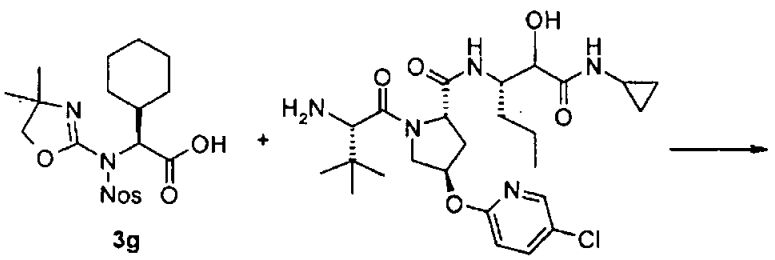
To a solution of **3i** (60 mg, 0.2 mmol) in $CH_3CN$ (2.0 mL) at 0 °C is added a solution of 2-chloro-3-ethylbenzoxazolium tetrafluroborate (81 mg, 0.3 mmol, 1.5 equiv) in $CH_3CN$ (1.0 mL). The solution is stirred at room temperature for 30 minutes after which TEA (0.139 mL, 1.0 mmol, 5.0 equiv) is added and the solution is stirred at room temperature for another

30 minutes. The solvent is then evaporated and the residue is purified by silica gel column chromatography (hexane/EtOAc, 4/1 to 0/1) to give 40 mg of **3j**. Found m/z in ES+ = 269.

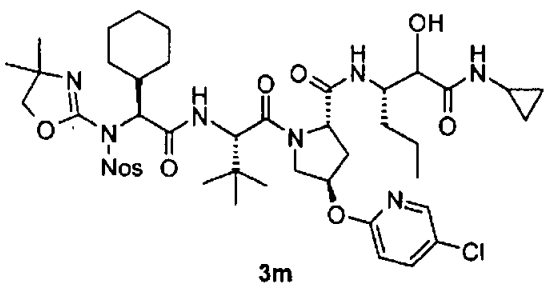
To a solution of **3j** (57 mg, 0.2 mmol) in $CH_2Cl_2$ (0.2 mL) added TEA (0.056 mL, 0.4 mmol, 2.0 equiv), 2-nitrobenzenesulfonyl chloride (66mg, 0.3 mmol, 1.5 equiv) and DMAP (10 mg). The solution is stirred at room temperature for 4 hours. The mixtures are then directly loaded to silica gel column and flushed with hexane/EtOAc (9/1 to 1/1) to give 67 mg of **3k**. Found m/z in ES+ = 454.

To a solution of **3k** (40 mg) in THF (0.3 mL), MeOH (0.3 mL) at 0 °C is added a solution of $LiOH•H_2O$ (12 mg) in water (0.3 mL). The solution is stirred at room temperature for 8 hours, after which aq. 1.0 N HCl solution is added. The mixtures are extracted with $CH_2Cl_2$. The combined organic layer is dried over $Na_2SO_4$ and concentrated to give **3g**. Found m/z in ES+ = 440, m/z in ES- = 438.

**Step 3-G:**



**3g** **3l**

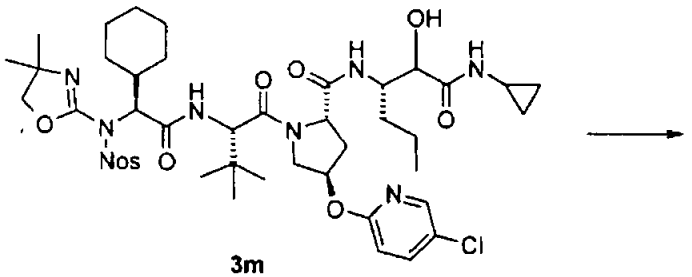


**3m**

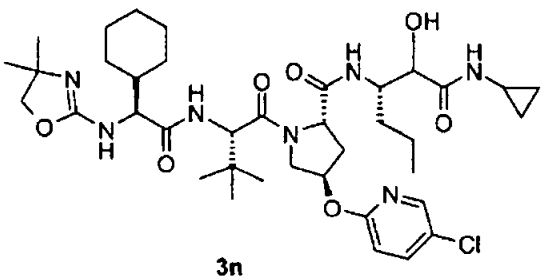
A solution of the acid **3g** (47 mg, 0.11 mmol) in anhydrous dichloromethane (0.5 mL) and anhydrous DMF (0.5 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 57 mg, 0.15 mmol). To the solution **3f** (1.2 eq, 62 mg, 0.12 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 0.047 mL, 0.43 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is

washed with water, aq. 1.0 N HCl solution, aq. sat. sodium bicarbonate solution, and brine. The organic layer is dried over $Na_2SO_4$, filtered and concentrated in vacuo. The residue is chromatographed on silica gel (eluent: acetone/hexane; 1:1) to afford the desired product **3m**. Found m/z ES+ = 945.

**Step 3-H:**



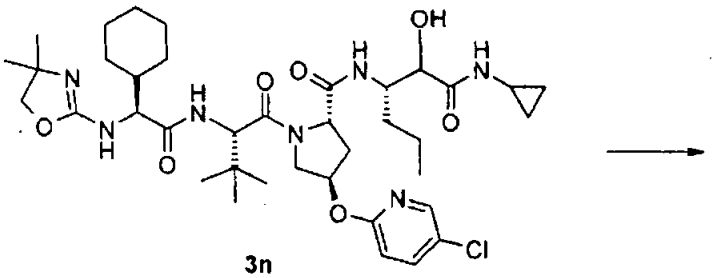

**3m**



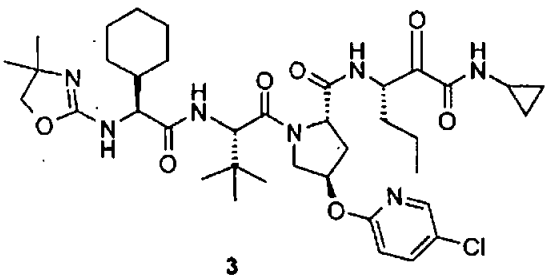

**3n**

To a solution of **3m** (50 mg, 0.05 mmol) in DMF (0.5 mL) is added mercaptoacetic acid (19 mg, 0.21 mmol) and monohydrate lithium hydroxide (18 mg, 0.42 mmol) at room temperature. The reaction mixture is stirred for 3 hours after which sat. aq. sodium bicarbonate solution is added. The phases are separated and the aqueous layer is extracted with ethyl acetate. The combined organic layers are washed with brine, dried over sodium sulfate, and concentrated to give the desired product **3n**. Found m/z ES+ = 760.

**Step 3-I:**



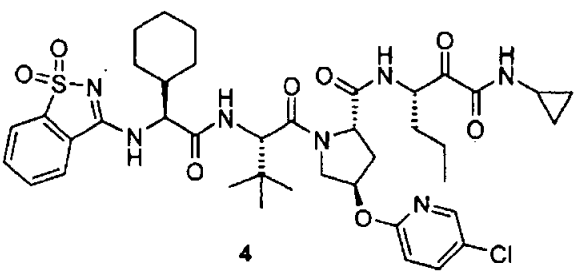
3n



3

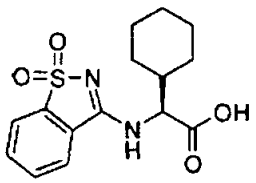
To a solution of **3n** (35 mg, 0.05 mmol) in anhydrous dichloromethane (0.5 mL) is added Dess-Martin periodinane (2.0 eq, 39 mg) and the mixtures are stirred at room temperature for 30 minutes. To the reaction mixtures is added aq. 1.0 M sodium thiosulfate solution (1 mL) and stirred for 5 minutes. Aq. sat. sodium bicarbonate solution (2 mL) is added and the stirring is continued for another 10 minutes. The mixtures are extracted with dichloromethane. The combined organic layers are dried over sodium sulfate, and concentrated. The residue is purified using silica gel preparative TLC plate (Eluent: acetone/hexanes, 1:1) to afford the desired product **3**. Found m/z ES+ = 758

**Example 4:**

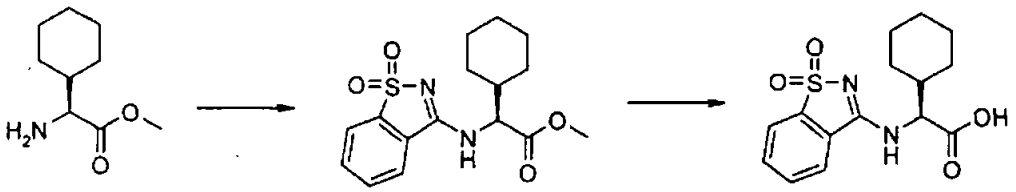


4

**Step 4-A:**



4a

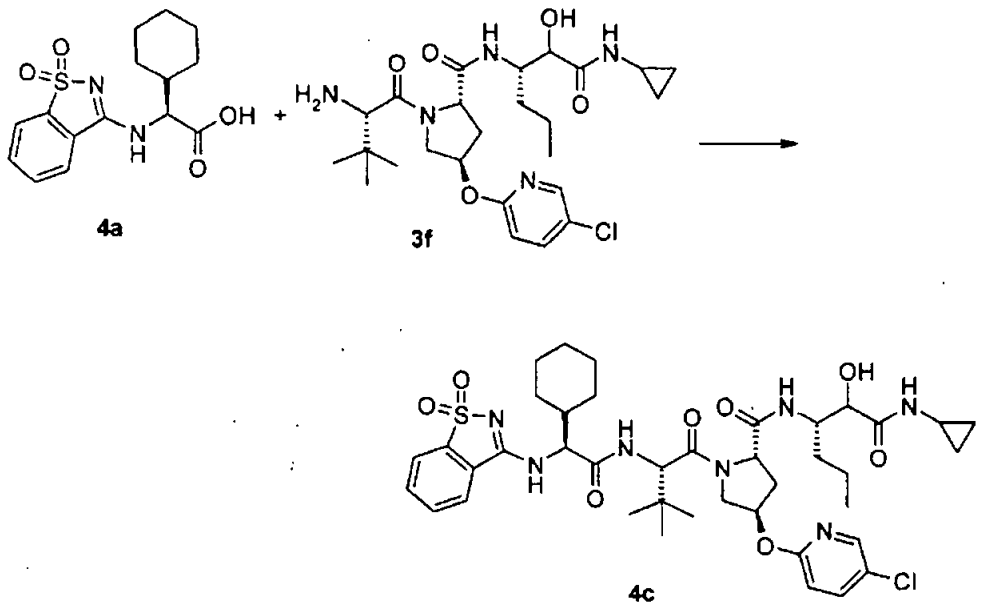


HCl 4b 4a

To a solution of H-cyclohexyl-gly-OMe•HCl in water (1.0 mL) and dioxane (1.0 mL) added NaOH (60 mg, 1.5 mmol, 3.0 equiv) and 3-chloro-benzoisothiazole 1,1-dioxide (220 mg, 1.0 mmol, 1.0 equiv). The solution is stirred at room temperature for 1 hour, after which the pH of the solution is adjusted to 5 by addition of 1.0 N HCl aqueous solution.. The two phases are separated and the aqueous phase is extracted with $CH_2Cl_2$. The organic layers are combined, washed with brine, dried over $Na_2SO_4$, concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give 150 mg of **4b**. Found m/z in ES+ = 337, m/z in ES- = 335.

To a solution of methyl ester **4b** (100 mg) in THF (0.3 mL) and MeOH (0.3 mL) at 0 °C is added a solution of $LiOH•H_2O$ (25 mg) in water (0.3 mL). The solution is stirred at room temperature for 3 hours. The pH of the solution is then adjusted to 6 by addition of 1.0 N HCl aqueous solution. $CH_2Cl_2$ is then added and the two phases are separated. The aqueous layer is extracted with $CH_2Cl_2$. The organic layers are combined, washed with brine, dried over $Na_2SO_4$ and concentrated to give 75 mg of **4a**. Found m/z in ES+ = 323, m/z in ES- = 321.

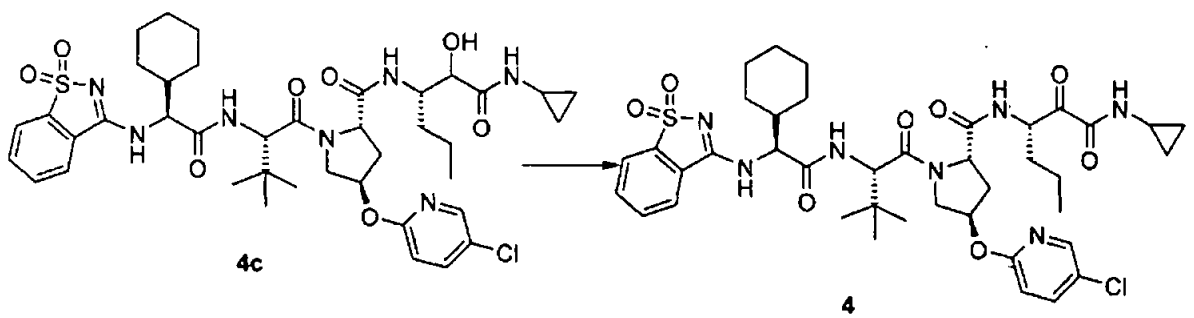
**Step 4-B:**



4a 3f 4c

A solution of **4a** (74 mg, 0.23 mmol) in anhydrous dichloromethane (1.0 mL) and anhydrous DMF (1.0 mL) is stirred at 0 °C and treated with HATU (1.4 eq, 105 mg, 0.27 mmol). To this solution is added **3f** (1 eq, 120 mg, 0.23 mmol) is added in small portions. Then, N-methylmorpholine (4.0 eq, 0.101 mL, 0.92 mmol) is added dropwise. The reaction mixture is gradually warmed to room temperature and stirred for overnight. All the volatiles are removed under vacuum and the residue is dissolved in ethylacetate. The organic layer is washed with water, aq. 1.0 N HCl solution, aqueous saturated sodium bicarbonate solution, and brine. The organic layer is dried over $Na_2SO_4$ and concentrated in vacuo. The residue is chromatographed on silica gel (eluent: acetone/hexane; 1:1) to afford the desired product **4c**. Found m/z ES+ = 828.

**Step 4-C:**

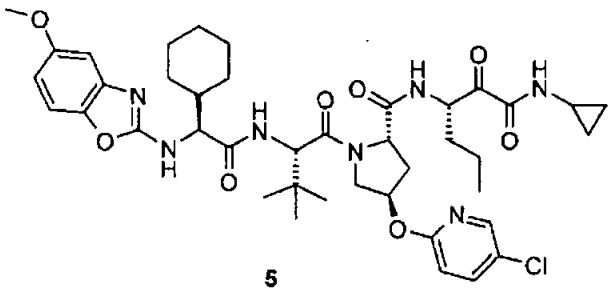


4c 4

A solution of **4c** (41 mg, 0.05 mmol) in anhydrous dichloromethane (3 mL) is treated with Dess-Martin periodinane (3.0 eq, 63 mg) and the reaction mixtures are stirred at room

temperature for 30 minutes. To the mixture is added aqueous 1.0 M sodium thiosulfate solution (2 mL) and stirred for 5 minutes. Aqueous saturated sodium bicarbonate solution (2 mL) is added and stirring is continued for another 10 minutes. The mixture is extracted with dichloromethane. The combined organic layers are dried over sodium sulfate, filtered and concentrated. The residue is purified by silica gel column chromatography (acetone/hexanes, 1:1) to afford the desired product **4**. Found m/z ES+ = 826 and m/z ES- = 824.

**Example 5:**



**5**

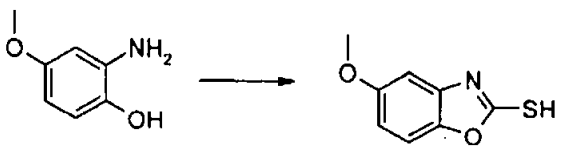
**Step 5-A:**



**5a** **5b**

To a solution of **5a** (5.0 g, 29.56 mmol) in ethanol (60 mL) is added Pd/C (20 %, 1.0 g). The reaction mixture is then stirred under 1.0 atm. of $H_2$ balloon for 12h. The reaction mixture is then filtered through celite 545 and the filtrate is concentrated to give 3.6 g of **5b**.

**Step 5-B:**



**5b** **5c**

Mixtures of **5b** (1.2 g, 8.62 mmol), potassium hydroxide (581 mg, 10.34 mmol) and carbon disulfide (10 mL, 173 mmol) in ethanol (17 mL) are heated to refluxed overnight. The solvent is then evaporated. To the residue aqueous 1.0 N HCl solution (10 mL) and ethylacetate (100 mL) are added. The phases are separated. The organic layer is washed with water, brine, dried over sodium sulfate and concentrated to give 1.2 g of **5c**.

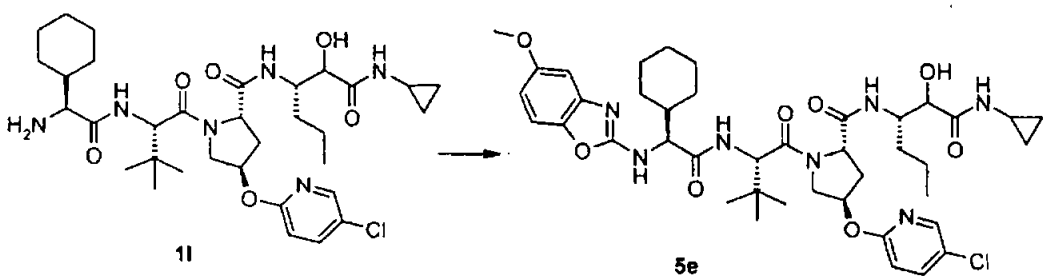
**Step 5-C:**



**5c** **5d**

To **5c** (1.0 g, 5.5 mmol) and thionyl chloride (6 mL, 66 mmol)is added two drops of DMF and the resulted mixtures are heated at 70 °C for 30 minutes. The solution is then cooled to room temperature and diluted with dichloromethane. The solvent is then evaporated. To the residue is added another 10 mL of dichloromethane and the solution is concentrated. The residue is dissolved in hot hexanes and then filtered. The filtrate is concentrated to give 1.0 g of **5d**.

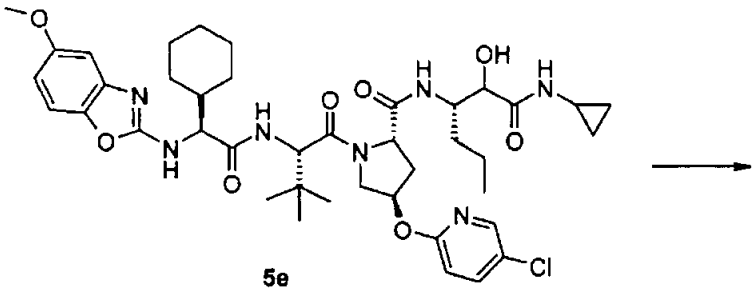
**Step 5-D:**



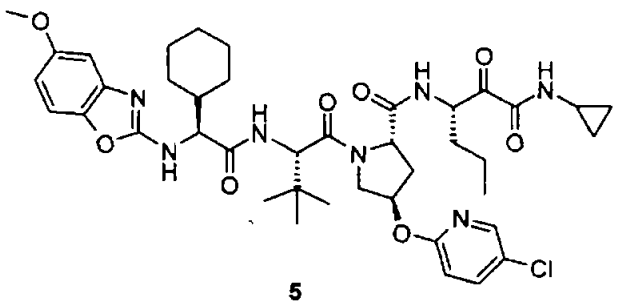
**1l** **5e**

To a solution of **1l** (75 mg, 0.11 mmol) in dioxane (0.4 mL) at room temperature is added **5d** (31 mg, 0.17 mmol ) and sodium bicarbonate (19 mg, 0.23 mmol). The mixtures are stirred at 65 °C for 12 hours. The mixtures are loaded directly to silica gel column and eluted with hexane/EtOH (from 95/5 to 85/15) to give **5e**. Found m/z ES+ = 810 and ES- = 808.

**Step 5-E:**



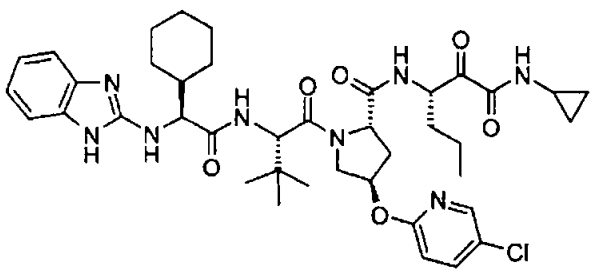
5e



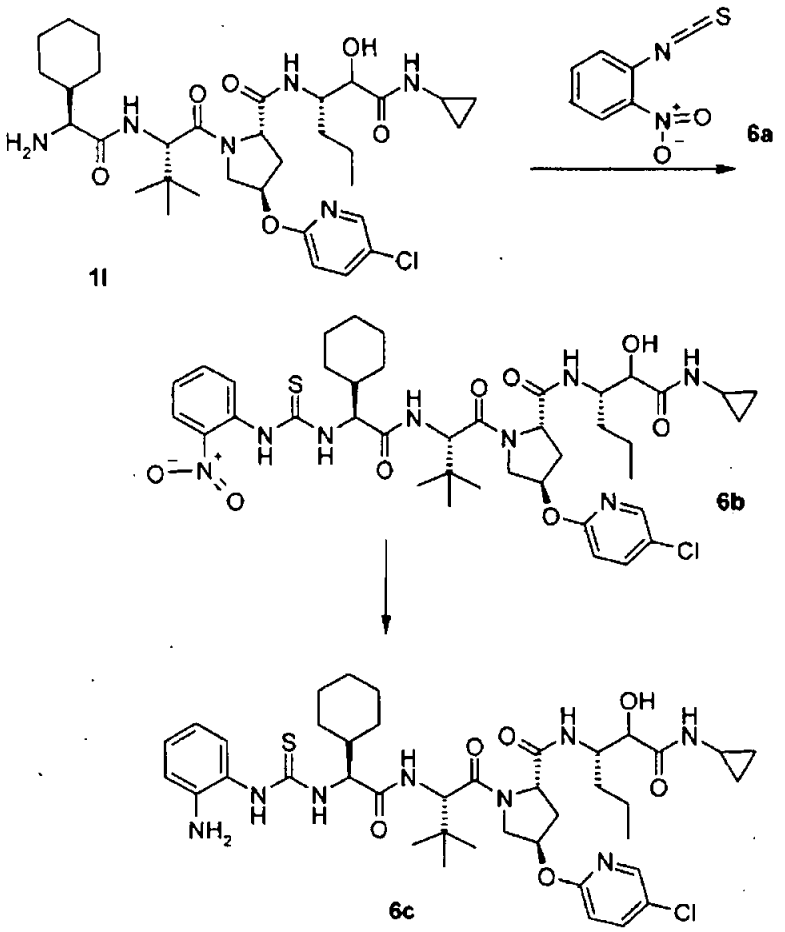
5

A solution of **5e** (62 mg, 0.08 mmol) in anhydrous dichloromethane (0.80 mL) is added Dess-Martin periodinane (2.0 eq, 65 mg). The reaction mixture is stirred at room temperature for 30 minutes. To the mixture is added aqueous 1.0 M sodium thiosulfate solution (2 mL) and stirred for 5 minutes. Aqueous saturated sodium bicarbonate solution (2 mL) is added and stirring is continued for another 10 minutes. The mixture is extracted with dichloromethane. The combined organic layers are dried over sodium sulfate, filtered and concentrated. The residue is purified using silica gel preparative TLC (gradient: acetone/hexanes, 3:7 to 1:1) to afford the desired product **5**. Found m/z ES+ = 808 and ES- = 806.

**Example 6:**

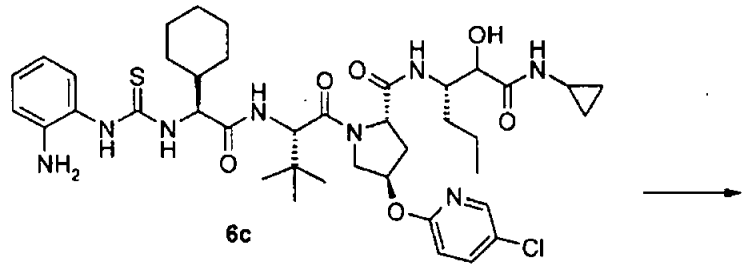


6

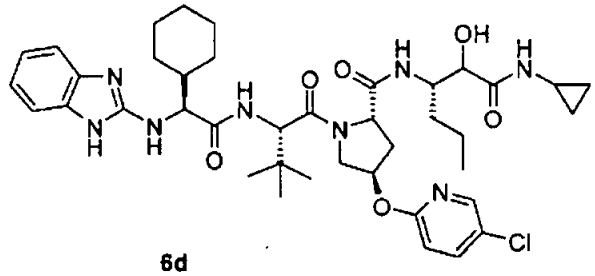



A solution of **1l** (100 mg, 0.15 mmol, 1.0 equiv) and **6a** (27 mg, 0.15 mmol, 1.0 equiv) in EtOH (0.5 mL) is stirred at room temperature for 1 hour. Found m/z for **6b** ES+ = 843, m/z in ES- = 841.

To the above solution added $SnCl_2$ (142 mg, 0.75 mmol) and the mixtures are heated at 70 °C for 30 minutes. The solution is then cooled at 0 °C. Ice is added followed by saturated aqueous $NaHCO_3$ and EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over $Na_2SO_4$, concentrated to give crude product **6c**, which is continued to the next step without further purification. Found m/z in ES+ = 813, m/z in ES- = 811..

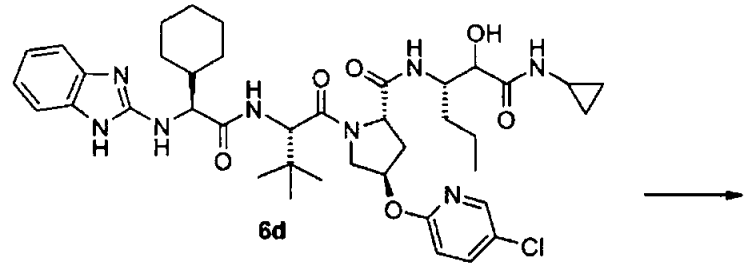


6c

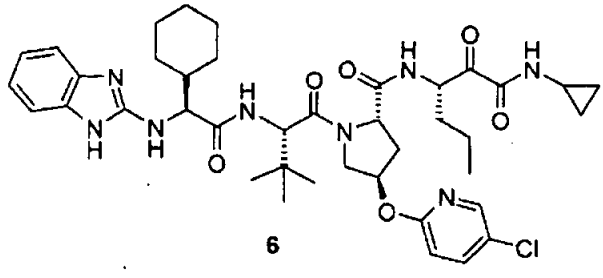


6d

To a solution of **6c** (120 mg, 0.15 mmol) in toluene (0.6 mL) added HgO (64.8 mg, 0.3 mmol, 2.0 equiv) and sulfur (4.8 mg, 0.15 mmol, 1.0 equiv) and the mixtures are stirred at 90 °C for 1 hour. The mixtures are filtered, washed with $CH_2Cl_2$ and the solution is concentrated. The residue is purified by silica gel column chromatography (hexane/EtOH = 4/1) to give desired product **6d** (54 mg). Found m/z in ES+ = 779.



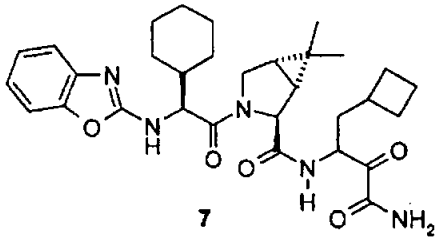
6d



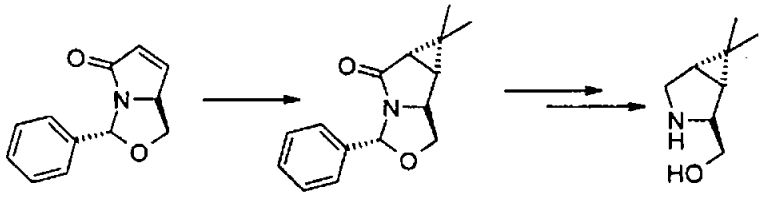
6

To a solution of alcohol **6d** (54 mg, 0.069 mmol) in $CH_2Cl_2$ (1.0 mL) at 0 °C is added DMP (58.7 mg, 0.138 mmol, 2.0 equiv). The solution is stirred at room temperature for 4 hours. The solution is then added saturated aqueous $NaHCO_3$ and 1.0 M $Na_2S_2O_3$ aqueous solution. The phases are separated and the aqueous layer is extracted with $CH_2Cl_2$. The organic layers combined, washed with brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel column chromatography (hexane/acetone 1/1) to give product **6**. Found m/z in ES+ = 777.

**Example 7:**

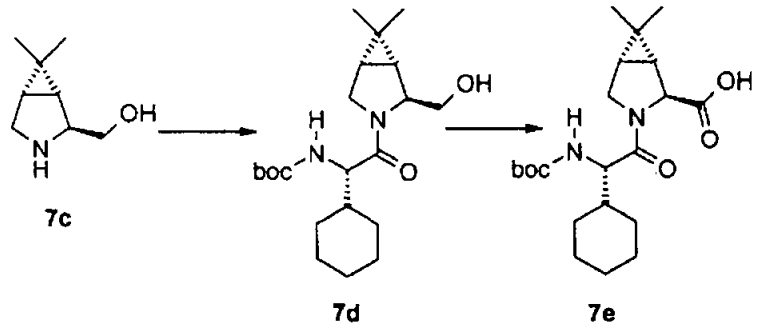


**7**



**7a** **7b** **7c**

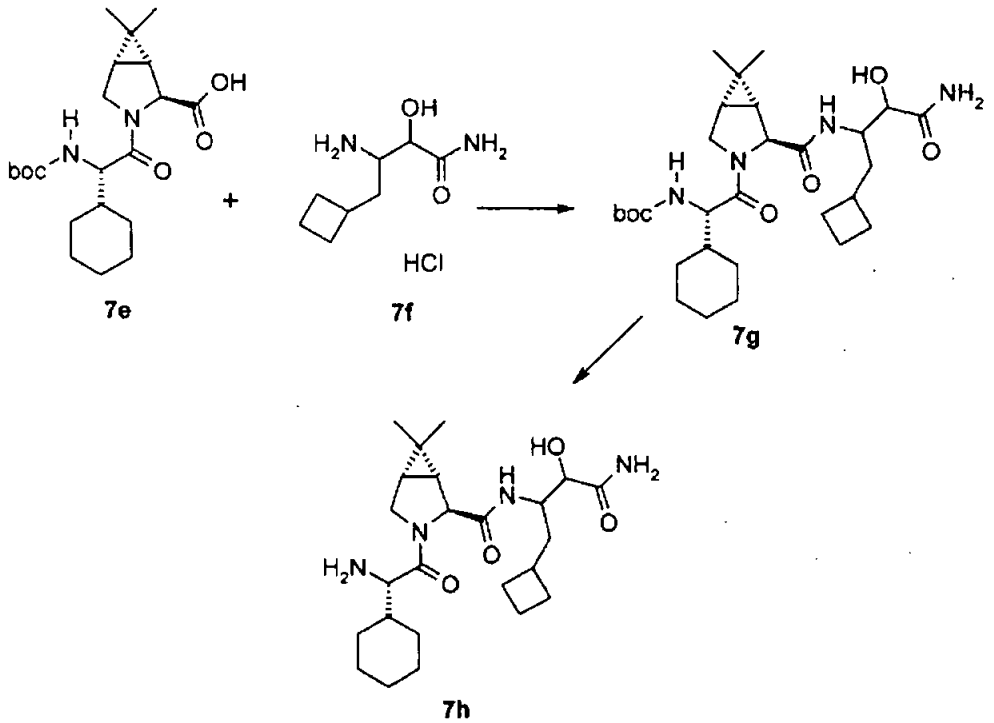
To a solution of isopropyldiphenylsulfonium tetrafluroborate (ref. Matsuyama, H. *et al. J. Org. Chem.* **2000**, *65*, 4796.) (13.4 g, 42.5 mmol, 1.7 equiv) in THF at -78 °C is added *t*-BuLi (22.0 mL, 37.5 mmol, 1.70 M in pentane, 1.5 equiv) and the solution is stirred at this temperature for 30 minutes. To the solution is then added a solution of **7a** (5.0 g, 25 mmol, 1.0 equiv) in THF (20 mL). The solution is stirred at -78 °C for 1 hour. The reaction is quenched by addition of saturated aqueous $NaHCO_3$. The solution is warmed to room temperature and diluted with EtOAc. The two phases are separated and the organic layer is washed with brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 9/1 to 3/1) to give 5.1 g of **7b**. **7b** is converted to the amino alcohol **7c** according to the reference: *J. Org. Chem.* **1999**, *64*, 330.



7c 7d 7e

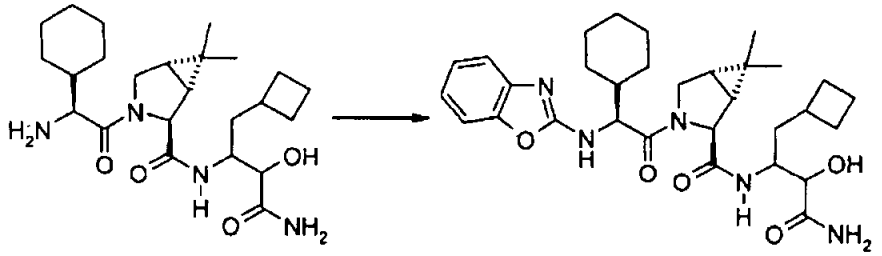
To a solution of Boc-L-cyclohexyl-gly-OH (2.57 g, 10 mmol, 1.0 equiv) in $CH_3CN$ (60.0 mL) at 0 °C is added HATU (3.878 g, 10.2 mmol, 1.02 equiv), HOAT (1.38g, 10.2 mmol, 1.02 equiv) followed by **7c** (1.39 g, 10 mmol, 1.0 equiv) and DIPEA (6.95 mL, 40 mmol, 4.0 equiv). The solution is stirred at room temperature for 12 hours, after which the solvent is evaporated. The residue is partitioned between EtOAc and water. The phases are separated and the organic layer is washed with saturated aqueous $NaHCO_3$, brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give product **7d** (3.43 g).

To a solution of **7d** (2.4 g, 6.5 mmol) in acetone (40.0 mL) at -5 °C is added a solution of Jones's reagent (3.0 M, 10.7 mL). The mixture is warmed to 0 °C and stirred at this temperature for 2 hours. The reaction is then quenched by slow addition of *i*-PrOH (10 mL) and the mixture is then filtered. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried ($Na_2SO_4$) and concentrated to give desired product **7e** 2.35 g. The material is continued to the next step with no further purification. Found m/z in ES+ = 395, m/z in ES- = 393.



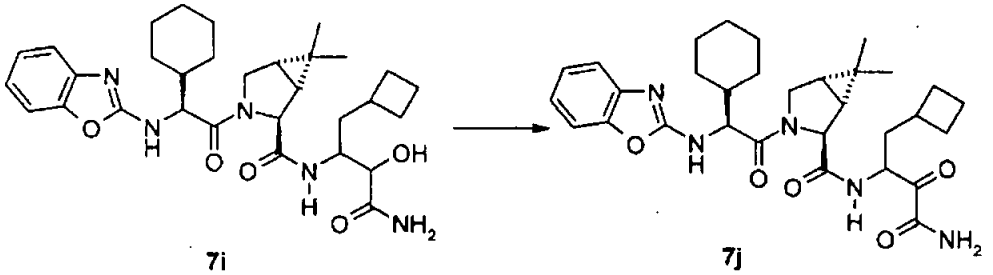

To a solution of **7e** (1.0 g, 2.5 mmol) in DMF (5.0 mL) and $CH_2Cl_2$ (5.0 mL) at 0 °C is added HATU (1.05 g, 2.75 mmol, 1.1 equiv), **7f** (0.53 g, 2.5 mmol, 1.0 equiv) and N-methyl-morpholine (0.825 mL, 7.5 mmol, 3.0 equiv). The solution is stirred at 0 °C for 30 minutes then at room temperature for 6 hours. To the reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over $Na_2SO_4$ and concentrated. The crude material is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give product **7g** (950 mg). Found m/z in ES+ = 549.

To a solution of **7g** (110 mg) in $CH_2Cl_2$ (2.0 mL) added TFA (2.0 mL) and the solution is stirred at room temperature for 1 hour. The solvent is then evaporated. The residue is added saturated aqueous $NaHCO_3$ solution and EtOAc. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, dried over $Na_2SO_4$ and concentrated to give desired product **7h** (67 mg). Found m/z in ES+ = 449.



7h 7i

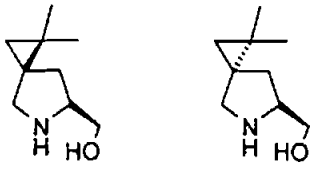
To a solution of **7h** (150 mg, 0.33 mmol)in dioxane (1.0 mL) at room temperature added 2-chlorobenzaxazole (76 mg, 0.50 mmol, 1.5 equiv) and $NaHCO_3$ (84 mg, 1.0 mmol, 3.0 equiv). The mixture is stirred at 60 °C for 6 hours. The mixture are then loaded directly to silica gel column and eluted with hexane/acetone (2/1) to give desired product **7i** (145 mg). Found m/z in ES+ = 566, m/z in ES- = 564.



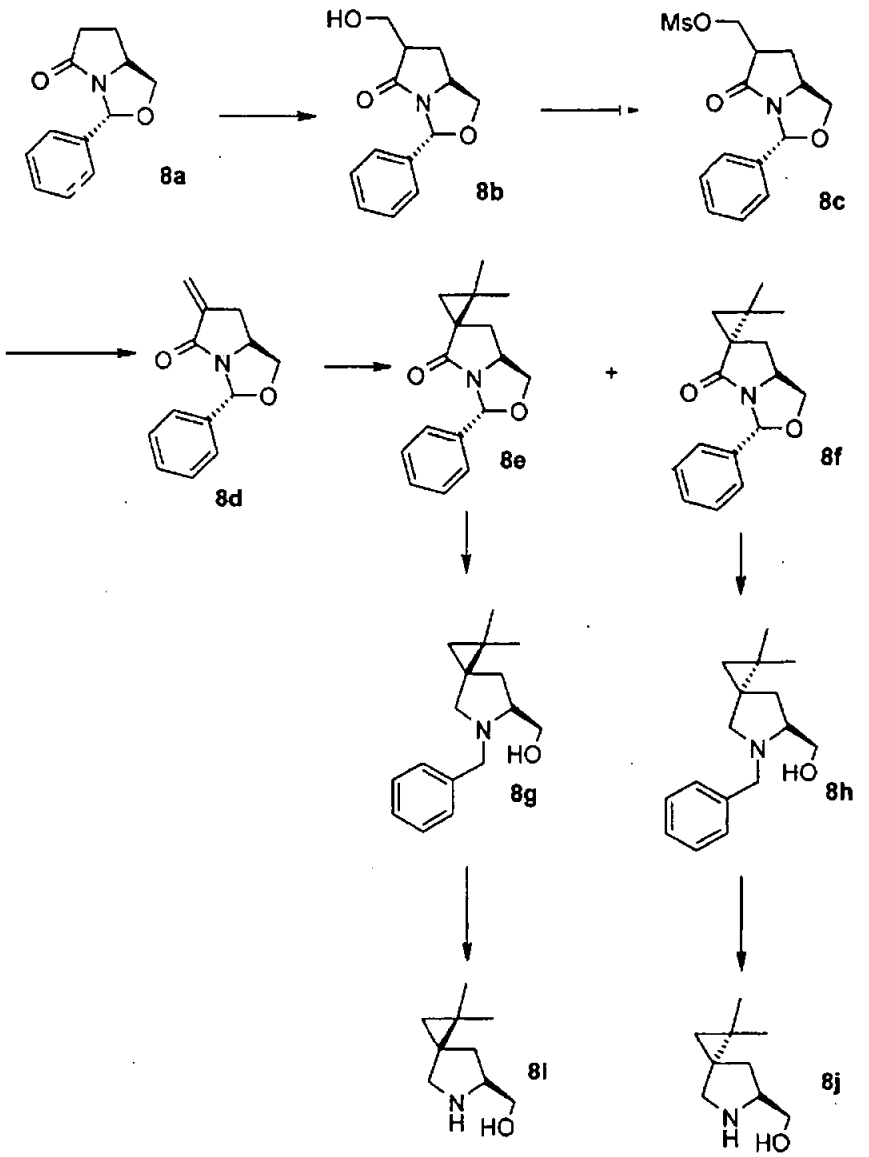
7i 7j

To a solution of **7i** (120 mg, 0.21 mmol) in $CH_2Cl_2$ (2.0 mL) at 0 °C is added DIPEA (0.148 mL, 0.848 mmol, 4.0 equiv) followed by a solution of $Py{\bullet}SO_3$ (67.6 mg, 0.424 mmol, 2.0 equiv) in DMSO (2.0 mL). The solution is then stirred at 0 °C for 10 minutes. To the solution is added EtOAc and saturated aqueous $NaHCO_3$ solution. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel column chromatography (hexane/Acetone, 1/1) to give product **7j** (108 mg). Found m/z in ES+ = 564, m/z in ES- = 562.

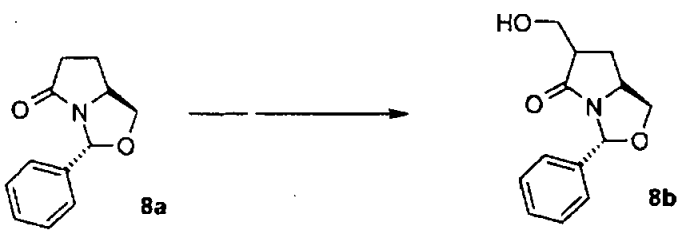
**Example 8:**



8i 8j



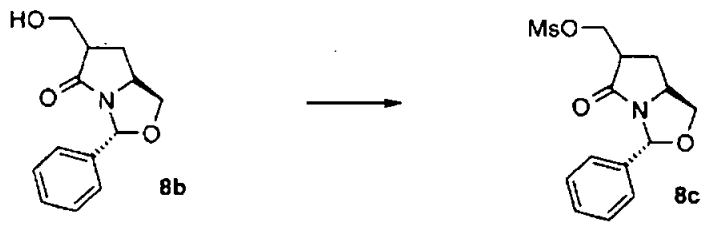

**Step 8-A:**




To a solution of DIPA (12.4 mL, 88.6 mmol, 1.2 equiv) in THF (400 mL) at -30 °C is added *n*-BuLi (50 mL, 1.60 M in hexane, 81.0 mmol, 1.10 equiv). The solution is stirred at this temperature for 30 minutes. A solution of **8a** (**8a** is prepared according to *J. Org. Chem.*

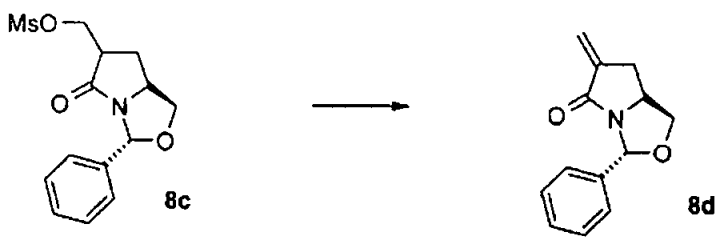
**1986**, *51*, 3140.) (15.0 g, 73.8 mmol, 1.0 equiv) is subsequently added to the solution, which is then stirred at -30 °C for 30 minutes. A stream of HCHO (22.0g, 738 mmol, 10 equiv) and $N_2$ gas is bubbled through this solution over 10 minutes. The reaction mixture is warmed up to 0 °C over 30 minutes and quenched by addition of 2.0 N HCl aqueous solution until pH=3. EtOAc is added and the phases are separated. The aqueous layer is extracted with EtOAc three times. The combined organic layer is washed with brine, dried over $Na_2SO_4$ and concentrated to give **8b**, which is used in the next step without purification.

**Step 8-B:**




To a solution of **8b** in $CH_2Cl_2$ (200 mL) at 0 °C is added TEA (30.9 mL, 222 mmol, 3.0 equiv), DMAP (902 mg, 7.4 mmol, 0.1 equiv) and MsCl (11.5 mL, 148 mmol, 2.0 equiv). The reaction temperature is maintained <5 °C. The solution is stirred at room temperature for 2 hours. Then saturated aqueous $NH_4Cl$ solution is added followed by 1/1 mixture of EtOAc/TBME. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried with $Na_2SO_4$ and concentrated to afford **8c**, which is continued to the next step with no purification.

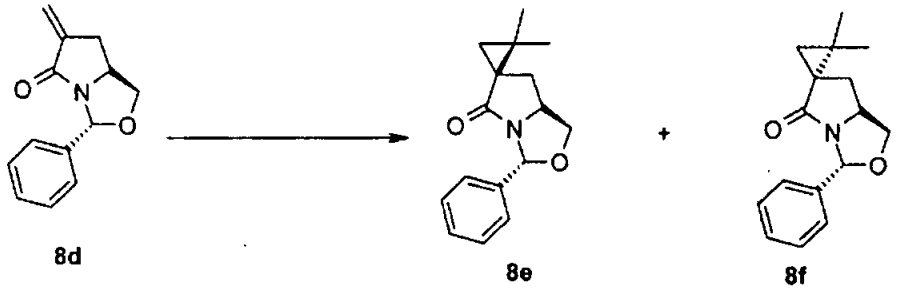
**Step 8-C:**




The residue **8c** from previous step is dissolved in $CH_2Cl_2$/toluene (20 mL/20 mL). At 0 °C, 15 mL of DBU is added. The internal temperature is kept below 20 °C. The solution is stirred at room temperature for 2 hours. The mixture is loaded directly to silica gel column and flushed with hexane/EtOAc (2/1 to 1/1) to give product **5** (7.4 g). The product **8d** is carried onto the next step immediately.

Found m/z in ES+ = 216; LC-MS (method A) $t_R$ = 0.86 min

**Step 8-D:**



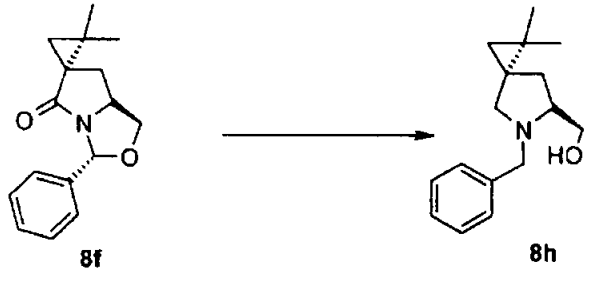

dr **8e/8f** = 1/2

To a solution of isopropyl triphenyl phosphine iodide (10.4 g, 24.1 mmol, 1.4 equiv) in THF (70 mL) at -30 °C is added *n*-BuLi (1.60 M, 13.9 mL, 22.4 mmol). The solution is stirred at 0 °C for 30 minutes, then cooled at -30 °C. A solution of **8d** (3.7 g, 17.2 mmol, 1.0 equiv) is added to above solution. The resulted reaction mixture are warmed up to room temperature over 1 hour and stirred at room temperature for 3 hour. The reaction is quenched by addition of saturated aqueous $NaHCO_3$ solution. After diluted with EtOAc, the mixture is filtered. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc 3/1 to 2/1) to give product **8e** (1.1 g), and **8f** (2.3 g).

TLC, Rf (EtOAc/heptane 1:2) = 0.53 (**8e**) and 0.46 (**8f**)

**Step 8-E:**

Procedure for the synthesis of **8j**.

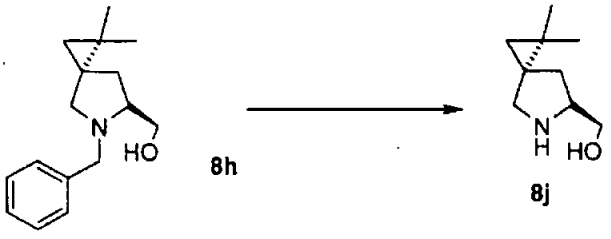



To a solution of **8f** (5.0 g, 19.5 mmol) in THF (75 mL) at 0 °C is added $LiAlH_4$ (2.2 g, 58.4 mmol, 3. equiv). The solution is heated to reflux for 5 hours. After cooled to 0 °C, the

reaction solution is slowly added 5.0 mL of saturated aqueous $Na_2SO_4$ solution. The mixtures are diluted with EtOAc and stirred at room temperature for 30 minutes. The mixture is filtered and the solution is concentrated to give product **8h** (~5.0 g).

HPLC (method B) $t_R$ = 2.64 min
TLC, Rf ($CH_2Cl_2$/MeOH 9:1) = 0.48
MS (method C): 246 [M+H]

**Step 8-F:**

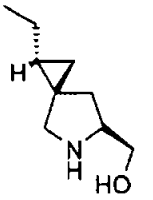



To a solution of **8h** (3.0 g) in EtOAc/HOAc (40 mL/40 mL) at room temperature added Pd (10% on carbon) 2.0 g. The mixture is placed under 40 psi $H_2$ parr shaker for 3 hours. The mixture is diluted with $CH_2Cl_2$ and filtered. The solution is concentrated. Most of the HOAc is removed under vacuum at 30 Torr, 40 °C. The solution is basified to pH = 13 with 6.0 M aqueous NaOH solution. After diluted with $CH_2Cl_2$, the solution is filtered. The two phases are separated and the aqueous layer is extracted with $CH_2Cl_2$. The organic layers are combined, washed with brine, dried over $Na_2SO_4$, $K_2CO_3$, concentrated to give product **8j** (1.8 g).

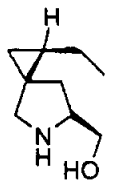
TLC, $R_f$ ($CH_2Cl_2$/MeOH 4:1) = 0.29
MS (method C): 156 [M+H]

Compound **8i** is prepared from **8g** by analogous procedure used to convert **8h** to **8j**.

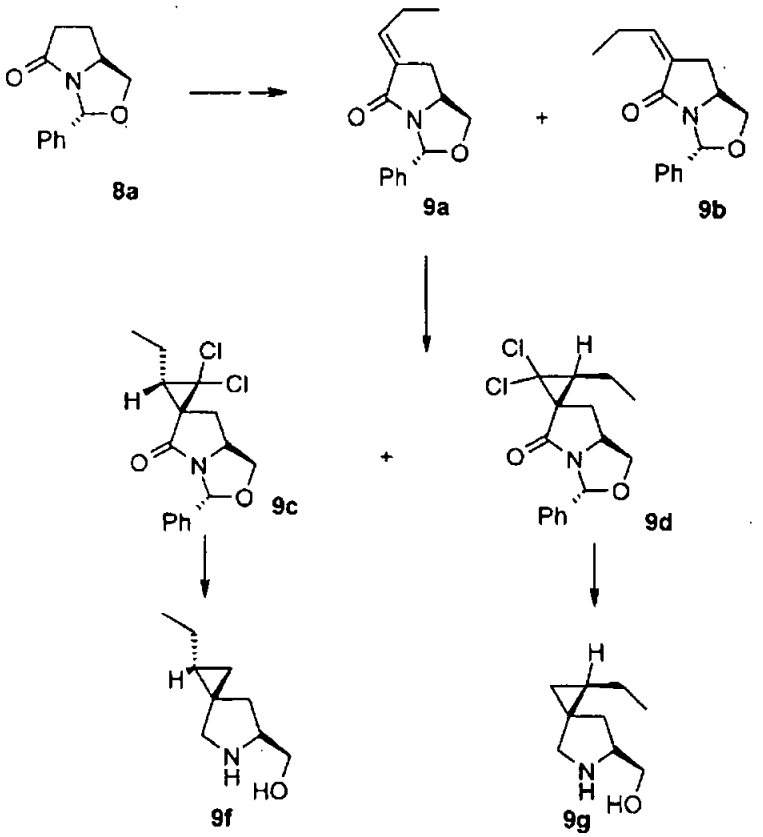
**Example 9:**



9e

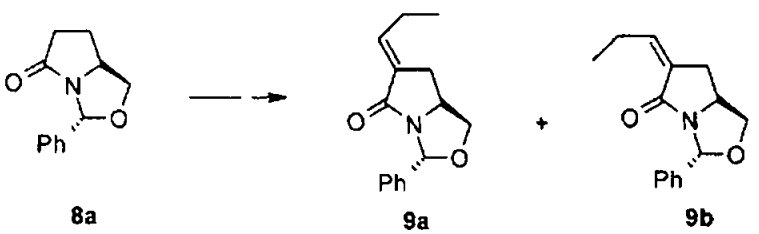


9f



8a 9a 9b 9c 9d 9f 9g

**Step 9-A:**



8a 9a 9b

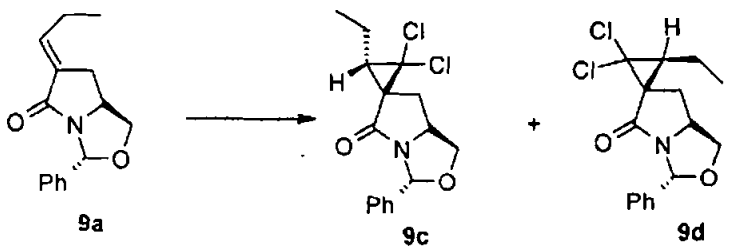
To a solution of DIPA (6.6 mL, 47.3 mmol, 1.2 equiv) in THF (200 mL) at -30 °C is added *n*-BuLi (27 mL, 1.60 M in hexane, 43.3 mmol, 1.10 equiv). The solution is stirred at this temperature for 30 minutes. Then a solution of **8a** (15.0 g, 73.8 mmol, 1.0 equiv), which

is prepared according to *J. Org. Chem.* **1986**, *51*, 3140, is added to the reaction and the solution is stirred at -78 °C for 30 minutes. To this solution is added propanal (3.4 mL, 47.3 mmol, 1.2 equiv). After 1.5 hours, the reaction is quenched by addition of 4.0 N HCl aqueous solution until pH=3. EtOAc is added and the phases are separated. The aqueous layer is extracted with EtOAc three times. The combined organic layer is washed with brine, dried over $Na_2SO_4$ and concentrated. The residue is continued to the next step with no further purification.

The product obtained from the previous step are dissolved in $CH_2Cl_2$ (40 mL). To this solution at 0 °C is added TEA (10.9 mL, 78.8 mmol, 2.0 equiv), DMAP (950 mg, 7.8 mmol, 0.2 equiv), followed by SLOW addition of MsCl (4.6 mL, 59.1 mmol, 1.5 equiv). The reaction temperature is maintained <5 °C. The solution is stirred at room temperature for 2 hours. Then saturated aqueous $NH_4Cl$ solution is added followed by 1/1 mixture of EtOAc/diethyl ether. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried with $Na_2SO_4$ and concentrated.

The residue from the previous step is dissolved in $CH_2Cl_2$ (30.0 mL). At 0 °C, 10 mL of DBU is added. The internal temperature is kept below 20 °C. The solution is stirred at room temperature for 2 hours. The mixture is loaded directly to silica gel column and flushed with hexane/EtOAc (2/1 to 1/1) to give products **9a** (3.7 g) and **9b** (4.2 g).

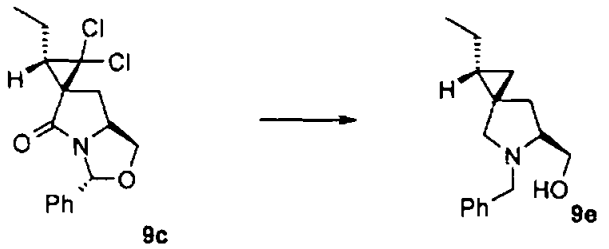
**Step 9-B:**




**9a** **9c** **9d**

To a solution of **9a** (1.7 g) in $CHCl_3$ (10 mL) at room temperature is added aq. NaOH solution (12 g, 1/1 mixtures) and benzyltriethylammonium chloride (227 mg). The solution is stirred at room temperature for 12 hours. Then the mixtures are partitioned between EtOAc and water. The aqueous layer is separated and extracted with EtOAc. The organic layers are combined, washed with brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by flash chromatography (9/1 heptane/EtOAc to 2/2 heptane/EtOAc) to give product **9c** and **9d**.

**Step 9-C:**

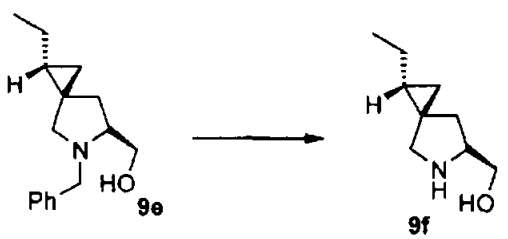



**9c** **9e**

To a solution of **9c** (1.8 g, 5.5 mmol) in THF (30 mL) at 0 °C is slowly added $LiAlH_4$ (1.05 g, 27.6 mmol, 5.0 equiv). The solution is heated to reflux for 5 hours. After cooled to 0 °C, the reaction solution is slowly added 2.5 mL of saturated aqueous $Na_2SO_4$ solution. The mixture is diluted with EtOAc and stirred at room temperature for 30 minutes. The mixture is filtered and the solution is concentrated. The residue is used in the subsequent step without further purification.

The isolated material (1.0 g) from previous step is dissolved in 18 mL of THF and 5.0 g of *t*-BuOH. To the solution is added small sodium pieces (1.6 g, 71 mmol, 20 equiv). The mixture is heated to reflux for about 6 hours. The sodium is taken out and quenched with EtOH. The solution is added 5 mL of EtOH and stirred at room temperature until there is no sodium left. The mixture is added ice and diluted with EtOAc. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel chromatography (heptane/EtOAc, 1/1) to give product **9e**.

**Step 9-D:**



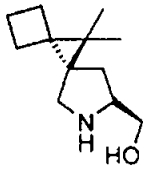

**9e** **9f**

Palladium on carbon (10%; 300 mg) is added to a solution of **9e** (500 mg) in EtOAc/HOAc (4.0 mL/3.0 mL) at room temperature. The mixture is placed under 40 PSI $H_2$ ($2.7x10^5$ Pa) in a Parr shaker for 3 hours. The mixture is diluted with $CH_2Cl_2$ and filtered. The solution is concentrated. Most of the HOAc is removed under vacuum at 30 Torr, 40 °C. The solution is basified to pH = 13 with 6.0 M aqueous NaOH solution. After diluted with

$CH_2Cl_2$, the solution is filtered. The two phases are separated and the aqueous layer is extracted with $CH_2Cl_2$. The organic layers are combined, washed with brine, dried over $Na_2SO_4$, $K_2CO_3$ and concentrated to give product **9f**.

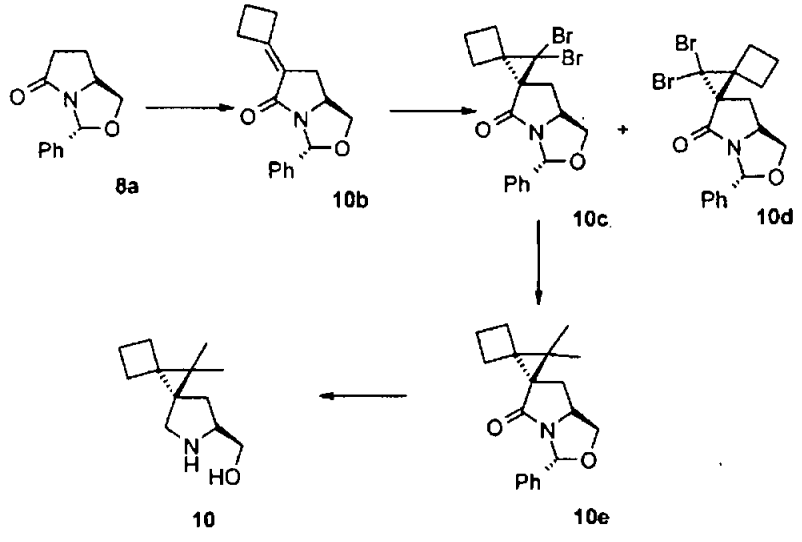
Compound **9g** is prepared from **9b** by analogous procedure used to convert **9a** to **9f**.

**Example 10:**

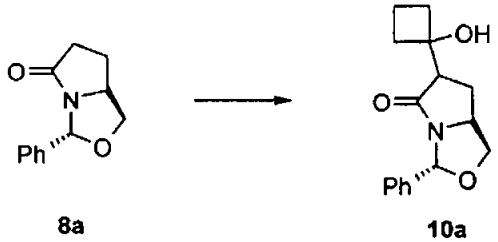


**10**

**Scheme:**




**Step 10-A:**

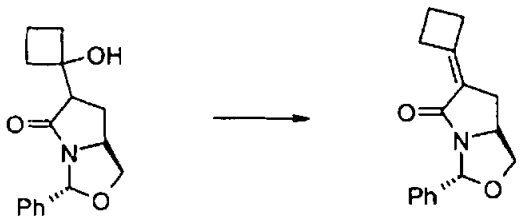


**8a** **10a**

To a solution of DIPA (7.66 mL, 54.2 mmol, 1.1 equiv) in THF (100 mL) at 0 °C is added *n*-BuLi (33.9 mL, 1.60 M in hexane 54.2 mmol, 1.10 equiv). The solution is stirred at this temperature for 30 minutes. A solution of **8a** (10.0 g, 49.3 mmol, 1.0 equiv) in THF (10.0 mL) is added to the mixture and the solution is stirred at -78 °C for 60 minutes.

Cyclobutanone (3.76 g, 49.3 mmol, 1.0 equiv) and $Et_2O{\cdot}BF_3$ (6.19 mL, 49.3 mmol) is added to this solution. The reaction mixture is stirred for another 2.5 hours and quenched by addition of saturated $NH_4Cl$ (100 mL). EtOAc is added and the phases are separated. The aqueous layer is extracted with EtOAc. The combined organic layers are washed with brine, dried over $Na_2SO_4$ and concentrated to afford **10a**, which is used in the subsequent reaction without further purification. Found m/z in ES+ = 274.

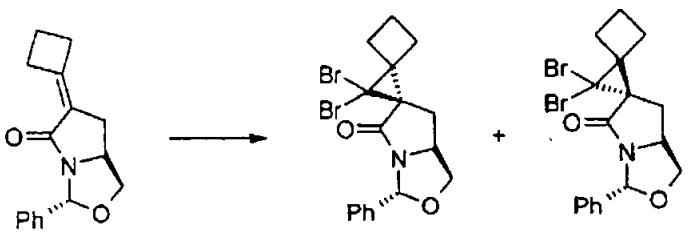
**Step 10-B:**



**10a** **10b**

The residue containing compound **10a** from the previous step is dissolved in $CH_2Cl_2$ (150 mL). Triethyl amine (TEA) (52.1 mL, 374 mmol) and MsCl (2.89 mL, 37.4 mmol) are added to the solution, which is stirred at reflux for 8 hours. The reaction mixture is then added water and the phases are separated. The aqueous layer is extracted with $CH_2Cl_2$. The organic layers are combined, washed with brine, dried with $Na_2SO_4$ and concentrated to afford compound **10b**. Found m/z in ES+ = 256.

**Step 10-C:**

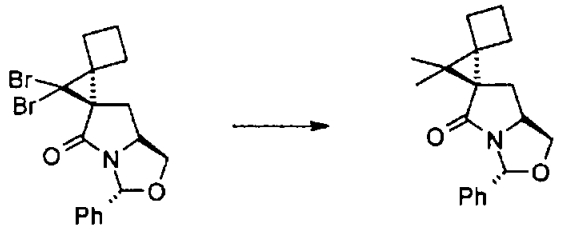


**10b** **10c** **10d**

To a solution of **10b** (2.54 g, 10 mmol) in $CHBr_3$ (25 mL) is added sequentially benzyl triethyl ammonium chloride (0.46 g, 2 mmol) and 50% NaOH/water (20 mL) at 0°C. The mixture is stirred at room temperature for 2 hours and then at 50°C for 1 hour. The reaction mixture is diluted with water and the aqueous phase is extracted at least twice with $CH_2Cl_2$. The combined organic phases are washed by brine, dried over $Na_2SO_4$ and concentrated. The isomers **10c** and **10d** are separated by flash chromatography

(Heptane/EtOAc, 4:1). The upper spot by thin layer chromatography is **10c** (1.43 g). Found m/z in ES+ = 428.

**Step 10-D:**



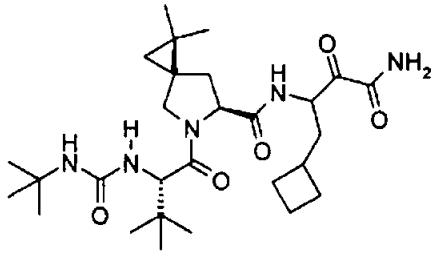

**10c** **10e**

MeLi ( 16.5 mL 1.6 M solution, 26.4 mmol) is added dropwise to a suspension of CuI in THF at 0°C to form a clear solution which is maintained at 0°C for 10 minutes. A solution of **10c** (800 mg) in THF (8.0 mL) is added dropwise to the mixture at a temperature of -50°C or less. After complete addition, the reaction mixture is warmed to 0°C over 20 minutes. The solution is then cooled at -78 °C. To this solution is added methyl iodide (10 mL). The reaction mixture is warmed to room temperature over 1 hour. Saturated aqueous $NH_4Cl$ solution (50 mL) is the added to the solution and the solution is stirred for 10 minutes. The precipitate removed by filtration. The filtrate is partitioned between EtOAc and water. The two phases are separated and the aqueous phase is extracted with EtOAc. The combined organic phases are dried over $Na_2SO_4$, concentrated. The residue is purified by silica gel column chromatography (heptane/EtOAc, 4/1) to give **10e** (380 mg). Found m/z ES+ = 298.

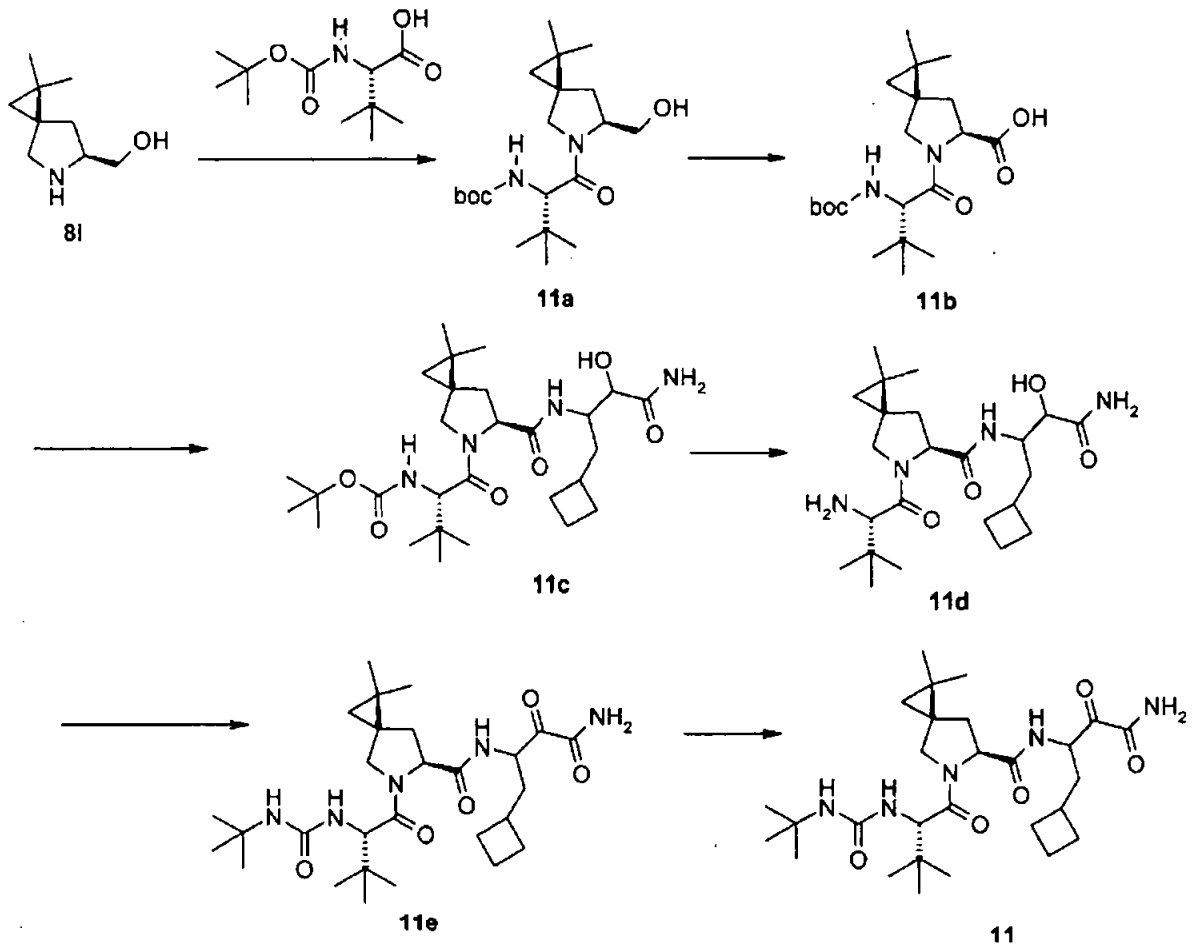
**Step 10-E:**

Compound **10e** is converted to amino alcohol **10** according to the procedure described for transforming compound **8f** to **8j**.

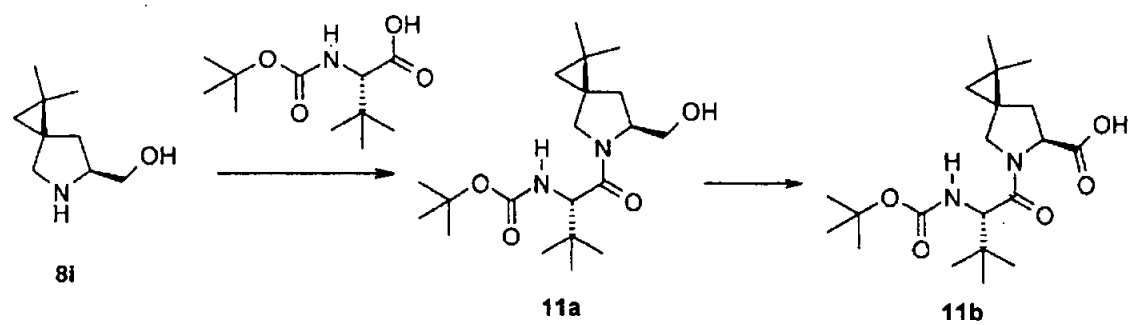
**Example 11:**




**11**




**Step 11-A:**

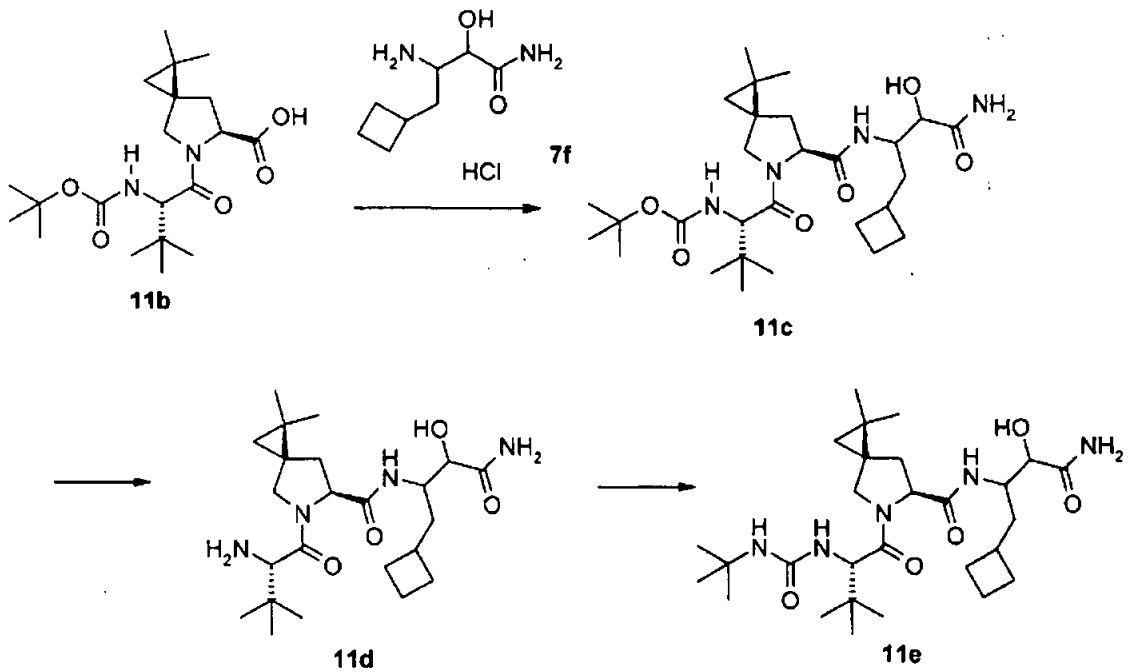



To a solution of Boc-L-t-butyl-gly-OH (907 mg, 3.92 mmol, 1.0 equiv) and amino alcohol **8i** (600 mg, 3.92 mmol, 1.0 equiv) in $CH_2Cl_2$ (20.0 mL) at 0 °C is added HATU (1.638 g, 4.31 mmol, 1.1 equiv) followed by and DIPEA (2.0 mL, 11.76 mmol, 3.0 equiv). The solution is stirred at -20 °C for 24 hours, 0 °C for 3 hour and room temperature for 1 hour. The reaction mixture is diluted with EtOAc and washed with 10 % citric acid. The

phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with saturated aqueous $HaHCO_3$, brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give product **11a** (1.2 g).

To a solution of alcohol **11a** (1.2 g) in acetone (20.0 mL) at -5 °C is added a solution of Jones' reagent (3.0 M, 5.0 mL). The mixture is warmed to 0 °C and stirred at this temperature for 2 hours. The reaction is then quenched by slow addition of *i*-PrOH (5.0 mL) and the mixture is then diluted with EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried ($Na_2SO_4$) and concentrated to give **11b** (1.16 g).

**Step 11-B:**



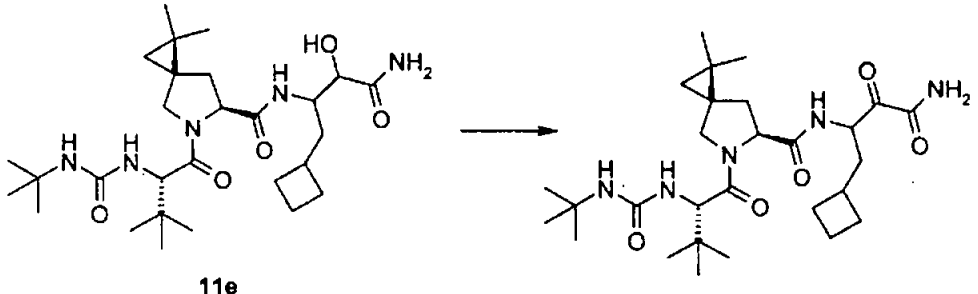

To a solution of **11b** (768 mg, 2.0 mmol) in DMF (2.0 mL) and $CH_2Cl_2$ (2.0 mL) at 0 °C is added HATU (836 mg, 2.2 mmol, 1.1 equiv), **7f** (417 mg, 2.0 mmol, 1.0 equiv) and N-methyl-morpholine (0.658 mL, 6.0 mmol, 3.0 equiv). The solution is stirred at room temperature for 3 hours. The reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc/diethyl ether 1/1. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl, brine, dried over

$Na_2SO_4$ and concentrated. The crude material is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give product **11c**.

Trifluoroacetic acid (3.0 mL) is added to a solution of **11c** in $CH_2Cl_2$ (3.0 mL) and the solution is stirred at room temperature for 1 hour. The solvent is then evaporated. Saturated aqueous $NaHCO_3$ solution and $CH_2Cl_2$ are added to the residue. The two phases are separated and the aqueous layer is extracted with $CH_2Cl_2$. The organic layers are combined, dried over $Na_2SO_4$ and concentrated to give **11d**.

To a solution of N-methyl-morpholine (0.028 mL) and *t*-butylisocyanate (25 mg) in $CH_2Cl_2$ is added **11d** (100 mg). The solution is stirred at room temperature for 4 hours. The solution is loaded to silica gel and flushed with heptane/acetone (1/1) to give product **11e** (91 mg).

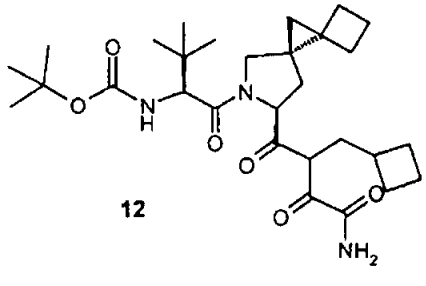
**Step 11-C:**



**11e** **11**

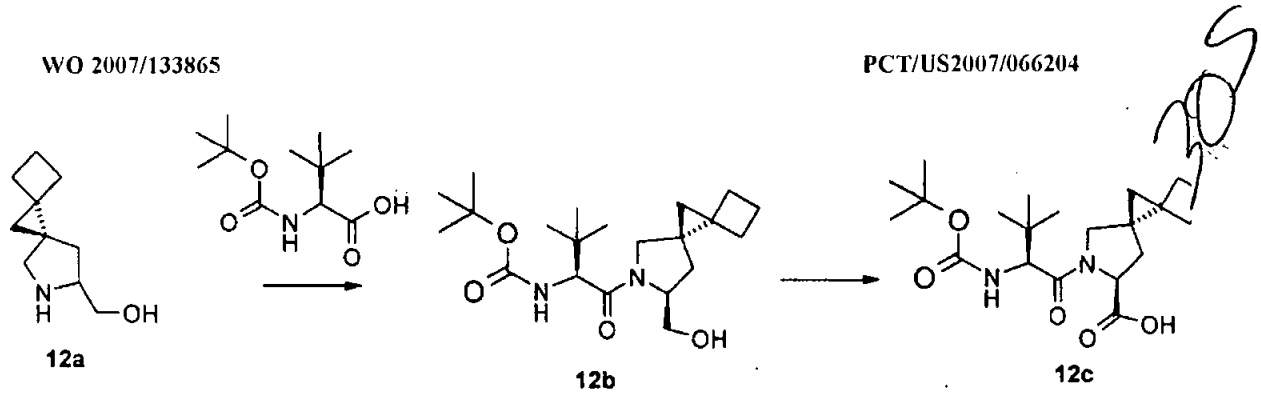
To a solution of alcohol **11e** (91 mg) in $CH_2Cl_2$ (0.6 mL) at 0 °C is added DIPEA (0.160 mL) followed by a solution of $Py{\bullet}SO_3$ (89 mg) in DMSO (0.6 mL). The solution is stirred at 0 °C for 10 minutes. The mixture is loaded directed to silica gel column and flushed with heptane/acetone (1/1) to give product **11** (65 mg). Found m/z ES+ = 534.

**Example 12:**



**12**

**Step 12-A:**

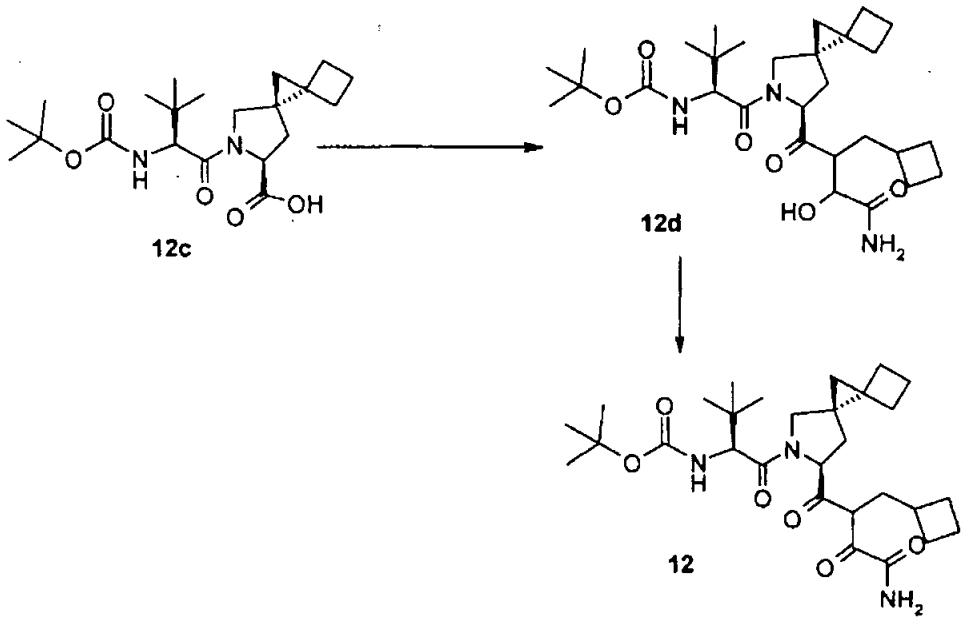



Amino alcohol **12** a is prepared from **8a** and cyclobutanone according to the procedure described for the synthesis of **9f** from **8a**.

To a solution of Boc-L-t-butyl-gly-OH (277 mg, 1.20 mmol, 1.0 equiv) and **12a** (200 mg, 1.20 mmol, 1.0 equiv) in $CH_2Cl_2$ (10.0 mL) at -20 °C is added HATU (0.55 g, 1.44 mmol, 1.2 equiv) followed by and DIPEA (0.63 mL, 3.60 mmol, 3.0 equiv). The solution is stirred at -20 °C for 24 hours and 0 °C for 1 h. The reaction mixture is diluted with EtOAc and washed with 10 % citric acid. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with saturated aqueous $NaHCO_3$, brine, dried ($Na_2SO_4$) and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give product **12b**.

To a solution of **12b** (0.40 g, 1.05 mmol) in acetone (10.0 mL) at 0 °C is added a solution of Jones' reagent (3.0 M, 2.1 mL, 5.3 mmol). The mixture is kept at 0 °C for 1 hour. The reaction is then quenched by slow addition of *i*-PrOH (3.0 mL) and the mixture is then diluted with EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried ($Na_2SO_4$) and concentrated to yield **12c**.

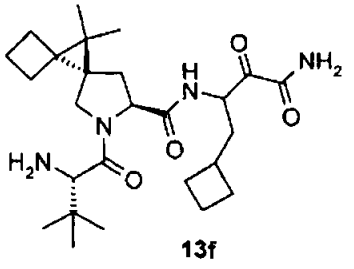
**Step 12-B:**



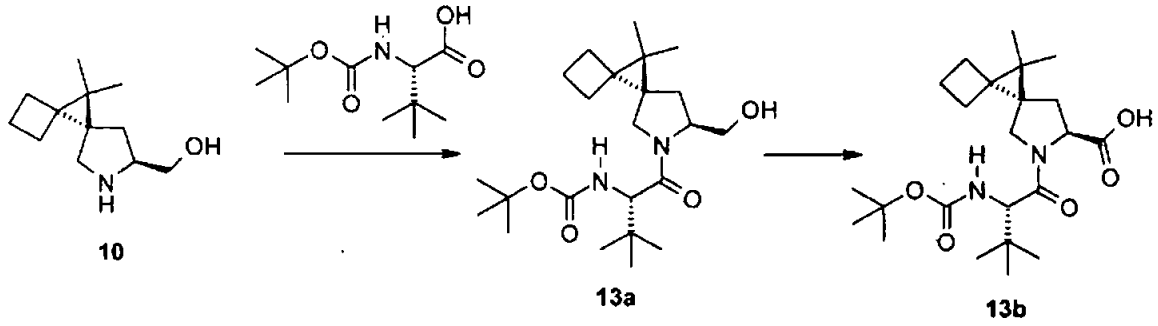

To a solution of acid **12c** (0.39 mg, 0.99 mmol) and **7f** (206 mg, 0.99 mmol, 1.0 equiv) in DMF (8.0 mL) and $CH_2Cl_2$ (8.0 mL) at 0 °C is added HATU (452 mg, 1.19 mmol, 1.2 equiv) and N-methyl-morpholine (0.33 mL, 2.97 mmol, 3.0 equiv). The solution is stirred at room temperature for 4 hours. To the reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc/diethyl ether (1/1). The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl aq. solution, brine, dried ($Na_2SO_4$) and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give product **12d**.

To a solution of **12d** (100 mg, 0.18 mmol) in $CH_2Cl_2$ (1.0 mL) and DMSO (1.0 mL) at 0 °C is added DIPEA (0.19 mL, 1.10 mmol, 6 eq) followed by Py•$SO_3$ (87 mg, 0.55 mmol, 3 eq). The solution is stirred at 0 °C for 10 minutes. The mixture is loaded directly to silica gel column and flushed with heptane/Acetone (1:1) to give 55 mg of product **12**. Found m/z ES+ = 532.

**Example 13:**



**Step 13-A:**

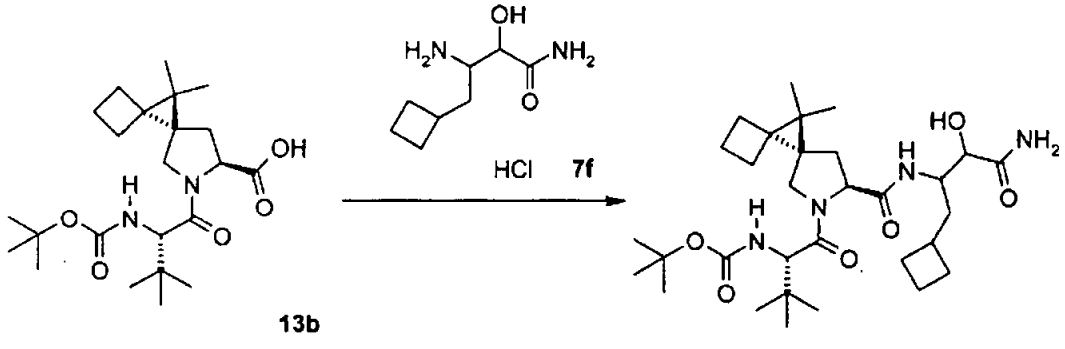


10 13a 13b

To a solution of Boc-L-t-butyl-gly-OH (711 mg, 3..08 mmol, 1.0 equiv) and amino alcohol **10** (600 mg, 3.08 mmol, 1.0 equiv) in $CH_2Cl_2$ (15.0 mL) at -20 °C is added HATU (1.4 g, 3.69 mmol, 1.2 equiv), followed by DIPEA (1.6 mL, 9.2 mmol, 3.0 equiv). The solution is stirred at -20 °C for 24 hours, 0 °C for 3 hours and room temperature for 1 hour. The reaction mixture is diluted with EtOAc and washed with 1.0 N HCl aq. solution. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined and washed with saturated aqueous $NaHCO_3$, brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give product **13a**. Found m/z ES+ = 409.

To a solution of alcohol **13a** (890 mg) in acetone (10.0 mL) at -5 °C is added a solution of Jones' reagent (3.0 M, 5.0 mL). The mixture is warmed to 0 °C and stirred at this temperature for 2 hours. The reaction is then quenched by slow addition of *i*-PrOH (5.0 mL) and the mixture is then diluted with EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried ($Na_2SO_4$) and concentrated to give product **13b**. Found m/z ES+ = 423.

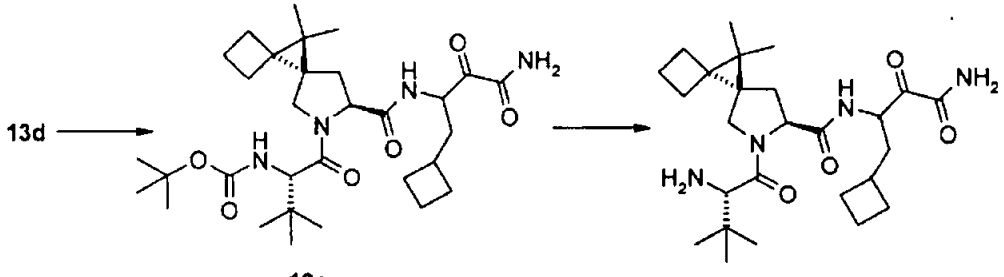
**Step 13-B:**



13b 7f 13d

To a solution of acid (906 mg, 2.1 mmol) in DMF (8.0 mL) and $CH_2Cl_2$ (8.0 mL) at 0 °C is added HATU (958 mg, 2.5 mmol, 1.2 equiv), amino alcohol (492 mg, 2.4 mmol, 1.1 equiv) and N-methyl-morpholine (0.692 mL, 6.3 mmol, 3.0 equiv). The solution is stirred at room temperature for 3 hours. The reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc/diethyl ether 1/1. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1N HCl, brine, dried over $Na_2SO_4$ and concentrated. The crude material is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give product **13d**. Found m/z ES+ = 577.

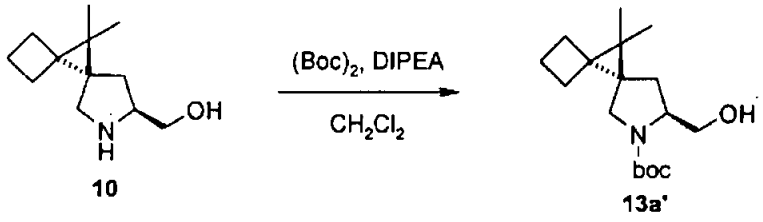
**Step 13-C:**




To a solution of alcohol **13d** (450 mg) in $CH_2Cl_2$ (0.6 mL) at 0 °C is added DIPEA (0.504 mL) followed by a solution of Py•$SO_3$ complex (372 mg) in DMSO (0.6 mL). The solution is stirred at 0 °C for 10 minutes. The mixture is loaded directed to silica gel column and flushed with heptane/Acetone to give product **13e**. Found m/z ES+ = 575.

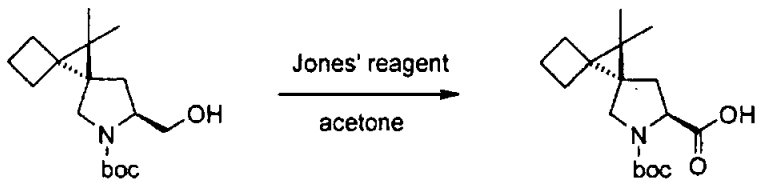
The product is dissolved in 15 mL of 4.0 M HCl in dioxane. The solution was stirred at room temperature for 2 hours. The solution is diluted with 50 mL heptane and concentrated to give crude product **13f**, which is carried on to the next step with no purification. Found m/z ES+ = 475.

**Alternative synthetic route from 10 to 13d.**



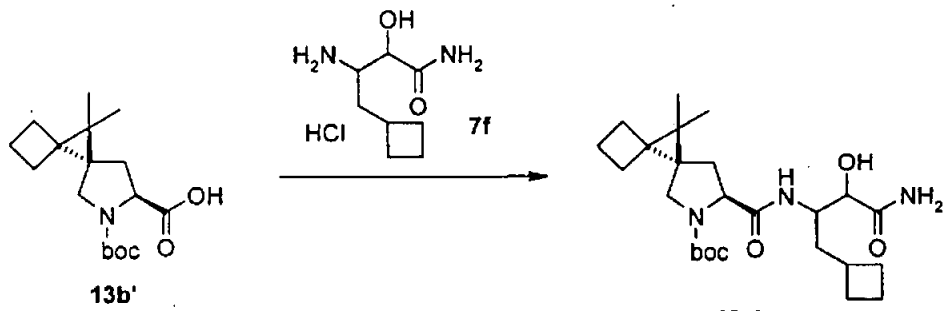

To a solution of **10** (1.95 g, 10 mmol) in $CH_2Cl_2$ (20.0 mL) at room temperature added Boc anhydride and DIPEA (0.434 mL, 10.5 mmol, 1.05 equiv). The solution is stirred

at room temperature for 2 hours. The solvent is evaporated and the residue is purified by silica gel chromatography (heptane/EtOAc, 2/1) to give product **13a'** 2.1 g.



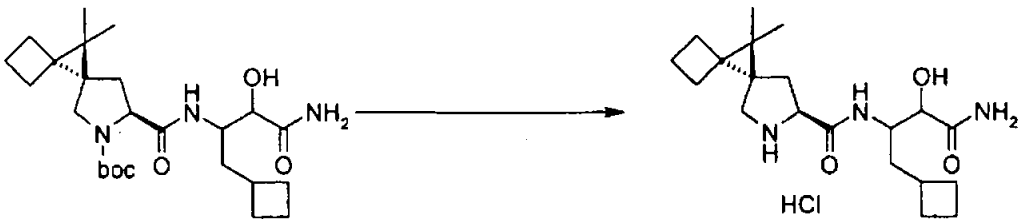

**13a'** **13b'**

To a solution of alcohol **13a'** (3.0 g, 10.2 mmol) in acetone (30.0 mL) at 0 °C added Jones' reagent (12.2 mL, 30.5 mmol, 3.0 equiv). The solution is stirred at 0 °C for 1.0 hour. The reaction is quenched by addition of i-PrOH (5.0 mL). The solution is then diluted with EtOAc and filtered. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with brine, dried over $Na_2SO_4$ and concentrated. The crude material is continued to the next step without further purification.



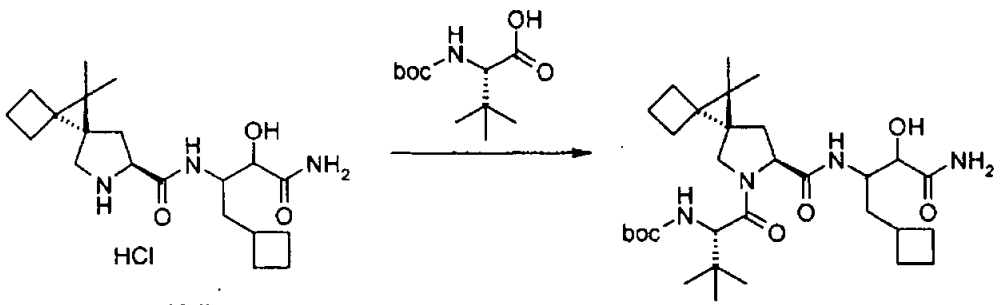

**13b'** **13c'**

To a solution of carboxylic acid **13b'** (1.0 g, 3.2 mmol) in $CH_2Cl_2$ (8.0 mL) and DMF (8.0 mL) at 0 °C added **11c** (673 mg, 3.2 mmol, 1.0 equiv) followed by HATU (1.45 g, 3.8 mmol, 1.2 equiv) and N-methyl morpholine (1.05 mL, 9.6 mmol, 3.0 equiv). The solution is stirred at room temperature for 4 hours. To the solution is added EtOAc and sat. aq. $NaHCO_3$. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl aq. solution, brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give product **13c'** 975 mg. Found MS ES+ = 464.



13c' 13d'

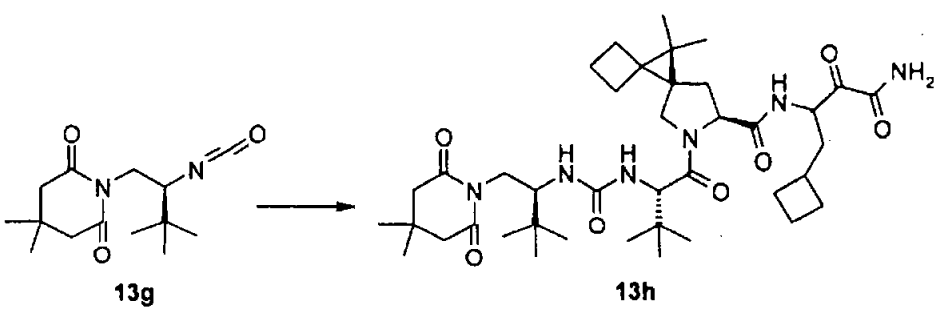
To a flask containing **13c'** added 10 mL of 4.0 N HCl in dioxane. The solution is stirred at room temperature for 1.0 hour. The solvent is then evaporated give crude product **13d'**, which is continued to the next step without purification. Found MS ES+ = 364, ES- = 362.



13d' 13d

To mixtures of Boc-L-t-butyl-gly-OH (297 mg, 1.29 mmol, 1.0 equiv), **13d'** (515 mg, 1.29 mmol, 1.0 equiv) in $CH_2Cl_2$ (7.0 mL) at -20 °C added HATU (585 mg, 1.54 mmol, 1.2 equiv) and DIPEA (0.696 mL, 4.0 mmol, 3.0 equiv). The solution is stirred at -20 °C for 12 hours then 0 °C for 1.0 hour. To the solution is added EtOAc and sat. aq. $NaHCO_3$ solution. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl aq. solution, brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give product 610 mg. Found MS ES+ = 577, ES- = 575.

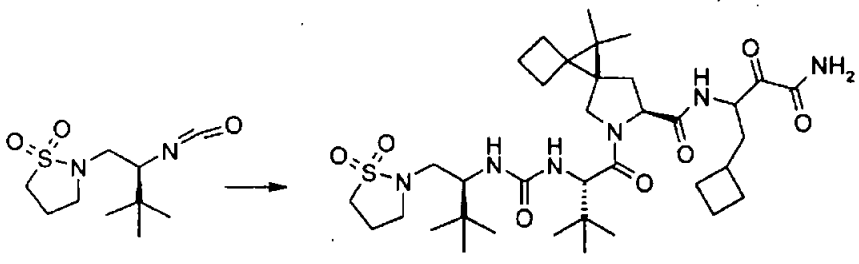
**Example 13h:**



13g 13h

To a solution of amine hydrochloride salt **13f** (37.5 mg) in $CH_2Cl_2$ (1.0 mL) is added DIPEA (0.012 mL) and a solution of **13g** (23 mg) in toluene (1.5 mL). The solution is stirred at room temperature for 2 hours. The solution is concentrated and the crude material is purified by silica gel column chromatography to give 20 mg of product **13h**. Found m/z ES+ = 741.

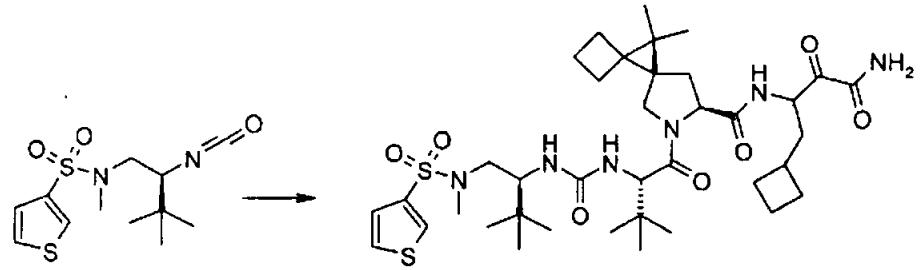
**Example 13j:**



**13i** **13j**

To a solution of amine hydrochloride salt **13f** (37 mg) in $CH_2Cl_2$ is added DIPEA (0.012 mL) and a solution of **13i** (21 mg) in toluene (1.5 mL). The solution is stirred at room temperature for 2 hours. The solution is concentrated and the crude material is purified by silica gel column chromatography to give 6 mg of product **13j**. Found m/z ES+ = 721.

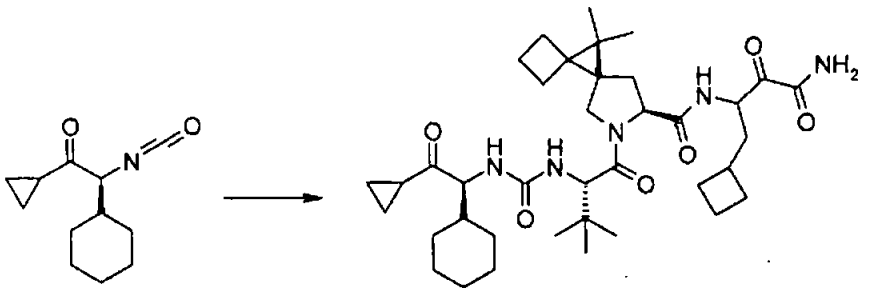
**Example 13l:**



**13k** **13l**

To a solution of amine hydrochloride salt **13f** (37 mg) in $CH_2Cl_2$ is added DIPEA (0.012 mL) and a solution of **13k** (26 mg) in toluene (1.5 mL). The solution is stirred at room temperature for 2 hours. The solution is concentrated and the crude material is purified by silica gel column chromatography to give 15 mg of product **13l**. Found m/z ES+ = 777.

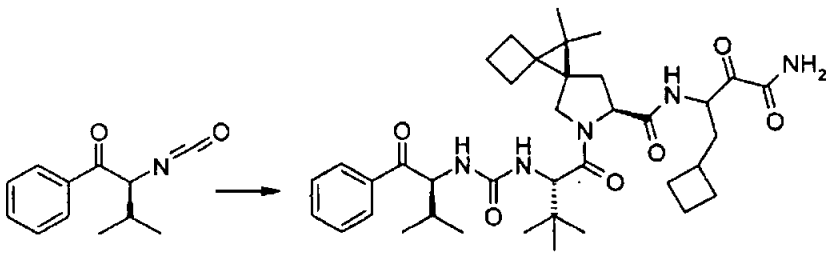
**Example 13n:**



13m 13n

To a solution of amine hydrochloride salt **13f** (37 mg) in $CH_2Cl_2$ is added DIPEA (0.012 mL) and a solution of **13m** (18 mg) in toluene (1.5 mL). The solution is stirred at room temperature for 2 hours. The solution is concentrated and the crude material is purified by silica gel column chromatography to give 29 mg of product **13n**. Found m/z ES+ = 682.

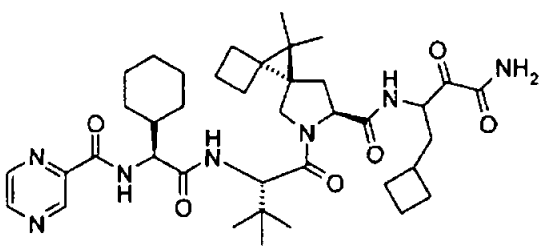
**Example 13p:**



13o 13p

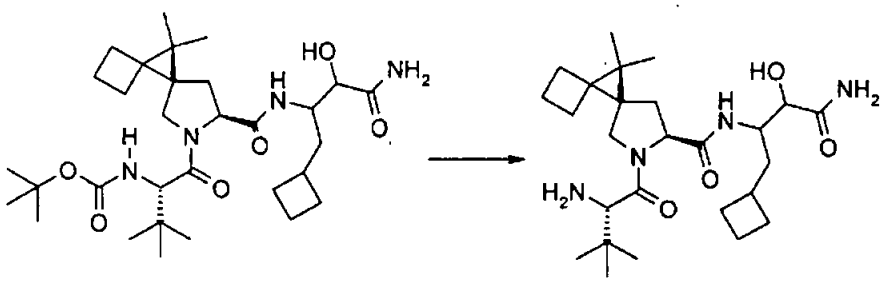
To a solution of amine hydrochloride salt **13f** (37 mg) in $CH_2Cl_2$ is added DIPEA (0.012 mL) and a solution of **13o** (18 mg) in toluene (1.5 mL). The solution is stirred at room temperature for 2 hours. The solution is concentrated and the crude material is purified by silica gel column chromatography to give 37.6 mg of product **13p**. Found m/z ES+ = 678.

**Example 14:**



14

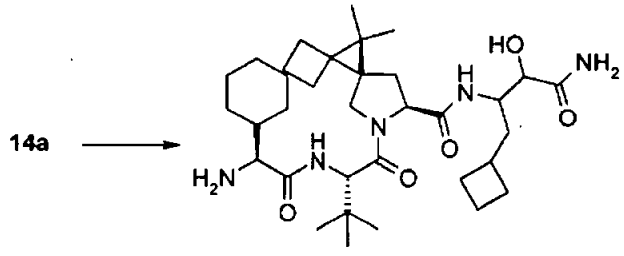
**Step 14-A:**



13d 14a

To a solution of N-Boc amine **13d** (690 mg) in dichloromethane (5.0 mL) at room temperature is added TFA (5.0 mL ). The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo and dichloromethane (100 mL) is added to the residue. The pH is adjusted to pH 8 by dropwise addition of saturated sodium bicarbonate. The layers are separated and the organic layer with washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give the product amine **14a**. Found m/z ES+ =477.

**Step 14-B:**

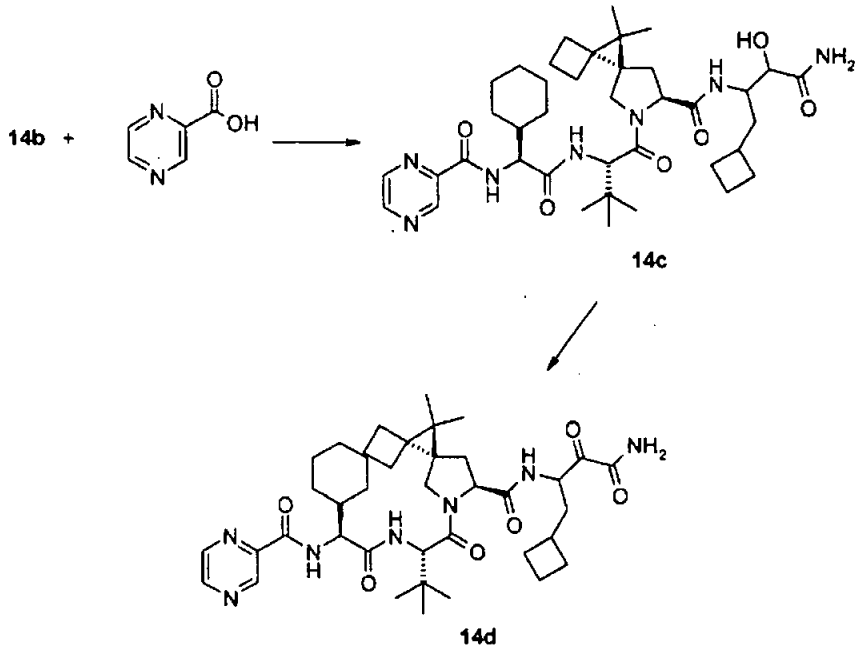


14a 14b

To a solution of (S)-2-(tert-butoxycarbonylamino)-2-cyclohexylacetic acid (51.4 mg, 0.2 mmol) in DMF (1.0 mL) and $CH_2Cl_2$ (1.0 mL) at 0 °C is added HATU (91 mg, 0.24 mmol, 1.2 equiv), amine **14a** (95 mg, 0.2 mmol, 1.0 equiv) and N-methyl-morpholine (0.066 mL, 0.6 mmol, 3.0 equiv). The solution is stirred at room temperature for 3 hours. To the reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc/diethyl ether 1/1. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1N HCl, brine, dried over $Na_2SO_4$ and concentrated. The crude material is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give Boc-protected amine (Found m/z ES+ =716). The product is dissolved in dichloromethane (5 mL) at room temperature and TFA (5 mL ) is added. The mixture is stirred for 3 hours after which the solvent is evaporated in vacuo. The residue is dissolved in dichloromethane (100 mL). The pH is adjusted to pH 8 by dropwise addition of saturated sodium bicarbonate. The layers are separated and the organic layer with washed with brine, dried over $Na_2SO_4$, filtered and concentrated to give the product **14b**. Found m/z ES+ =616.

314

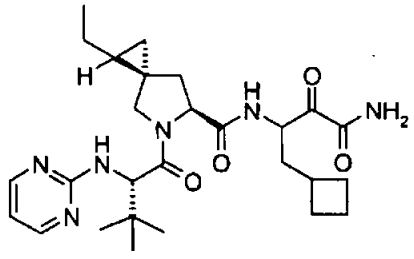
**Step 14-C:**




To a solution of pyrazine-2-carboxylic acid (20 mg, 0.16 mmol) in DMF (1.0 mL) and $CH_2Cl_2$ (1.0 mL) at 0 °C is added HATU (73 mg, 0.19 mmol, 1.2 equiv), amine **14b** (100 mg, 0.16 mmol, 1.0 equiv) and N-methyl-morpholine (0.053 mL, 0.48 mmol, 3.0 equiv). The solution is stirred at room temperature for 3 hours. To the reaction mixture is added saturated aqueous $NaHCO_3$ solution and EtOAc/diethyl ether 1/1. The two phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1N HCl, brine, dried over $Na_2SO_4$ and concentrated. The crude material is purified by silica gel column chromatography (hexane/EtOH, 9/1) to give product **14c**. Found m/z ES+ =722.

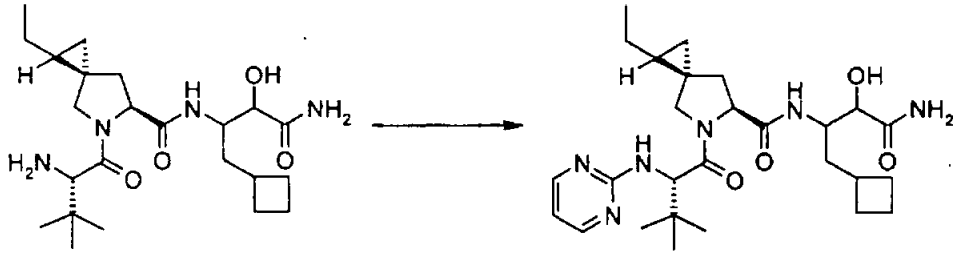
To a solution of alcohol **14c** (110 mg) in $CH_2Cl_2$ (0.6 mL) at 0 °C is added DIPEA (0.160 mL) followed by a solution of sulfur trioxide pyridine complex (89 mg) in DMSO (0.6 mL). The solution is stirred at 0 °C for 10 mines. The mixture is loaded directly onto a silica gel column and flushed with heptane/Acetone to give product **14d** (71 mg). Found m/z ES+ = 720.

**Example 15:**

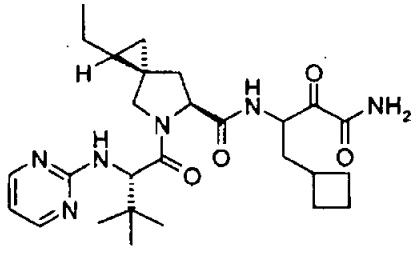


15

**Scheme:**



15a



15

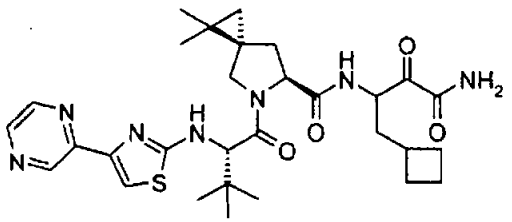
**Step 15-A:**

To a solution of amine (87 mg, 0.2 mmol, 1.0 equiv) in IPA (0.4 mL) at room temperature is added 2-bromo-pyrimidine (32 mg, 0.2 mmol, 1.0 equiv) and DIPEA (0.034 mL, 0.2 mmol, 1.0 equiv). The solution is heated at 80 °C for 24 hours. The crude material is purified by silica gel chromatography (heptane/acetone, 1/1) to give desired product. Found m/z ES+ = 515.

**Step 15-B:**

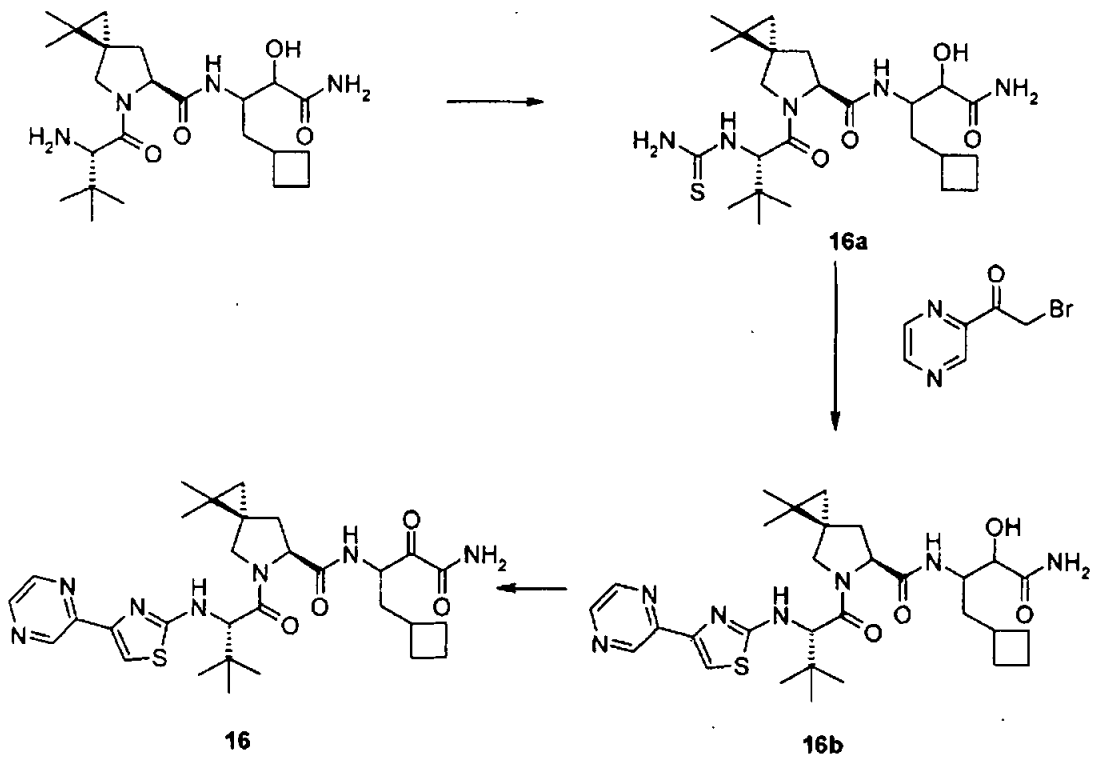
To a solution of **15a** (90 mg) in $CH_2Cl_2$ (0.6 mL) add DIPEA (0.12 mL) and a solution of $Py{\cdot}SO_3$ (80 mg) in DMSO (0.6 mL). The solution is stirred at rt for 10 mins. The solution is loaded to silica gel and flushed with heptane/acetone (1/1) to give 28 mg of product **15**. Found m/z ES+ = 513.

**Example 16:**



**16**

**Synthesis of thiazole:**




**Step 16-A:**

Benzoyl isothiocyanate (162 mg) is added to a solution of amine (400 mg) in acetone (4.0 mL) . The solution is heated at 70 °C for 2 hours. Potassium carbonate (40 mg), water (0.4 mL) and MeOH (4.0 mL) are then added to the solution. The solution is then heated at 80 °C for 4 hours. The mixture is concentrated and the crude residue is purified by silica gel chromatography ($CH_2Cl_2$/MeOH, 4/1) to give thiourea intermediate **16a**. Found m/z ES+ = 497.

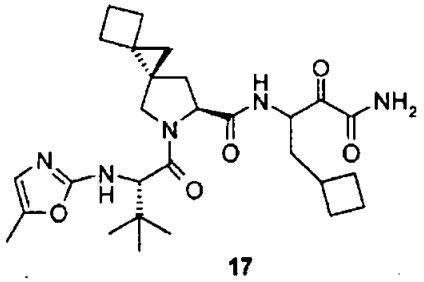
**Step 16-B:**

The thiourea (70 mg) and 2-bromo-1-pyrazin-2yl-ethanone (30 mg) are dissolved in ethanol (0.5 mL) and the solution is heated to reflux for 1 hour. The crude material is purified by silica gel chromatography ($CH_2Cl_2$/EtOH, 9/1) to give product **16b**. Found m/z ES+ = 598.

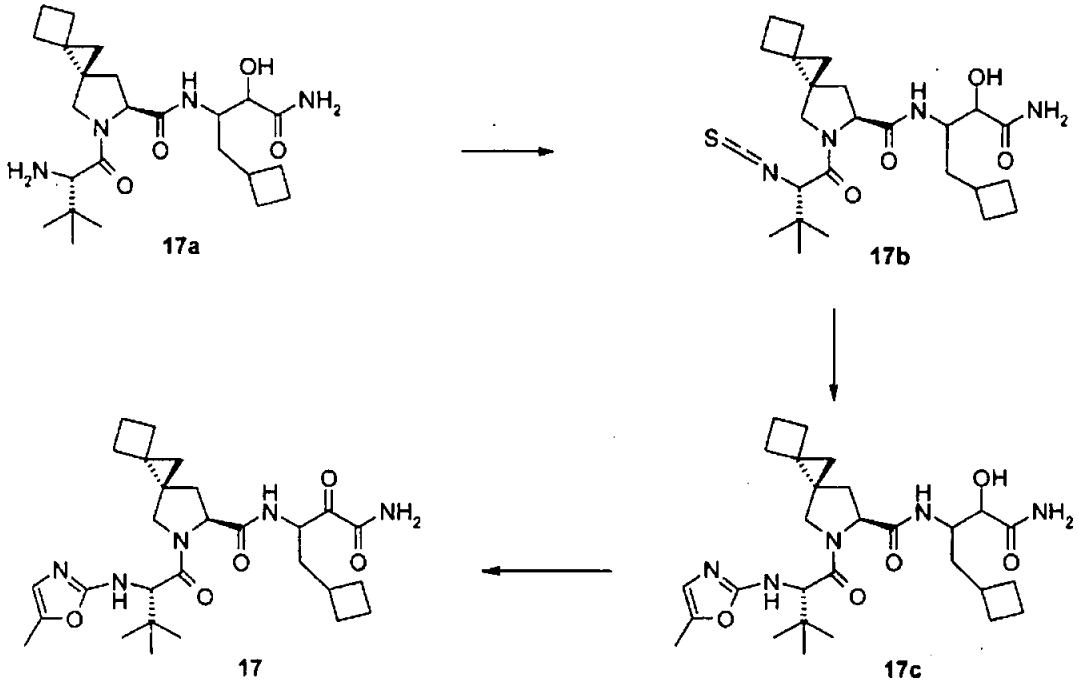
**Step 16-C:**

To a solution of **16b** (70 mg) in $CH_2Cl_2$ (1.0 mL) add DIPEA (0.12 mL) and a solution of Py•$SO_3$ (80 mg) in DMSO (0.6 mL). The solution is stirred at rt for 10 mins. The solution is loaded to silica gel and flushed with heptane/acetone (1/1) to give 25 mg of product **16**. Found m/z ES+ = 513.

**Example 17:**



**17**




**Step 17-A:**

To a solution of **17a** (5.31 g, 11.86 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C add sat. aq. $NaHCO_3$ ( 40 mL) and $CSCl_2$ (1.1 mL, 14.23 mmol) is added. The mixture is stirred at room temperature for 30 minutes. The phases are separated and the organic layer is washed with brine, dried over $Na_2SO_4$, and concentrated. The crude material is purified by silica gel chromatography (heptane/EtOAc, 1/1) to give product **17b** (1.20 g, 21% yield) as light yellow solid. Found m/z ES+ = 491.

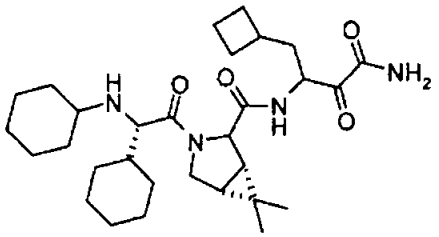
**Step 17-B:**

To a solution of **17b** (60 mg, 0.122 mmol) in dioxane is added $PPh_3$ (38.6 mg, 0.147 mmol) and followed by 1-azidopropan-2-one (14.5 mg, 0.147 mmol). The solution is heated at 90 °C for 1 hour. Then 2-methyl-propane-1,2 diamine (0.20 mL) is added and the solution is heated at 50 °C for 30 minutes. The crude mixture is separated by silica gel column chromatography ($CH_2Cl_2$/EtOH, 4/1) to afford **17c** (22 mg). Found m/z ES+ = 530.

**Step 17-C:**

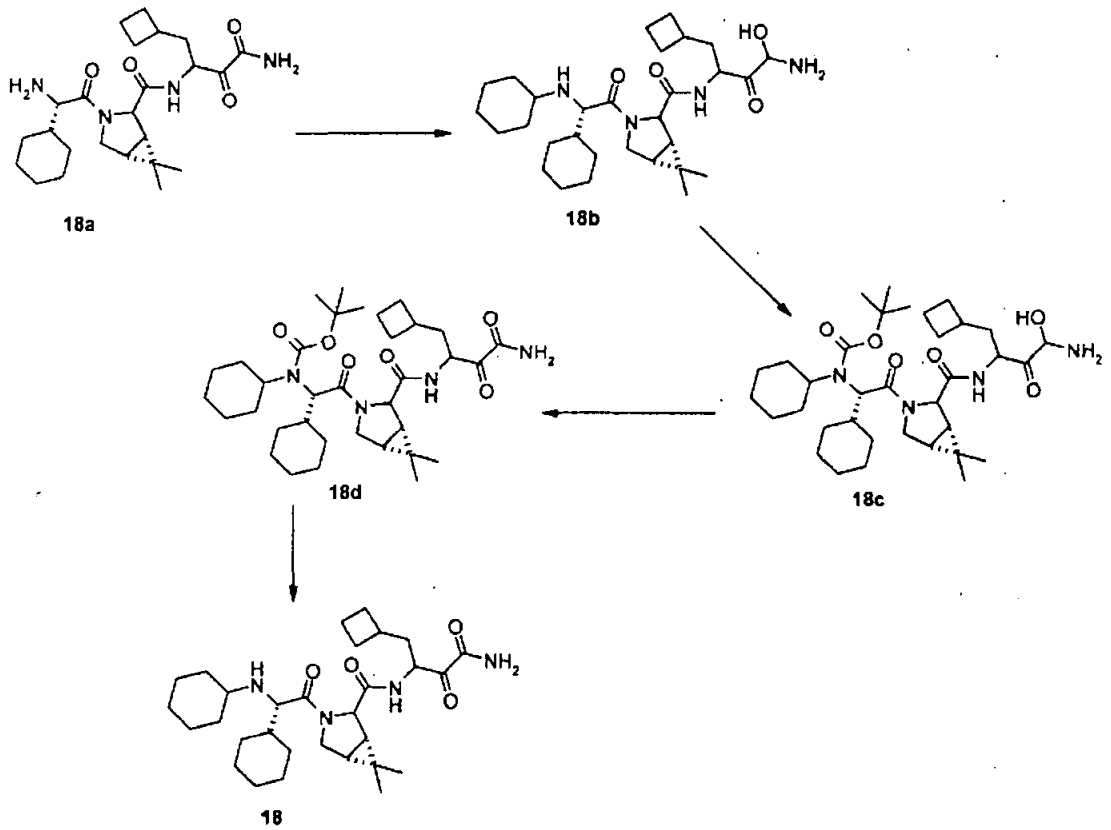
To a solution of **17c** (22 mg, 0.042 mmol) in $CH_2Cl_2$ add DIPEA (0.044 mL, 0.252 mmol) and DMSO ( 0.5 mL). Then the solution is cooled to 0 °C and Py•$SO_3$ ( 20 mg, 0.125 mmol) is added. The solution is stirred at 0 °C for 10 minutes. The mixtures are separated by chromatography ( Heptane/Acetone, 1/1) to afford **17** (5 mg). Found m/z ES+ =528.

**Example18:**



18

**Scheme:**




**Step 18-A:**

A solution of **18a** (89 mg, 0.2 mmol) in $CH_2Cl_2$ (1.0 mL) is added cyclohexanone (0.22 mmol, 0.023 mL). The solution is stirred for 20 minutes at room temperature after which sodium triacetoxy borohydride (0.4 mmol, 84 mg) is added and stirred for another 20 minutes. To the reaction mixtures add sat. aq. $NaHCO_3$ solution. The organic layer is separated from aqueous layer and the aqueous layer is extracted with dichloromethane (3 X

10 mL). The organic layers are combined, dried ($Na_2SO_4$) and concentrated to give 97 mg of **18b**.

**Step 18-B:**

A solution of **18b** (97 mg, 0.183 mmol) in DCM is added $Et_3N$ (0.366 mmol, 51 μL) and $(Boc)_2O$ (0.274 mmol, 60 mg). The solution is stirred at room temperature for an hour after which it is washed with 1.0 N HCl aq. solution (1 mL), sat. aq. $NaHCO_3$ solution (1 mL) and brine. The organic layer is dried over $Na_2SO_4$, and concentrated. The residue is purified by silica gel column chromatography (eluent: acetone/heptane, 1:1) to give 95 mg of **18c**.

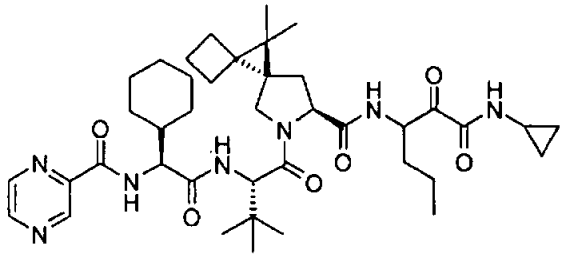
**Step 18-C:**

To a solution of **18c** (73 mg, 0.12mmol) in $CH_2Cl_2$ (0.5 mL), DIPEA (81 μL, 0.46 mmol) and DMSO ( 0.5 mL) are added. Then the solution is cooled to 0 °C and Py•$SO_3$ ( 37 mg, 0.23 mmol) is added. The solution is stirred at 0 °C for 10 minutes. The mixtures are separated by silica gel chromatography ( Heptanes/Acetone, 1/1) to afford 67 mg of **18d**.

**Step 18-D:**

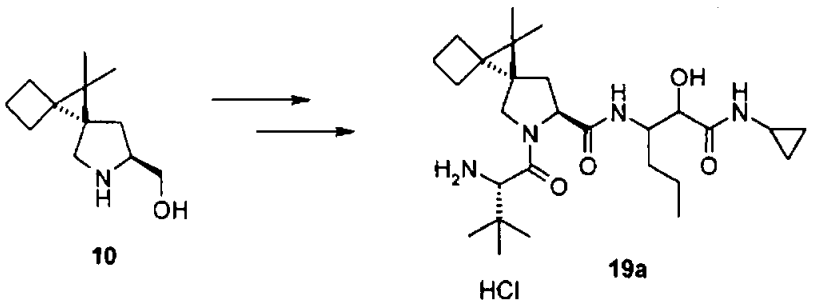
The product **18d** (66 mg, 0.104 mmol) is dissolved in dioxane (0.2 mL) and the solution is added 4.0 N HCl in dioxane (0.105 mL) at 0 °C. The reaction mixture is stirred at rt for 24 hours after which the reaction mixture is concentrated. The residue is dissolved in DCM and the solution is washed with sat. $NaHCO_3$ aq. solution, brine. The organic layer is dried over $Na_2SO_4$, chromatographed (Eluent: Acetone/heptane, 1:1) to give 33.5 mg of **18**.

**Example 19:**



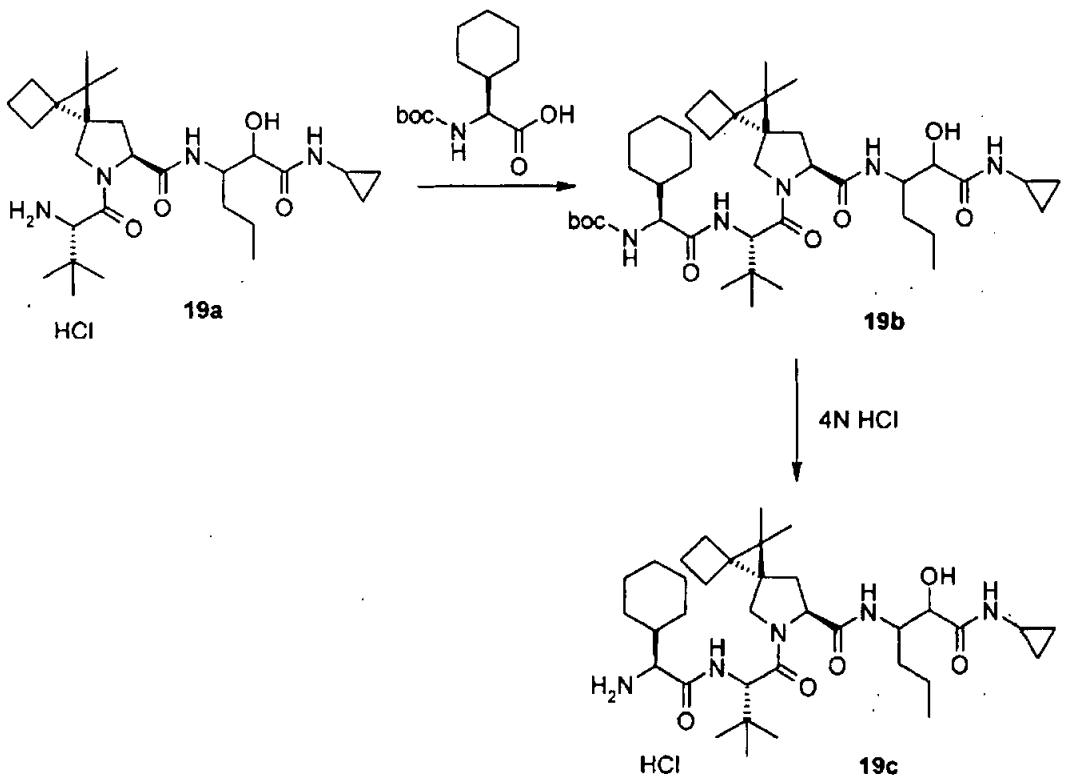
**19**

**Step 19-A:**




Intermediate **19a** is prepared according to the procedure described for the synthesis of **13d**. Found MS ES+ = 491.

**Step 19-B:**

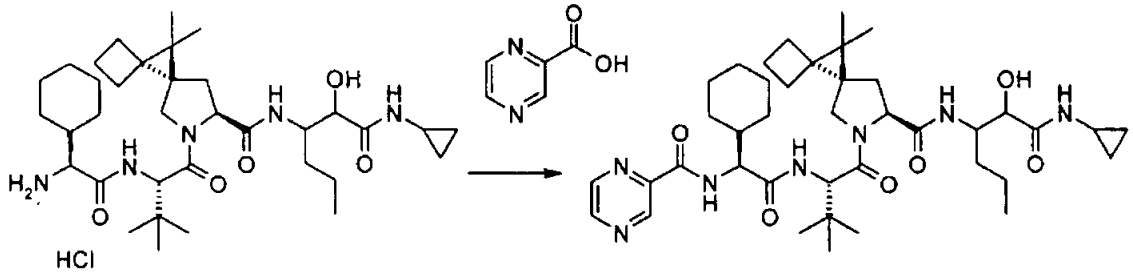



To a solution of Boc-L-cyclohexyl-gly-OH (0.391 g, 1.53 mmol) and **19a** (800 mg, 1.53 mmol, 1.0 equiv) in $CH_2Cl_2$ (7.0 mL) and DMF (7.0 mL) at 0 °C added HATU (697 mg, 1.8 mmol, 1.2 equiv) and N-methyl morpholine (0.505 mL, 4.6 mmol, 3.0 equiv). The solution is stirred at room temperature for 4 hours. To the solution is added EtOAc and sat. aq. $NaHCO_3$. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl aq. solution, brine, dried over $Na_2SO_4$

and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give product **19b**. Found MS ES+ = 730, ES- = 728.

To a flask containing **19b** (1.02 g) added 4.0 N HCl in dioxane (10.0 mL). The solvent is evaporated to give crude material **19c**, which is continued to the next step without purification. Found MZ ES+ = 630, ES- = 628.

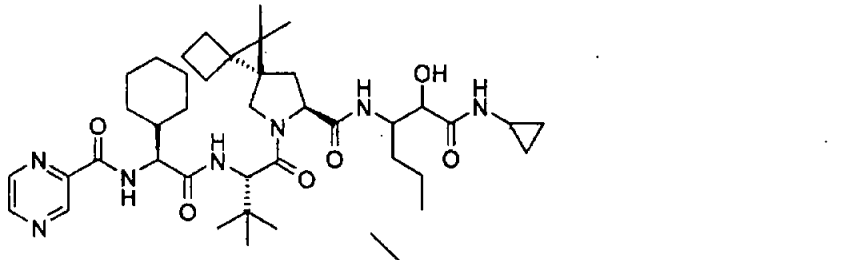
**Step 19-C:**



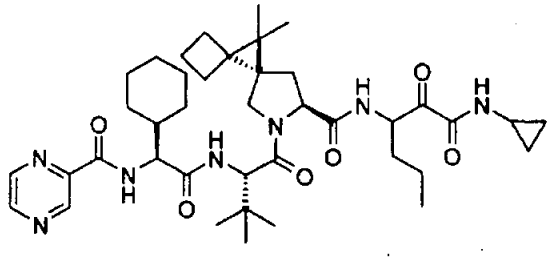
**19c** **19d**

To a solution of pyrazine-2-carboxylic acid (0.175 g, 1.40 mmol) and **19c** (938 mg, 1.40 mmol, 1.0 equiv) in $CH_2Cl_2$ (7.0 mL) and DMF (3.0 mL) at 0 °C added HATU (639 mg, 1.7 mmol, 1.2 equiv) and N-methyl morpholine (0.461 mL, 4.2 mmol, 3.0 equiv). The solution is stirred at room temperature for 4 hours. To the solution is added EtOAc and sat. aq. $NaHCO_3$. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, washed with 1.0 N HCl aq. solution, brine, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give product **19d**. Found MZ ES+ = 736, ES- = 734.

**Step 19-D:**



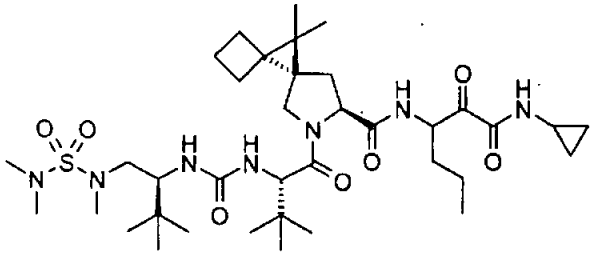
19d



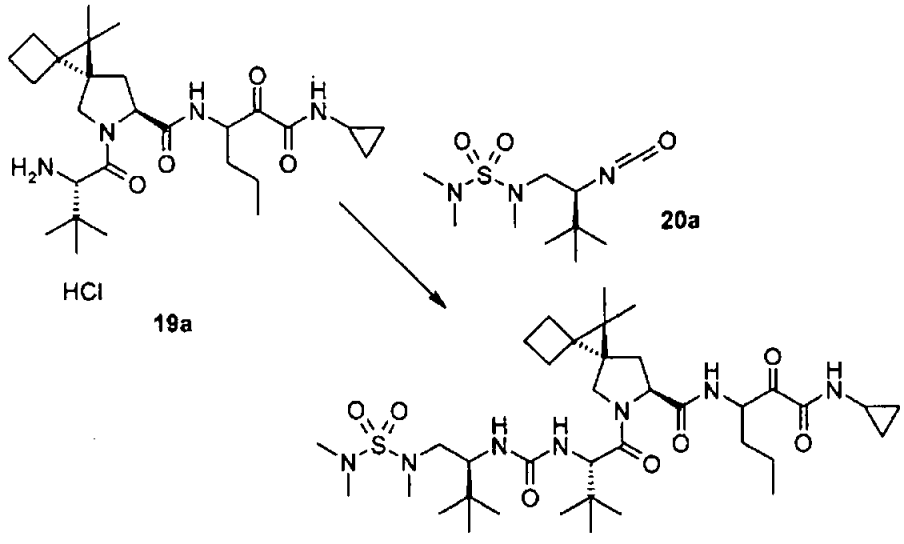
19

To a solution of **19d** (670 mg, 0.91 mmol) in $CH_2Cl_2$ (2.0 mL) at 0 °C added DIPEA (0.95 mL, 5.46 mmol, 6.0 equiv) followed by a solution of Py•$SO_3$ (440 mg, 2.73 mmol, 2.0 equiv) in DMSO (2.0 mL). The solution is stirred at 0 °C for 10 minutes, after which it is added sat. aq. $NH_4Cl$ solution and EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The organic layers are combined, dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give 71 mg of **19**. Found MZ ES+ = 734, ES- = 732.

**Example 20:**

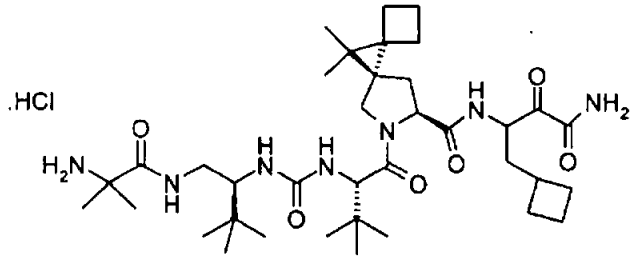


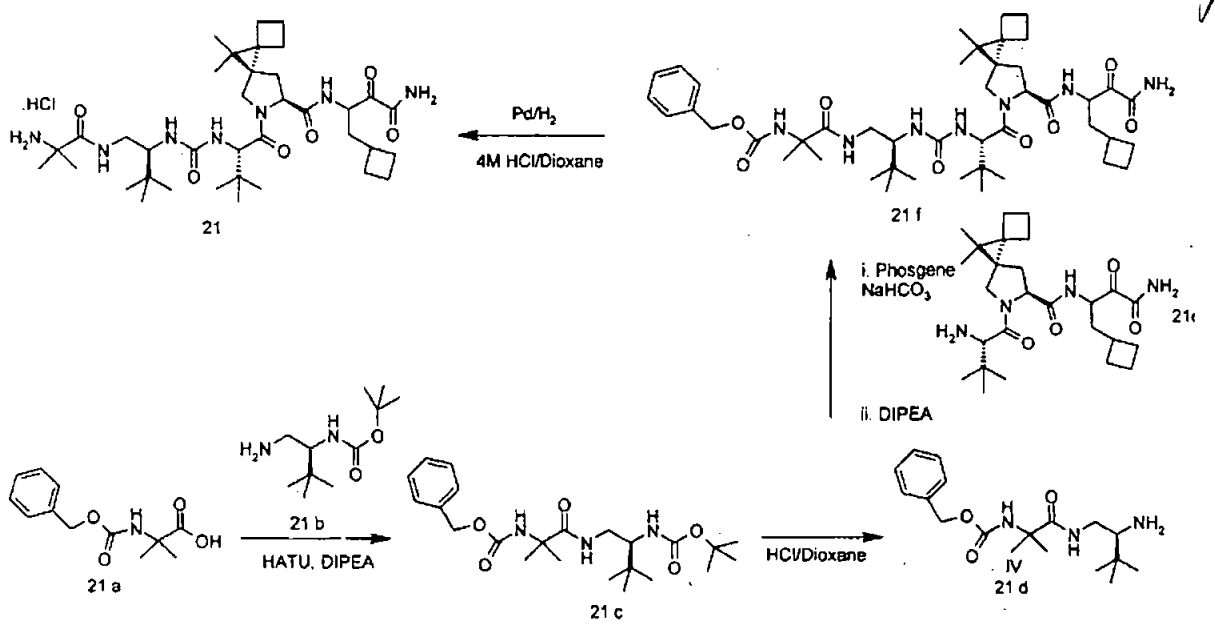
20



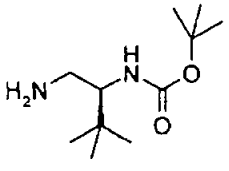

To mixtures of **19a** (75 mg, 0.14 mmol) in $CH_2Cl_2$ (1 mL) added DIPEA (0.05 mL, 0.29 mmol) at 0 °C, **20a** ( 0.18 mmol, in toluene solution ). The solution is stirred at 0°C for 30 min after which it is quenched by addition of citric acid (10% aq. solution, 5 mL) and EtOAc. The phases are separated and the aqueous layer is extracted with EtOAc. The combined organic layers are washed with brine, dried over $Na_2SO_4$, filtered and concentrated. The residue is purified by silica gel chromatography (heptane/acetone, 1/1) to give 59 mg of **20**. Found MZ, ES+ = 752, ES- = 750.

**Example 21:**





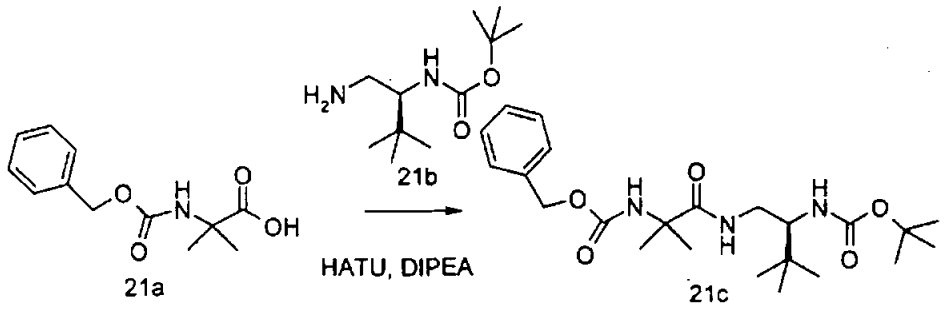

**Step 21-A:**



21b

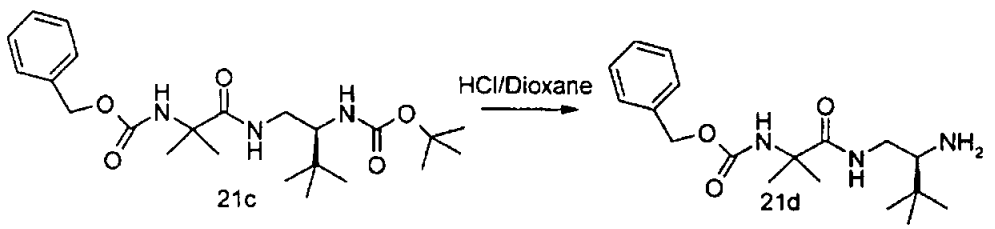
Synthesis of compound **21b** is carried out in a three step sequence following a literature procedure by Busacca, C. A. ; Grossbach, D. Spinelli, E. *Tetrahedron: Asymmetry*, **2000,** 11(9), 1907-1910.

**Step 21-B:**



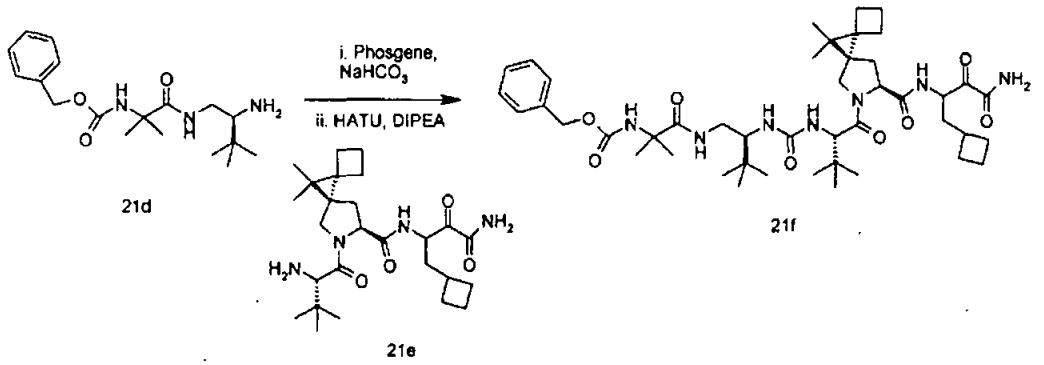

To a solution of N-Carbobenzyloxy-2-methylalanine **21a** (817 mg, 3.44 mmol, 1.2 equiv) and amine **21b** (620 mg, 2.87 mmol, 1.0 equiv) in $CH_2Cl_2$ (15.0 mL) at 0 °C is added HATU (1.31 g, 3.44 mmol, 1.2 equiv), followed by DIPEA (1.25 mL, 7.16 mmol, 2.5 equiv). The solution is stirred overnight at RT. The reaction mixture is diluted with EtOAc (75 mL) and washed with 1.0 N HCl (2 X 10 mL). The phases were separated and the aqueous layer extracted with EtOAc (2 x 50 mL). The organic layers are combined and washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel column chromatography (hexane/EtOAc, 1/1) to give1g of the product **21c**. ESMS; $[M + H]^+ = 436$.

**Step 21-C:**




The N-Boc protected amine **21c** (388 mg, 0.89 mmol) is dissolved in HCl (2.5 mL, 4.0 M HCl in dioxane) and the solution stirred at room temperature for 2 hours. The solution is diluted with 50 mL heptane and concentrated to give crude product **21d**, This compound did not require purification and is used directly in the next step. ESMS; $[M + H]^+ = 335$.

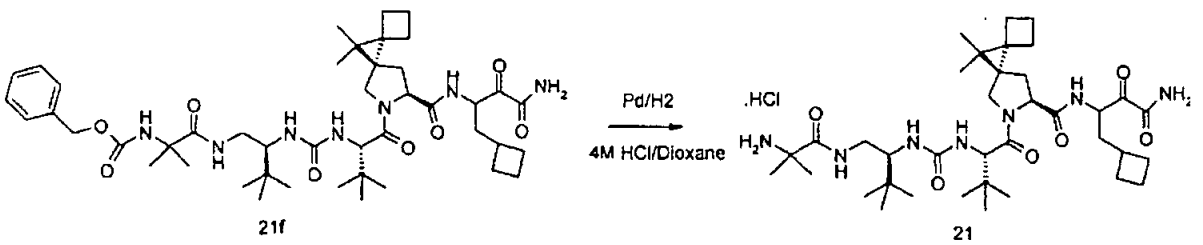
**Step 21-D:**




Amine **21d** (169 mg, 0.46 mmol) is dissolved in Dichloromethane (2.3 mL) and the solution cooled to 0 °C. Saturated $NaHCO_3$ (2.3 mL) is added and the solution stirred vigorously for 5 min. Stirring is stopped and Phosgene (0.46 mL, 0.92 mmol of 2M solution in Toluene) is added to the lower Dichloromethane layer and vigorous stirring is continued for 1 h at room temperature. The solution is diluted with Dichloromethane (10 mL), the layers separated and the organic layer collected and dried over $Na_2SO_4$. The solution is then evaporated to dryness and is used directly in the next step.

A solution of the isocyanate of **21d** in $CH_2Cl_2$ (7 mL) generated above is added to a cooled solution (0 °C) of amine hydrochloride salt **21e** (82 mg, 0.17 mmol) in $CH_2Cl_2$ (7 mL). DIPEA (0.24 mL) is then added and the solution stirred at room temperature for 2 hours. The solution is then concentrated and the crude material purified by silica gel column chromatography (Acetone: Heptane 40 %-75 % acetone) to give 50 mg of product **21f**. ESMS; $[M + H]^+ = 836$.

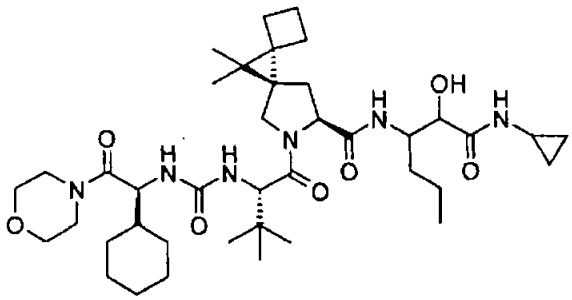
**Step 21-E:**




Benzyloxycarbamate **21f** (11 mg, 0.013 mmol) is dissolved in EtOAc (3 mL). Air was evacuated and flask purged with $N_2$. Palladium (10 % on C, 2 mg) is added and the mixture

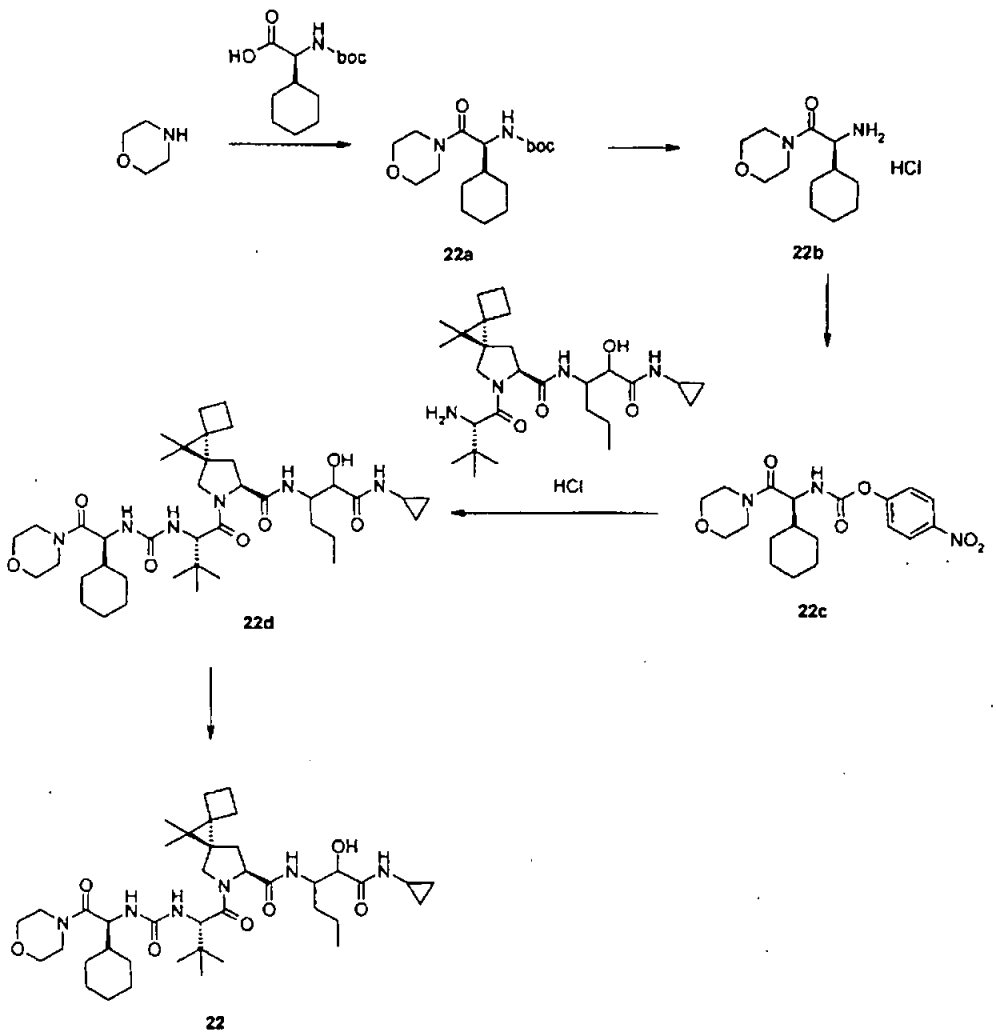
fitted with $H_2$ balloon. The reaction is allowed to proceed for 5 h and then stopped by filtering the mixture through a celite bed. The filtrate is then concentrated. HCl (4M HCl in Dioxane, 2 mL) is added and the solution stirred for 2 min and then evaporated to dryness. The solid sample is washed with heptane (5 mL) and EtOAc ( 2 mL) then dissolved in $H_2O$ (3 mL) and lyophilized overnight to afford 7 mg of a white solid **21.** ESMS; $[M + H]^+ = 702$.

**Example 22:**



**22**

**Scheme:**




**Step 22-A:**

To a solution of Boc-L-cyclohexyl-gly-OH (2.0 g, 7.8 mmol) in $CH_2Cl_2$ (15.0 mL) at room temperature add HATU (3.5 g, 9.3 mmol, 1.2 equiv), morpholine (0.679 mL, 7.8 mmol, 1.0 equiv) and N-methyl-morpholine (2.6 mL, 23.4 mmol, 3.0 equiv). The solution is stirred at room temperature for 3 hours. The solution is then added EtOAc and sat. aq. $NaHCO_3$. The phases are separated and the organic phase is washed with 1.0 N aq. HCl, and brine. The solution is dried over $Na_2SO_4$ and concentrated. The residue is purified by silica gel column chromatography, heptane/EtOAc, 1/1 to give product **22a** 1.2 g.

**Step 22-B:**

The product **22a** is dissolved in 4.0 N HCl in dioxane and the solution is stirred at room temperature for 1 hour. The solution is then concentrated to dryness to give product **22b**.

To a solution of 4-nitrophenyl chloroformate (201 mg, 1.1 mol, 1.0 equiv) in $CH_2Cl_2$ at room temperature added **22b** (263 mg, 1.0 mmol, 1.0 equiv) and pyridine (0.242 mL, 3.0 mmol, 3.0 equiv). After stirred at room temperature for 1h, the solution is directly loaded to silica gel column and the column is flushed with heptane/EtOAc (1/1 to 100% EtOAc) to give product **22c** 315 mg. Found ES+ = 392.

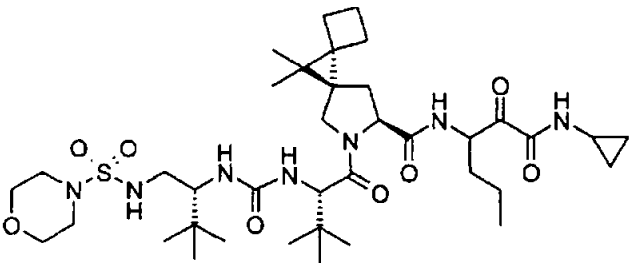
**Step 22-C:**

To a solution of **22c** (49 mg 0.127 mmol, 1.0 equiv) in $CH_2Cl_2$ (0.5 mL) added **19c** (67 mg, 0.127 mmol, 1.0 equiv) and TEA (0.042 mL, 0.3 mmol, 3.0 equiv). The solution is stirred at room temperature for 2 hours. The solution is then loaded to silica gel column and the column is flushed with heptane/acetone (1/1) to give product **22d** 80 mg. Found m/z, ES+ = 743

**Step 22-D:**

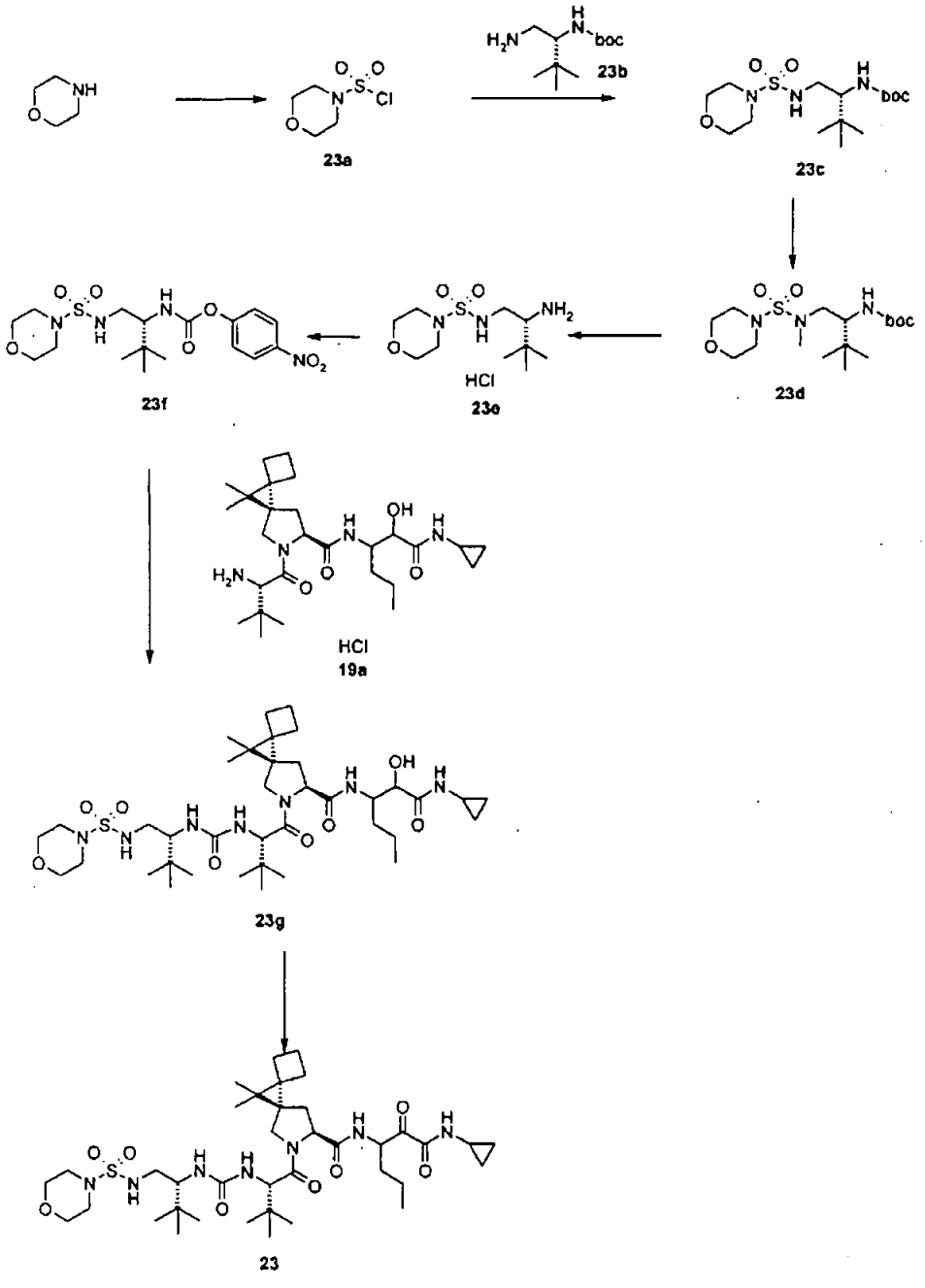
To a solution of **22d** (80 mg, 0.107 mmol) in $CH_2Cl_2$ (1.0 mL) add DIPEA (0.093 mL, 0.535 mmol, 5.0 equiv) and a solution of $Py{\bullet}SO_3$ (51 mg, 0.323 mmol, 3.0 equiv) in DMSO (0.5 mL). The solution is stirred at room temperature for 10 minutes. The solution is loaded to silica gel column and the column is flushed with heptane/acetone (1/1) to give product **22** 75 mg. Found m/z, ES+ = 741.

**Example 23:**



**23**

**Scheme:**




**Step 23-A:**

To a solution of sulfuryl chloride (1.62 mL, 20.0 mmol, 1.0 equiv) in $CHCl_3$ (20.0 mL) at 0 °C slowly added a solution of morpholine (1.7 mL, 20.0 mmol, 1.0 equiv) and TEA (2.78 mL) in $CHCl_3$ (5.0 mL) over 1 hour. The solution is stirred at 0 °C for 1 hour then room temperature for 1 hour. The solution is concentrated and then partitioned between ether

and 1.0 N aq. HCl solution. The phases are separated and the organic layer is washed with brine. The organic layer is dried over $Na_2SO_4$ and concentrated to give product **23a** (2.5 g).

**Step 23-B:**

To a solution of **23a** (559 mg, 3.0 mmol, 1.0 equiv) in $CH_2Cl_2$ (10.0 mL) at -20 °C added **23b** (648 mg, 3.0 mmol, 1.0 equiv) and TEA (0.836 mL, 6.0 mmol, 2.0 equiv). The solution is stirred at room temperature for 24 hours and at 40 °C for 4 hours. The solution is loaded to silica gel column and the column is flushed with heptane/EtOAc (1/1) to give product **23c** (760 mg).

**Step 23-C:**

To a solution of **23c** (760 mg, 2.07 mmol, 1.0 equiv) in DMF (6.0 mL) at 0 °C add $Cs_2CO_3$ (2.0 g, 6.2 mmol, 3.0 equiv) and MeI (0.154 mL, 2.48 mmol, 1.2 equiv). The solution is stirred at room temperature for 1.0 hours. The solution is filtered and the solvent is evaporated. The residue is purified by silica gel column chromatography, heptane/EtOAc (1/2) to give product **23d** (510 mg).

**Step 23-D:**

The product **23d** is dissolved in 4.0 N HCl in dioxane and stirred at room temperature for 1 hour. The solution is then concentrated to dryness to give product **23e**.

To a solution of 4-nitrophenyl chloroformate (179 mg, 0.89 mol, 1.0 equiv) in $CH_2Cl_2$ (4.0 mL) at room temperature added **23e** (270 mg, 0.89 mmol, 1.0 equiv) and pyridine (0.144 mL, 2.0 mmol, 2.0 equiv). The solution is stirred at room temperature for 1 hour. The solution is loaded to silica gel column and the column is flushed with heptane/EtOAc (1/1 to 100% EtOAc) to give product **23f** (210 mg).

**Step 23-E:**

To a solution of **23f** (63 mg, 0.14 mmol, 1.0 equiv) in $CH_2Cl_2$ (1.0 mL) added **19c** (75 mg, 0.14 mmol, 1.0 equiv) and TEA (0.031 mL, 0.42 mmol, 3.0 equiv). The solution is stirred at room temperature for 2 hours. The solution is then loaded to silica gel column and the column is flushed with heptane/acetone (1/1 to 100% acetone) to give product **23g** 101 mg. Found m/z, ES+ = 796.

**Step 23-F:**

To a solution of **23g** (101 mg) in $CH_2Cl_2$ (1.0 mL) add DIPEA (0.120 mL) and a solution of $Py{\bullet}SO_3$ (70 mg) in DMSO (0.5 mL). The solution is stirred at room temperature for 10 minutes. The solution is loaded to silica gel column and the column is flushed with heptane/acetone (1/1) to give product **22** 71 mg. Found m/z, ES+ = 794.

## BIOLOGICAL ACTIVITY

**Example 24: HCV NS3-4A protease assay**

The inhibitory activity of certain compounds of Table A against HCV NS3-4A serine protease is determined in a homogenous assay using the full-length NS3-4A protein (genotype 1a, strain HCV-1) and a commercially available internally-quenched fluorogenic peptide substrate as described by Taliani, M., et al. 1996 Anal. Biochem. 240:60-67, which is incorporated by reference in its entirety.

**Example 25: Luciferase-based HCV replicon assay**

The antiviral activity and cytotoxicity of certain compounds of Table A is determined using a subgenomic genotype 1b HCV replicon cell line (Huh-Luc/neo-ET) containing a luciferase reporter gene, the expression of which is under the control of HCV RNA replication and translation. Briefly, 5,000 replicon cells are seeded in each well of 96-well tissue culture plates and are allowed to attach in complete culture media without G418 overnight. On the next day, the culture media are replaced with media containing a serially diluted compound of Table A in the presence of 10% FBS and 0.5% DMSO. After a 48-h treatment with the compound of Table A, the remaining luciferase activities in the cells are determined using BriteLite reagent (Perkin Elmer, Wellesley, Massachusetts) with a LMaxII plate reader (Molecular Probe, Invitrogen). Each data point represents the average of four replicates in cell culture. $IC_{50}$ is the concentration of the at which the luciferase activity in the replicon cells is reduced by 50%. The cytotoxicity of the compound of Table A is evaluated using an MTS-based cell viability assay.

Compounds in Table A *supra* have been tested in at least one of the protease assay of Example 24 or the replicon assay of Example 25 and exhibit an $IC_{50}$ of less than about 10 μM or less in at least one of the assays recited in Example 24 and 25.

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments and methods described herein. Such equivalents are intended to be encompassed by the scope of the following claims.

***Incorporation by Reference***

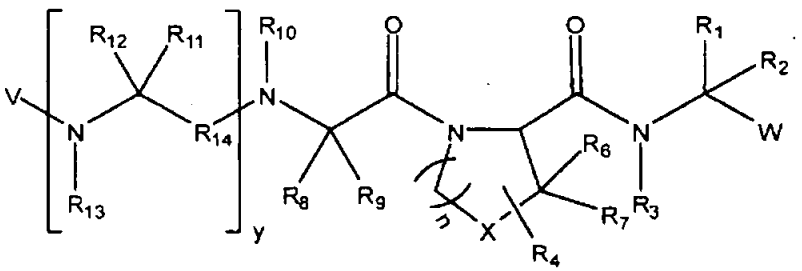
The entire contents of all patents, published patent applications and other references cited herein are hereby expressly incorporated herein in their entireties by reference. The

entire contents of copending provisional patent applications U.S.S.N. 60/791,611, U.S.S.N. 60/791,578, and U.S.S.N. 60/791,320, each of which was filed on April 11, 2006, and non-provisional patent applications claiming the benefit therefrom are expressly incorporated herein, in their entirety, as applied to the compounds of the present invention.

## CLAIMS

What is claimed is:

1. A compound of the Formula I:



I

and pharmaceutically acceptable salts and stereoisomers thereof;

wherein

y is 0 or 1;

n and p are each independently selected from 0, 1 or 2;

$R^{14}$ is C(O) or $SO_2$;

$R^1$, $R^2$, W, $R^{13}$ and V are each, independently, selected from hydrogen or from the group consisting of alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, carboxyalkylamino, mono- and di-alkylcarboxamide, aralkyloxy and heterocyclylamino; each of which may be further independently substituted one or more times with $X^1$ and $X^2$; wherein $X^1$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, aryloxy, arylthio, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaralkyl; wherein $X^1$ can be independently substituted with one or more $X^2$ moieties which can be the same or different and are independently selected; wherein $X^2$ is hydroxy, oxo, alkyl, cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, thio, alkylthio, amino, mono- and di-alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyl, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each $X_2$ residue selected to be alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are

independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl and heteroaralkyl;

W is also selected from the group consisting of C(O)-C(O)H, C(=N-O-$R_{24}$)-C(O)-amine, C(O)-C(O)-amine, C(O)$NR_{24}S(O)_pR_{24}$, C(O)$NR_{24}S(O)_pN(R_{24})_2$ and C(O)-$[C(O)]_a$-heterocycle, wherein the heterocycle may be independently substituted one or more times with aryl, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, and $C_{3-6}$-cycloalkyl, wherein a is 0 or 1, wherein each $R_{24}$ is independently selected from hydrogen or the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, each of which may be independently substituted one or more times with a halogen atom or $C_{1-4}$-alkyl;

V is also selected from the group consisting of $-Q^1$-$Q^2$, wherein $Q^1$ is absent, C(O), N(H), N($C_{1-4}$-alkyl), C=N(CN), C=N($SO_2CH_3$), C=N-COH-$C_{1-4}$-alkyl, or C=N-COH, and $Q^2$ is hydrogen or is selected from the group consisting of $C_{1-4}$-alkyl, O-$C_{1-4}$-alkyl, $NH_2$, N(H)-$C_{1-4}$-alkyl, N($C_{1-4}$-alkyl)$_2$, $SO_2$-aryl, $SO_2$-$C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl-$C_{0-4}$-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, or $C_{3-6}$-cycloalkyl;

or $R^1$ and $R^2$ may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

$R^3$ is selected from the group consisting of hydrogen, $C_{1-4}$-alkyl and $C_{3-6}$cycloalkyl$C_{0-4}$alkyl;

X is O, S, N, $NR^5$, $CR^5$ or $CR^5R^{5a}$;

$R^4$ represents 0-4 substituents, each of which is independently selected from hydrogen or from the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times with a halogen atom or $C_{1-4}$-alkyl;

$R^5$ is selected from hydrogen or oxo or from the group consisting of hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heterocycle-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl , $C_{3-8}$-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

$R^{5a}$ is hydrogen or is selected from the group consisting of hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-

alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl and heteroaryl-$C_{0-4}$-alkyl,

or $R^4$ and $R^5$ may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

or $R^5$ and $R^6$ may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

or $R^5$ and $R^{5a}$ may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide, or two of said 0-4 substitutents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide;

$R^6$ and $R^7$ are each, independently, selected from the group consisting of hydrogen, hydroxy, amino, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, and mono- and di-$C_{1-4}$alkylamino, and $C_{3-6}$cycloalkyl$C_{0-4}$alkyl;

$R^8$, $R^9$, $R^{10}$, $R^{11}$ and $R^{12}$ are each, independently, selected from the group consisting of hydrogen, $C_{1-4}$-alkyl and $C_{3-6}$cycloalkyl$C_{0-4}$alkyl;

or $R^6$ and $R^7$ may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-

$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, mono- and di-$C_{1-4}$-alkylamino, mono- and di-$C_{1-4}$-alkyl-carboxamide, $C_{1-4}$-alkoxycarbonyl, and phenyl;

or $R^3$ and W may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; and

or when y is 0, $R^{10}$ and V may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times.

2. The compound of claim 1,

wherein

y is 0 or 1;

n is 0 or 1;

$R^{14}$ is C(O) or $SO_2$

$R^1$ is selected from the group consisting of H and $C_{1-4}$-alkyl;

$R^2$ is selected from the group consisting of $C_{1-4}$-alkyl, $C(O)C_{1-4}$-alkyl, $C(O)OC_{1-4}$-alkyl, and $C_{3-6}$cycloalkyl$C_{0-4}$alkyl;

or $R^1$ and $R^2$ together form a cyclopropane ring;

W is also selected from the group consisting of C(O)-C(O)H, C(=N-O-$R_{24}$)-C(O)-amine, C(O)-C(O)-amine, C(O)$NR_{24}S(O)_pR_{24}$, C(O)$NR_{24}S(O)_pN(R_{24})_2$ and C(O)-$[C(O)]_a$-heterocycle, wherein the heterocycle may be independently substituted one or more times with aryl, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, and $C_{3-6}$-cycloalkyl, wherein a is 0 or 1, wherein each $R_{24}$ is independently selected from hydrogen or from the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$cycloalkyl$C_{0-4}$alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle, each of which may be independently substituted one or more times with a halogen atom or $C_{1-4}$-alkyl;

p is 0, 1 or 2;

$R^3$ is selected from the group consisting of H and $C_{1-4}$-alkyl;

X is O, $NR^5$ or $CR^5R^{5a}$;

$R^4$ is selected from hydrogen or from the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-

cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times with a halogen atom or $C_{1-4}$-alkyl;

$R^5$ is selected from hydrogen or oxo or from the group consisting of hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heterocycle-$C_{0-4}$-alkyl and heteroaryl-$C_{0-4}$-alkyl, each of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

$R^{5a}$ is selected from hydrogen or from the group consisting of hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl and heteroaryl-$C_{0-4}$-alkyl,

or $R^4$ and $R^5$ may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

or $R^5$ and $R^{5a}$ may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, mono- and di-$C_{1-4}$-alkylamino, mono- and di-$C_{1-4}$-alkyl-carboxamide, $C_{1-4}$-alkoxycarbonyl, and phenyl;

$R^8$, $R^{10}$ and $R^{11}$ are each, independently, selected from the group consisting of H and $C_{1-4}$-alkyl;

$R^6$ and $R^7$ are each, independently, selected from the group consisting of hydrogen, hydroxy, amino, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, and mono- and di-$C_{1-4}$alkylamino;

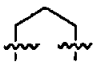
$R^{13}$ is H;

$R^9$ and $R^{12}$ are each, independently, selected from the group consisting of hydrogen, $C_{1-4}$-alkyl and $C_{3-6}$-cycloalkyl; and

V is also selected from the group consisting of $-Q^1$-$Q^2$, wherein $Q^1$ is absent, C(O), N(H), N($C_{1-4}$-alkyl), C=N(CN), C=N($SO_2CH_3$), C=N-COH-$C_{1-4}$-alkyl, or C=N-COH, and $Q^2$ is hydrogen or is selected from the group consisting of $C_{1-4}$-alkyl, O-$C_{1-4}$-alkyl, $NH_2$, N(H)-$C_{1-4}$-alkyl, N($C_{1-4}$-alkyl)$_2$, $SO_2$-aryl, $SO_2$-$C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl-$C_{0-4}$-alkyl, aryl,

heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, or $C_{3-6}$-cycloalkyl;

or $R^3$ and W can together form a 6-membered ring of the formula II:



II

wherein formula II may be further substituted;

or when y is 0, $R^{10}$ and V can form a cyclopropyl ring that may be further substituted by an amide group.

3. The compound of claim 1, wherein $R^{14}$ is C(O).

4. The compound of claim 1, wherein y is 0, and $R^{10}$ and V form a cyclopropyl ring that is substituted with C(O)N(H)-pyrazine.

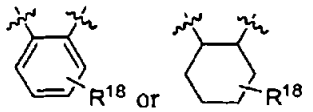
5. The compound of claim 1, wherein $R^4$, $R^6$ and $R^7$ are hydrogen, and $R^5$ is aryl$C_{0-3}$alkyl, heteroaryloxy, or heteroaryl$C_{0-3}$alkyl, wherein aryl and heteroaryl may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, $C_{3-6}$-cycloalkyl or $C_{1-4}$-alkyl.

6. The compound of claim 1, wherein $R^1$ and $R^2$, are independently selected from hydrogen or from the group consisting of $C_{1-4}$alkyl, $C_{2-4}$alkenyl, $C_{2-4}$alkynyl, $C_{3-6}$cycloalkyl$C_{0-4}$alkyl, $C_{3-6}$cycloalkenyl$C_{0-4}$alkyl, $C_{1-4}$alkoxy$C_{0-4}$alkyl, and heterocycloalkyl$C_{0-4}$alkyl, each of which is unsubstituted or substituted with one or more groups selected from fluoro, chloro, hydroxy, $C_{1-2}$alkylS, $C_{1-2}$alkylS(O), and $C_{1-2}$alkylS$(O)_2$, and wherein the heterocycloalkyl is a 3 to 6 membered ring having one or two N, O or S ring atoms.

7. The compound of claim 1, wherein $R_1$ is hydrogen and $R_2$ is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl, allyl, propargyl, 3-fluoro-n-propyl, n-butyl, n-pentyl, iso-propyl, sec-butyl, iso-butyl, 3-methyl-n-butyl, 3,3,3-trifluoro-n-propyl, 2,2-difluoroethyl, trifluoromethyl, 1,1-difluoro-n-propyl, 2,2,2-trifluoroethyl, 2,2-difluoro-n-but-3-enyl, 4-pentenyl, 3,3-difluoro-allyl, 2-methyl-allyl, 3-butenyl, 2-cyanoethyl, 3,3-difluoropropyl, 2,2-difluoro-3-butenyl, 2,2-difluoro-n-propyl, 4,4,4-trifluorobutyl, $C_{3-6}$cycloalkyl, oxetan-2-ylmethyl, thietan-2-ylmethyl, 3-fluorocyclobutylmethyl, 3-

hydroxycyclobutylmethyl, 3-butynyl, methoxymethyl, 2-methoxyethyl, methyl-$S(O)_{0-2}C_{1-2}$alkyl, 3,3-difluorocyclobutylmethyl, oxetan-3-ylmethyl, $C_{3-6}$cycloalkylmethyl, 1-methylcyclopropylmethyl, $C_{3-6}$cycloalkyl-difluoromethyl, $C_{3-6}$cycloalkylethyl, thietan-3-ylmethyl, 1-fluorocyclobutylmethyl, 1-fluorocyclopropylmethyl, 2,2-difluorocyclopropylmethyl, and cyclopenten-2-ylmethyl.

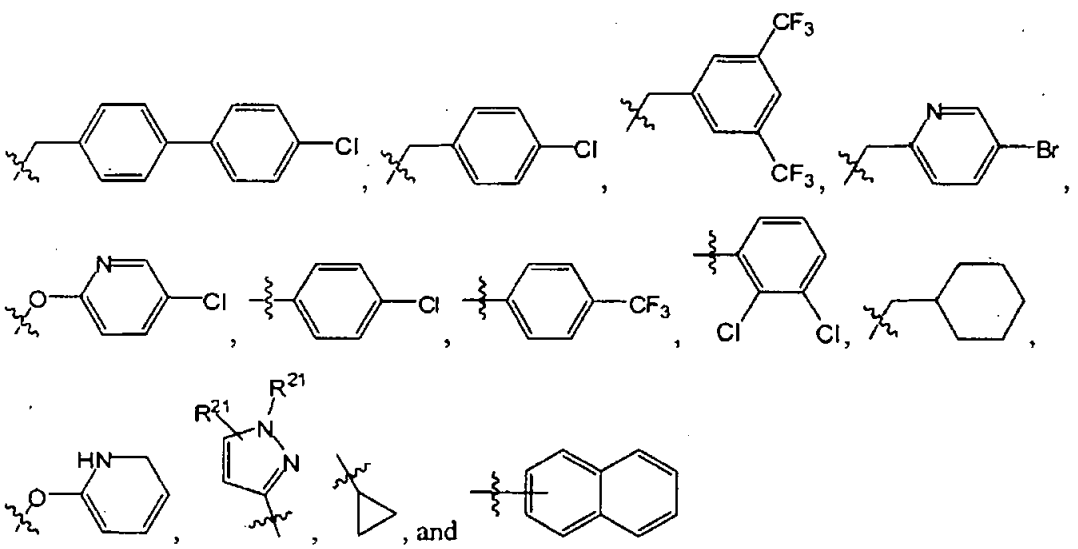
8. The compound of claim 1, wherein n is 1, and $R^4$ and $R^5$ together form a fused ring system selected from:




wherein $R^{18}$ is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and $C_{1-4}$-alkyl.

9. The compound of claim 1, wherein X is $CR^5R^{5a}$, $R^{5a}$ is hydrogen, and $R^5$ is selected from the group consisting of piperidine, phenyl, pyridinyl, pyridinyloxy and pyridinylmethyl, wherein the phenyl and pyridinyl groups may be independently substituted one or more times with a halogen atom or $C_{1-4}$-alkyl.

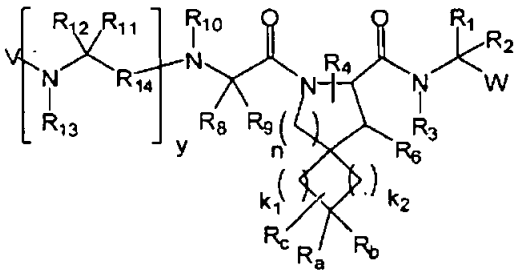
10. The compound of claim 9, wherein X is $CR^5R^{5a}$, $R^{5a}$ is hydrogen, and $R^5$ is selected from the group consisting of




wherein $R^{21}$ is independently selected from the group consisting of $C_{1-4}$-alkyl and aryl.

11. The compound of claim 1, wherein X is $CR^5R^{5a}$, $R^4$ is hydrogen, and $R^5$ and $R^{5a}$ taken in combination form a 3 to 6 member spirocyclic carbocycle substituted with 0-2 substituents selected from halogen, $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl, $C_{2-6}$-alkynyl, $C_{1-6}$-alkoxy, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, phenyl-$C_{0-4}$-alkyl, naphthyl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, or two substituents taken together form a fused or spirocyclic 3 to 7 membered carbocyclic ring, each of which is substituted with 0-3 independently selected halogen atoms or $C_{1-4}$-alkyl groups.

12. A compound of claim 1 according to the formula:



wherein

$k_1$ and $k_2$ are 0 or 1 such that a sum of $k_1$ and $k_2$ equals 1 or 2;

$R_a$ is hydrogen, $C_{1-4}$alkyl, or phenyl;

$R_b$ is hydrogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy-$C_{0-4}$alkyl, mono- and di-$C_{1-4}$alkylamino$C_{0-4}$alkyl, mono- and di-$C_{1-4}$alkyl carboxamide, $C_{1-4}$alkanoyl, $C_{1-4}$alkoxycarbonyl, or phenyl;

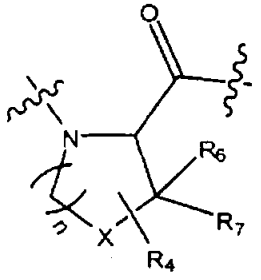
or $R_a$ and $R_b$, taken together, form a spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, and phenyl;

$R_c$ represents 0 to 4 substituents which are independently selected at each occurrence of $R_c$ from the group consisting of halogen, $C_{1-4}$alkyl, and phenyl, or two *geminal* $R_c$ substituents, taken in combination form a 3 to 6 member spirocyclic ring;

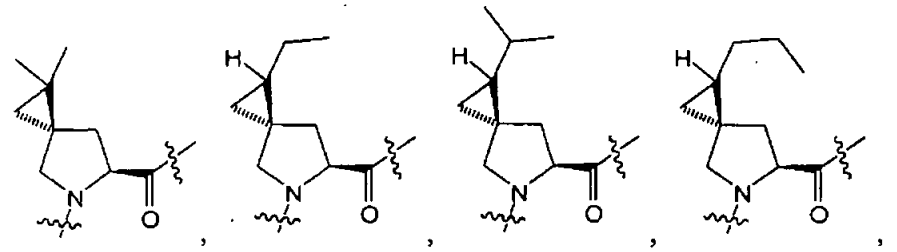
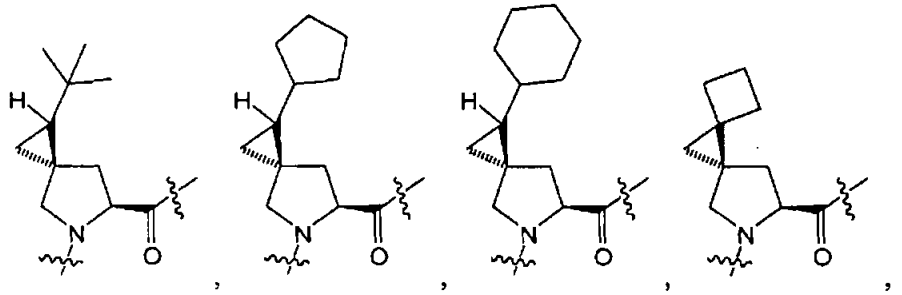
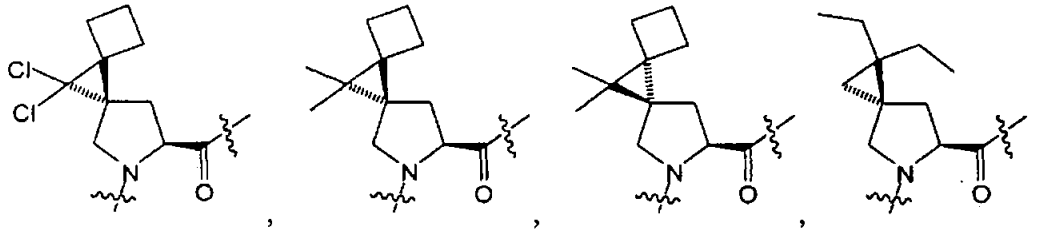
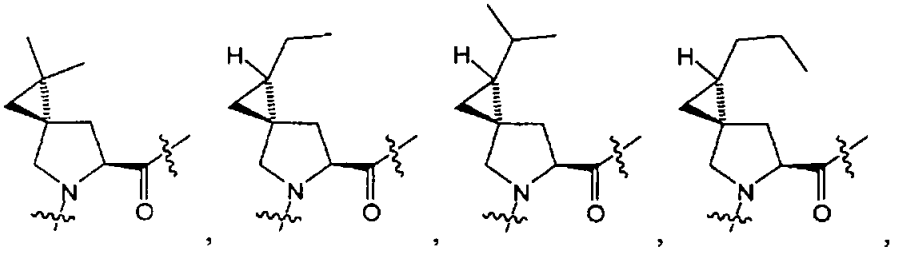
$R_4$ represents 0, 1, or 2 substituents each of which is independently selected from H and $C_{1-4}$-alkyl; and

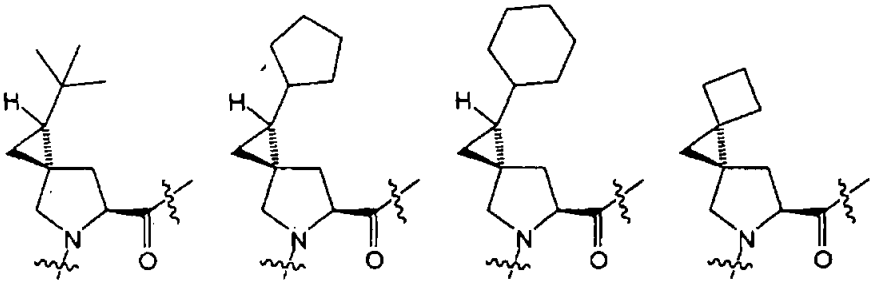
$R_6$ is hydrogen or $C_{1-4}$alkyl.

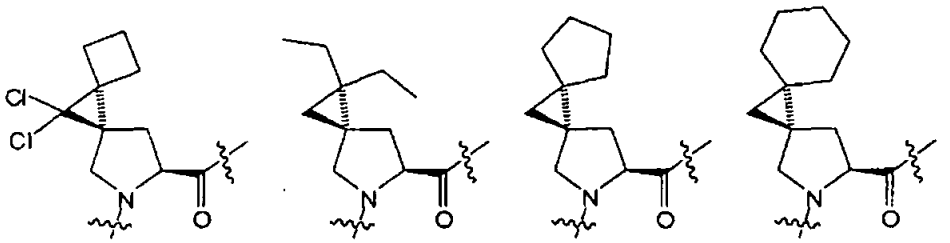
13. The compound of claim 1, wherein the divalent residue:

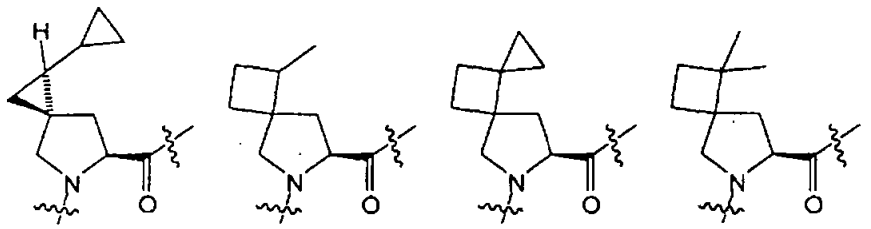


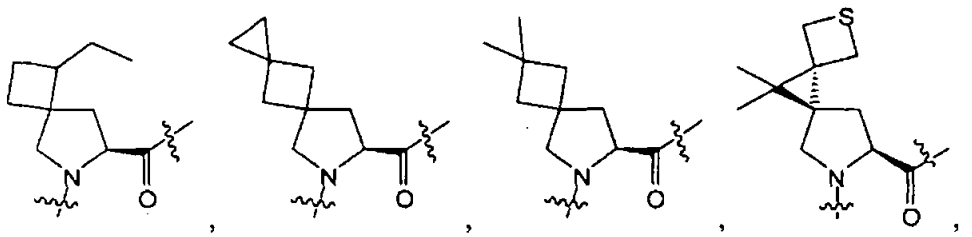
is selected from the group consisting of:

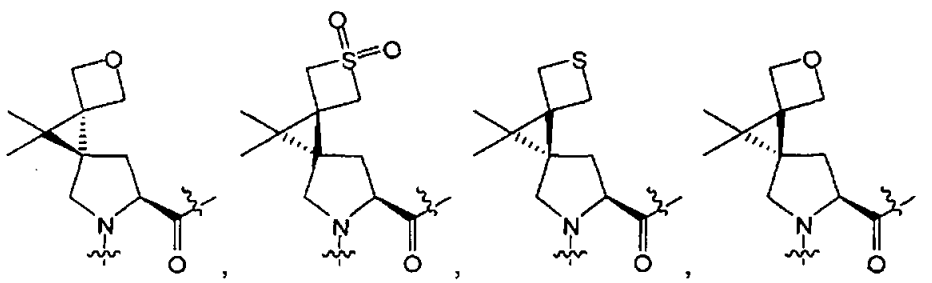





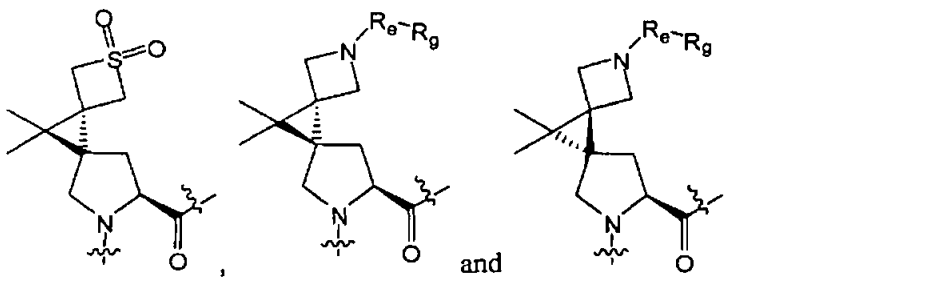

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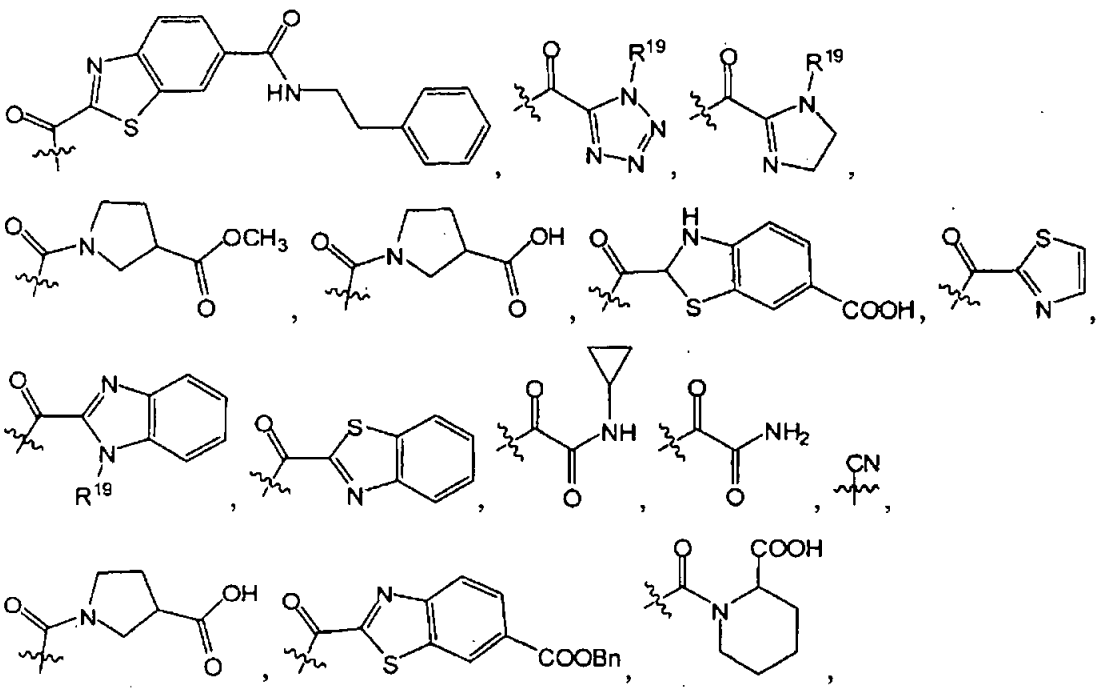

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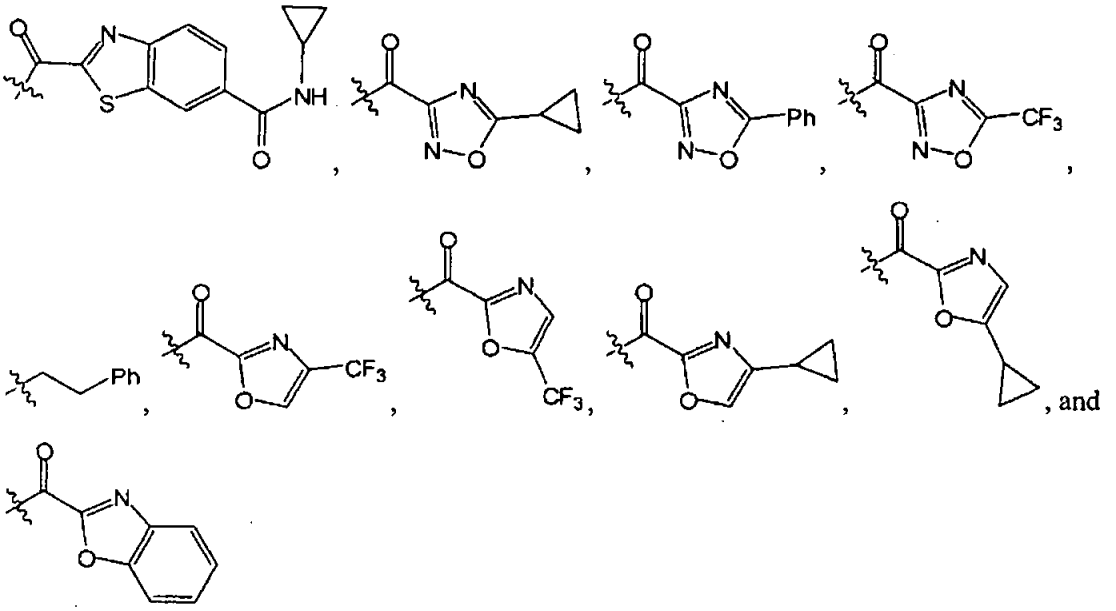

and

wherein $R_e$ is absent, C(O), or $S(O)_2$; and $R_g$ is selected hydrogen or selected from the group consisting of $C_{1-6}$alkyl, aryl$C_{0-4}$alkyl, heteroaryl$C_{0-4}$alkyl, heterocyclyl$C_{0-4}$alkyl, and $C_{3-7}$cycloalkyl$C_{0-4}$alkyl, each of which is substituted with 0 to 4 independently selected substituents selected from the group consisting of cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide.

14. The compound of claim 1, wherein W is selected from the group consisting of $C(O)$-$C(O)NH_2$, C(O)-C(O)N(H)-cyclopropyl, C(O)-benzothiazole, C(O)-benzoimidazole, C(O)-oxazole, C(O)-imidazole, and C(O)-oxadiazole, wherein the benzothiazole, benzoimidazole, oxazole and oxadiazole groups may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, $C_{3-6}$-cycloalkyl or $C_{1-4}$-alkyl.

15. The compound of claim 14, wherein W is selected from the group consisting of

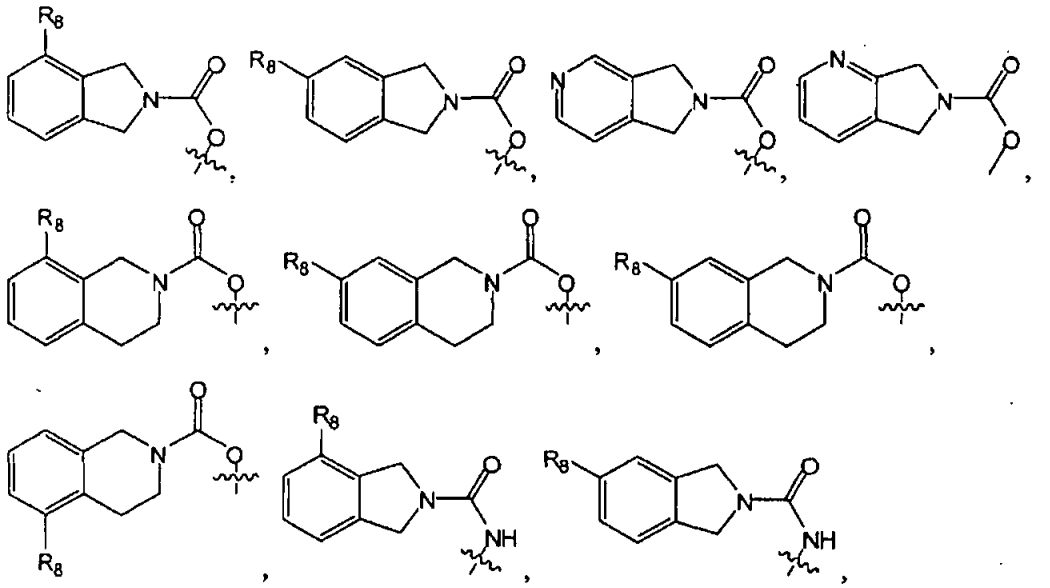


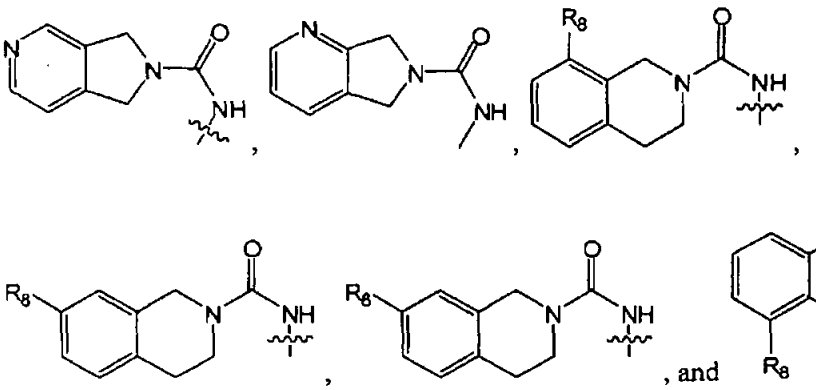


wherein $R^{19}$ is selected from the group consisting of hydrogen, aryl, trihalomethyl, and $C_{1-4}$-alkyl.

16. The compound of claim 1, wherein $R^2$ is selected from the group consisting of propyl and $(CH_2)_2$-cyclobutyl.

17. The compound of claim 1, wherein X is $CR_5R_{5a}$, $R_{5a}$ is hydrogen or methyl, and $R_5$ is a residue selected from the group consisting of:





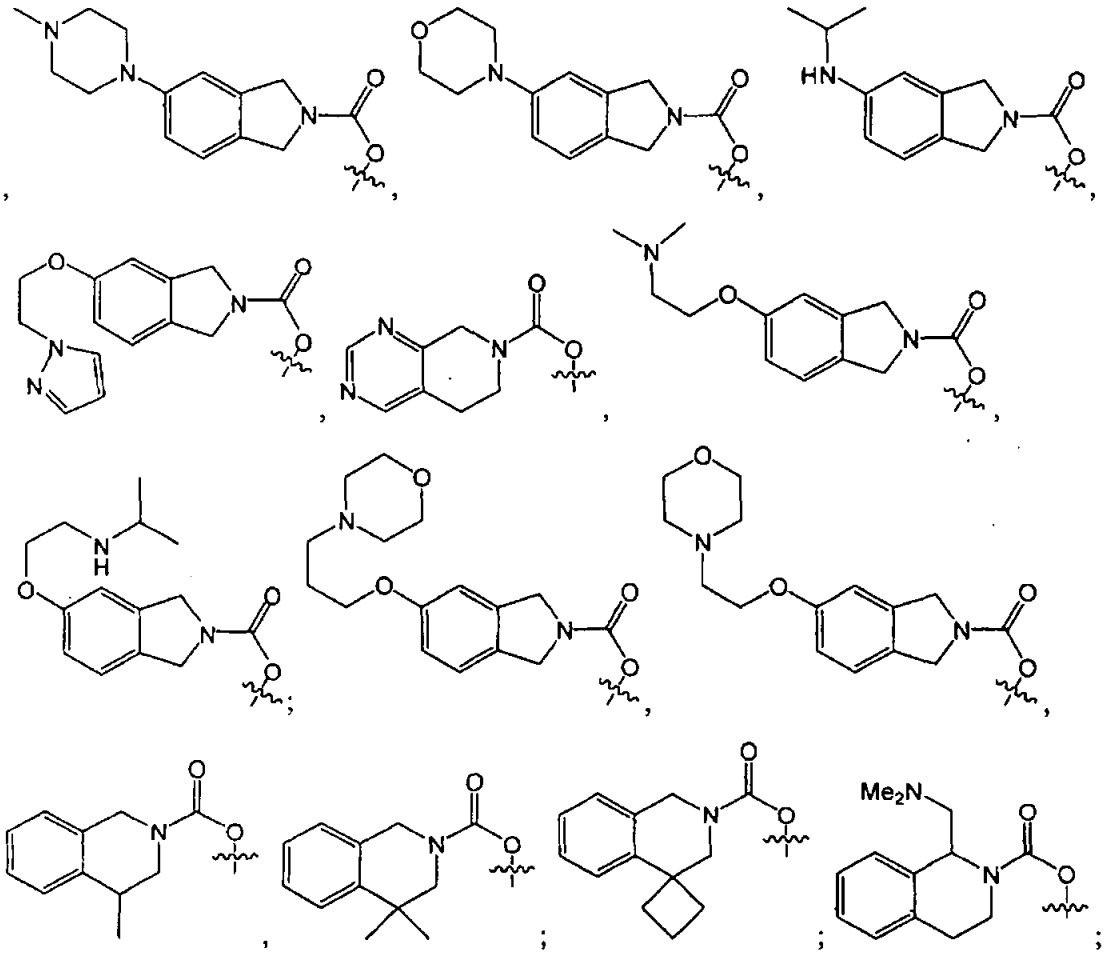
wherein $R_8$ is selected from hydrogen, methyl, ethyl, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-fluoromethoxy, fluoro, and chloro.

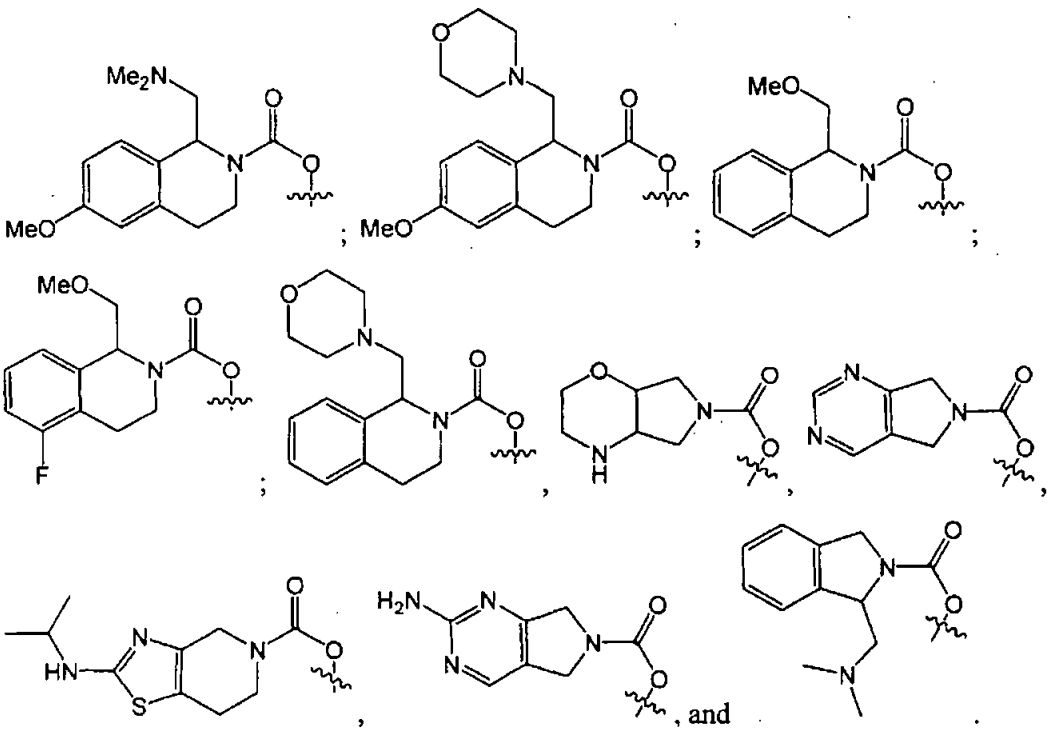
18. The compound of claim 1, wherein X is $CR_5R_{5a}$;

$R_{5a}$ is hydrogen or methyl;

$R_6$ is hydrogen, methyl, ethyl, and mono-, di-, and tri-fluoromethyl;

$R_5$ is a residue selected from the group consisting of:

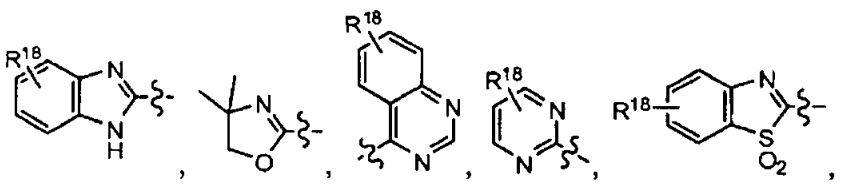


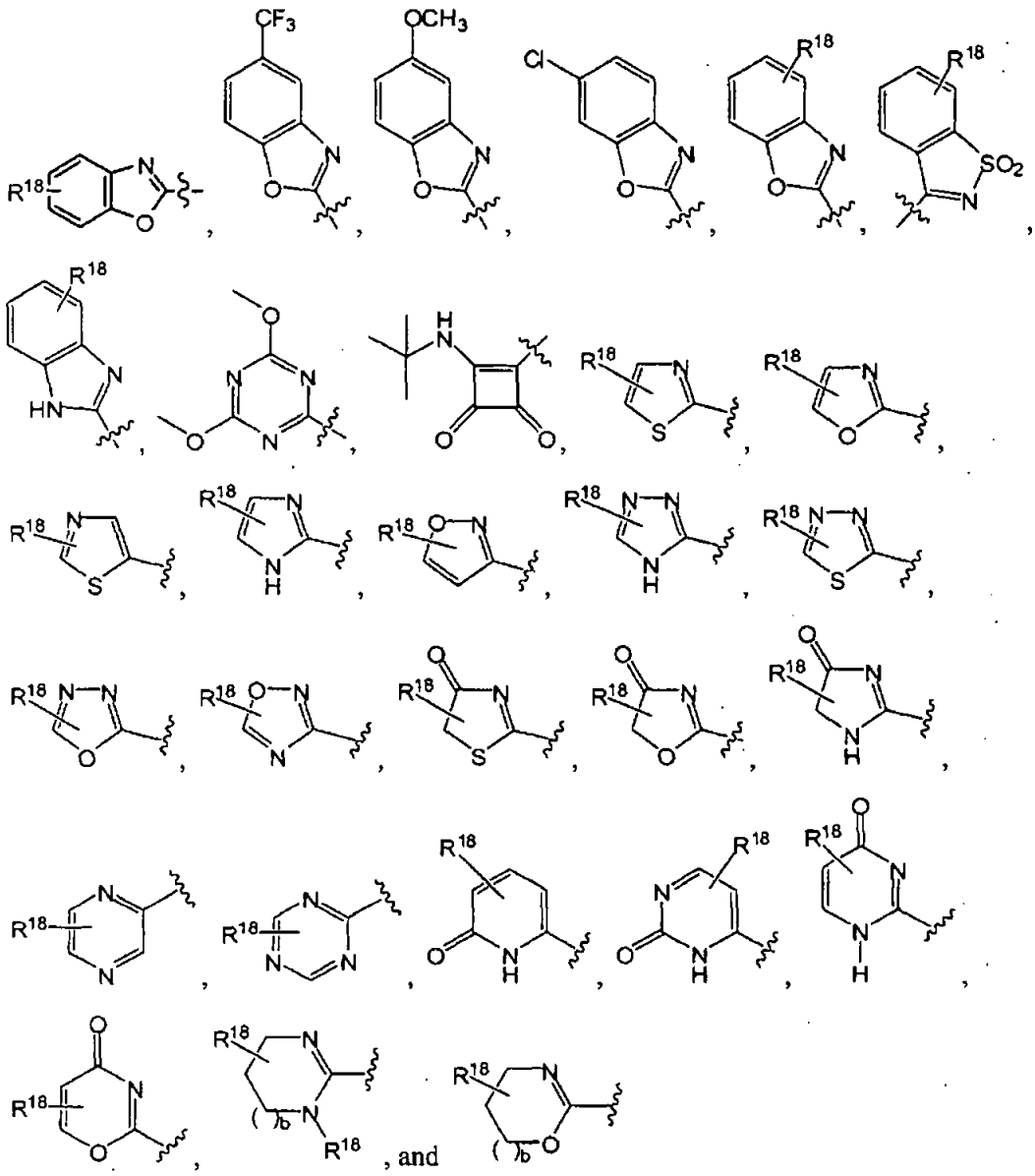


19. The compound of claim 1, wherein $R^{11}$ is H and $R^{12}$ is $C_{3-6}$-cycloalkyl.

20. The compound of claim 1, wherein V is $R^{20}$ or C(O)-$R^{20}$, wherein $R^{20}$ is selected from the group consisting of $C_{3-6}$-cycloalkyl, mono- and di-$C_{1-4}$alkylamino, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, $CF_3$, $C_{1-4}$-alkyl or $C_{3-6}$-cycloalkyl.

21. The compound of claim 1, wherein V is selected from $R^{20}$ or C(O)$R^{20}$, wherein $R^{20}$ is selected from the group consisting of





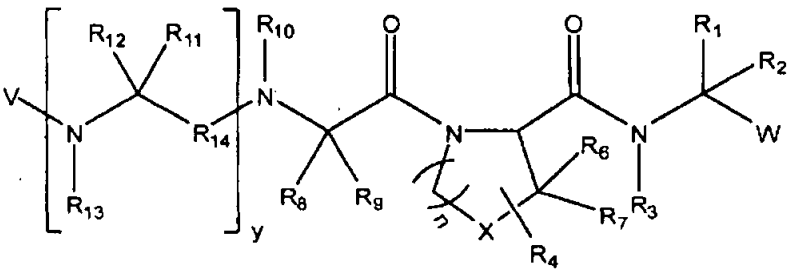
wherein b is 0, 1, or 2; and $R_{18}$ is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and $C_{1-4}$-alkyl.

22. The compound of claim 1, wherein X is $CR^5R^{5a}$, $R^4$ and $R^{5a}$ are hydrogen, and $R^5$ is aryl-$C_{0-3}$-alkyl, -O-heterocycle, or heterocycle-$C_{0-3}$-alkyl, wherein aryl and heterocycle may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, $C_{3-6}$-cycloalkyl or $C_{1-4}$-alkyl.

23. The compound of claim 1, wherein W is selected from the group consisting of $C(O)$-$C(O)N(R^{23})_2$, wherein $R^{23}$ is independently selected from hydrogen or from the group

consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl, aryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom or $C_{1-4}$-alkyl.

24. A compound of the formula III:



III

and pharmaceutically acceptable salts and stereoisomers thereof;

wherein

y is 0 or 1;

n is 0, 1 or 2;

$R^{14}$ is C(O) or $SO_2$;

$R^1$, $R^2$, W, $R^{13}$ and V are each, independently, selected from hydrogen or from the group consisting of alkyl, alkyl-aryl, heteroalkyl, heterocyclyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocyclyloxy, cycloalkyloxy, amino, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, mono and dialkylcarboxamide, carboxyalkylamino, arlylalkyloxy and heterocyclylamino; each of which may be further independently substituted one or more times with $X^1$ and $X^2$; wherein $X^1$ is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, aryloxy, arylthio, arylheteroaryl, heteroaryl, heterocyclylamino, alkylheteroaryl, or heteroaralkyl; wherein $X^1$ can be independently substituted with one or more $X^2$ moieties which can be the same or different and are independently selected; wherein $X^2$ is hydroxy, oxo, alkyl, cycloalkyl, spirocycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkoxy, aryloxy, thio, alkylthio, amino, mono- and di-alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyl, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro; wherein each $X_2$ residue selected to be alkyl, alkoxy, and aryl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different and are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, aralkyl, arylheteroaryl, heteroaryl,

heterocyclylamino, alkylheteroaryl and heteroaralkyl;

W is also selected from the group consisting of C(O)OH, $C(O)OR_{24}$, C(O)-amine, $P(O)(OR_{24})_2$, C(O)-C(O)OH, $C(=N\text{-}O\text{-}R_{24})$-C(O)-amine, $C(O)NHS(O)_2R_{24}$, $C(O)NHS(O)_pN(R_{24})_2$, $C(O)NR_{24}S(O)_pN(R_{24})_2C(O)$-C(O)-amine, $CON(H)SO_2$-amine and $C(O)\text{-}[C(O)]_a$-heterocycle, wherein the heterocycle may be substituted or unsubstituted, wherein a is 0 or 1, wherein each $R_{24}$ is independently selected from the group consisting of hydrogen, halogen, hydroxyl, formyl, carboxylate, amide, amino, substituted or unsubstituted-$C_{1-4}$-alkyl, substituted or unsubstituted-$C_{1-4}$-alkoxy, substituted or unsubstituted-$C_{1-4}$-alkanoyl, substituted or unsubstituted-$C_{1-4}$-alkoxycarbonyl, substituted or unsubstituted-$C_{1-4}$-alkanoyloxy, substituted or unsubstituted mono- and di-$C_{1-4}$-alkylamino, substituted or unsubstituted-$C_{3-6}$cycloalkyl-$C_{0-4}$alkyl, substituted or unsubstituted aryl-$C_{0-4}$alkyl, and substituted or unsubstituted heterocycle-$C_{0-4}$alkyl;

V is also selected from the group consisting of $-Q^1\text{-}Q^2$, wherein $Q^1$ is absent, C(O), N(H), $N(C_{1-4}$-alkyl), C=N(CN), $C=N(SO_2CH_3)$, or C=N-COH, and $Q^2$ is hydrogen or is selected from the group consisting of $C_{1-4}$-alkyl, O-$C_{1-4}$-alkyl, $NH_2$, N(H)-$C_{1-4}$-alkyl, $N(C_{1-4}$-alkyl$)_2$, $SO_2$-aryl, $SO_2$-$C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl-$C_{0-4}$-alkyl, aryl, heteroaryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom, $C_{1-4}$-alkyl, $C_{1-4}$-alkyl substituted by one or more halogen atoms, or $C_{3-6}$-cycloalkyl;

or $R^1$ and $R^2$ may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times;

$R^3$ is selected from the group consisting of hydrogen, $C_{1-4}$-alkyl and $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl;

X is $CR^5R^{5a}$;

$R^4$ represents 0-4 substituents, each of which is independently selected from hydrogen or from the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl, aryl, heterocycle and heteroaryl, each of which may be independently substituted one or more times with a halogen atom or $C_{1-4}$-alkyl;

$R^5$ is selected from hydrogen or oxo or from the group consisting of hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heterocycle-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl , $C_{3-8}$-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

$R^{5a}$ is selected from the group consisting of hydrogen, hydroxyl, $C_{1-8}$-alkyl, $C_{2-8}$-

alkenyl, $C_{2-8}$-alkynyl, $C_{3-8}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl and heteroaryl-$C_{0-4}$-alkyl, or $R^4$ and $R^5$ may together form a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or $C_{1-4}$-alkyl;

or $R^5$ and $R^{5a}$ may together form a spirocyclic ring having between 3 and 7 ring atoms or $R^5$ and $R^{5a}$ may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide, or two of said 0-4 substitutents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide;

$R^6$ and $R^7$ are each, independently, selected from the group consisting of hydroxy, amino, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, and mono- and di-$C_{1-4}$alkylamino, and $C_{3-6}$cycloalkyl$C_{0-4}$alkyl;

$R^8$, $R^9$, $R^{10}$, $R^{11}$ and $R^{12}$ are each, independently, selected from the group consisting of hydrogen, $C_{1-4}$-alkyl and $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl;

or $R^6$ and $R^7$ may together form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which is optionally substituted by 0-4 substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide, or two substituents taken together form a fused or spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S,

which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, mono- and di-$C_{1-4}$-alkylamino, mono- and di-$C_{1-4}$-alkyl-carboxamide, $C_{1-4}$-alkoxycarbonyl, and phenyl;

wherein at least one of $R^5$ and $R^{5a}$ or $R^6$ and $R^7$, taken in combination, form a spirocyclic ring having at least one spirocyclic ring substituent;

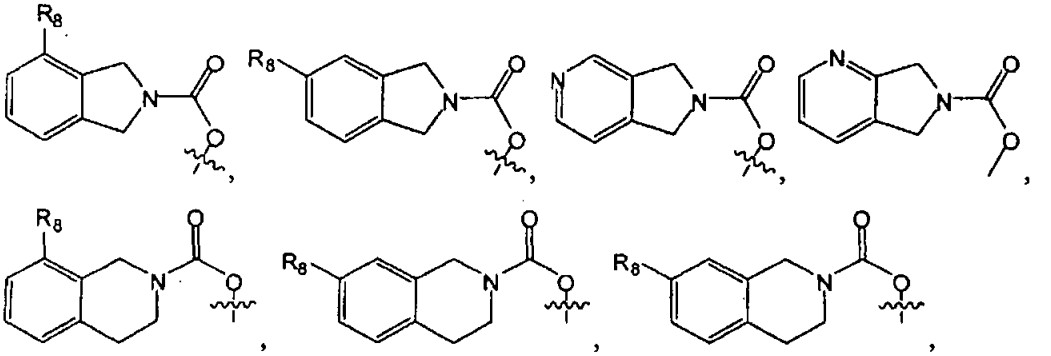
or $R^3$ and W may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times; and

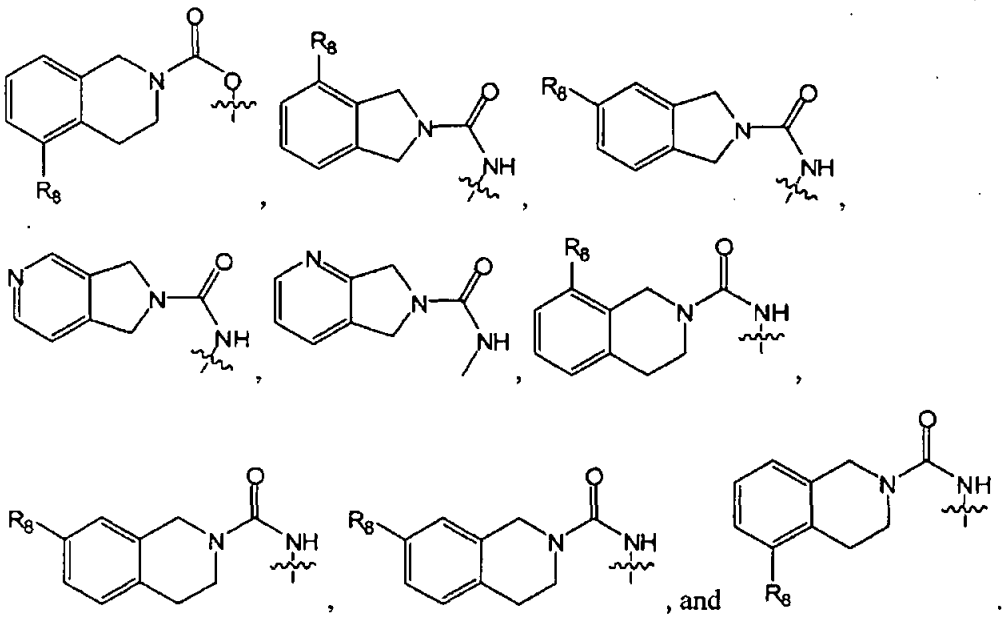
or when y is 0, $R^{10}$ and V may together form a 3, 4, 5, 6 or 7-membered ring that is aromatic or non-aromatic and may contain one or more heteroatoms, wherein the ring may be further substituted one or more times.

25. The compound of claim 24, wherein $R^5$ and $R^{5a}$, taken in combination, form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1, or 2 ring heteroatoms, which spirocyclic ring is substituted with a spirocyclic 3 to 7 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, and wherein each of the spirocyclic rings has 0 to 2 independently selected substituents selected from cyano, halogen, hydroxyl, amino, thiol, $C_{1-8}$-alkyl, $C_{2-8}$-alkenyl, $C_{2-8}$-alkynyl, $C_{1-8}$-alkoxy-$C_{0-4}$alkyl, $C_{1-8}$-haloalkyl, $C_{2-8}$-haloalkenyl, $C_{2-8}$-haloalkynyl, $C_{1-8}$-haloalkoxy, $C_{1-8}$-alkylthio, $C_{1-8}$-alkylsulfonyl, $C_{1-8}$-alkylsulfoxy, $C_{1-8}$-alkanoyl, $C_{1-8}$-alkoxycarbonyl, $C_{3-7}$-cycloalkyl-$C_{0-4}$-alkyl, aryl-$C_{0-4}$-alkyl, heteroaryl-$C_{0-4}$-alkyl, COOH, $C(O)NH_2$, mono- and di-$C_{1-4}$-alkyl-carboxamide, mono- and di-$C_{1-4}$-alkyl-amino-$C_{0-4}$alkyl, $SO_3H$, $SO_2NH_2$, and mono-and di-$C_{1-4}$-alkylsulfonamide.

26. The compound of claim 24, wherein $R^{14}$ is C(O).

27. The compound of claim 24, wherein X is $CR_5R_{5a}$, $R_{5a}$ is hydrogen or methyl, and $R_5$ is a residue selected from the group consisting of:





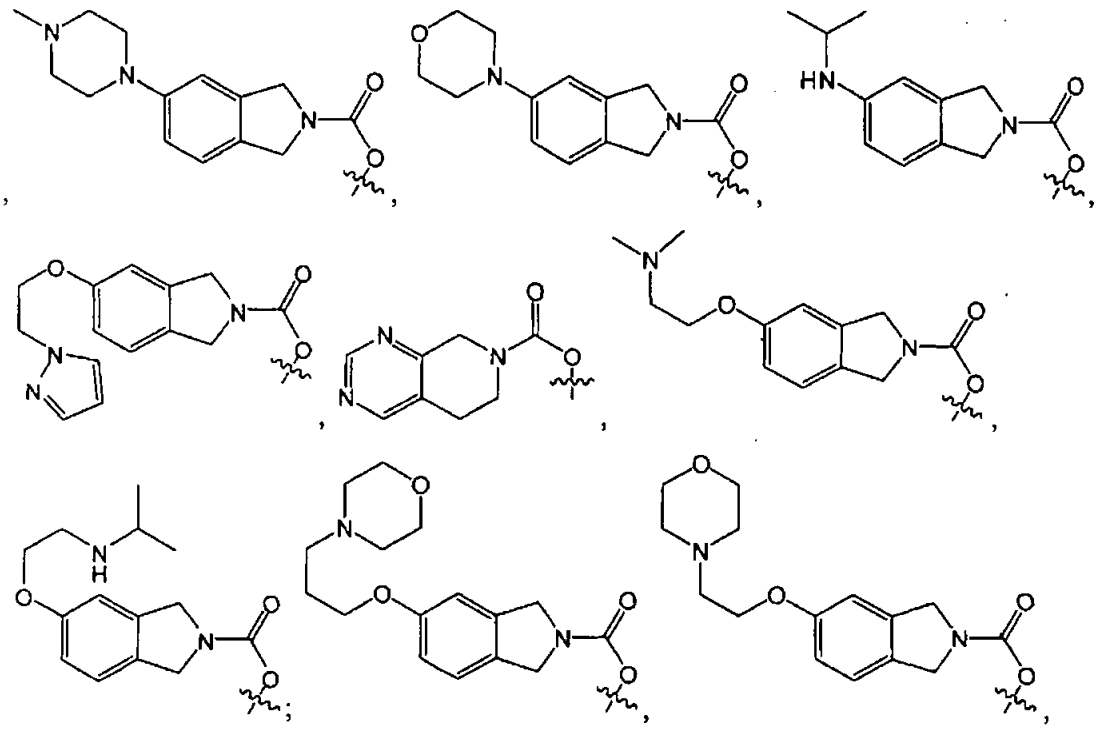
wherein $R_8$ is selected from hydrogen, methyl, ethyl, mono-, di-, or tri-fluoromethyl, mono-, di-, or tri-fluoromethoxy, fluoro, and chloro.

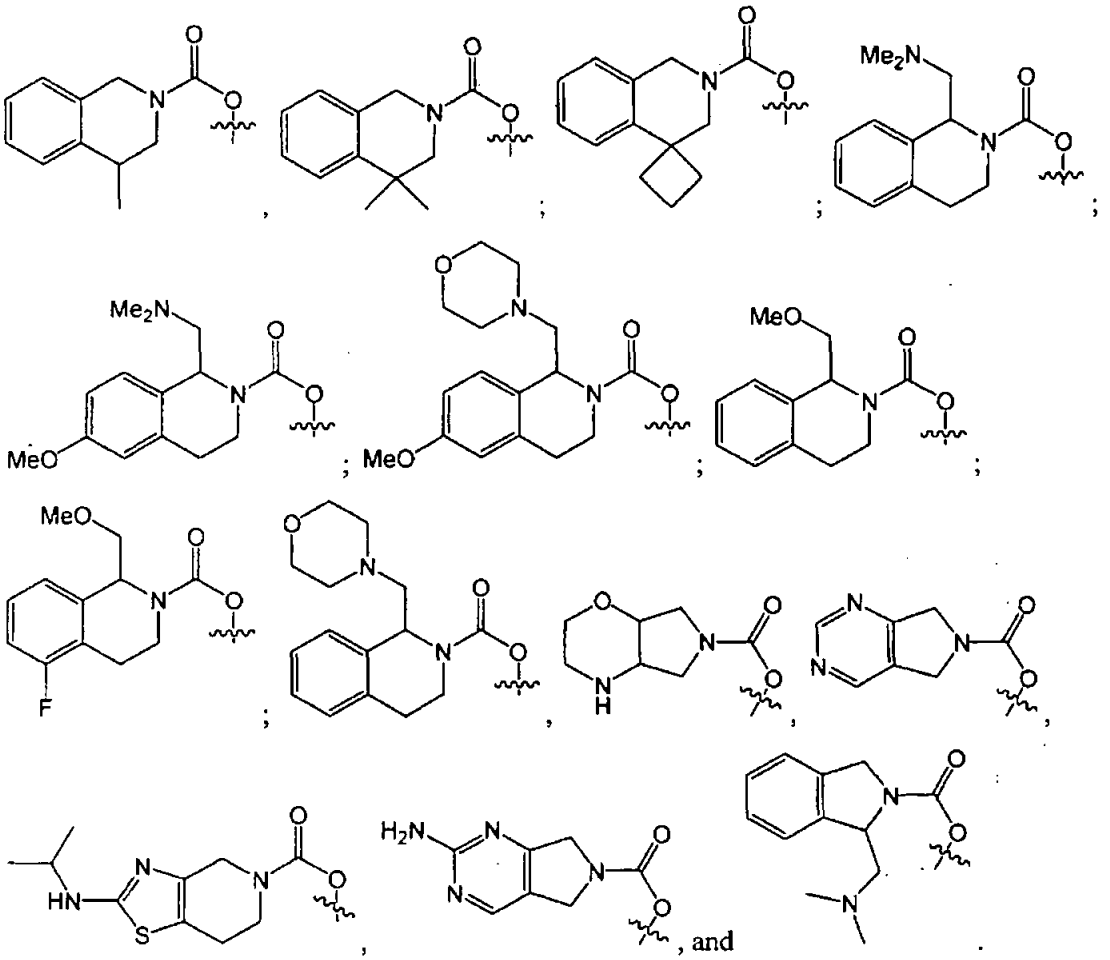
28. The compound of claim 24, wherein X is $CR_5R_{5a}$;

$R_{5a}$ is hydrogen or methyl;

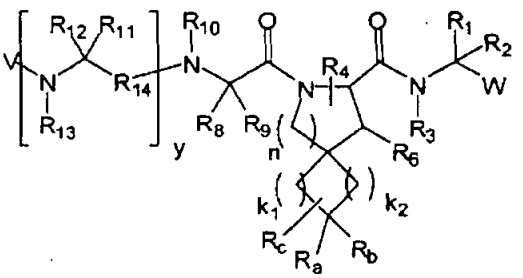
$R_6$ is hydrogen, methyl, ethyl, and mono-, di-, and tri-fluoromethyl;

$R_5$ is a residue selected from the group consisting of:





29. A compound of claim 24, according to the formula:



wherein

$k_1$ and $k_2$ are 0 or 1 such that a sum of $k_1$ and $k_2$ equals 1 or 2;

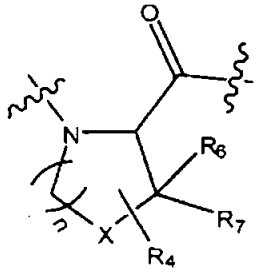
$R_a$ and $R_b$ taken together form a spirocyclic 3 to 6 membered ring having 0, 1 or 2 ring heteroatoms selected from N, O and S, which fused or spirocyclic ring has 0 to 2 independently selected substituents selected from halogen, $C_{1-4}$alkyl, $C_{1-4}$alkoxy, $C_{1-4}$alkanoyl, and phenyl;

$R_c$ represents 0 to 2 substituents which are independently selected at each occurrence of $R_c$ from the group consisting of halogen, $C_{1-4}$alkyl, and phenyl, or two *geminal* $R_c$ substituents, taken in combination form a 3 to 6 member spirocyclic ring;

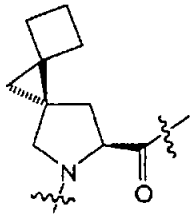
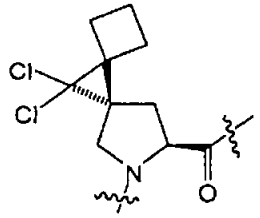
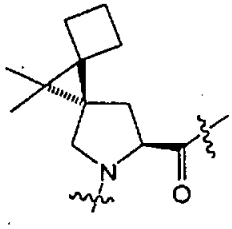
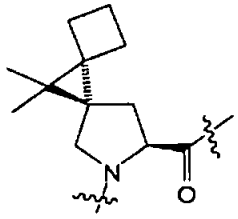
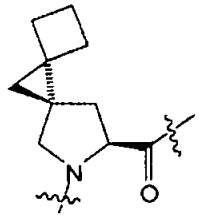
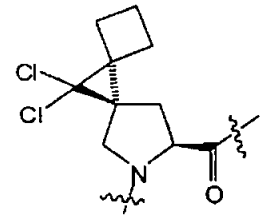
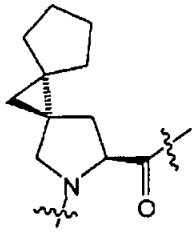
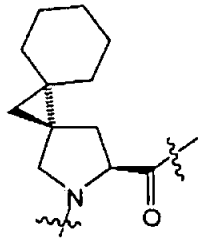
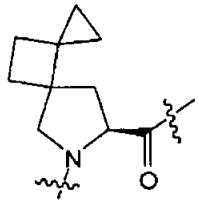
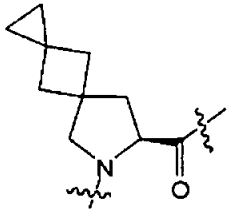
$R_4$ represents 0, 1, or 2 substituents each of which is independently selected from H and $C_{1-4}$-alkyl; and

$R_6$ is hydrogen or $C_{1-4}$alkyl.

30. The compound of claim 24, wherein the divalent residue:



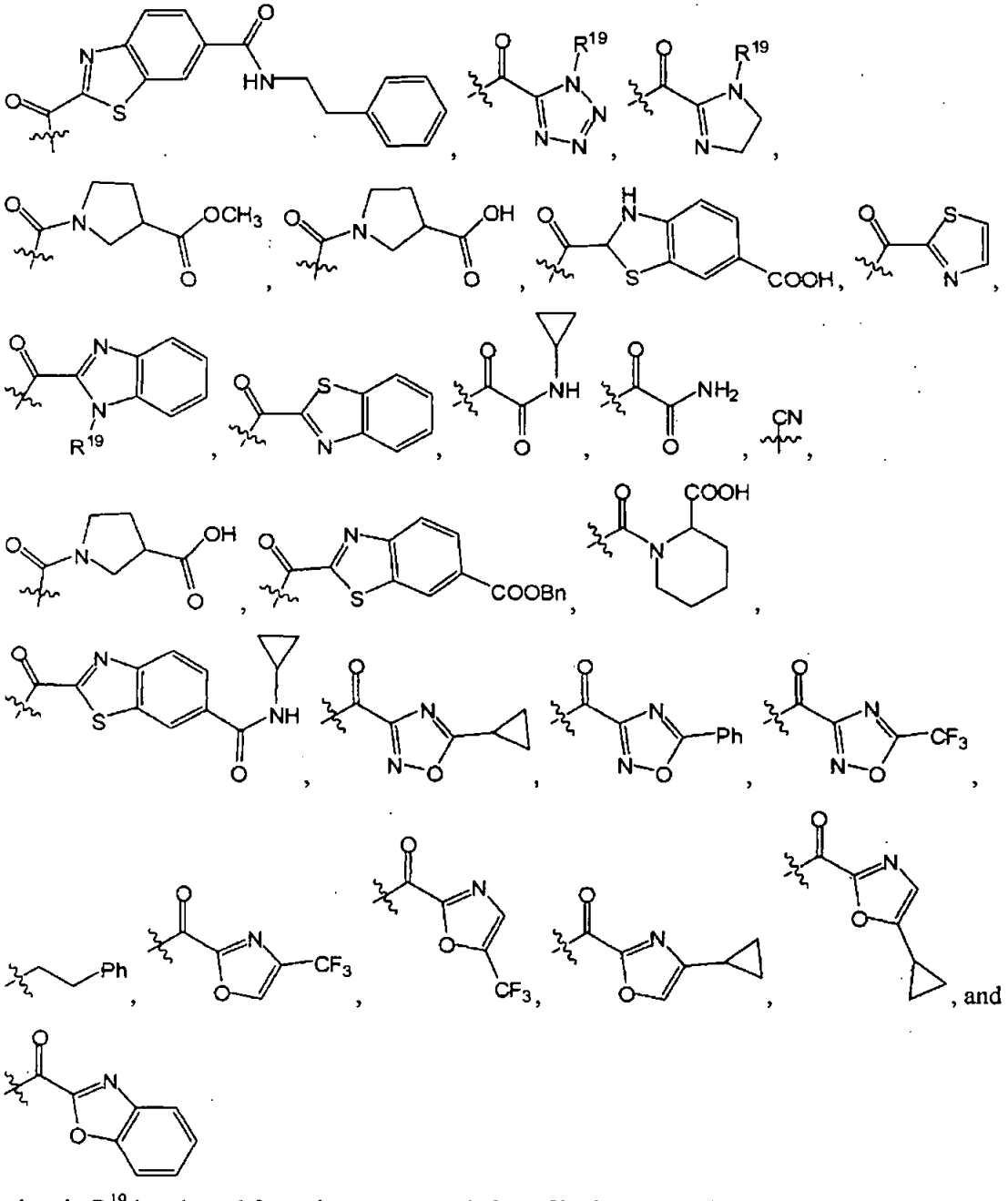
is selected from the group consisting of:


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,


, and

31. The compound of claim 24, wherein W is selected from the group consisting of C(O)-C(O)$NH_2$, C(O)-C(O)N(H)-cyclopropyl, C(O)-benzothiazole, C(O)-benzoimidazole, C(O)-oxazole, C(O)-imidazole, and C(O)-oxadiazole, wherein the benzothiazole, benzoimidazole, oxazole and oxadiazole groups may be independently substituted one or

more times with a halogen atom, aryl, trihalomethyl, $C_{3-6}$-cycloalkyl or $C_{1-4}$-alkyl.

32. The compound of claim 24, wherein W is selected from the group consisting of



wherein $R^{19}$ is selected from the group consisting of hydrogen, aryl, trihalomethyl, and $C_{1-4}$-alkyl.

33. The compound of claim 24, wherein $R^2$ is selected from the group consisting

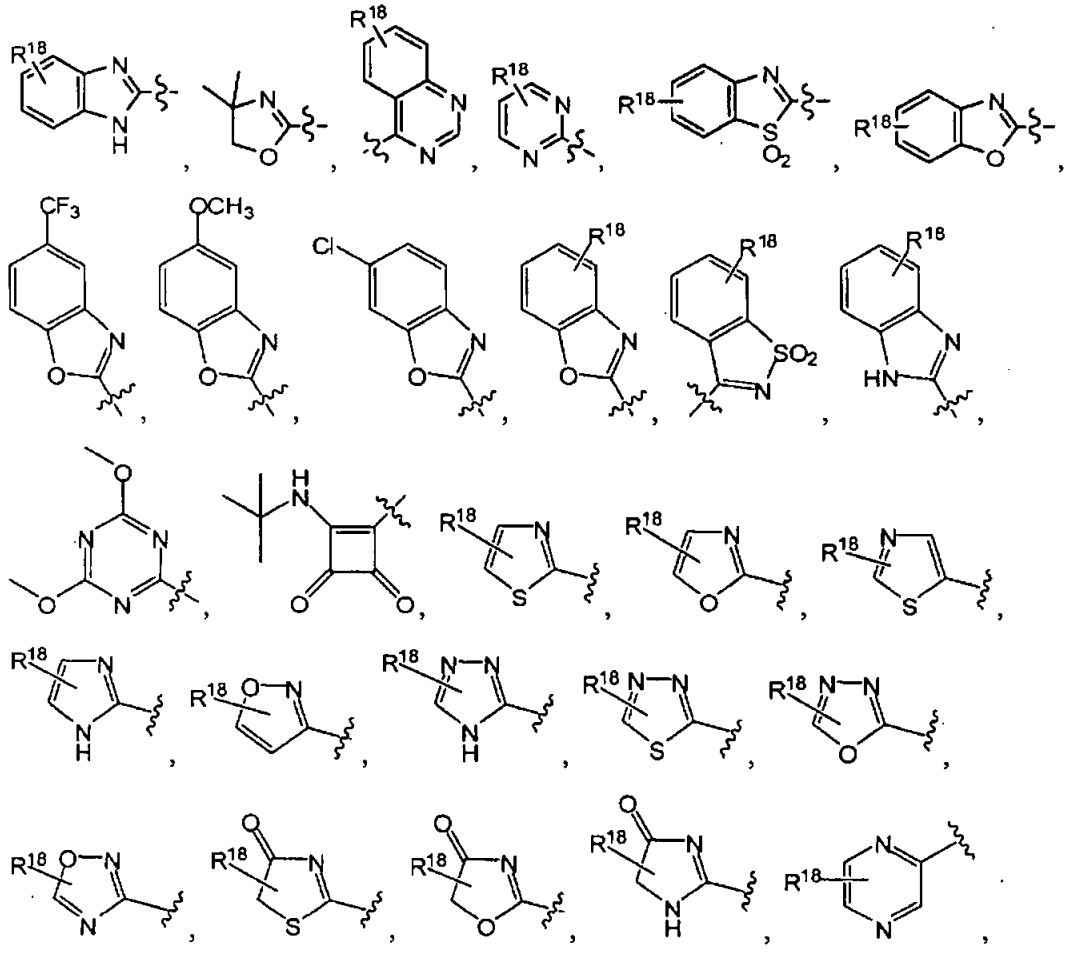
of propyl and $(CH_2)_2$-cyclobutyl.

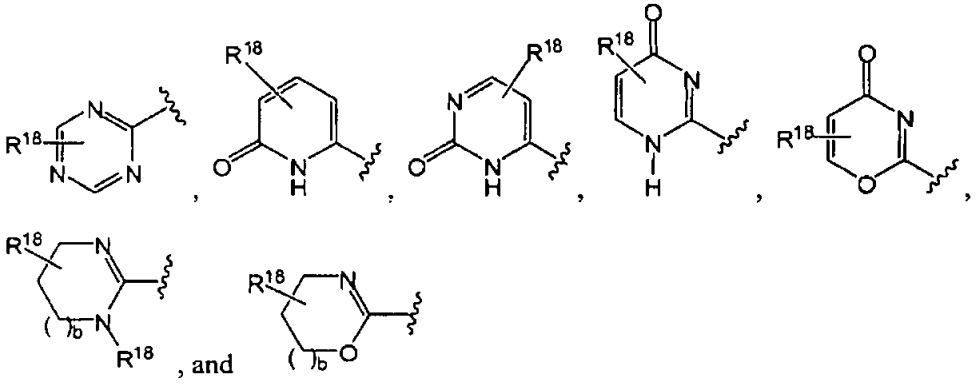
34. The compound of claim 24, wherein $R^{11}$ is H and $R^{12}$ is $C_{3-6}$-cycloalkyl.

35. The compound of claim 24, wherein $R^{12}$ is cyclohexyl.

36. The compound of claim 24, wherein V is $R^{20}$ or C(O)-$R^{20}$, wherein $R^{20}$ is selected from the group consisting of $C_{3-6}$-cycloalkyl, mono- and di-$C_{1-4}$alkylamino, phenyl, pyrazine, benzooxazole, 4,4-dimethyl-4,5-dihydro-oxazole, benzoimidazole, pyrimidine, benzothiazole 1,1-dioxide and quinazoline, each of which may be further independently substituted with a halogen atom, $CF_3$, $C_{1-4}$-alkyl or $C_{3-6}$-cycloalkyl.

37. The compound of claim 24, wherein V is $R^{20}$ or C(O)-$R^{20}$, wherein $R^{20}$ is selected from the group consisting of





wherein b is 0, 1, or 2; and $R_{18}$ is selected from the group consisting of hydrogen, a halogen atom, aryl, trihalomethyl, and $C_{1-4}$-alkyl.

38. The compound of claim 24, wherein X is $CR^5R^{5a}$, $R^4$ and $R^{5a}$ are hydrogen, and $R^5$ is aryl-$C_{0-3}$-alkyl, -O-heterocycle, or heterocycle-$C_{0-3}$-alkyl, wherein aryl and heterocycle may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, $C_{3-6}$-cycloalkyl or $C_{1-4}$-alkyl.

39. The compound of claim 24, wherein W is selected from the group consisting of C(O)-C(O)N($R^{23}$)$_2$, wherein $R^{23}$ is independently selected from hydrogen or the group consisting of $C_{1-4}$-alkyl, $C_{3-6}$-cycloalkyl$C_{0-4}$alkyl, aryl and heterocycle, each of which may be independently substituted one or more times with a halogen atom or $C_{1-4}$-alkyl.

40. A method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of claim 1 or claim 24, such that the HCV-associated disorder is treated.

41. The method of claim 40, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

42. A method of treating an HIV infection comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of claim 1 or claim 24.

43. A method of treating, inhibiting or preventing the activity of HCV in a subject

in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of claim 1 or claim 24.

44. A method of inhibiting the activity of a serine protease, comprising the step of contacting said serine protease with a compound according to claim 1 or claim 24.

45. The method of claim 44, wherein the activity of the NS2 protease is inhibited.

46. The method of claim 44, wherein the activity of the NS3 protease is inhibited.

47. The method of claim 44, wherein the activity of the NS3 helicase is inhibited.

48. The method of claim 44, wherein the activity of the NS5a protein is inhibited.

49. The method of claim 44, wherein the activity of the NS5b polymerase is inhibited.

50. The method of claim 44, wherein the interaction between the NS3 protease and NS4A cofactor is disrupted.

51. The method of claim 44 wherein the severing of one or more of the NS4A-NS4B, NS4B-NS5A and NS5A-NS5B junctions of the HCV is prevented or altered.

52. The method of any one of claims 44-51, wherein an HCV-associated disorder is treated in a subject in need thereof.

53. The method of claim 52, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

54. A method of treating, inhibiting or preventing the activity of HCV in a subject in need thereof, comprising administering to the subject a pharmaceutically acceptable amount of a compound of claim 1 or claim 24,wherein the compound interacts with any

target in the HCV life cycle.

55. The method of claim 54, wherein the target is selected from the group consisting of NS2 protease, NS3 protease, NS3 helicase, NS5a protein andNS5b polymerase.

56. A method of decreasing the HCV RNA load in a subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of claim 1 or claim 24, such that the HCV RNA load in the subject is decreased.

57. A compound exhibiting HCV protease activity, wherein the compound is a compound of claim 1 or claim 24.

58. The compound of claim 57, wherein the compound is a HCV NS3-4A protease inhibitor.

59. A method of treating an HCV-associated disorder in a subject, comprising administering to a subject in need thereof a pharmaceutically acceptable amount of a compound of claim 1 or claim 24 and a pharmaceutically acceptable carrier, such that the HCV-associated disorder is treated.

60. A method of treating an HCV-associated disorder comprising administering to a subject in need thereof a pharmaceutically effective amount of a compound of claim 1 or claim 24, in combination with a pharmaceutically effective amount of an additional HCV-modulating compound, such that the HCV-associated disorder is treated.

61. The method of claim 60, wherein the additional HCV-modulating compound is selected from the group consisting of Sch 503034 and VX-950.

62. The method of claim 60 wherein the additional HCV-modulating compound is interferon or derivatized interferon.

63. The method of claim 62, wherein the interferon is selected from the group consisting of interferon alpha 2B, pegylated interferon alpha, consensus interferon, interferon alpha 2A, lymphoblastoid interferon, and interferon tau; and said compound having anti-

hepatitis C virus activity is selected from the group consisting of interleukin 2, interleukin 6, interleukin 12, a compound that enhances the development of a type 1 helper T cell response, double stranded RNA, double stranded RNA complexed with tobramycin, Imiquimod, ribavirin, an inosine 5'-monophosphate dehydrogenase inhibitor, amantadine, and rimantadine.

64. The method of claim 60, wherein the additional HCV-modulating compound is a cytochrome P450 monooxygenase inhibitor.

65. The method of claim 64, wherein the cytochrome P450 inhibitor is selected from the group consisting of ritonavir, ketoconazole, troleandomycin, 4-methyl pyrazole, cyclosporin, and clomethiazole.

66. The method of claim 59 or claim 60, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

67. A method of inhibiting hepatitis C virus replication in a cell, comprising contacting said cell with a compound of claim 1 or claim 24.

68. A packaged HCV-associated disorder treatment, comprising an HCV-modulating compound of claim 1 or claim 24, packaged with instructions for using an effective amount of the HCV-modulating compound to treat an HCV-associated disorder.

69. The treatment of claim 68, wherein the HCV-associated disorder is selected from the group consisting of HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and a suppressed innate intracellular immune response.

70. A method of treating HCV infection, liver cirrhosis, chronic liver disease, hepatocellular carcinoma, cryoglobulinaemia, non-Hodgkin's lymphoma, and/or a suppressed innate intracellular immune response in subject in need thereof comprising administering to the subject a pharmaceutically acceptable amount of a compound of claim 1 or claim 24.

# COMPUESTOS ORGÁNICOS Y SUS USOS

## Antecedentes

El virus de hepatitis C (HCV) es un virus de ARN de una sola cadena en sentido-(+) que se ha implicado como el principal agente causante de la hepatitis no-A, no-B (NANBH), en particular en la NANBH asociada con la sangre (BB-NANBH). La NANBH se va a distinguir de otros tipos de enfermedad hepática viralmente inducida, tal como el virus de hepatitis A (HAV), el virus de hepatitis B (HBV), el virus de hepatitis delta (HDV), el citomegalovirus (CMV), y el virus Epstein-Barr (EBV), así como de otras formas de enfermedad hepática, tales como alcoholismo y cirrosis biliar primaria.

Recientemente se ha identificado, clonado y expresado una proteasa del HCV necesaria para el procesamiento de polipéptidos y la réplica viral. (Ver, por ejemplo, la Patente de los Estados Unidos de Norteamérica Número 5,712,145). Esta poliproteína de aproximadamente, 3,000 aminoácidos contiene, desde el término amino hasta el término carboxilo, una proteína de nucleocapsida (C), proteínas de envoltura (E1 y E2), y varias proteínas no estructurales (NS1, 2, 3, 4a, 5a, y 5b). NS3 es una proteína de aproximadamente 68 kda, codificada por aproximadamente 1893 nucleótidos del genoma de HCV, y tiene dos dominios distintos: (a) un dominio de proteasa de serina que consiste en aproximadamente 200 de los aminoácidos N-terminales; y (b) un dominio de ATPasa dependiente del ARN en el término C de la proteína. La proteasa NS3 se

considera como un miembro de la familia de quimiotripsina, debido a las similitudes en la secuencia de la proteína, sobre todo la estructura tridimensional y el mecanismo de catalización. La proteasa de serina NS3 de HCV es responsable de la proteólisis del polipéptido (poliproteina) en las uniones NS3/NS4a, NS4a/NS4b, NS4b/NS5a, y NS5a/NS5b, y por consiguiente, es responsable de la generación de cuatro proteínas virales durante la réplica viral. Esto ha hecho que la proteasa de serina NS3 de HCV sea un objetivo atractivo para la quimioterapia anti-viral.

Se ha determinado que la proteína NS4a, un polipéptido de aproximadamente 6 kda, es un co-factor para la actividad de proteasa de serina de NS3. La auto-disociación de la unión NS3/NS4a por parte de la proteasa de serina NS3/NS4a se presenta intramolecularmente (es decir, *cis*), mientras que los otros sitios de disociación se procesan intermolecularmente (es decir, *trans*).

El virus de hepatitis C se ha implicado en la cirrosis del hígado y en la inducción del carcinoma hepatocelular. El pronóstico para los pacientes que sufren de infección por hepatitis C actualmente es pobre. La infección por el virus de hepatitis C es más difícil de tratar que otras formas de hepatitis, debido a la falta de inmunidad o remisión asociada con la infección por el virus de hepatitis C. Los datos actuales indican un índice de sobrevivencia menor al 50 por ciento a los cuatro años después del diagnóstico de cirrosis. Los pacientes diagnosticados con carcinoma hepatocelular resectable localizado tienen un índice de sobrevivencia de cinco

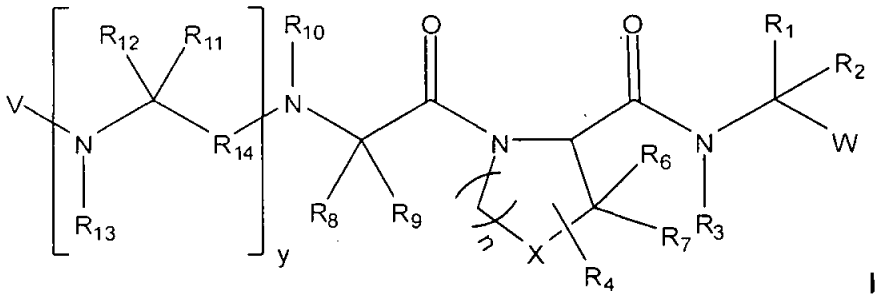
años del 10 al 30 por ciento, mientras que aquéllos con carcinoma hepatocelular no resectable localizado tienen un índice de sobrevivencia de cinco años de menos del 1 por ciento.

Las terapias actuales para hepatitis C incluyen el interferón-α (INFα) y la terapia de combinación con ribavirina e interferón. Ver, por ejemplo, Beremguer y colaboradores (1998) Proc. Assoc. Am. Physicians 110 (2): 98-112. Estas terapias sufren de un bajo índice de respuesta sostenido y de frecuentes efectos secundarios. Ver, por ejemplo, Hoofnagle y colaboradores (1997) N. Engl. J. Med. 336: 347. En la actualidad, no hay una vacuna disponible para la infección por el virus de hepatitis C.

**Breve Descripción de la Invención**

Sigue existiendo una necesidad de nuevos tratamientos y terapias para la infección por el virus de hepatitis C, así como los trastornos asociados con el virus de hepatitis C. También existe una necesidad de compuestos útiles en el tratamiento o en la prevención o disminución de uno o más síntomas del virus de hepatitis C, así como una necesidad de métodos de tratamiento o de prevención o disminución de uno o más síntomas del virus de hepatitis C. Adicionalmente, existe una necesidad de métodos para modular la actividad de las proteasas de serina del virus de hepatitis C, en particular la proteasa de serina NS3/NS4a del virus de hepatitis C, utilizando los compuestos proporcionados en la presente.

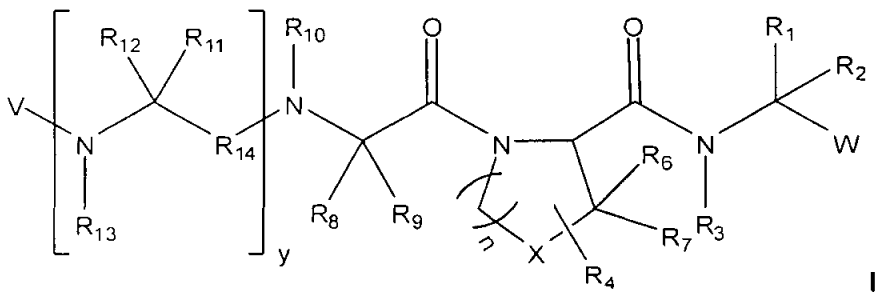
En un aspecto, la invención proporciona compuestos de la Fórmula I:



I

y las sales farmacéuticamente aceptables y estereoisómeros de los mismos.

En otro aspecto, la invención proporciona compuestos de la Fórmula III:



III

y las sales farmacéuticamente aceptables y estereoisómeros de los mismos, en donde X o $R_6$ y $R_7$, tomados en combinación, comprenden un sistema de anillo espirocíclico, el cual es espiro para el anillo que comprende la variable X.

En una modalidad, la invención proporciona un método para el tratamiento de un trastorno asociado con el virus de hepatitis C, el cual comprende administrar a un sujeto que lo necesite, una cantidad farmacéuticamente aceptable de un compuesto de la invención, de manera que se trate el trastorno asociado con el virus de hepatitis C.

En otra modalidad, la invención proporciona un método para el tratamiento de una infección por el virus de inmunodeficiencia

humana (VIH), el cual comprende administrar a un sujeto que lo necesite, una cantidad farmacéuticamente aceptable de un compuesto de la invención.

En todavía otra modalidad, la invención proporciona un método para el tratamiento, la inhibición, o la prevención de la actividad del virus de hepatitis C en un sujeto que lo necesite, el cual comprende administrar al sujeto, una cantidad farmacéuticamente aceptable de un compuesto de la invención. En una modalidad, los compuestos de la invención inhiben la actividad de la proteasa NS2, la proteasa NS3, la helicasa NS3, la proteína NS5a, y/o la polimerasa NS5b. En otra modalidad, se interrumpe la interacción entre la proteasa NS3 y el co-factor NS4A. En todavía otra modalidad, los compuestos de la invención previenen o alteran la ruptura de una o más de las uniones NS4A-NS4B, NS4B-NS5A y NS5A-NS5B del virus de hepatitis C. En otra modalidad, la invención proporciona un método para la inhibición de la actividad de una proteasa de serina, el cual comprende el paso de poner en contacto esta proteasa de serina con un compuesto de la invención. En otra modalidad, la invención proporciona un método para el tratamiento, la inhibición, o la prevención de la actividad del virus de hepatitis C en un sujeto que lo necesite, el cual comprende administrar al sujeto una cantidad farmacéuticamente aceptable de un compuesto de la invención, en donde el compuesto interactúa con cualquier objetivo en el ciclo de vida del virus de hepatitis C. En una modalidad, el objetivo del ciclo de vida del virus de hepatitis C se selecciona a

partir del grupo que consiste en proteasa NS2, proteasa NS3, helicasa NS3, proteína NS5a, y polimerasa NS5b.

En otra modalidad, la invención proporciona un método para disminuir la carga de ARN del virus de hepatitis C en un sujeto que lo necesite, el cual comprende administrar al sujeto una cantidad farmacéuticamente aceptable de un compuesto de la invención.

En otra modalidad, los compuestos de la invención exhiben actividad de proteasa del virus de hepatitis C. En una modalidad, los compuestos son un inhibidor de proteasa NS3-4A del virus de hepatitis C.

En otra modalidad, la invención proporciona un método para el tratamiento de un trastorno asociado con el virus de hepatitis C en un sujeto, el cual comprende administrar a un sujeto que lo necesite, una cantidad farmacéuticamente aceptable de un compuesto de la invención, y un vehículo farmacéuticamente aceptable, de tal manera que se trate el trastorno asociado con el virus de hepatitis C.

En todavía otra modalidad, la invención proporciona un método para el tratamiento de un trastorno asociado con el virus de hepatitis C, el cual comprende administrar a un sujeto que lo necesite, una cantidad farmacéuticamente efectiva de un compuesto de la invención, en combinación con una cantidad farmacéuticamente efectiva de un compuesto modulador del virus de hepatitis C adicional, tal como interferón o interferón derivado, o un inhibidor de mono-oxigenasa del citocromo P450, de tal manera que se trate el trastorno asociado con el virus de hepatitis C. En una modalidad, el

compuesto modulador del virus de hepatitis C adicional se selecciona a partir del grupo que consiste en Sch 503034 y VX-950.

En otra modalidad, la invención proporciona un método para inhibir la réplica del virus de hepatitis C en una célula, el cual comprende poner en contacto esta célula con un compuesto de la invención.

En todavía otra modalidad, la invención proporciona el tratamiento de un trastorno asociado con el virus de hepatitis C empacado, el cual comprende un compuesto modulador del virus de hepatitis C de la invención, empacado con instrucciones para utilizar una cantidad efectiva del compuesto modulador del virus de hepatitis C con el fin de tratar un trastorno asociado con el virus de hepatitis C.

En ciertas modalidades, el trastorno asociado con el virus de hepatitis C se selecciona a partir del grupo que consiste en infección por el virus de hepatitis C, cirrosis hepática, enfermedad crónica del hígado, carcinoma hepatocelular, crioglobulinemia, linfoma que no es de Hodgkin, y respuesta inmune intracelular innata suprimida.

En otra modalidad, la invención proporciona un método para el tratamiento de infección por el virus de hepatitis C, cirrosis hepática, enfermedad crónica del higado, carcinoma hepatocelular, crioglobulinemia, linfoma que no es de Hodgkin, y/o respuesta inmune intracelular innata suprimida, en un sujeto que lo necesite, el cual comprende administrar al sujeto una cantidad

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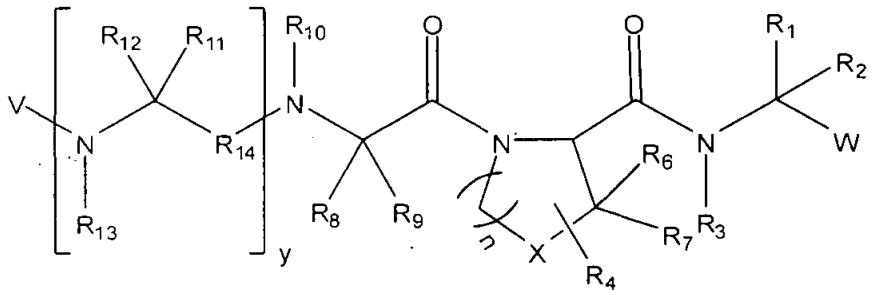
farmacéuticamente aceptable de un compuesto de la invención.

En una modalidad, el virus de hepatitis C que se va a tratar se selecciona a partir del cualquier genotipo del virus de hepatitis C. En otra modalidad, el virus de hepatitis C se selecciona a partir de los genotipos 1, 2, y/o 3 del virus de hepatitis C.

**Descripción Detallada de la Invención**

Esta invención se refiere a compuestos, por ejemplo compuestos peptídicos, y a intermediarios para los mismos, así como a composiciones farmacéuticas que contienen los compuestos, para utilizarse en el tratamiento de infección por el virus de hepatitis C. Esta invención también se refiere a los compuestos de la invención o composiciones de los mismos como inhibidores de proteasa, en particular como inhibidores de proteasa de serina, y más particularmente como inhibidores de la proteasa NS3 del virus de hepatitis C. Los compuestos son particularmente útiles para interferir con el ciclo de vida del virus de hepatitis C, y en el tratamiento o en la prevención de una infección por el virus de hepatitis C, o de las condiciones fisiológicas asociadas con la misma. La presente invención también se refiere a métodos de terapia de combinación para inhibir la réplica del virus de hepatitis C en las células, o para el tratamiento o la prevención de una infección por el virus de hepatitis C en los pacientes, utilizando los compuestos de la invención, o composiciones farmacéuticas o kits de los mismos.

En un aspecto, los compuestos de la invención son de la Fórmula I:



I

y sales farmacéuticamente aceptables y estereoisómeros de los mismos;

en donde:

**y** es 0 ó 1;

**n** es 0, 1, ó 2;

$R_{14}$ es C(O) ó $SO_2$;

$R_1$, $R_2$, W, $R_{13}$, y V se seleccionan cada uno independientemente a partir de hidrógeno o a partir del grupo que consiste en alquilo, alquil-arilo, heteroalquilo, heterociclilo, heteroarilo, aril-heteroarilo, alquil-heteroarilo, cicloalquilo, alquiloxilo, alquil-ariloxilo, ariloxilo, heteroariloxilo, heterociclíloxilo, cicloalquiloxilo, amino, alquil-amino, aril-amino, alquil-aril-amino, aril-amino, heteroaril-amino, cicloalquil-amino, carboxi-alquil-amino, mono- y di-alquil-carboxamida, aril-alquiloxilo, y heterociclil-amino; cada uno de los cuales puede estar además independientemente sustituido una o más veces por $X^1$ y $X^2$ (o más preferiblemente, cada uno de los cuales puede estar adicionalmente sustituido con 1, 2, 3, 4, ó 5 residuos independientemente seleccionados a partir de $X^1$ y $X^2$); en donde $X^1$ es alquilo, alquenilo, alquinilo, cicloalquilo,

cicloalquil-alquilo, heterociclilo, heterociclil-alquilo, arilo, alquil-arilo, aralquilo, ariloxilo, tioarilo, aril-heteroarilo, heteroarilo, heterociclil-amino, alquil-heteroarilo, o heteroaralquilo; en donde $X^1$ puede estar independientemente sustituido con una o más fracciones $X^2$ (o más preferiblemente con 1, 2, 3, 4, ó 5 fracciones), las cuales pueden ser iguales o diferentes, y se seleccionan de una manera independiente; en donde $X^2$ es hidroxilo, oxo, alquilo, cicloalquilo, espiro-cicloalquilo, heterociclo-alquilo, arilo, heteroarilo, alcoxilo, ariloxilo, tio, tioalquilo, amino, mono- y di-alquil-amino, aril-amino, alquil-sulfonilo, aril-sulfonilo, alquil-sulfonamido, aril-sulfonamido, carboxilo, carbalcoxilo, carboxamido, alcoxi-carbonil-amino, alcoxi-carbonilo, alcoxi-carboniloxilo, alquil-ureido, aril-ureido, halógeno, ciano, o nitro; en donde cada residuo $X^2$ seleccionado como alquilo, alcoxilo, y arilo puede estar insustituido o de manera opcional independientemente sustituido con una o más fracciones (o más preferiblemente con 1, 2, 3, 4, ó 5 fracciones), las cuales pueden ser iguales o diferentes, y se seleccionan independientemente a partir de alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquil-alquilo, heterociclilo, heterociclil-alquilo, arilo, alquil-arilo, aralquilo, aril-heteroarilo, heteroarilo, heterociclil-amino, alquil-heteroarilo, y heteroaralquilo;

W también se selecciona a partir del grupo que consiste en C(O)-C(O)H, C(=N-O-$R_{24}$)-C(O)-amina, C(O)-C(O)-amina, C(O)N$R_{24}$S(O)$_p$$R_{24}$, C(O)N$R_{24}$S(O)$_p$N($R_{24}$)$_2$ y C(O)-[C(O)]$_a$-heterociclo, en donde el heterociclo puede estar independientemente sustituido

una o más veces (o de preferencia entre una y cinco veces) con arilo, alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono sustituido por uno o más átomos de halógeno, y cicloalquilo de 3 a 6 átomos de carbono, en donde a es 0 ó 1, en donde cada $R_{24}$ se selecciona independientemente a partir de hidrógeno o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo sustituido o insustituido, y heterociclo sustituido o insustituido, cada uno de los cuales puede estar independientemente sustituido una o más veces (de preferencia entre una y cinco veces) con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono;

V también se selecciona a partir del grupo que consiste en $-Q^1-Q^2$, en donde $Q^1$ está ausente, o es C(O), N(H), N(alquilo de 1 a 4 átomos de carbono), C=N(CN), C=N($SO_2CH_3$), C=N-COH-alquilo de 1 a 4 átomos de carbono, o C=N-COH, y $Q^2$ es hidrógeno, o se selecciona a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, O-alquilo de 1 a 4 átomos de carbono, $NH_2$, N(H)-alquilo de 1 a 4 átomos de carbono, N(alquilo de 1 a 4 átomos de carbono)$_2$, $SO_2$-arilo, $SO_2$-alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo, heteroarilo, y heterociclo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno, alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono sustituido por uno o más átomos de halógeno, o cicloalquilo de 3 a 6 átomos de carbono;

o $R_1$ y $R_2$ pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces (o de preferencia entre una y cinco veces);

$R_3$ se selecciona a partir del grupo que consiste en hidrógeno, alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

X es O, S, N, $NR^5$, $CR^5$, ó $CR^5R^{5a}$;

$R_4$ se selecciona a partir de hidrógeno, o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, arilo, heterociclo, y heteroarilo, cada uno de los cuales puede estar independientemente sustituido una o más veces (de preferencia entre una y cinco veces) con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono;

$R^5$ se selecciona a partir de hidrógeno u oxo, o a partir del grupo que consiste en hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heterociclo-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, cicloalquiloxilo de 3 a 8 átomos de carbono, ariloxilo, y hetero-ariloxilo, cada uno de los cuales puede estar independientemente sustituido una o más veces (de preferencia entre una y cinco veces) con un átomo de halógeno, arilo, trihalo-

metilo, o alquilo de 1 a 4 átomos de carbono;

$R^{5a}$ se selecciona a partir del grupo que consiste en hidrógeno, hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, y heteroaril-alquilo de 0 a 4 átomos de carbono;

o $R_4$ y $R^5$ pueden formar juntos un anillo de dimetil-ciclopropilo fusionado, un anillo de ciclopentano fusionado, un anillo de fenilo fusionado, o un anillo de piridilo fusionado, cada uno de los cuales puede estar sustituido con un átomo de halógeno, arilo, trihalometilo, o alquilo de 1 a 4 átomos de carbono;

o $R^5$ y $R_6$ pueden formar juntos un anillo de dimetil-ciclopropilo fusionado, un anillo de ciclopentano fusionado, un anillo de fenilo fusionado, o un anillo de piridilo fusionado, cada uno de los cuales puede estar sustituido con un átomo de halógeno, arilo, trihalometilo, o alquilo de 1 a 4 átomos de carbono;

o $R^5$ y $R^{5a}$ pueden formar juntos un anillo espirocíclico que tiene entre 3 y 7 átomos del anillo, y que tiene 0, 1, ó 2 heteroátomos del anillo, el cual está opcionalmente sustituido por 0 a 4 sustituyentes seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8

átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida, o dos de estos 0 a 4 sustituyentes, tomados juntos, forman un anillo fusionado o espirocíclico de 3 a 7 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de

carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida;

$R_6$, $R_7$, $R_8$, $R_9$, $R_{10}$, $R_{11}$ y $R_{12}$ se seleccionan cada uno independientemente a partir del grupo que consiste en hidrógeno, alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

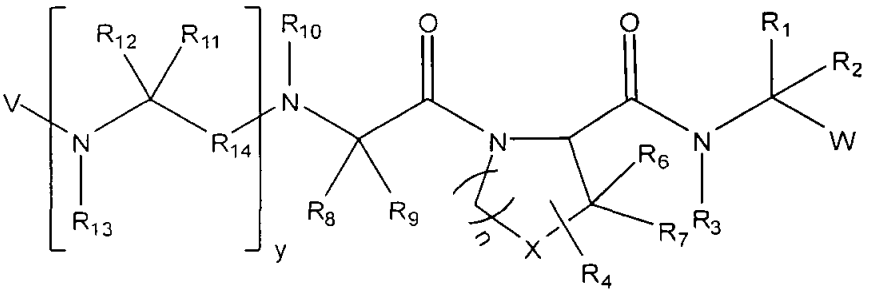
o $R_6$ y $R_7$ pueden formar juntos un anillo espirociclico que tiene entre 3 y 7 átomos del anillo, y que tiene 0, 1, ó 2 heteroátomos del anillo, el cual está opcionalmente sustituido por 0 a 4 sustituyentes seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoilo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-

alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida, o dos sustituyentes, tomados juntos, forman un anillo fusionado o espirocíclico de 3 a 7 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alcanoílo de 1 a 4 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-amino, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, alcoxilo de 1 a 4 átomos de carbono-carbonilo, y fenilo;

o $R_3$ y W pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces (o de preferencia entre una y cinco veces); y

o cuando y es 0, $R_{10}$ y V pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces (o de preferencia entre una y cinco veces).

En otro aspecto, los compuestos de la invención son de la Fórmula III:



III

y sales farmacéuticamente aceptables y estereoisómeros de los mismos;

en donde:

**y** es 0 ó 1;

**n** es 0, 1, ó 2;

$R_{14}$ es C(O) ó $SO_2$;

$R_1$, $R_2$, W, $R_{13}$, y V se seleccionan cada uno independientemente a partir de hidrógeno o a partir del grupo que consiste en alquilo, alquil-arilo, heteroalquilo, heterociclilo, heteroarilo, aril-heteroarilo, alquil-heteroarilo, cicloalquilo, alquiloxilo, alquil-ariloxilo, ariloxilo, heteroariloxilo, heterocicliloxilo, cicloalquiloxilo, amino, alquil-amino, aril-amino, alquil-aril-amino, aril-amino, heteroaril-amino, cicloalquil-amino, carboxi-alquil-amino, mono- y di-alquil-carboxamida, aril-alquiloxilo, y heterociclil-amino; cada uno de los cuales puede estar además independientemente sustituido una o más veces por $X^1$ y $X^2$ (o más preferiblemente, cada uno de los cuales puede estar adicionalmente sustituido con 1, 2, 3,

4, ó 5 residuos independientemente seleccionados a partir de $X^1$ y $X^2$); en donde $X^1$ es alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquil-alquilo, heterociclilo, heterociclil-alquilo, arilo, alquil-arilo, aralquilo, ariloxilo, tioarilo, aril-heteroarilo, heteroarilo, heterociclil-amino, alquil-heteroarilo, o heteroaralquilo; en donde $X^1$ puede estar independientemente sustituido con una o más fracciones $X^2$ (o más preferiblemente con 1, 2, 3, 4, ó 5 fracciones), las cuales pueden ser iguales o diferentes, y se seleccionan de una manera independiente; en donde $X^2$ es hidroxilo, oxo, alquilo, cicloalquilo, espiro-cicloalquilo, heterociclo-alquilo, arilo, heteroarilo, alcoxilo, ariloxilo, tio, tioalquilo, amino, mono- y di-alquil-amino, aril-amino, alquil-sulfonilo, aril-sulfonilo, alquil-sulfonamido, aril-sulfonamido, carboxilo, carbalcoxilo, carboxamido, alcoxi-carbonil-amino, alcoxi-carbonilo, alcoxi-carboniloxilo, alquil-ureido, aril-ureido, halógeno, ciano, o nitro; en donde cada residuo $X^2$ seleccionado como alquilo, alcoxilo, y arilo puede estar insustituido o de manera opcional independientemente sustituido con una o más fracciones (o más preferiblemente con 1, 2, 3, 4, ó 5 fracciones), las cuales pueden ser iguales o diferentes, y se seleccionan independientemente a partir de alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquil-alquilo, heterociclilo, heterociclil-alquilo, arilo, alquil-arilo, aralquilo, aril-heteroarilo, heteroarilo, heterociclil-amino, alquil-heteroarilo, y heteroaralquilo;

W también se selecciona a partir del grupo que consiste en $C(O)OH$, $C(O)OR_{24}$, C(O)-amina, $P(O)(OR_{24})_2$, C(O)-C(O)OH, C(=N-

O-$R_{24}$)-C(O)-amina, C(O)NHS$(O)_2R_{24}$, C(O)NHS$(O)_2N(R_{24})_2$, C(O)-C(O)-amina, $CONHSO_2$-amina, y C(O)-$[C(O)]_a$-heterociclo, en donde el heterociclo puede estar sustituido o insustituido, en donde **a** es 0 ó 1, en donde cada $R_{24}$ se selecciona independientemente a partir del grupo que consiste en hidrógeno, halógeno, hidroxilo, formilo, carboxilato, amida, amino, alquilo de 1 a 4 átomos de carbono sustituido o insustituido, alcoxilo de 1 a 4 átomos de carbono sustituido o insustituido, alcanoílo de 1 a 4 átomos de carbono sustituido o insustituido, alcoxilo de 1 a 4 átomos de carbono-carbonilo sustituido o insustituido, alcanoiloxilo de 1 a 4 átomos de carbono sustituido o insustituido, mono- y di-alquilo de 1 a 4 átomos de carbono-amino sustituido o insustituido, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono sustituido o insustituido, aril-alquilo de 0 a 4 átomos de carbono sustituido o insustituido, y heterociclo-alquilo de 0 a 4 átomos de carbono sustituido o insustituido;

V también se selecciona a partir del grupo que consiste en -$Q^1$-$Q^2$, en donde $Q^1$ está ausente, o es C(O), N(H), N(alquilo de 1 a 4 átomos de carbono), C=N(CN), C=N($SO_2CH_3$), C=N-COH-alquilo de 1 a 4 átomos de carbono, o C=N-COH, y $Q^2$ es hidrógeno, o se selecciona a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, O-alquilo de 1 a 4 átomos de carbono, $NH_2$, N(H)-alquilo de 1 a 4 átomos de carbono, N(alquilo de 1 a 4 átomos de carbono)$_2$, $SO_2$-arilo, $SO_2$-alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo,

heteroarilo, y heterociclo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno, alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono sustituido por uno o más átomos de halógeno, o cicloalquilo de 3 a 6 átomos de carbono;

o $R_1$ y $R_2$ pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces (o de preferencia entre una y cinco veces);

$R_3$ se selecciona a partir del grupo que consiste en hidrógeno, alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

X es $CR^5R^{5a}$;

$R_4$ representa de 0 a 4 sustituyentes, cada uno de los cuales se selecciona independientemente a partir de hidrógeno, o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, arilo, heterociclo, y heteroarilo, cada uno de los cuales puede estar independientemente sustituido una o más veces (de preferencia entre una y cinco veces) con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono;

$R^5$ se selecciona a partir de hidrógeno u oxo, o del grupo que consiste en hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4

átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heterociclo-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, cicloalquiloxilo de 3 a 8 átomos de carbono, ariloxilo, y hetero-ariloxilo, cada uno de los cuales puede estar independientemente sustituido una o más veces (de preferencia entre una y cinco veces) con un átomo de halógeno, arilo, trihalometilo, o alquilo de 1 a 4 átomos de carbono;

$R^{5a}$ se selecciona a partir del grupo que consiste en hidrógeno, hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, y heteroaril-alquilo de 0 a 4 átomos de carbono;

o $R_4$ y $R^5$ pueden formar juntos un anillo de dimetil-ciclopropilo fusionado, un anillo de ciclopentano fusionado, un anillo de fenilo fusionado, o un anillo de piridilo fusionado, cada uno de los cuales puede estar sustituido con un átomo de halógeno, arilo, trihalometilo, o alquilo de 1 a 4 átomos de carbono;

o $R^5$ y $R^{5a}$ pueden formar juntos un anillo espirociclico que tiene entre 3 y 7 átomos del anillo, y que tiene 0, 1, ó 2 heteroátomos del anillo, el cual está opcionalmente sustituido por 0 a 4 sustituyentes seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono,

haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida, o dos de estos 0 a 4 sustituyentes, tomados juntos, forman un anillo fusionado o espirocíclico de 3 a 7 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo,

alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida;

$R_6$ y $R_7$ se seleccionan cada uno independientemente a partir del grupo que consiste en hidroxilo, amino, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, y mono- y di-alquilo de 1 a 4 átomos de carbono-amino, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

$R_8$, $R_9$, $R_{10}$, $R_{11}$ y $R_{12}$ se seleccionan cada uno independientemente a partir del grupo que consiste en hidrógeno, alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

o $R_6$ y $R_7$ pueden formar juntos un anillo espirocíclico que tiene entre 3 y 7 átomos del anillo, y que tiene 0, 1, ó 2 heteroátomos del anillo, el cual está opcionalmente sustituido por 0 a 4 sustituyentes seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8

átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida, o dos sustituyentes, tomados juntos, forman un anillo fusionado o espirocíclico de 3 a 7 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alcanoílo de 1 a 4 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-amino, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, alcoxilo de 1 a 4 átomos de carbono-carbonilo, y fenilo;

en donde cuando menos uno de $R^5$ y $R^{5a}$, o $R_6$ y $R_7$, tomados en combinación, forman un anillo espirocíclico que tiene cuando menos un sustituyente del anillo espirocíclico;

o $R_3$ y W pueden formar juntos un anillo de 3, 4, 5, 6, ó 7

miembros, que es aromático o no aromático, y puede contener uno o más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces (o de preferencia entre una y cinco veces); y

o cuando **y** es 0, $R_{10}$ y V pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces (o de preferencia entre una y cinco veces).

En una modalidad de la fórmula I, **y** es 0 ó 1;

**n** es 0 ó 1;

$R_{14}$ es C(O) ó $SO_2$;

$R_1$ se selecciona a partir del grupo que consiste en H y alquilo de 1 a 4 átomos de carbono;

$R_2$ se selecciona a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, C(O)-alquilo de 1 a 4 átomos de carbono, C(O)O-alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

o $R_1$ y $R_2$ forman juntos un anillo de ciclopropano;

W también se selecciona a partir del grupo que consiste en C(O)-C(O)H, C(=N-O-$R_{24}$)-C(O)-amina, C(O)-C(O)-amina, y C(O)-$[C(O)]_a$-heterociclo, en donde el heterociclo puede estar independientemente sustituido una o más veces (o de preferencia entre una y cinco veces) con arilo, alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono sustituido por uno o

más átomos de halógeno, y cicloalquilo de 3 a 6 átomos de carbono, en donde **a** es 0 ó 1, en donde cada $R_{24}$ se selecciona independientemente a partir de hidrógeno, o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo sustituido o insustituido, y heterociclo sustituido o insustituido, cada uno de los cuales puede estar independientemente sustituido una o más veces (o de preferencia entre una y cinco veces) con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono;

$R_3$ se selecciona a partir del grupo que consiste en H y alquilo de 1 a 4 átomos de carbono;

X es O, $NR^5$ o $CR^5R^{5a}$;

$R_4$ se selecciona a partir del hidrógeno, o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, arilo, heterociclo, y heteroarilo, cada uno de los cuales puede estar independientemente sustituido una o más veces (o de preferencia entre una y cinco veces) con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono;

$R^5$ se selecciona a partir de hidrógeno u oxo, o del grupo que consiste en hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heterociclo-alquilo de 0 a 4 átomos de carbono, y heteroaril-alquilo de 0 a 4 átomos de carbono, cada uno de los cuales puede estar

independientemente sustituido una o más veces (o de preferencia entre una y cinco veces) con un átomo de halógeno, arilo, trihalo-metilo, o alquilo de 1 a 4 átomos de carbono;

$R^{5a}$ se selecciona a partir del grupo que consiste en hidrógeno, hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, y heteroaril-alquilo de 0 a 4 átomos de carbono;

o $R_4$ y $R^5$ pueden formar juntos un anillo de dimetil-ciclopropilo fusionado, un anillo de ciclopentano fusionado, un anillo de fenilo fusionado, o un anillo de piridilo fusionado, cada uno de los cuales puede estar sustituido con un átomo de halógeno, arilo, trihalo-metilo, o alquilo de 1 a 4 átomos de carbono;

o $R^5$ y $R^{5a}$ pueden formar juntos un anillo espiro-carbocíclico saturado que tiene entre 3 y 6 átomos de carbono del anillo, el cual está opcionalmente sustituido por 0 a 2 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, fenil-alquilo de 0 a 4 átomos de carbono, naftil-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, o dos sustituyentes tomados juntos forman un anillo carbocíclico fusionado o espirocíclico de 3 a 7 miembros, cada uno de los cuales está

sustituido con 0 a 3 átomos de halógeno o grupos alquilo de 1 a 4 átomos de carbono independientemente seleccionados;

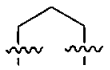
$R_8$, $R_{10}$, y $R_{11}$ se seleccionan cada uno independientemente a partir del grupo que consiste en H y alquilo de 1 a 4 átomos de carbono;

$R_6$, $R_7$, y $R_{13}$ son H;

$R_9$ y $R_{12}$ se seleccionan cada uno independientemente a partir del grupo que consiste en hidrógeno, alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono; y

V también se selecciona a partir del grupo que consiste en $-Q^1-Q^2$, en donde $Q^1$ está ausente, o es C(O), N(H), N(alquilo de 1 a 4 átomos de carbono), C=N(CN), C=N($SO_2CH_3$), C=N-COH-alquilo de 1 a 4 átomos de carbono, o C=N-COH, y $Q^2$ es hidrógeno, o se selecciona a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, O-alquilo de 1 a 4 átomos de carbono, $NH_2$, N(H)-alquilo de 1 a 4 átomos de carbono, N(alquilo de 1 a 4 átomos de carbono)$_2$, $SO_2$-arilo, $SO_2$-alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo, heteroarilo, y heterociclo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno, alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono sustituido por uno o más átomos de halógeno, o cicloalquilo de 3 a 6 átomos de carbono;

o $R_3$ y W pueden formar juntos un anillo de 6 miembros de la fórmula II:



II

en donde la fórmula II puede estar adicionalmente sustituida;

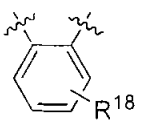
o cuando y es 0, $R^{10}$ y V pueden formar un anillo de ciclo-propilo que puede estar adicionalmente sustituido por un grupo amida.

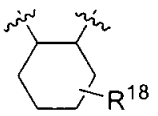
En otra modalidad de la Fórmula I o de la Fórmula III, $R^{14}$ es C(O).

En todavía otra modalidad de la Fórmula I o de la Fórmula III, y es 0, y $R_{10}$ y V forman un anillo de ciclo-propilo que está sustituido con C(O)N(H)-pirazina.

En todavía otra modalidad de la Fórmula I, en donde $R_4$, $R_6$, y $R_7$ son hidrógeno, y $R^5$ es aril-alquilo de 0 a 3 átomos de carbono, -O-heteroarilo, o heteroaril-alquilo de 0 a 3 átomos de carbono, en donde arilo y heteroarilo pueden estar independientemente sustituidos una o más veces (o de preferencia entre una y cinco veces) con un átomo de halógeno, arilo, trihalo-metilo, cicloalquilo de 3 a 6 átomos de carbono, o alquilo de 1 a 4 átomos de carbono.

En una modalidad de la Fórmula I, n es 1, y $R_4$ y $R^5$ forman juntos los siguientes sistemas de anillos fusionados:



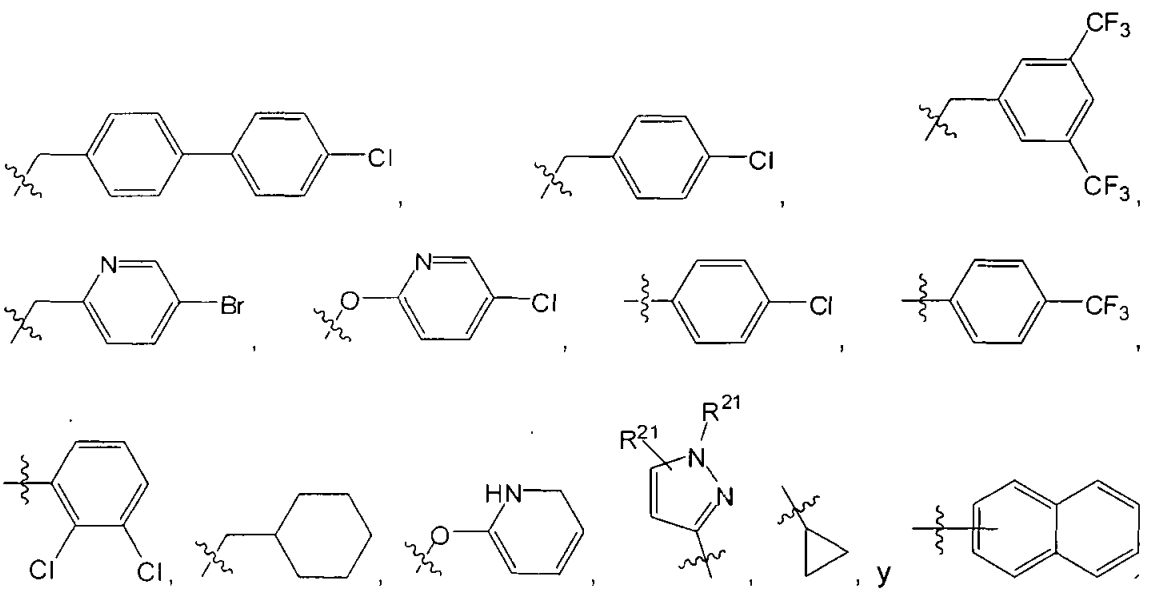

en donde $R^{18}$ se selecciona a partir del grupo que consiste en hidrógeno, un átomo de halógeno, arilo, trihalo-metilo, y alquilo

de 1 a 4 átomos de carbono.

En otra modalidad de la Fórmula I, $R^5$ se selecciona a partir del grupo que consiste en piperidina, fenilo, -O-piridinilo, y $CH_2$-piridinilo, en donde los grupos fenilo y piridinilo pueden estar independientemente sustituidos una o más veces (o de preferencia entre una y cinco veces) con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono.

En todavía otra modalidad de la Fórmula I, $R^5$ es 5-cloro-piridin-2-ilo.

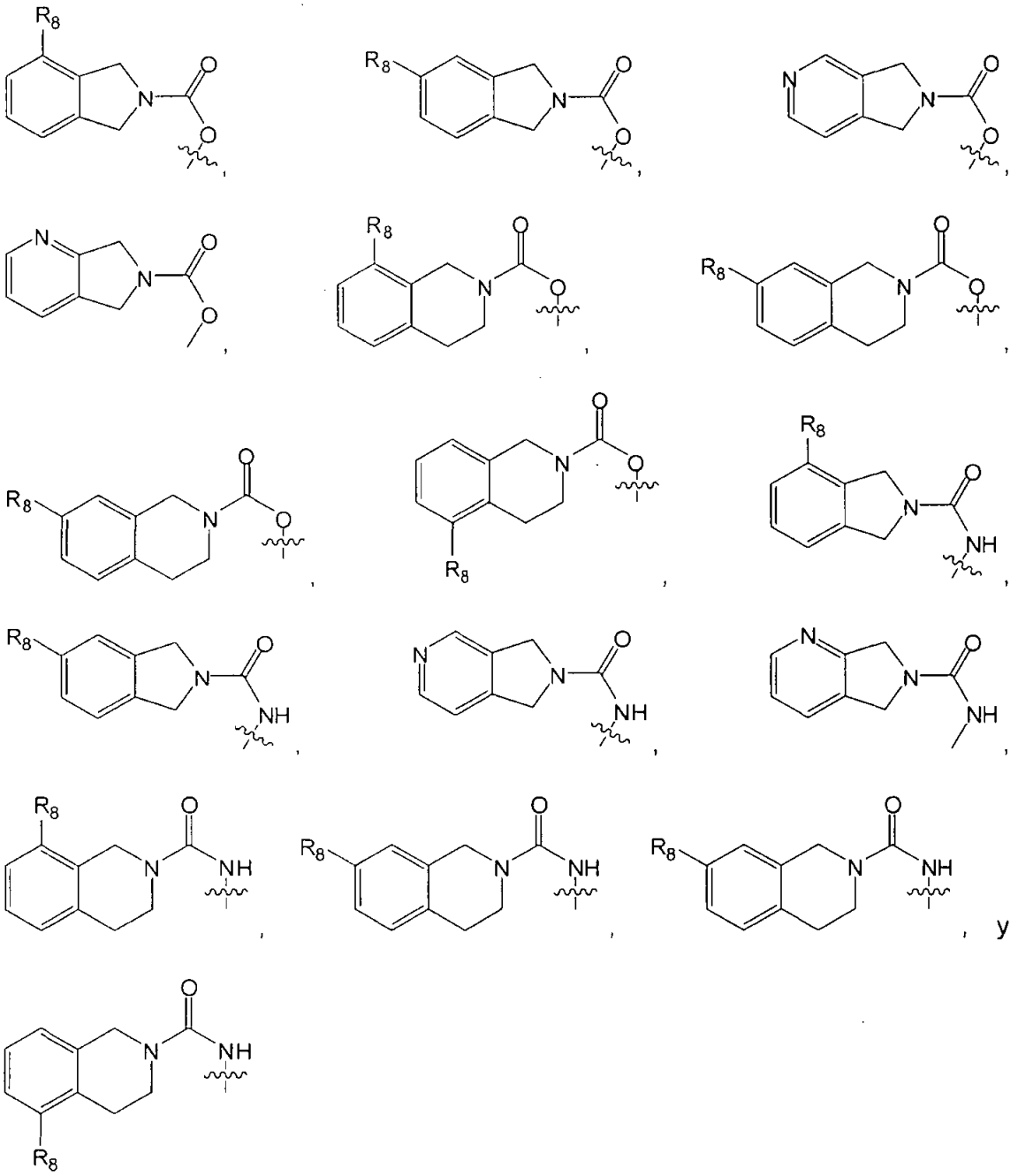
En todavía otra modalidad de la Fórmula I, $R^5$ se selecciona a partir del grupo que consiste en:



en donde $R^{21}$ se selecciona independientemente a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono y arilo.

Todavía otros compuestos de la Fórmula I o de la Fórmula III incluyen los compuestos en donde X es $CR_{5a}$, $R_{5a}$ es hidrógeno o

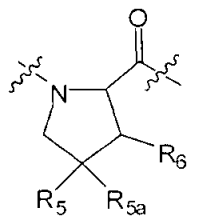
metilo, y $R_5$ es un residuo seleccionado a partir del grupo que consiste en:



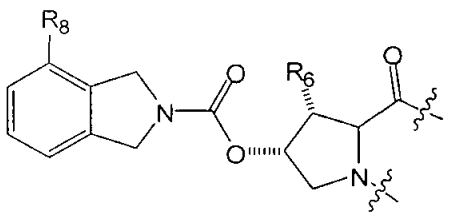
en donde $R_8$ se selecciona a partir de hidrógeno, metilo,

etilo, mono-, di-, o tri-fluoro-metilo, mono-, di-, o tri-fluoro-metoxilo, flúor, y cloro.

En todavía otra modalidad, los compuestos de la Fórmula I o de la Fórmula III incluyen los compuestos en donde el residuo

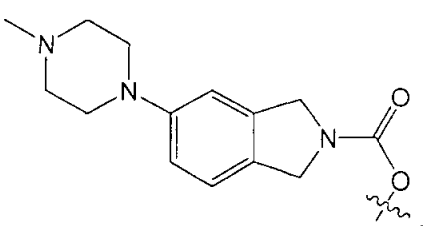


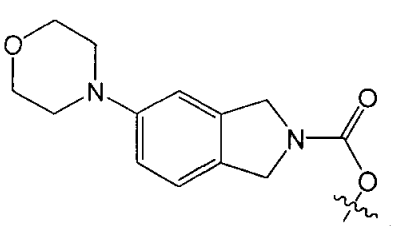
es un residuo de la fórmula:

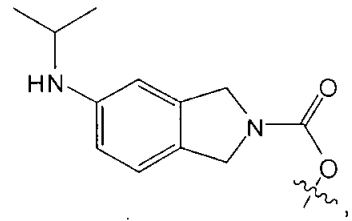


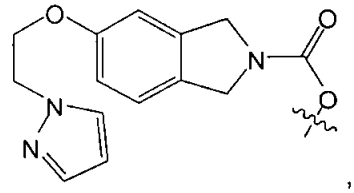
en donde $R_6$ es hidrógeno, metilo, etilo, y mono-, di-, y tri-fluoro-metilo; $R_8$ se selecciona a partir de hidrógeno, metilo, etilo, mono-, di-, o tri-fluoro-metilo, mono-, di-, o tri-fluoro-metoxilo, flúor, y cloro.

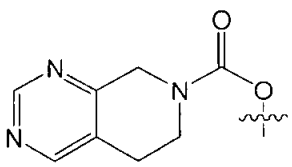
Todavía otros compuestos de la Fórmula I o de la Fórmula III incluyen los compuestos en donde X es $CR_{5a}$, $R_{5a}$ es hidrógeno o metilo, y $R_5$ es un residuo seleccionado a partir del grupo que consiste en:

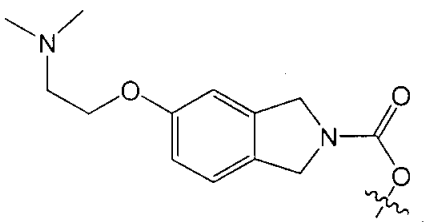


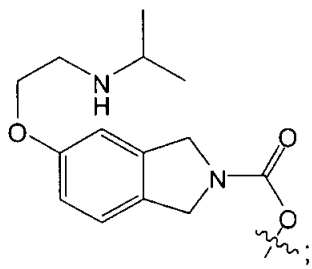


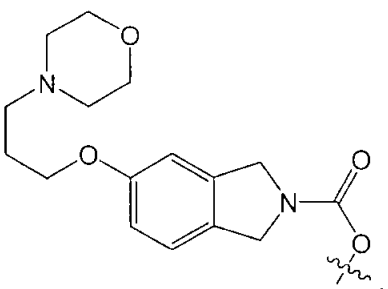


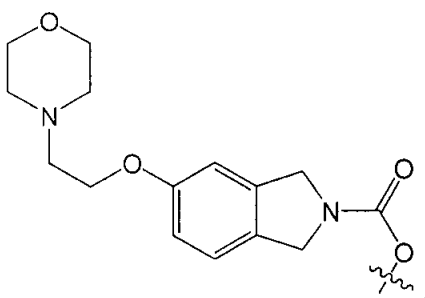


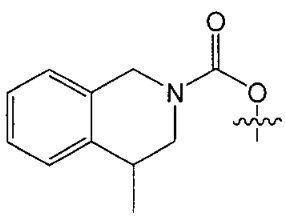


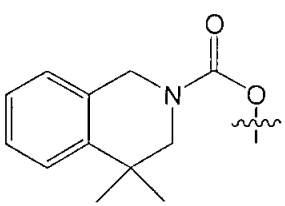


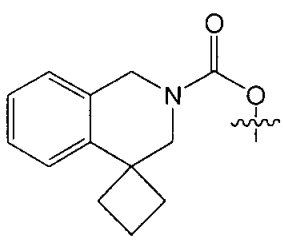


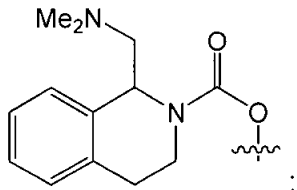


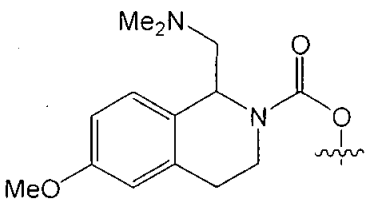


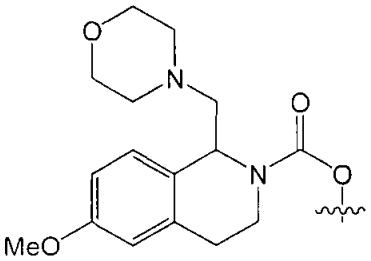


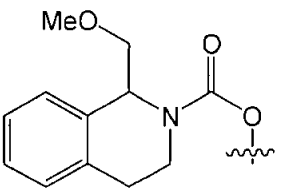




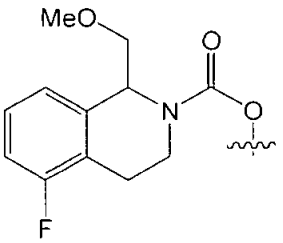


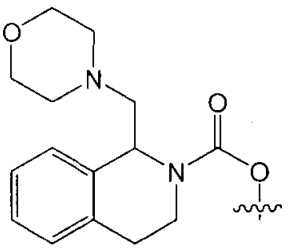


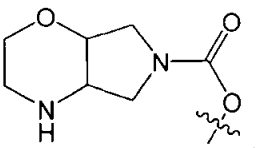
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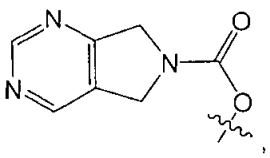
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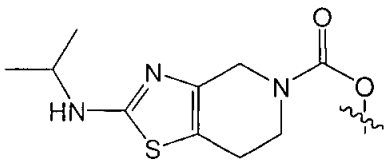


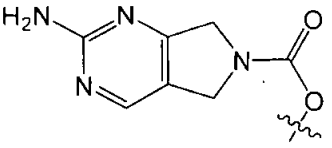
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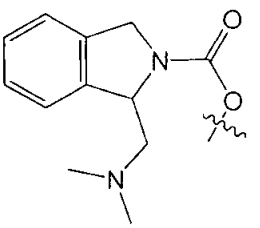
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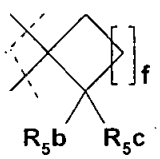
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En todavía otras modalidades, los compuestos de la Fórmula I incluyen los compuestos en donde $CR^5R^{5a}$, cuando se toman en combinación, forman un anillo carbocíclico espirocíclico de 3 a 6 miembros. Ciertos anillos espirocíclicos incluyen grupos de la fórmula:



en donde:

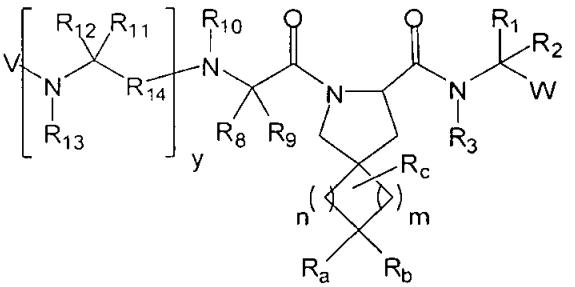
**f** es 0, 1, 2, 3, 4, ó 5;

$R_{5b}$ y $R_{5c}$ se seleccionan independientemente a partir de hidrógeno, halógeno, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, fenil-alquilo de 0 a 4 átomos de carbono, naftil-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, o dos sustituyentes, tomados juntos, forman un anillo carbocíclico fusionado o espirocíclico de 3 a 7 miembros, cada uno de los cuales está sustituido con 0 a 3 átomos de halógeno o grupos alquilo de 1 a 4 átomos de carbono independientemente seleccionados.

En todavía otras modalidades, los compuestos de la Fórmula I incluyen los compuestos en donde X es $CR^5R^{5a}$, $R^4$ es hidrógeno, y $R^5$ y $R^{5a}$ tomados en combinación forman un carbociclo espirocíclico de 3 a 6 miembros sustituido con 0 a 2 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, fenil-alquilo de 0 a 4 átomos de carbono, naftil-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, o dos sustituyentes tomados juntos forman un anillo carbocíclico fusionado o espirocíclico de 3 a 7 miembros, cada uno de los cuales

está sustituido con 0 a 3 átomos de halógeno o grupos alquilo de 1 a 4 átomos de carbono independientemente seleccionados.

Ciertos compuestos de la Fórmula I incluyen los compuestos de la fórmula:



en donde:

**m** y **n** son 0 ó 1, de tal manera que la suma de **m** y **n** es igual a 1 ó 2;

$R_a$ es hidrógeno, alquilo de 1 a 4 átomos de carbono, o fenilo;

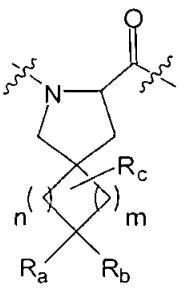
$R_b$ es hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono-alquilo de 0 a 4 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, alcanoílo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono-carbonilo, o fenilo,

o $R_a$ y $R_b$ tomados juntos forman un anillo fusionado o espirocíclico de 3 a 6 miembros, que tiene 0, 1, o 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente

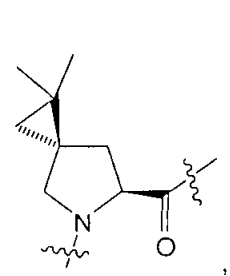
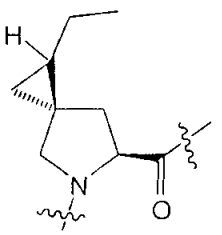
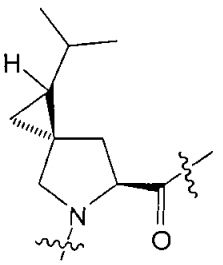
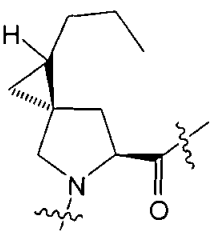
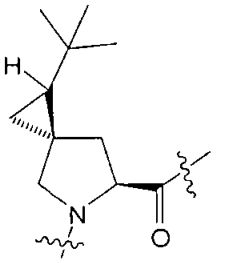
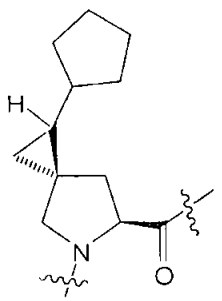
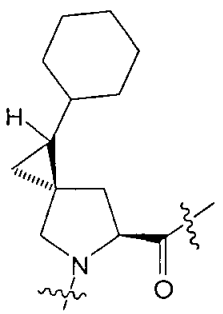
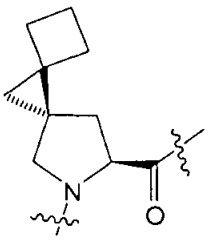
seleccionados a partir de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alcanoílo de 1 a 4 átomos de carbono, y fenilo; y

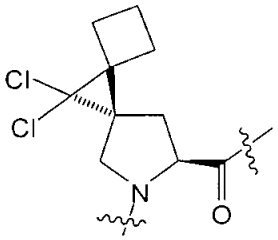
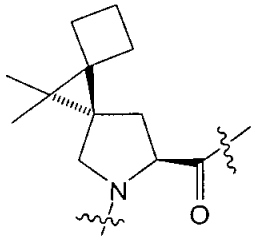
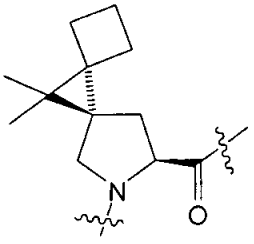
$R_c$ representa de 0 a 4 sustituyentes, los cuales se seleccionan independientemente en cada presentación de $R_c$ a partir del grupo que consiste en halógeno, alquilo de 1 a 4 átomos de carbono, y fenilo, o dos sustituyentes $R_c$ *geminales*, tomados en combinación, forman un anillo espirocíclico de 3 a 6 miembros.

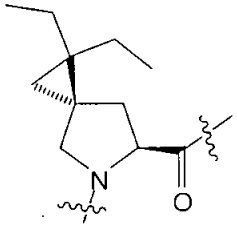
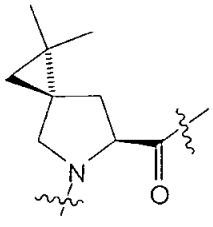
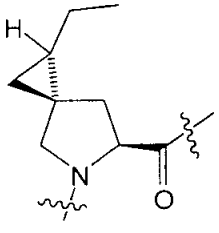
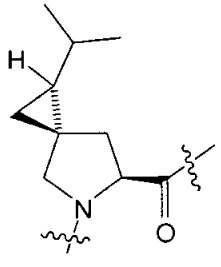
En algunas otras modalidades, los compuestos de la Fórmula I incluyen los compuestos en donde el residuo divalente:

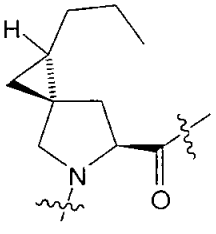
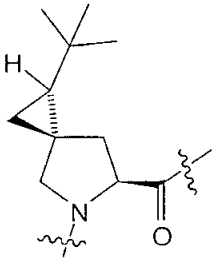
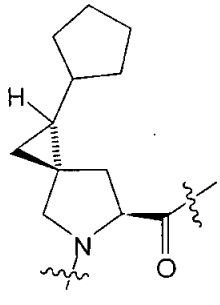
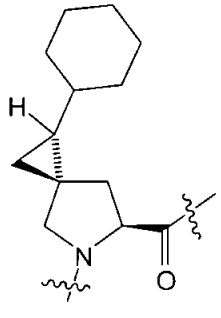


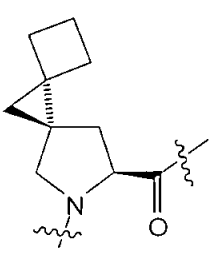
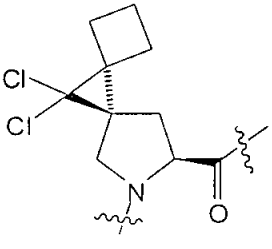
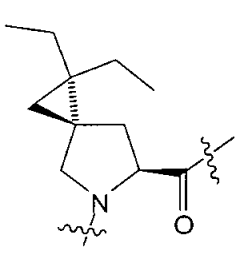
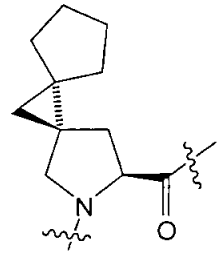

se selecciona a partir del grupo que consiste en:

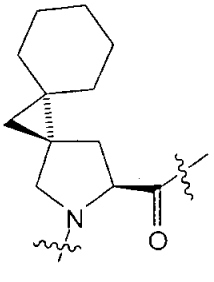
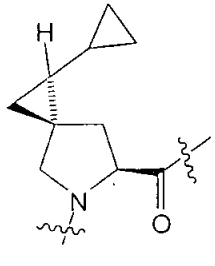
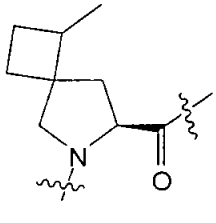
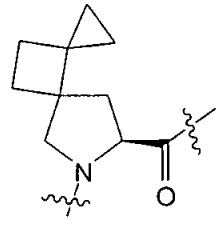









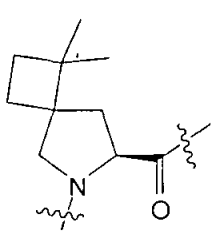
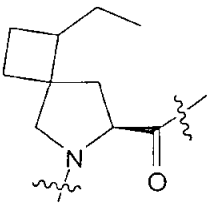
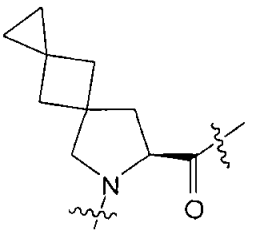
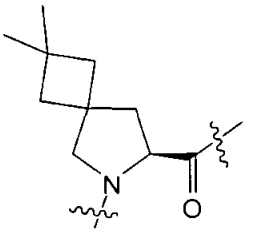




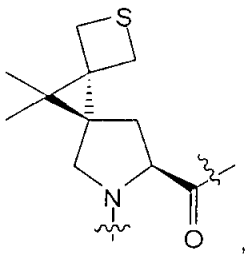
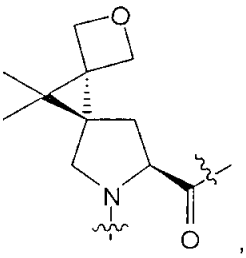
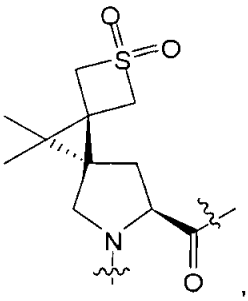
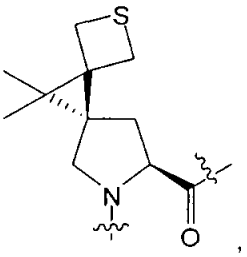





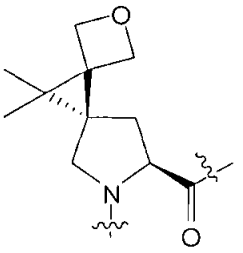
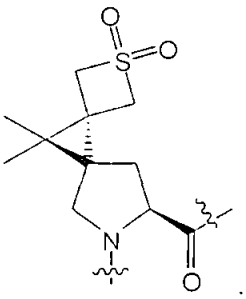





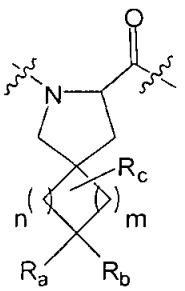






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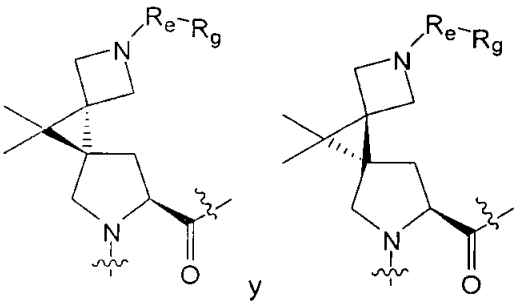

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y

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En algunas otras modalidades, los compuestos de la Fórmula I incluyen los compuestos en donde el residuo divalente:



se selecciona a partir del grupo que consiste en:



y

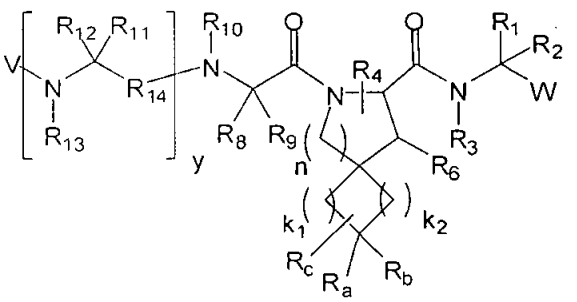
en donde $R_e$ está ausente, o es C(O), o $S(O)_2$; y $R_g$ es hidrógeno o se selecciona a partir del grupo que consiste en alquilo de 1 a 6 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, heterociclil-alquilo de 0 a 4 átomos de carbono, y cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, cada uno de los cuales está sustituido con 0 a 4 sustituyentes independientemente seleccionados a partir del grupo que consiste en ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-

carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida.

En ciertas modalidades, los compuestos de la Fórmula III incluyen los compuestos en donde $R^5$ y $R^{5a}$, tomados en combinación, forman un anillo espirocíclico que tiene entre 3 y 7 átomos del anillo, y que tiene 0, 1, ó 2 heteroátomos del anillo, cuyo anillo espirocíclico está sustituido con un anillo espirocíclico de 3 a 7 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, y en donde cada uno de los anillos espirocíclicos tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos

de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida.

En otra modalidad, los compuestos de la Fórmula III incluyen los compuestos de la fórmula:



en donde:

$k_1$ y $k_2$ son 0 ó 1, de tal manera que la suma de $k_1$ y $k_2$ es igual a 1 ó 2;

$R_a$ y $R_b$ tomados juntos forman un anillo espirocíclico de 3 a 6 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alcanoilo de 1 a 4 átomos de carbono, y fenilo;

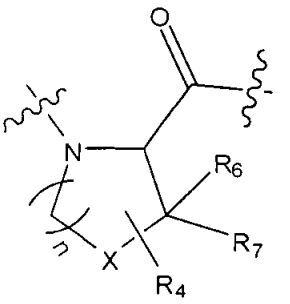
$R_c$ representa de 0 a 2 sustituyentes, los cuales se seleccionan independientemente en cada presentación de $R_c$, a partir del grupo que consiste en halógeno, alquilo de 1 a 4 átomos de carbono, y fenilo, o dos sustituyentes $R_c$ *geminales*, tomados en combinación, forman un anillo espirocíclico de 3 a 6 miembros;

$R_4$ representa 0, 1, ó 2 sustituyentes, cada uno de los

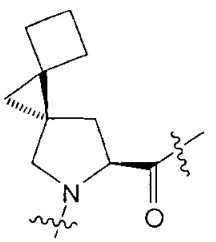
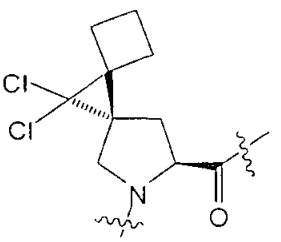
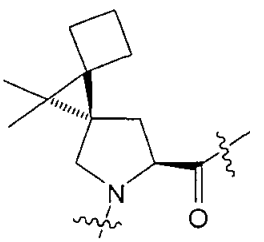
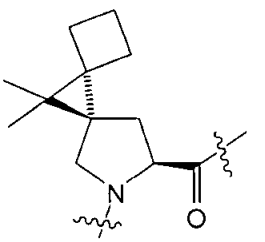
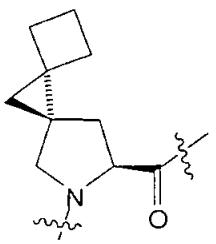
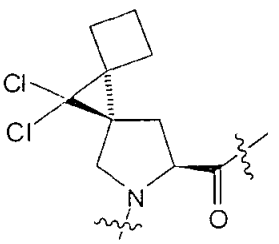
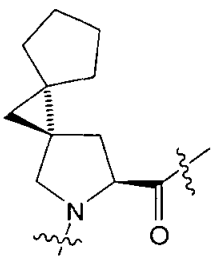
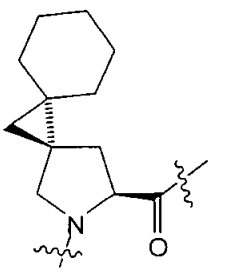
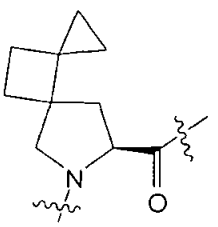
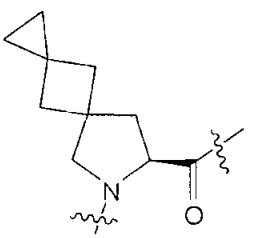
cuales se selecciona independientemente a partir de H y alquilo de 1 a 4 átomos de carbono; y

$R_6$ es hidrógeno o alquilo de 1 a 4 átomos de carbono.

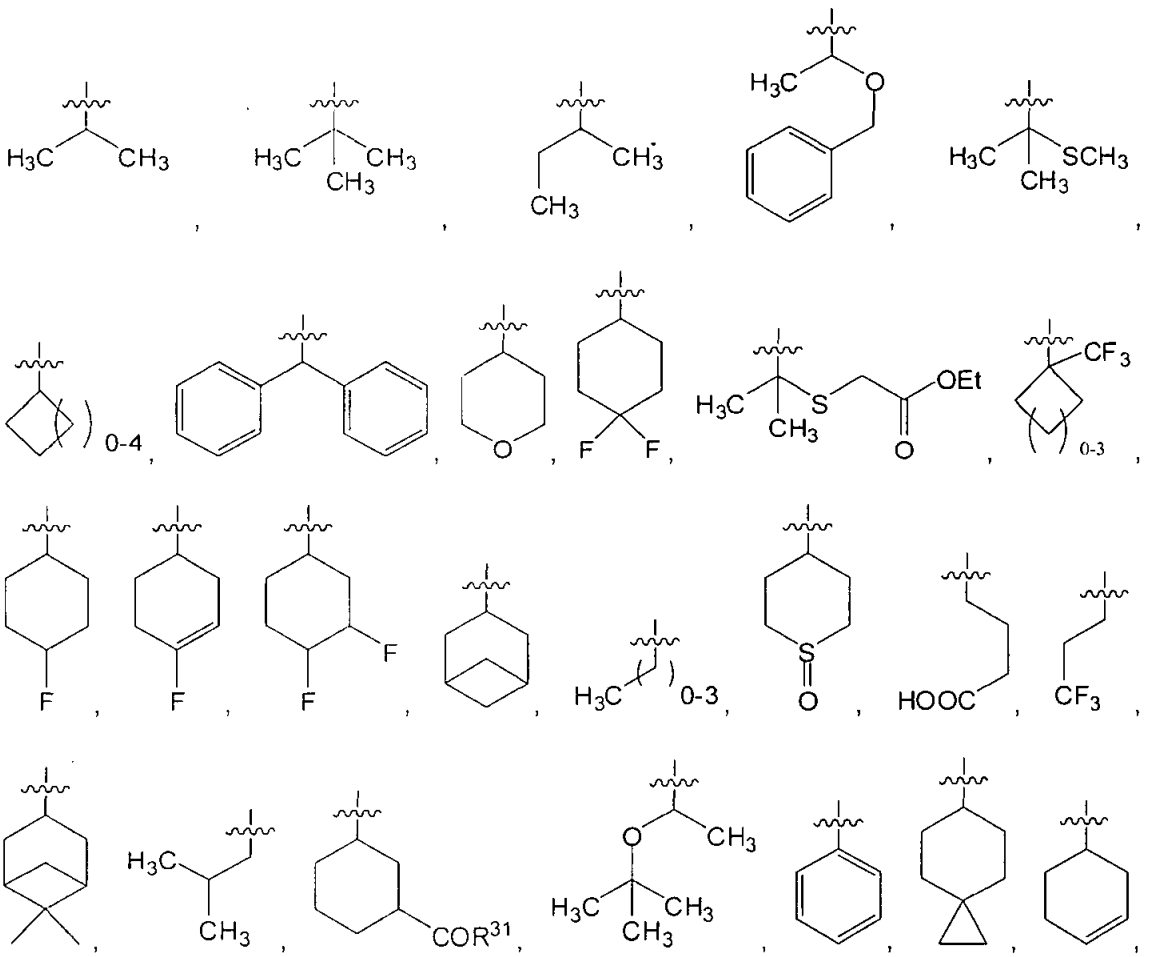
En todavía otro aspecto, los compuestos de la Fórmula III incluyen los compuestos en donde el residuo divalente:

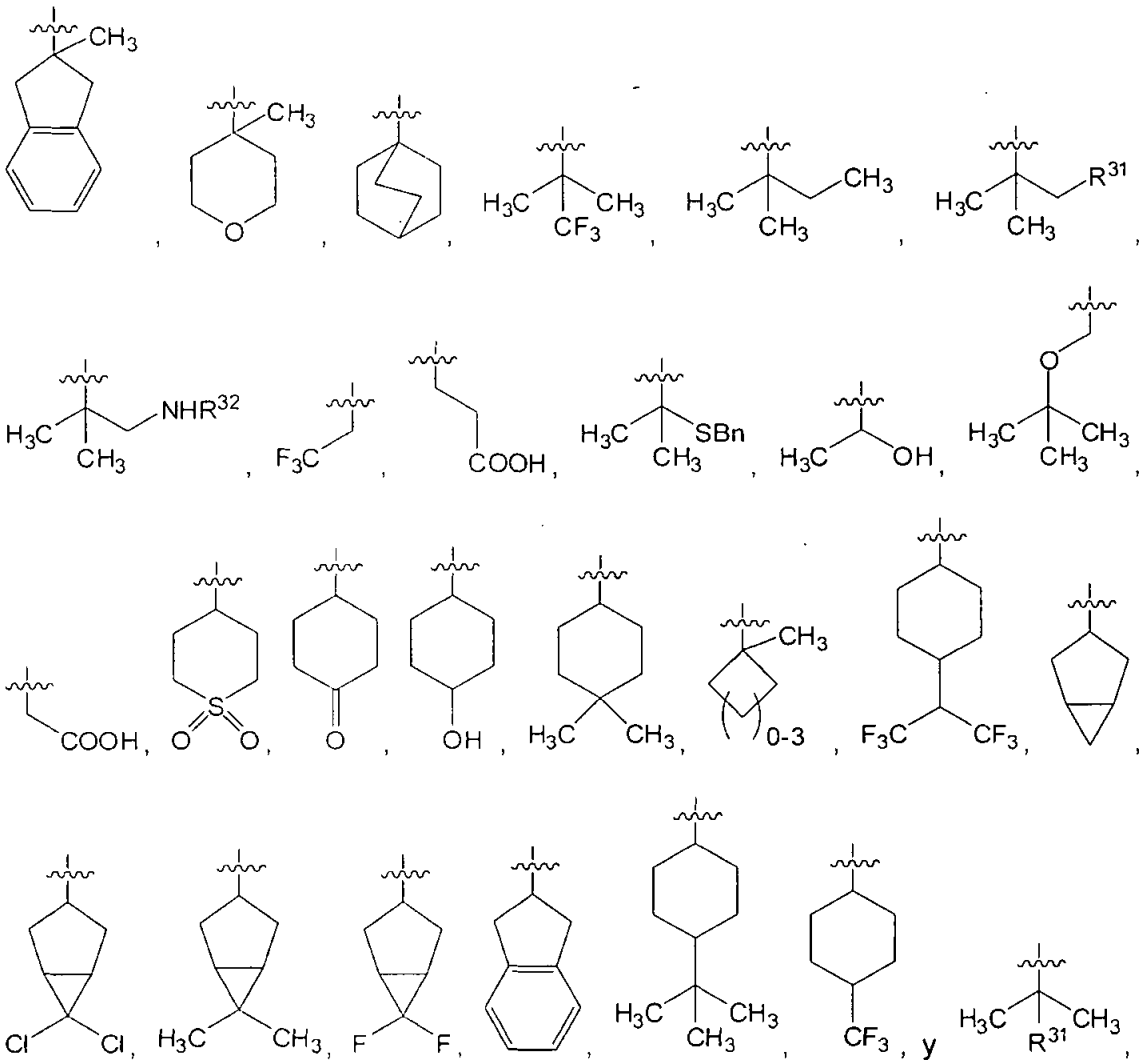


se selecciona a partir del grupo que consiste en:


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En todavia otras modalidades, los compuestos que tienen la estructura de la Fórmula I o de la Fórmula III, tienen sustituyentes en $R_6$, $R_9$, $R_{11}$, y $R_{12}$, los cuales se seleccionan cada uno independientemente a partir del grupo que consiste en:

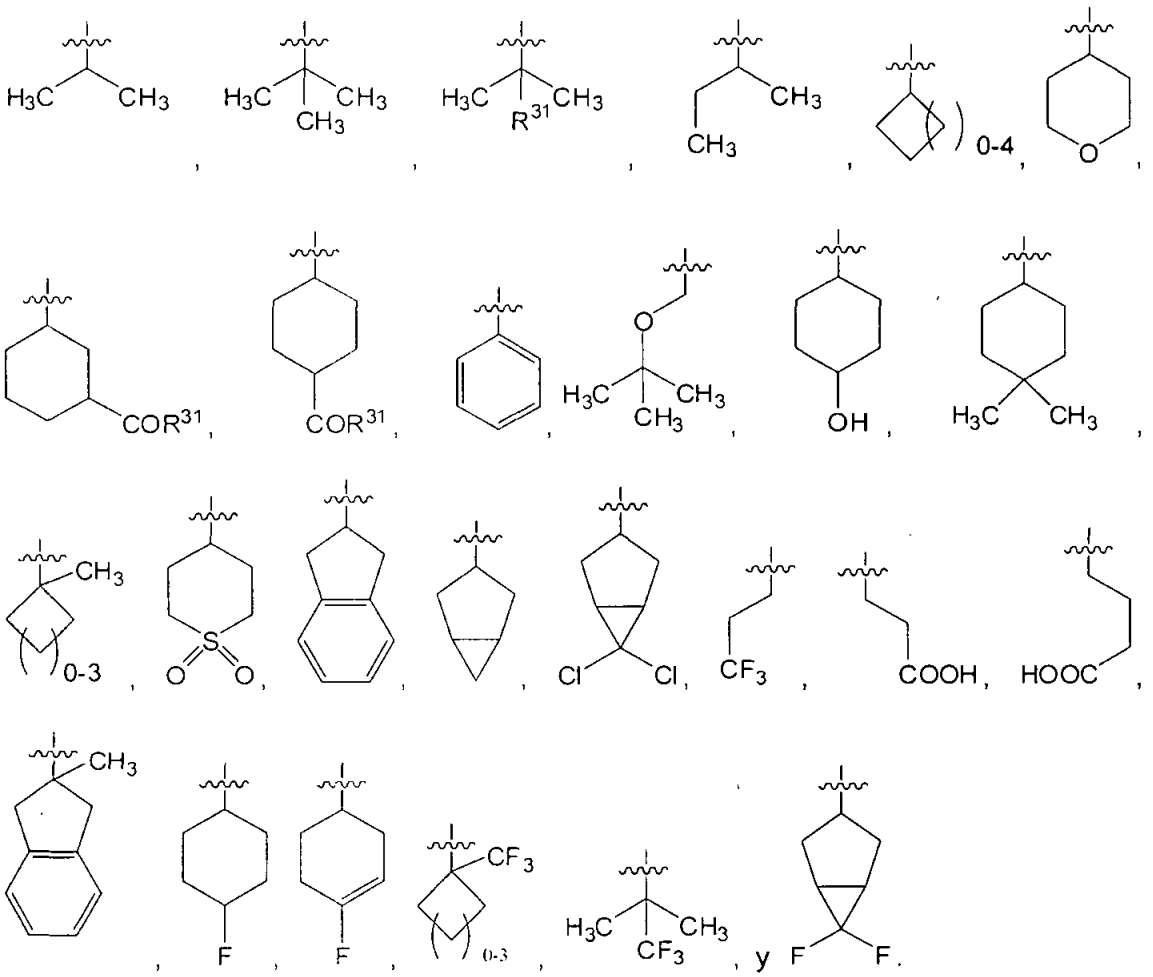




en donde $R^{31}$ es hidroxilo o alcoxilo de 1 a 6 átomos de carbono; y

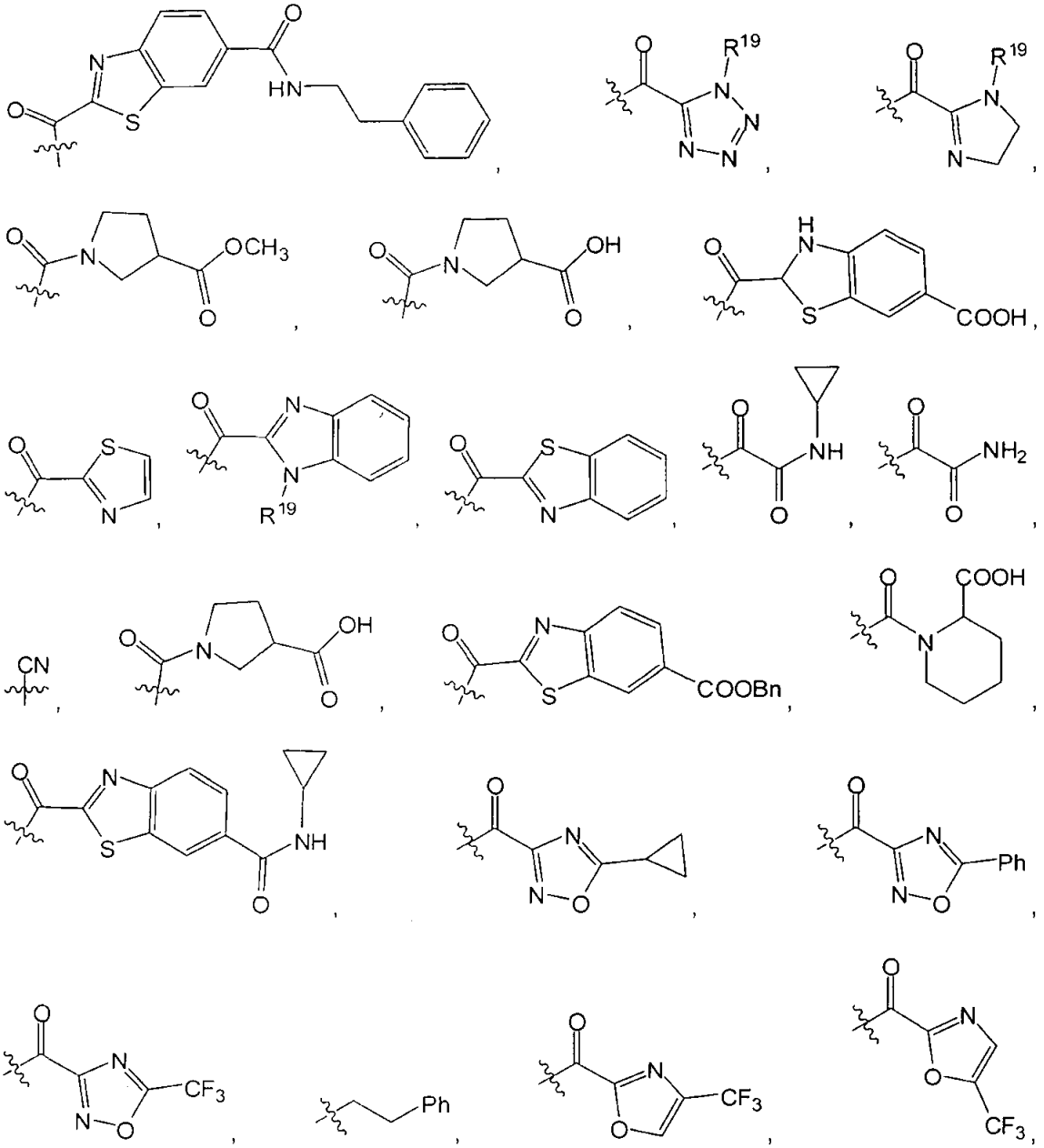
$R^{32}$ es hidrógeno, acetilo, C(O)O$^t$Bu, o C(O)N(H)$^t$Bu.

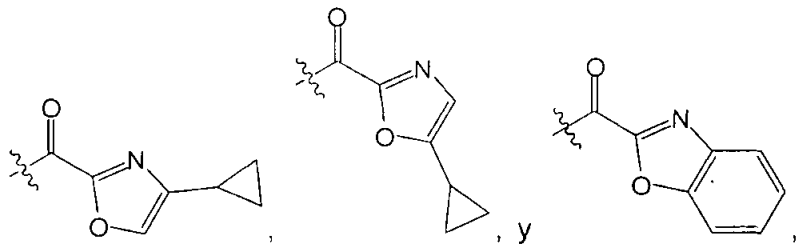
En algunas otras modalidades, los compuestos que tienen la estructura de la Fórmula I o de la Fórmula III, están sustituidos en $R_3$ con un sustituyente seleccionado a partir del grupo que consiste en:



En una modalidad de la Fórmula I o de la Fórmula III, W se selecciona a partir del grupo que consiste en C(O)-C(O)$NH_2$, C(O)-C(O)N(H)-ciclopropilo, C(O)-benzotiazol, C(O)-benzoimidazol, C(O)-oxazol, C(O)-imidazol, y C(O)-oxadiazol, en donde los grupos benzotiazol, benzoimidazol, oxazol, y oxadiazol pueden estar independientemente sustituidos una o más veces (o de preferencia entre una y cinco veces) con un átomo de halógeno, arilo, trihalometilo, cicloalquilo de 3 a 6 átomos de carbono, o alquilo de 1 a 4 átomos de carbono.

En otra modalidad de la Fórmula I o de la Fórmula III, W se selecciona a partir del grupo que consiste en:





en donde $R^{19}$ se selecciona a partir del grupo que consiste en hidrógeno, arilo, trihalo-metilo, y alquilo de 1 a 4 átomos de carbono.

En todavía otra modalidad de la Fórmula I o de la Fórmula III, $R^2$ se selecciona a partir del grupo que consiste en propilo y $(CH_2)_2$-ciclo-butilo.

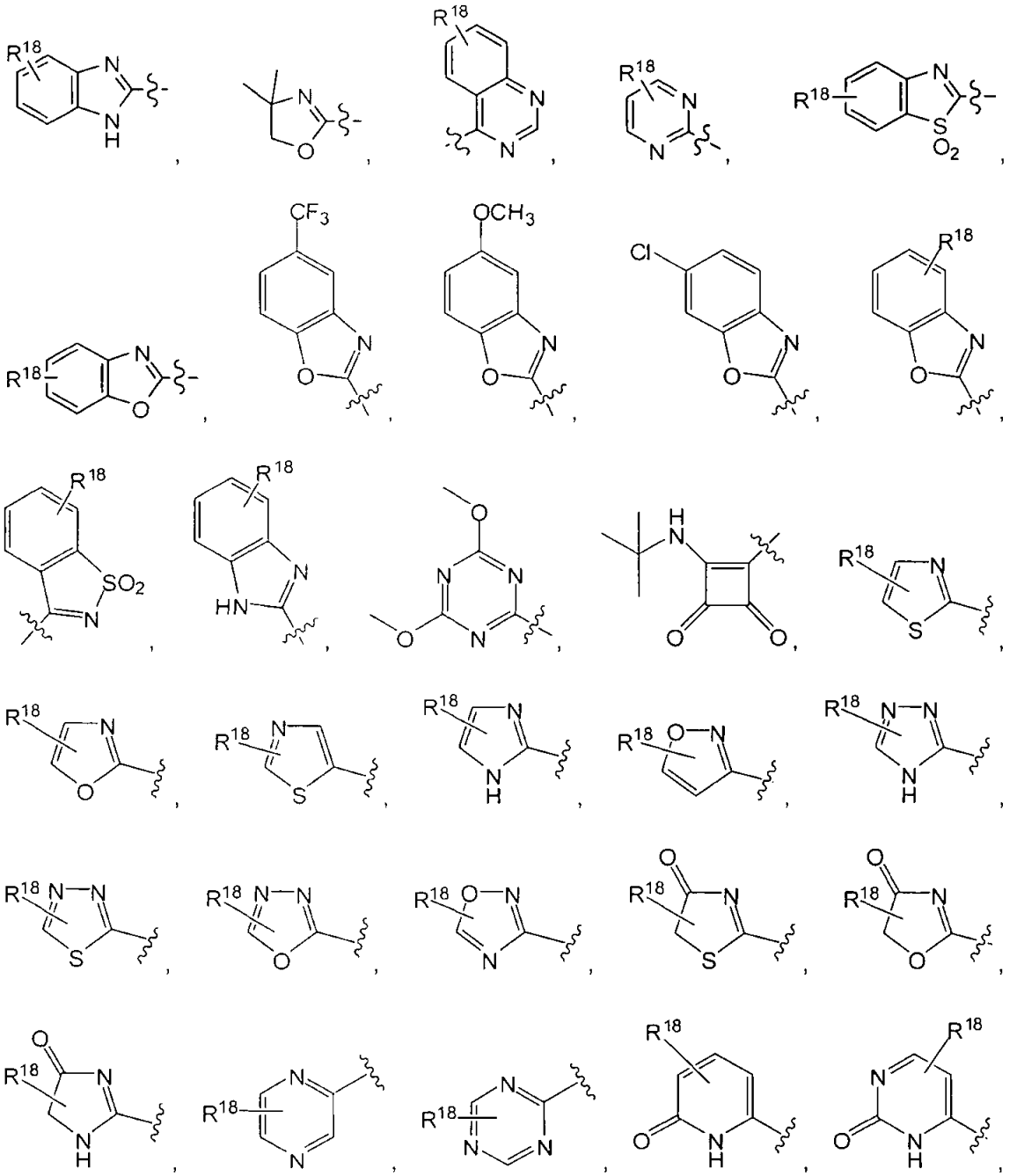
En todavía otra modalidad de la Fórmula I o de la Fórmula III, $R_{11}$ es H, y $R_{12}$ es cicloalquilo de 3 a 6 átomos de carbono.

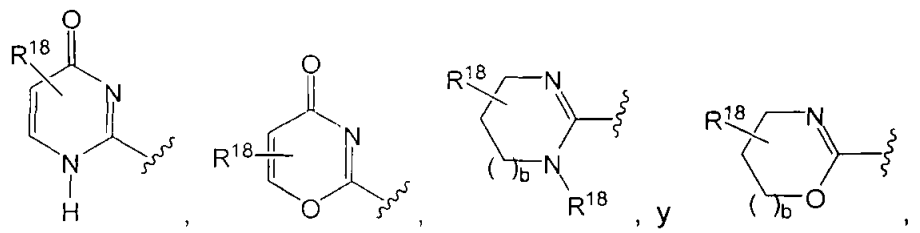
En una modalidad de la Fórmula I o de la Fórmula III, $R^{12}$ es ciclohexilo.

En otra modalidad de la Fórmula I o de la Fórmula III, V se selecciona a partir del grupo que consiste en C(O)-N(H)-terbutilo.

En todavía otra modalidad de la Fórmula I o de la Fórmula III, V es C(O)-$R^{20}$, en donde $R^{20}$ se selecciona a partir del grupo que consiste en cicloalquilo de 3 a 6 átomos de carbono, fenilo, pirazina, benzoxazol, 4,4-dimetil-4,5-dihidro-oxazol, benzoimidazol, pirimidina, 1,1-dióxido de benzotiazol, y quinazolina, cada uno de los cuales puede estar además independientemente sustituido con un átomo de halógeno, $CF_3$, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono.

En todavía otra modalidad de la Fórmula I o de la Fórmula III, V es $R^{20}$ o $C(O)-R^{20}$, en donde $R^{20}$ se selecciona a partir del grupo que consiste en:

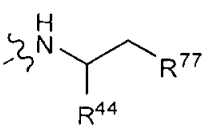




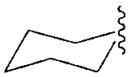
en donde b es 0, 1, ó 2; y $R^{18}$ se selecciona a partir del grupo que consiste en hidrógeno, un átomo de halógeno, arilo, trihalo-metilo, y alquilo de 1 a 4 átomos de carbono.

En otra modalidad de la Fórmula I o de la Fórmula III, V se selecciona a partir del grupo que consiste en cicloalquilo de 3 a 6 átomos de carbono, fenilo, pirazina, benzo-oxazol, 4,4-dimetil-4,5-dihidro-oxazol, benzoimidazol, pirimidina, 1,1-dióxido de benzotiazol, y quinazolina, cada uno de los cuales puede estar además independientemente sustituido con un átomo de halógeno, $CF_3$, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono.

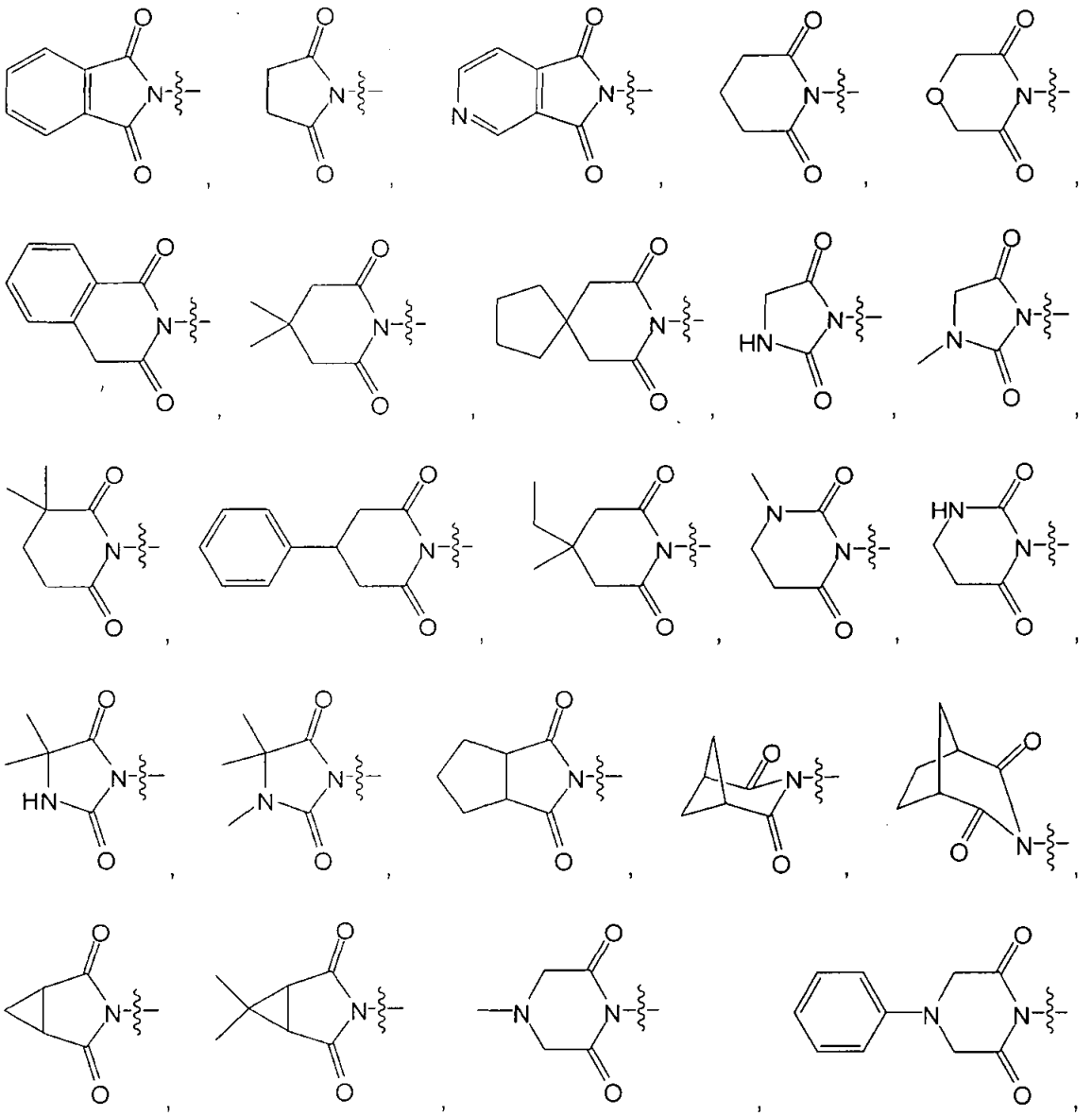
En ciertas modalidades, los compuestos de la Fórmula I o de la Fórmula III comprenden un grupo V seleccionado a partir de residuos que tienen la fórmula -C(O)-$R^{20}$, en donde $R^{20}$ es un residuo de la fórmula (i):

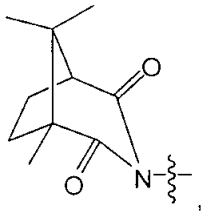
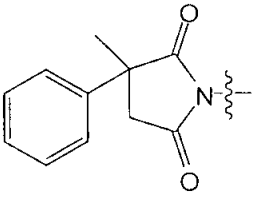
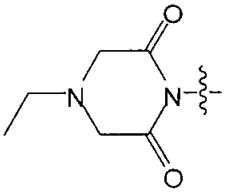
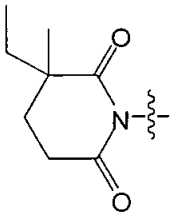


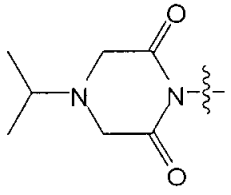
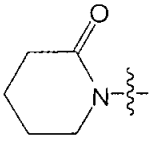
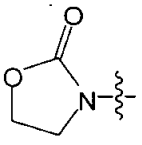
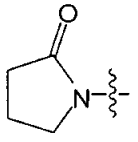
en donde $R^{44}$ se selecciona a partir del grupo que consiste en: butilo terciario, isopropilo, ciclohexilo, espiro-ciclohexilo (por

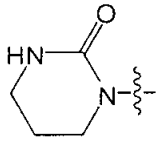
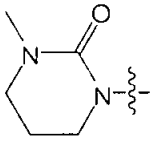
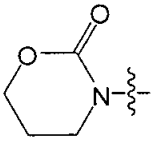
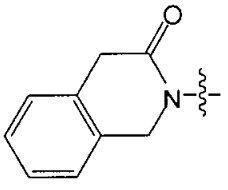
ejemplo,  ), y 1-metil-ciclohexilo;

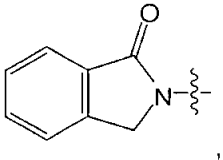
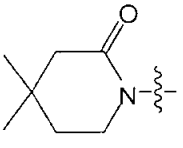
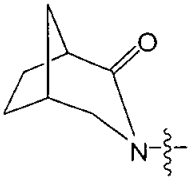
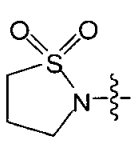
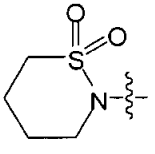
y $R^{77}$ se selecciona a partir del grupo que consiste en:

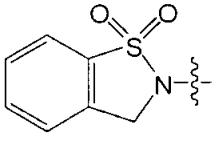
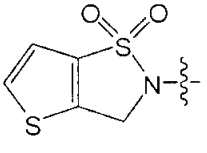
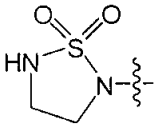
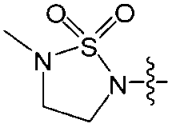
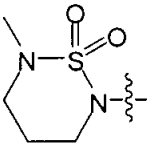


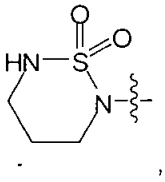
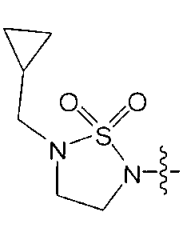
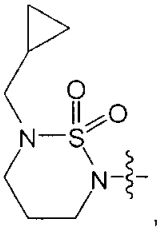
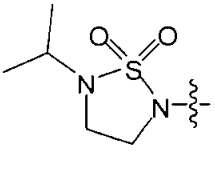
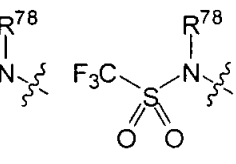





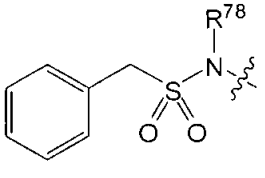
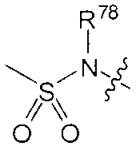
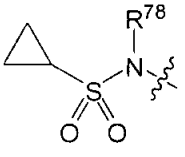
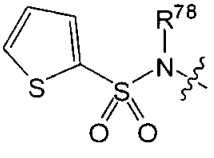





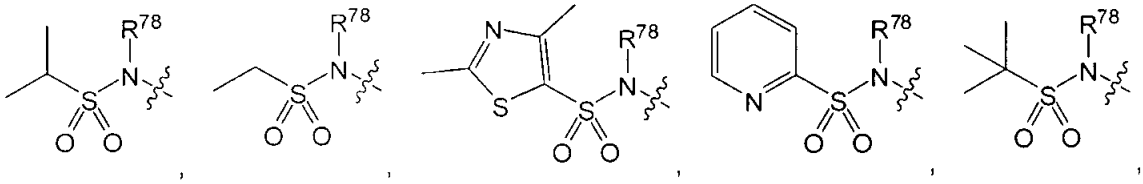





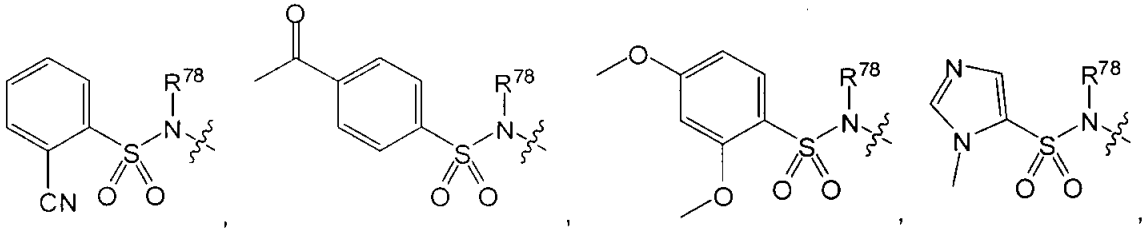






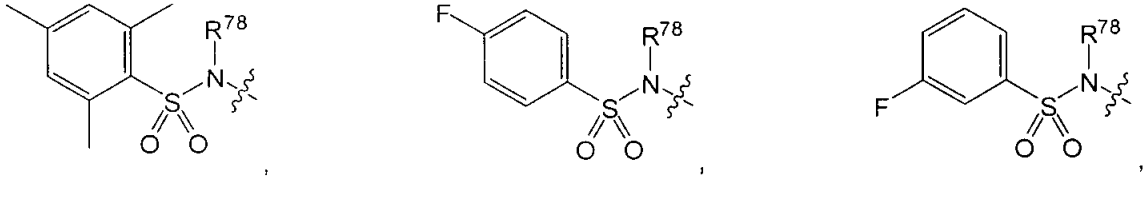






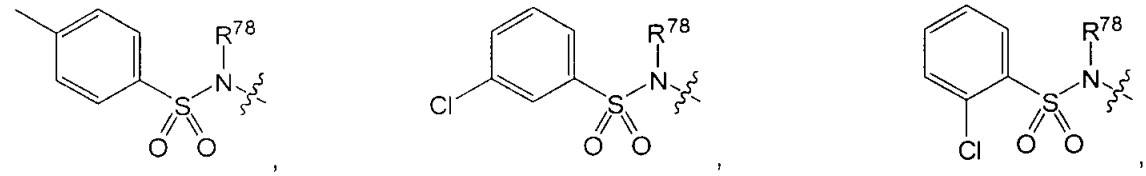






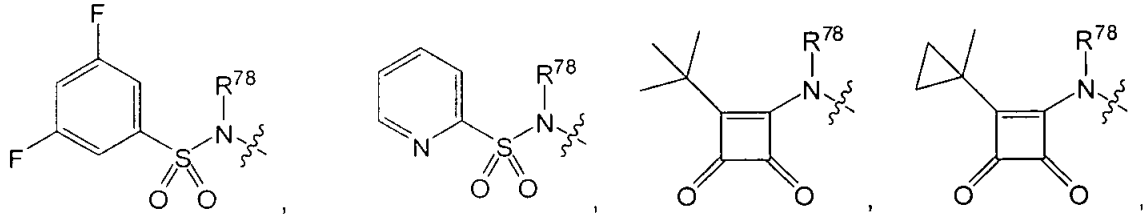





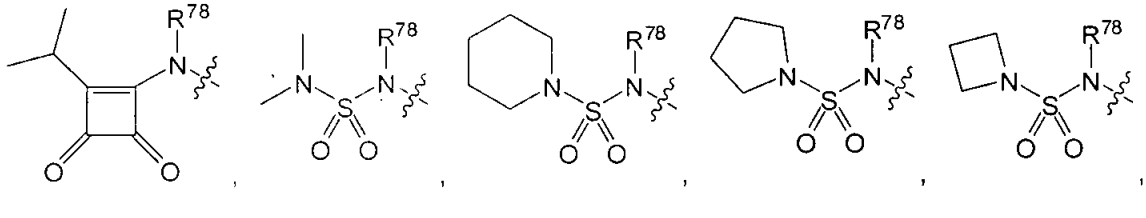


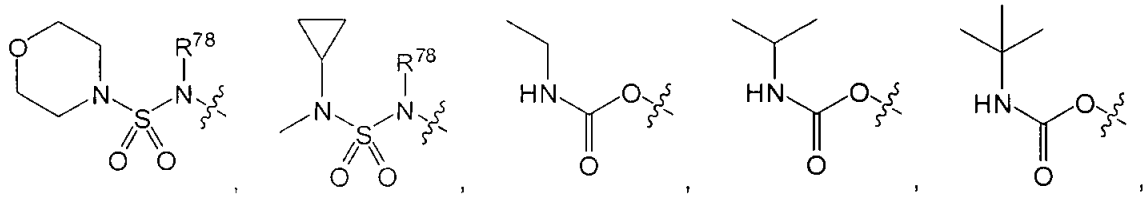


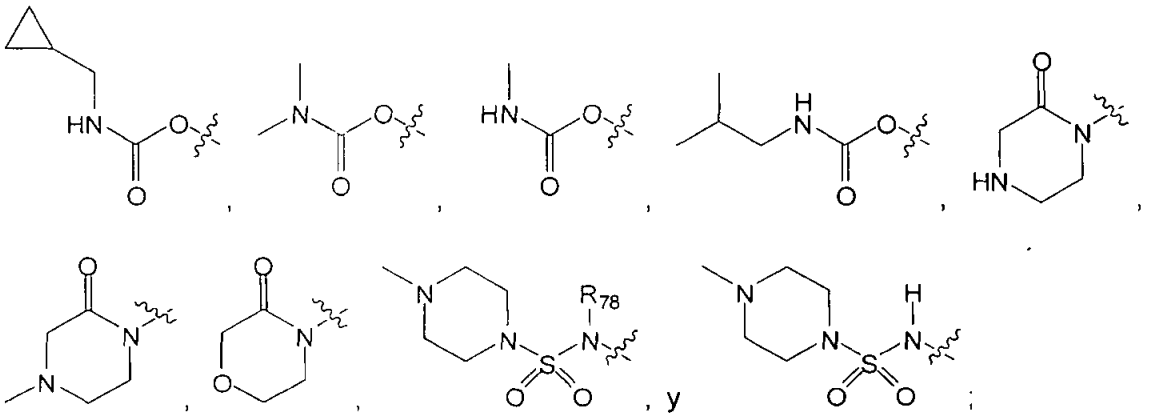






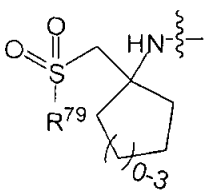






en donde $R^{78}$ se selecciona a partir de metilo, etilo, isopropilo, butilo terciario, y fenilo.

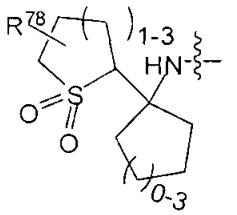
En todavía otras modalidades, los compuestos de la Fórmula I o de la Fórmula III comprenden un grupo V seleccionado a partir de residuos que tienen la fórmula -C(O)-V', en donde V' es un residuo de la fórmula (ii):



en donde $R^{79}$ se selecciona a partir del grupo que consiste en metilo, etilo, isopropilo, butilo terciario, butilo secundario, 4-metil-butilo, 1,1-dimetil-propilo, 1,1-dimetil-butilo, fenilo, bencilo, ciclo-pentilo, ciclo-hexilo, furil-metilo, y piridilo (por ejemplo, 2-piridilo, 3-piridilo, o 4-piridilo).

En algunas otras modalidades, los compuestos de la Fórmula I o de la Fórmula III comprenden un grupo V seleccionado a partir de residuos que tienen la fórmula -C(O)-V', en donde V' es un

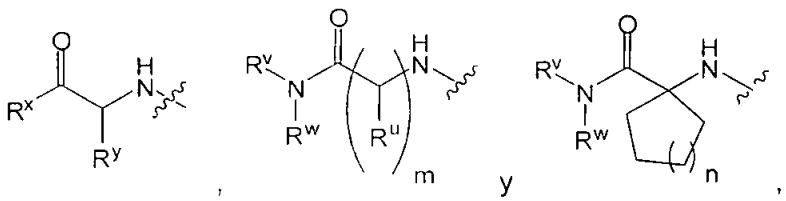
residuo de la fórmula (iii):



(iii)

en donde $R^{78}$ representa de 0 a 3 grupos independientemente seleccionados a partir de alquilo de 1 a 6 átomos de carbono y cicloalquilo de 3 a 6 átomos de carbono.

En ciertas modalidades, los compuestos de la Fórmula I o de la Fórmula III comprenden un grupo V seleccionado a partir de residuos que tienen la fórmula -C(O)-V', en donde V' es un residuo de la fórmula (iv):



en donde **m** es 1 ó 2; **n** es 0, 1, 2, ó 3;

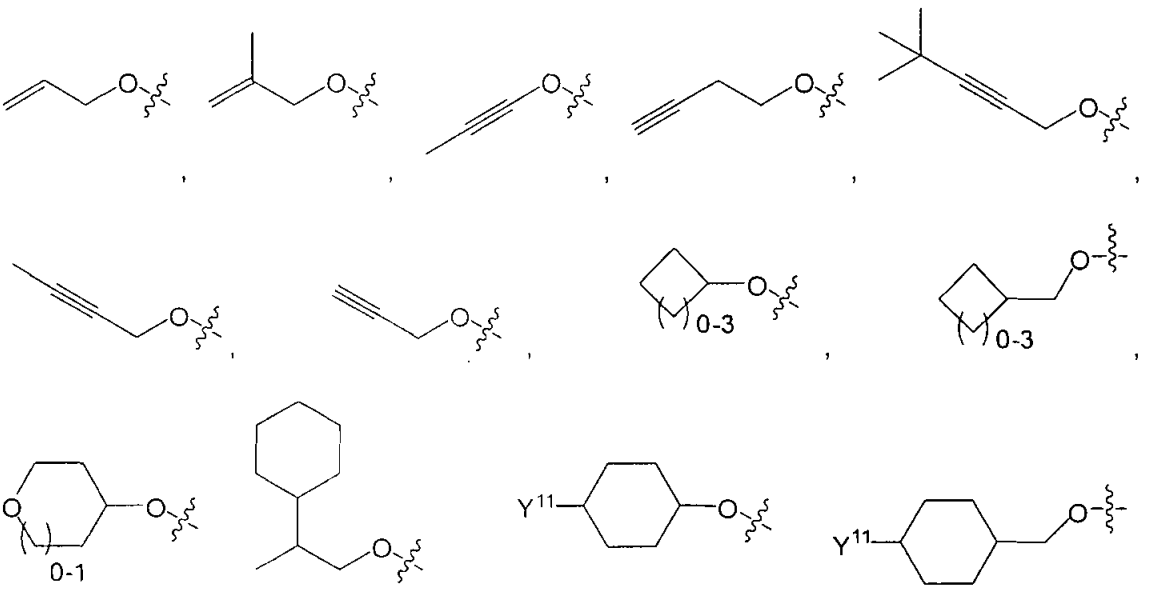
$R^u$, $R^v$, y $R^w$ se seleccionan independientemente en cada presentación a partir del grupo que consiste en hidrógeno, alquilo de 1 a 6 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, hetero-aril-alquilo de 0 a 4 átomos de carbono, heterociclil-alquilo de 0 a 4 átomos de carbono, y cicloalquil-alquilo de 0 a 4 átomos de carbono; o

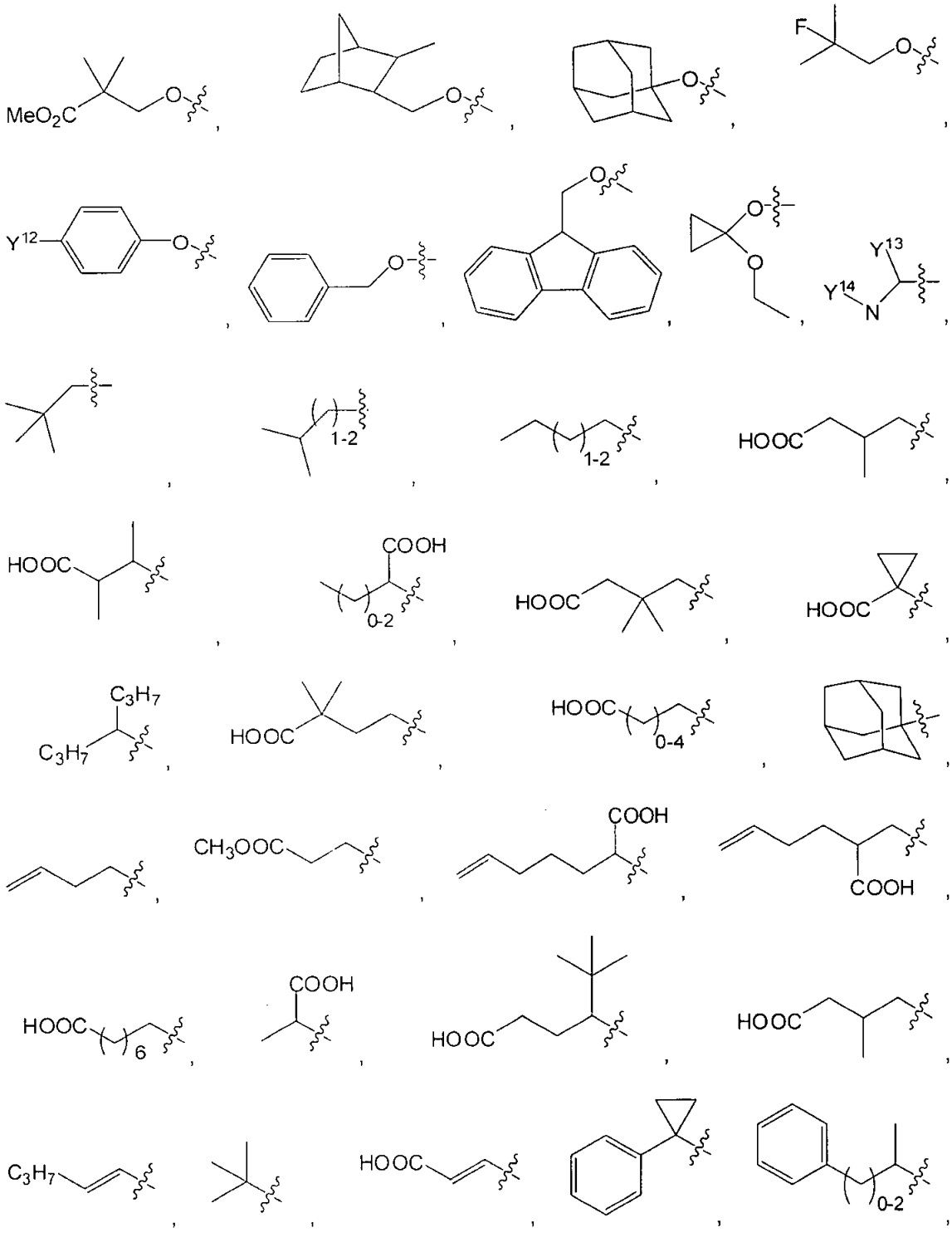
$R^v$ y $R^w$, tomados en combinación, forman un anillo que tiene entre 3 y 7 átomos del anillo, y que tiene 0, 1, ó 2 hetero-átomos, el cual está sustituido con 0 a 2 grupos alquilo y de 0 a 1

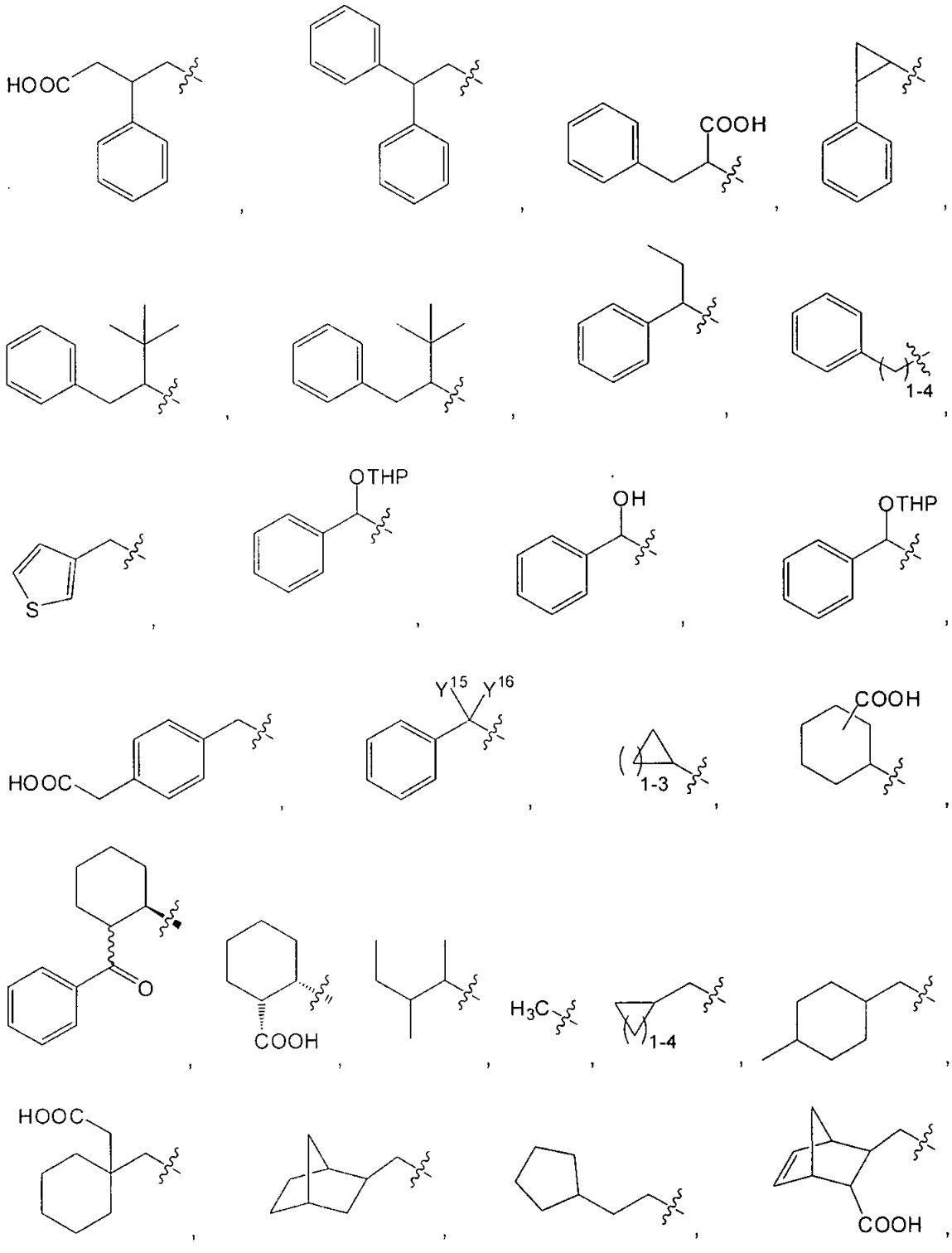
grupo espirocíclico.

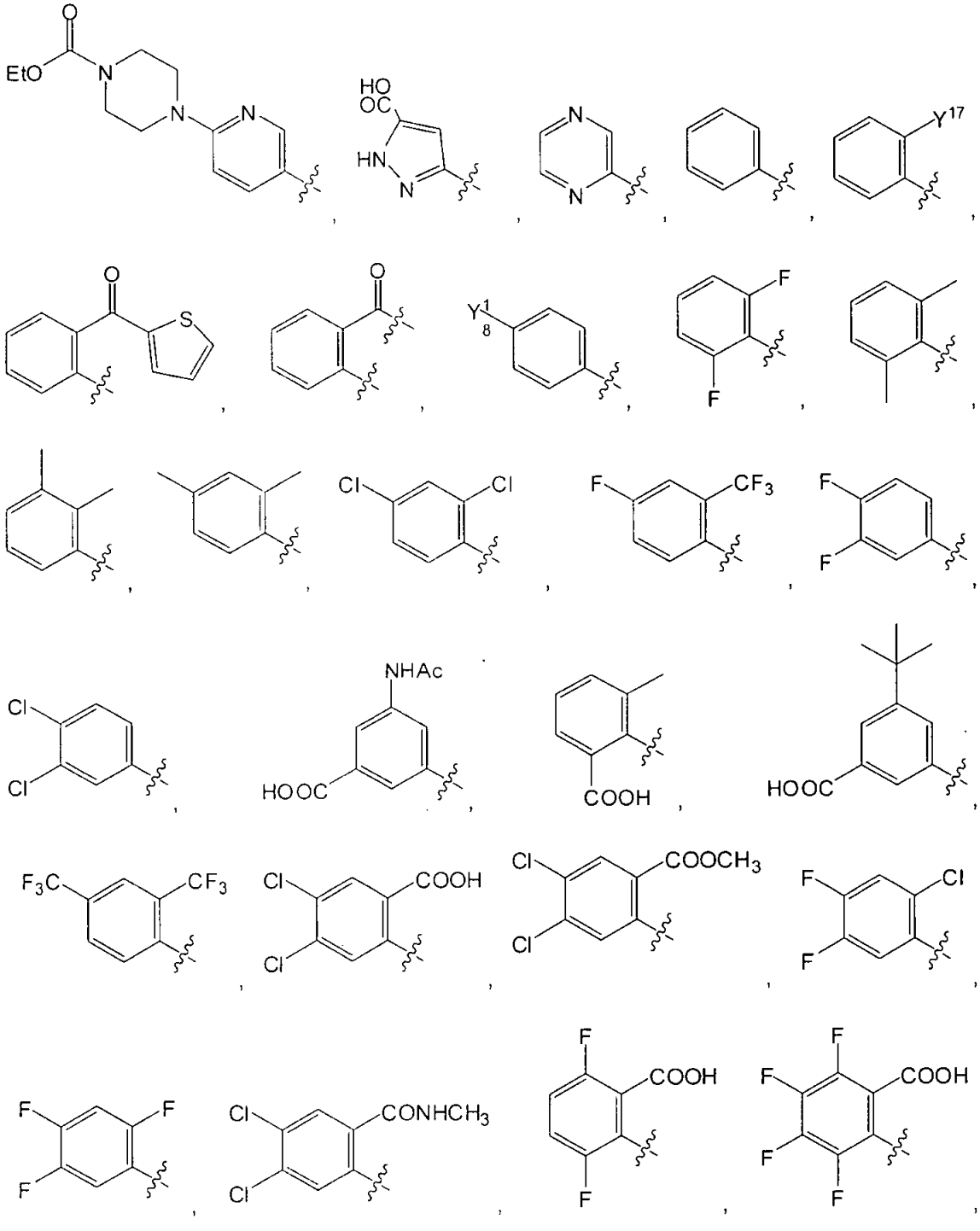
$R^x$ y $R^y$ se seleccionan cada uno independientemente a partir del grupo que consiste en fenilo, alquilo de 1 a 6 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono, o $R^x$ y $R^y$ se seleccionan cada uno independientemente a partir del grupo que consiste en fenilo, ciclopropilo, isopropilo, butilo terciario, y ciclohexilo.

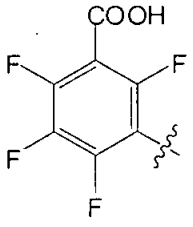
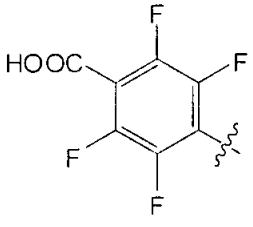
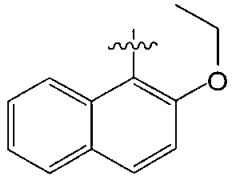
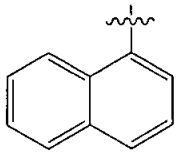
En ciertas modalidades, los compuestos de la Fórmula I o de la Fórmula III comprenden un grupo V seleccionado a partir de residuos que tienen la fórmula -C(O)-V', en donde V' es un residuo seleccionado a partir del grupo que consiste en butoxilo terciario, 2,2-dimetil-propoxilo, butoxilo secundario, 1,2-dimetil-propoxilo, 3-pentoxilo, isopropoxilo, alcoxilo de 1 a 9 átomos de carbono, 2,2,2-tricloro-etoxilo,

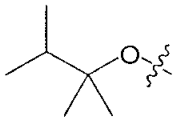
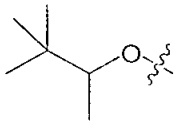
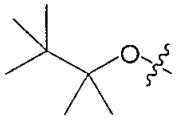
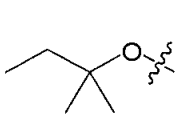
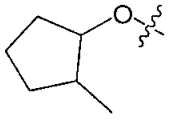


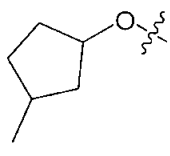
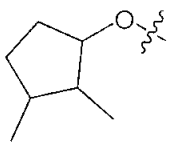
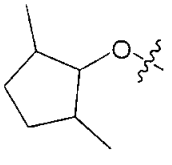
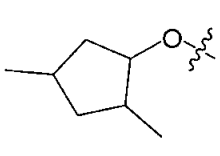
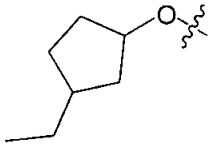

MeO2C
F
Y12
1-2
1-2
HOOC
Y13
Y14
N
COOH
0-2
HOOC
HOOC
C3H7
C3H7
HOOC
HOOC
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6
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C3H7
HOOC
0-2

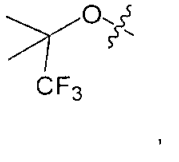
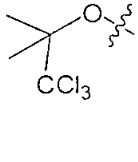
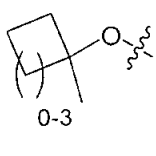
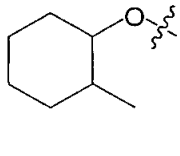
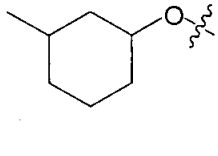

HOOC
COOH
1-4
OTHP
OH
OTHP
S
HOOC
Y15
Y16
1-3
COOH
O
COOH
H3C
1-4
HOOC
COOH

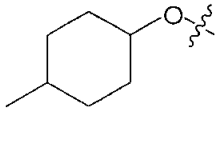
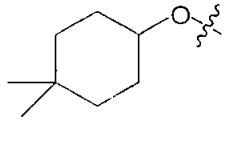
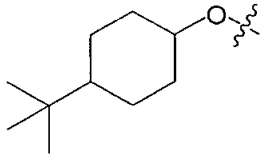
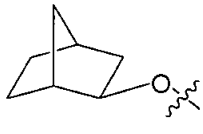

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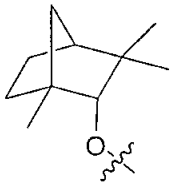
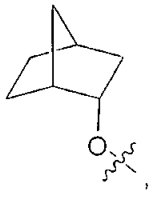
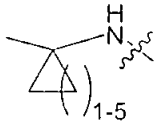
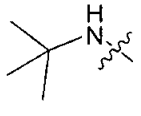
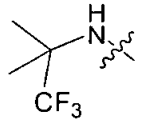
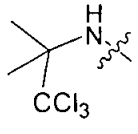

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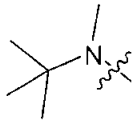
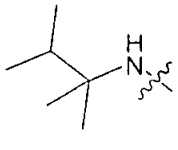
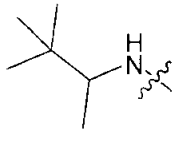
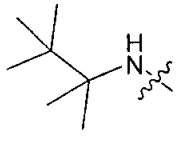
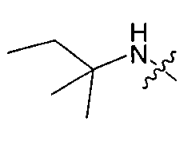
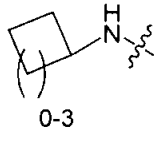

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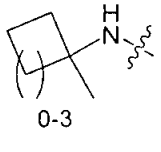
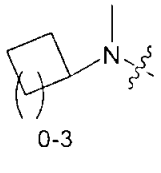
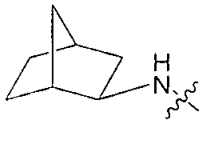
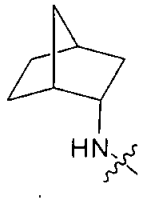
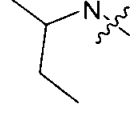
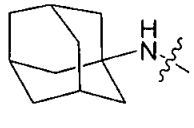

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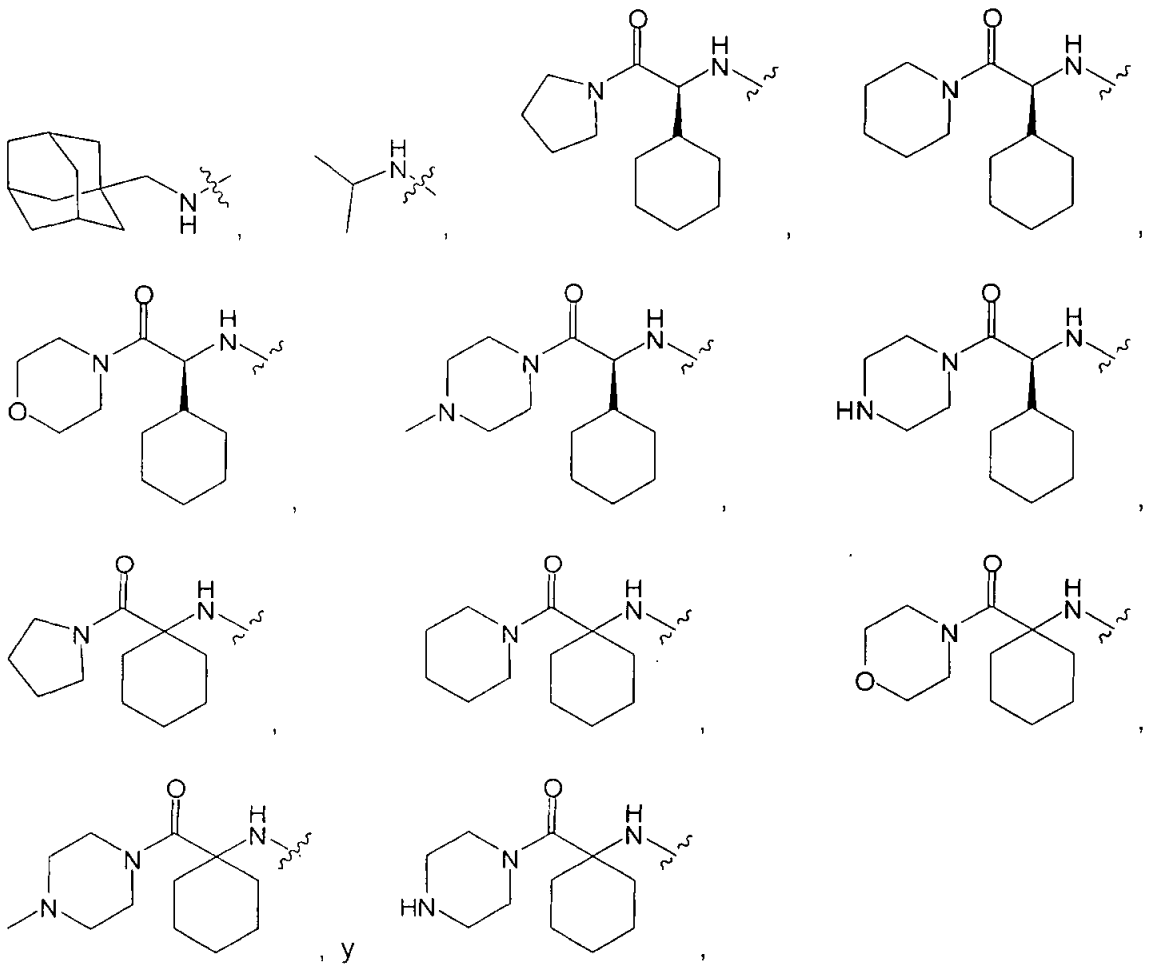

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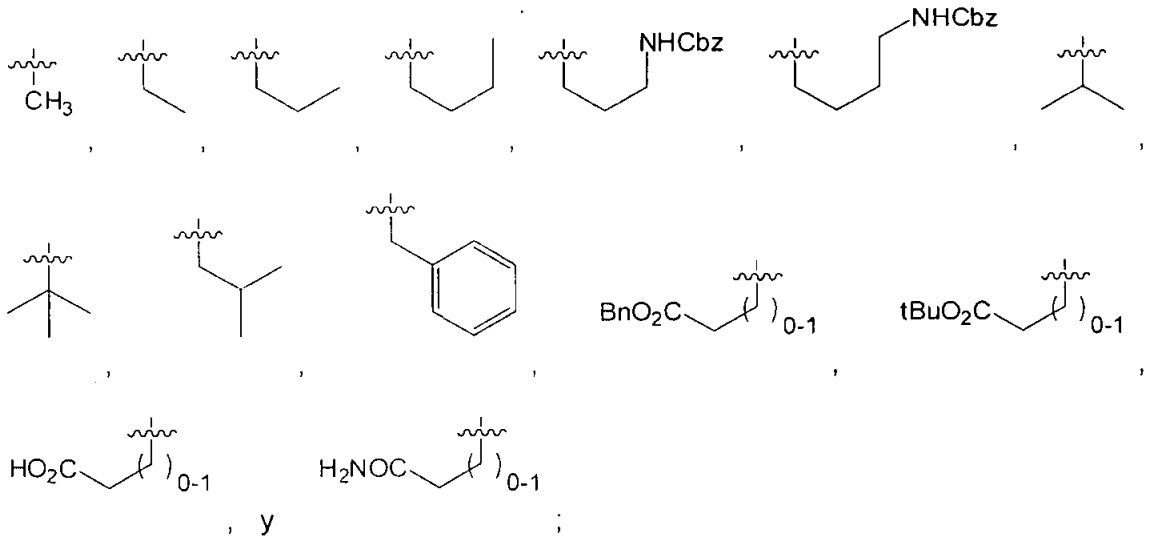


en donde:

$Y^{11}$ se selecciona a partir del grupo que consiste en hidrógeno, -C(O)OH, -C(O)OEt, -OMe, -Ph, -OPh, -NHMe, -NHAc, -NHPh, $-CH(Me)_2$, 1-triazolilo, 1-imidazolilo, y $-NHCH_2COOH$;

$Y^{12}$ se selecciona a partir del grupo que consiste en hidrógeno, -C(O)OH, -C(O)OMe, -OMe, F, Cl, y Br;

$Y^{13}$ se selecciona a partir del grupo que consiste en las siguientes fracciones:




$Y^{14}$ es $S(O)_2Me$, -C(O)Me, -Boc, -iBoc, Cbz, o –Alloc;

$Y^{15}$ y $Y^{16}$ pueden ser iguales o diferentes, y se seleccionan independientemente a partir del grupo que consiste en alquilo, arilo, hetero-alquilo, y hetero-arilo;

$Y^{17}$ es $-CF_3$, $-NO_2$, $-C(O)NH_2$, -OH, $-C(O)OCH_3$, $-OCH_3$, $-OC_6H_5$, $-C_6H_5$, $-C(O)C_6H_5$, $-NH_2$, o –C(O)OH; y

$Y^{18}$ es $-C(O)OCH_3$, $-NO_2$, $-N(CH_3)_2$, F, $-OCH_3$, $-C(H)_2C(O)OH$, -C(O)OH, $-S(O)_2NH_2$, o $-N(H)C(O)CH_3$.

En una modalidad, cualquiera de los grupos cicloalquilo de 3 a 6 átomos de carbono puede estar independientemente sustituido una o más veces (o de preferencia entre una y cinco veces) con un átomo de halógeno, arilo, trihalo-metilo, o alquilo de 1 a 4 átomos de carbono.

En otra modalidad de la fórmula I, $R_4$ es H, y $R^5$ es aril-alquilo de 0 a 3 átomos de carbono, -O-heterociclo, o heterociclo-alquilo de 0 a 3 átomos de carbono, en donde arilo y heterociclo

pueden estar independientemente sustituidos una o más veces (de preferencia entre una y cinco veces) con un átomo de halógeno, arilo, trihalo-metilo, cicloalquilo de 3 a 6 átomos de carbono, o alquilo de 1 a 4 átomos de carbono.

En todavia otra modalidad de la Fórmula I o de la Fórmula III, W se selecciona a partir del grupo que consiste en C(O)-C(O)N($R^{23}$)$_2$, en donde $R^{23}$ se selecciona independientemente a partir de hidrógeno, o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo, y heterociclo, cada uno de los cuales puede estar independientemente sustituido una o más veces (o de preferencia entre una y cinco veces) con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono.

En todavia otra modalidad de la Fórmula I o de la Fórmula III, W es C(O)-C(O)-ciclopropilo.

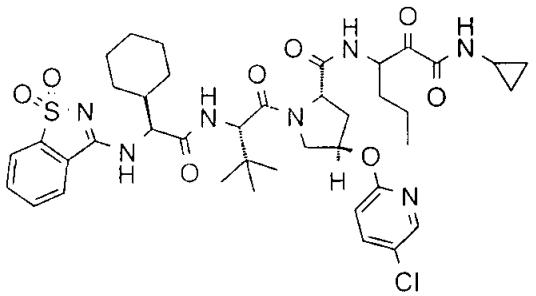
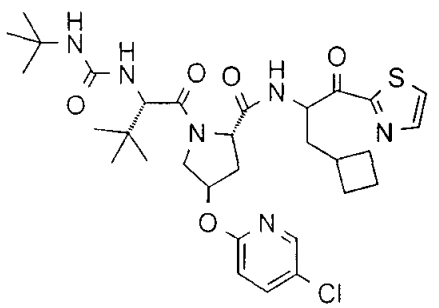
En una modalidad de la Fórmula I o de la Fórmula III, cualquiera de los grupos heterociclo se selecciona independientemente a partir del grupo que consiste en acridinilo, carbazolilo, cinolinilo, quinoxalinilo, pirazolilo, indolilo, benzotriazolilo, furanilo, tienilo, benzotienilo, benzofuranilo, quinolinilo, isoquinolinilo, oxazolilo, isoxazolilo, indolilo, pirazinilo, piridazinilo, piridinilo, pirimidinilo, pirrolilo, tetrahidroquinolina, benzoimidazolilo, benzofuranilo, benzofurazanilo, benzopirazolilo, benzotriazolilo, benzotiofenilo, benzoxazolilo, carbazolilo, carbolinilo, cinolinilo, furanilo, imidazolilo, indolinilo, indolilo, indolazinilo,

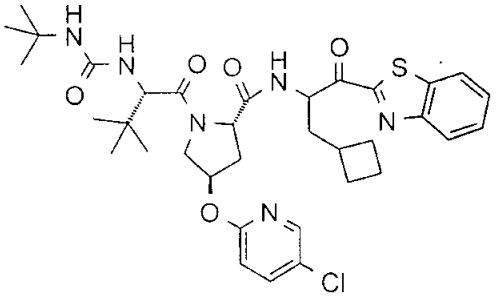
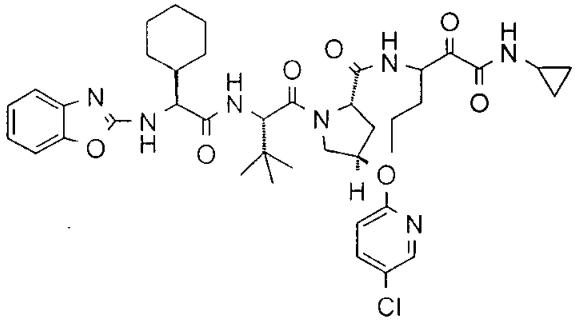
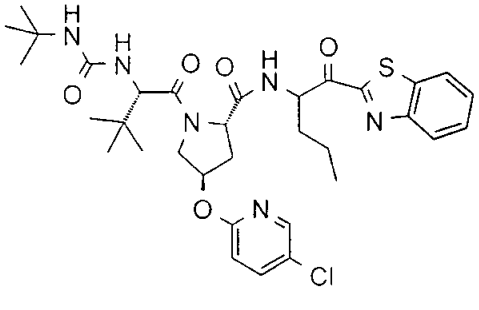
indazolilo, isobenzofuranilo, isoindolilo, isoquinolilo, isotiazolilo, isoxazolilo, naftpiridinilo, oxadiazolilo, oxazolilo, oxazolina, isoxazolina, oxetanilo, piranilo, pirazinilo, pirazolilo, piridazinilo, piridopiridinilo, piridazinilo, piridilo, pirimidilo, pirrolilo, quinazolinilo, quinolilo, quinoxalinilo, tetrahidropiranilo, tetrazolilo, tetrazolo-piridilo, tiadiazolilo, tiazolilo, tienilo, triazolilo, azetidinilo, 1,4-dioxanilo, hexahidroazepinilo, piperazinilo, piperidinilo, piridin-2-onilo, pirrolidinilo, morfolinilo, tiomorfolinilo, dihidro-benzo-imidazolilo, dihidro-benzo-furanilo, dihidro-benzo-tiofenilo, dihidro-benzoxazolilo, dihidro-furanilo, dihidro-imidazolilo, dihidro-indolilo, dihidro-iso-oxazolilo, dihidro-isotiazolilo, dihidro-oxadiazolilo, dihidro-oxazolilo, dihidro-pirazinilo, dihidro-pirazolilo, dihidro-piridinilo, dihidro-pirimidinilo, dihidro-pirrolilo, dihidro-quinolinilo, dihidro-tetrazolilo, dihidro-tiadiazolilo, dihidro-tiazolilo, dihidro-tienilo, dihidro-triazolilo, dihidro-azetidinilo, metilen-dioxibenzoílo, tetrahidro-furanilo, y tetrahidro-tienilo, y los N-óxidos de los mismos, cada uno de los cuales puede estar además independientemente sustituido una o más veces (o de preferencia entre una y cinco veces) con un átomo de halógeno, alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono sustituido por uno o más átomos de halógeno, o cicloalquilo de 3 a 6 átomos de carbono.

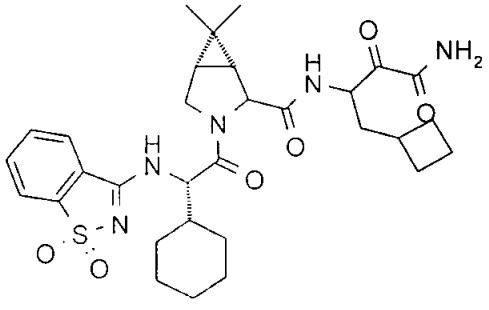
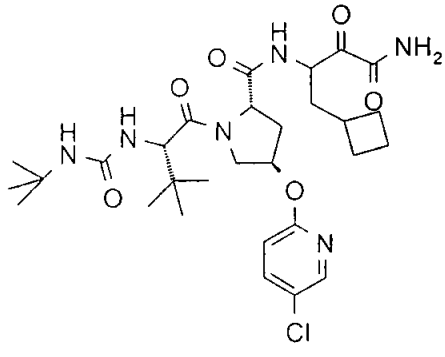
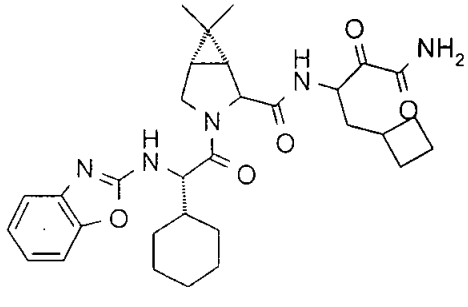
Las modalidades preferidas de los compuestos de la invención (incluyendo las sales farmacéuticamente aceptables de los mismos, así como los enantiómeros, estereoisómeros, rotámeros, tautómeros, diaestereómeros, o racematos de los mismos),s e

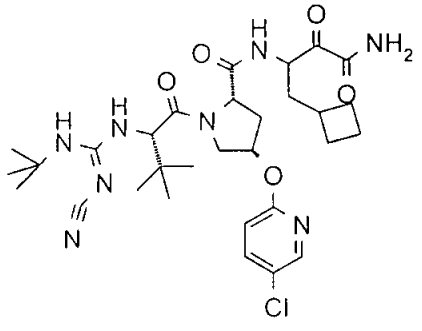
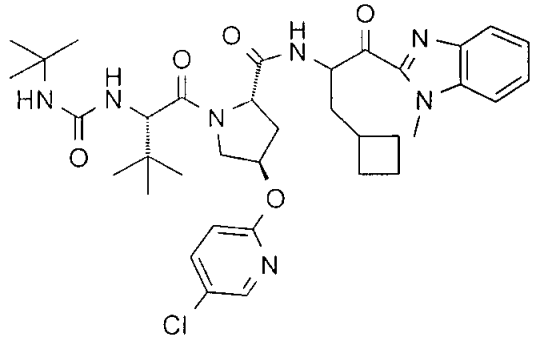
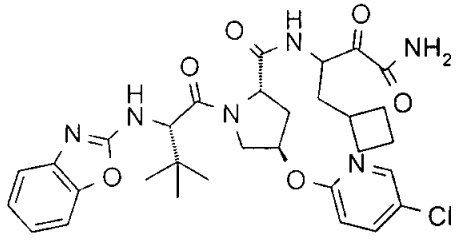
muestran más adelante en la Tabla A y en la Tabla B, y también se consideran como "compuestos de la invención".

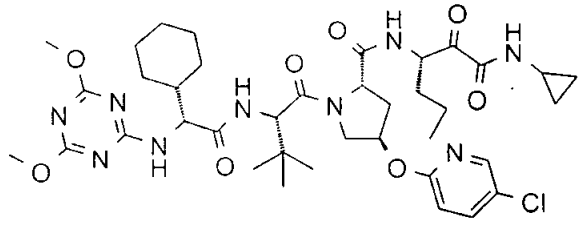
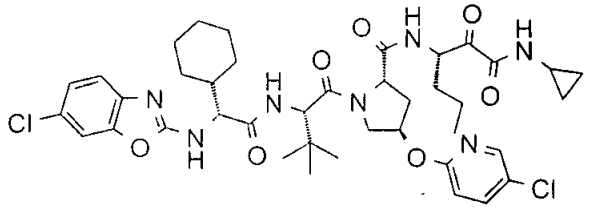
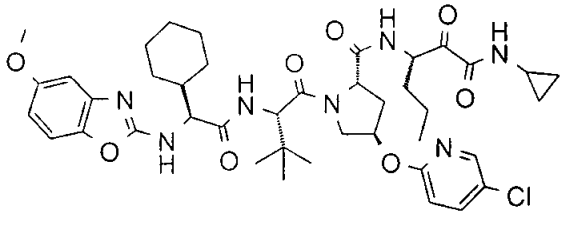
TABLA A

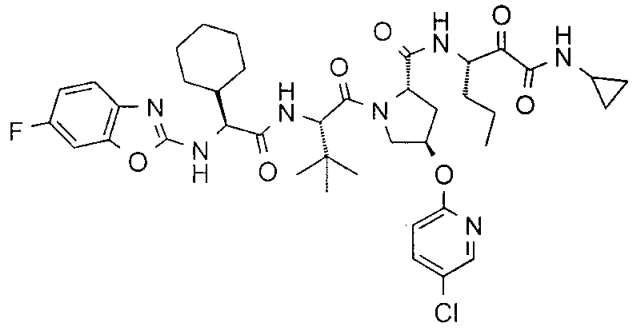
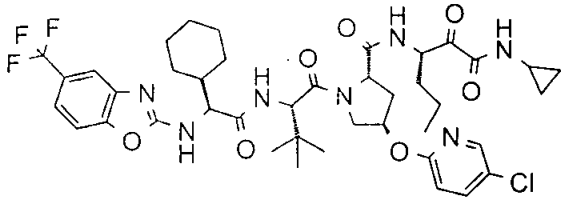
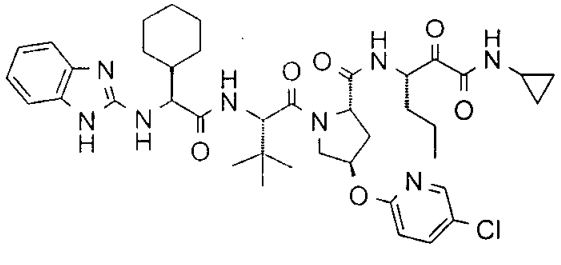
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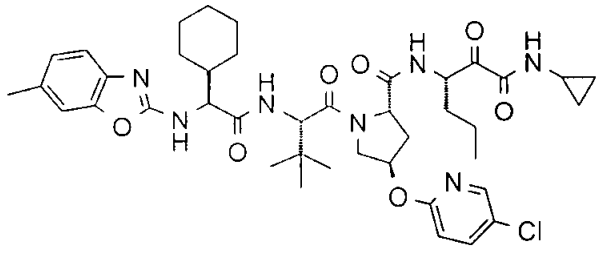
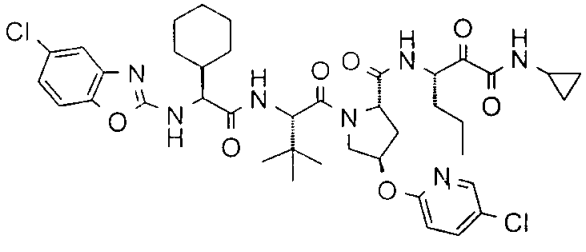
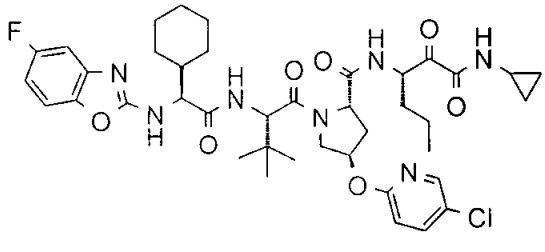
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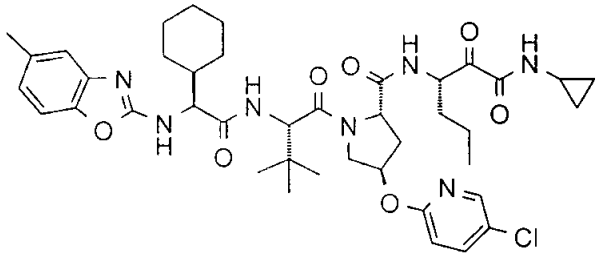
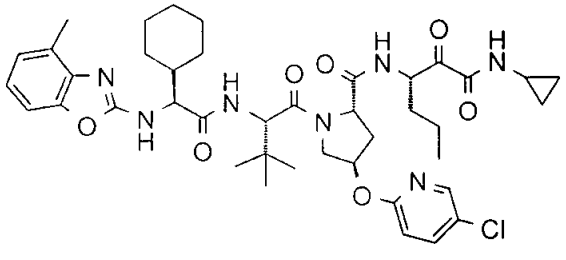
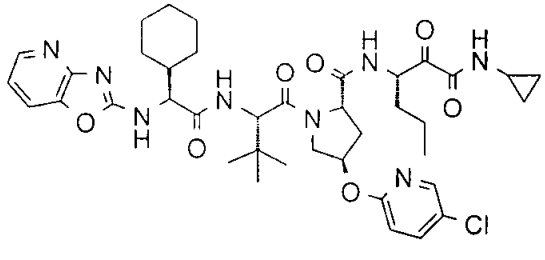
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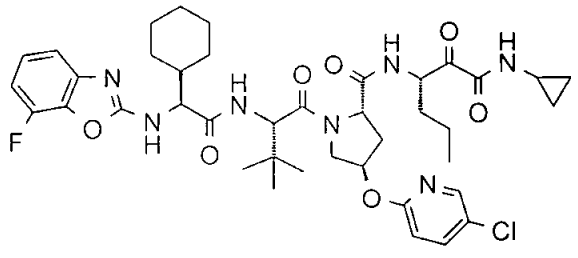
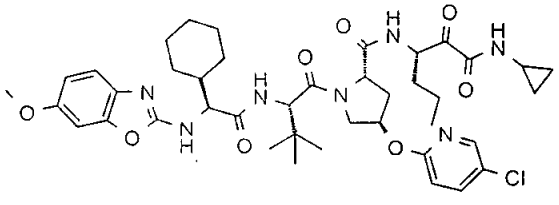
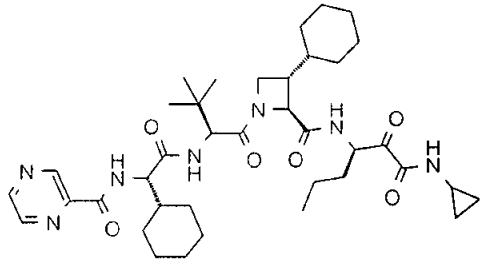
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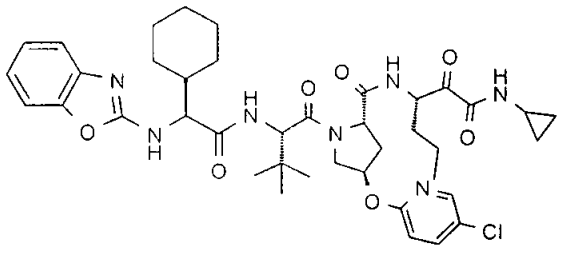
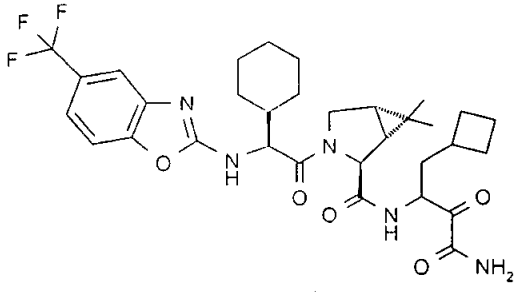
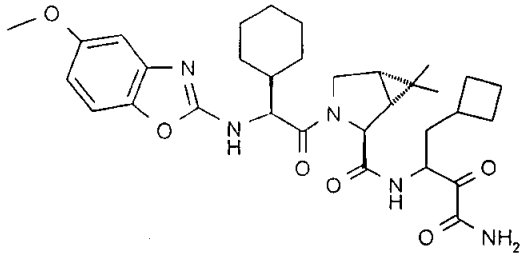
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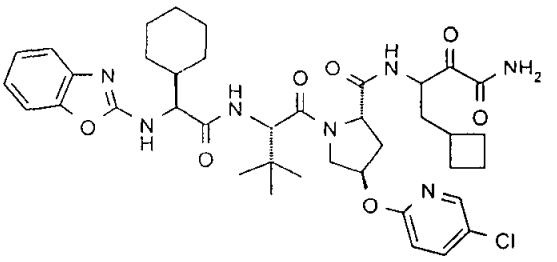
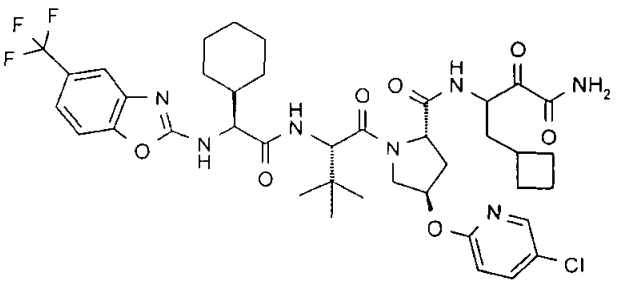
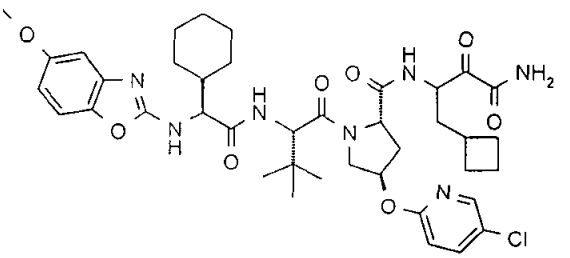
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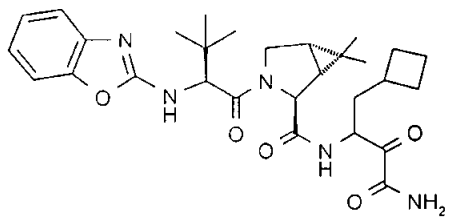
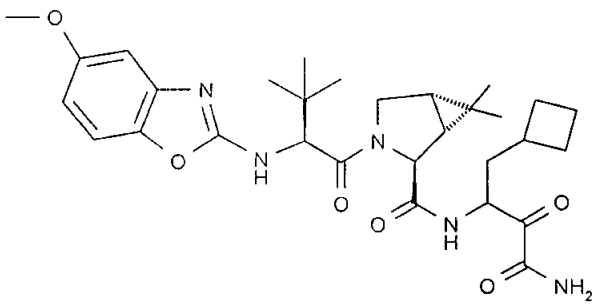
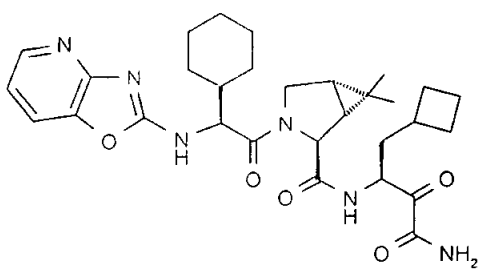
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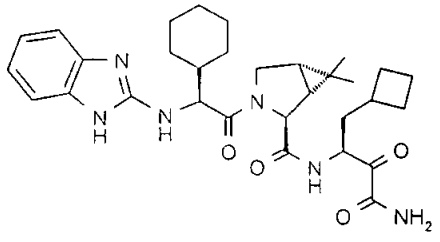
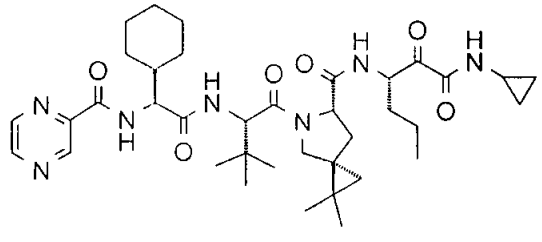
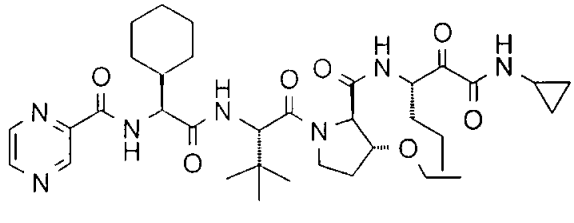
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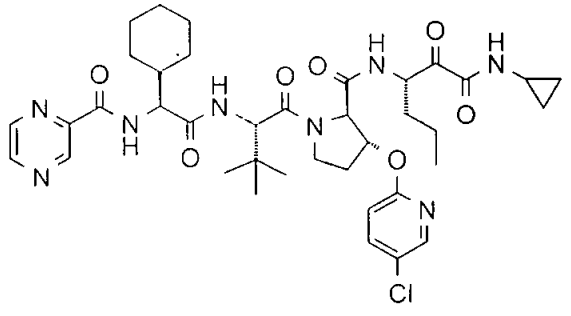
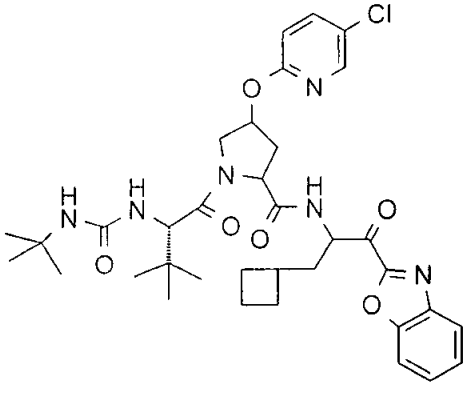
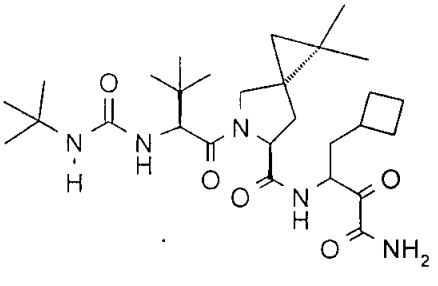
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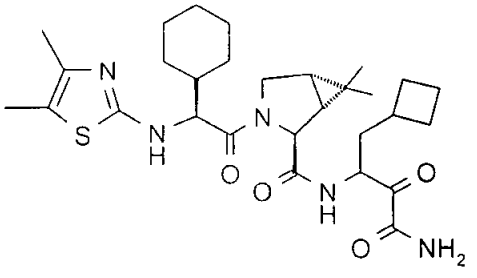
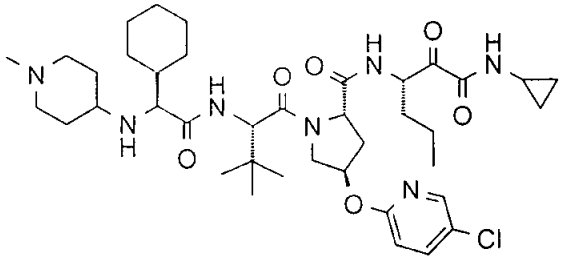
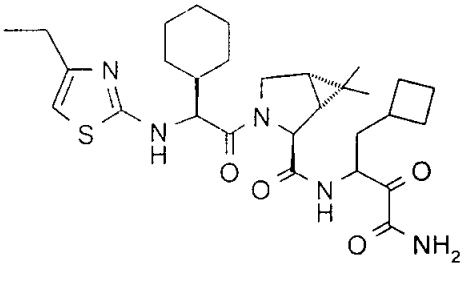
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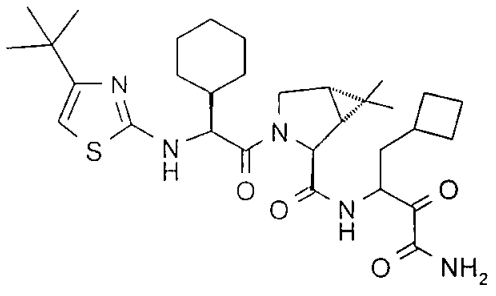
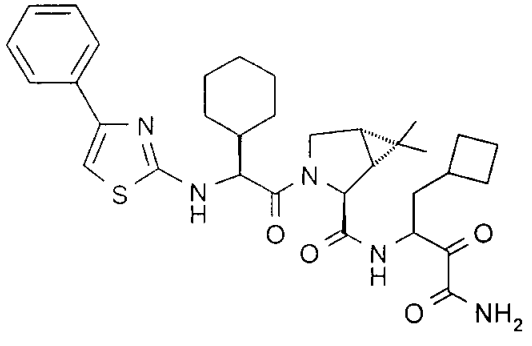
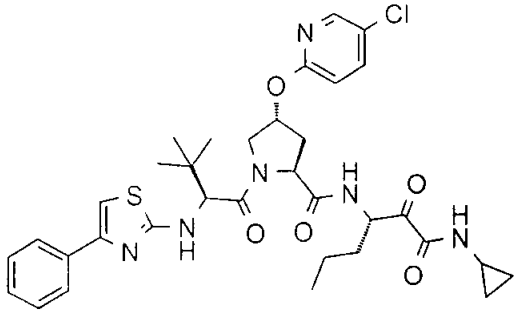
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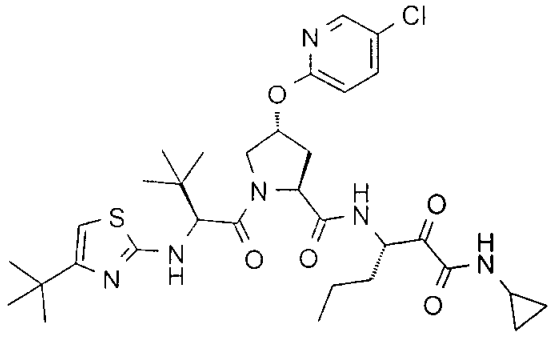
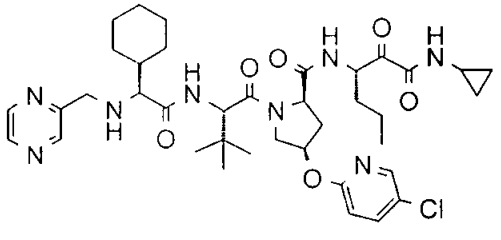
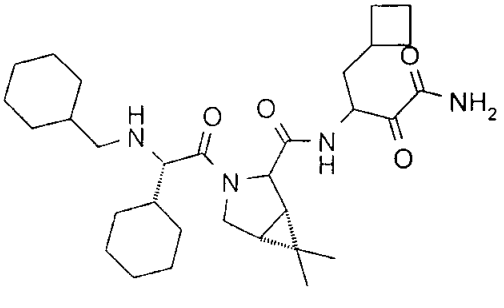
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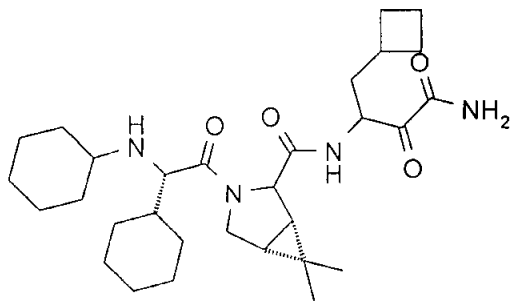
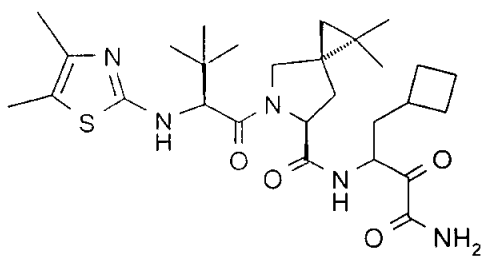
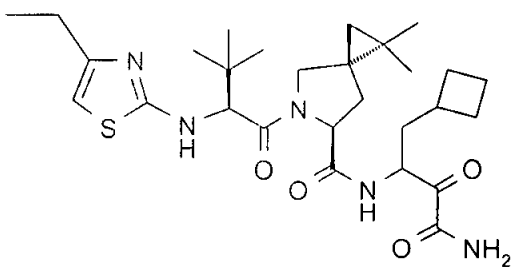
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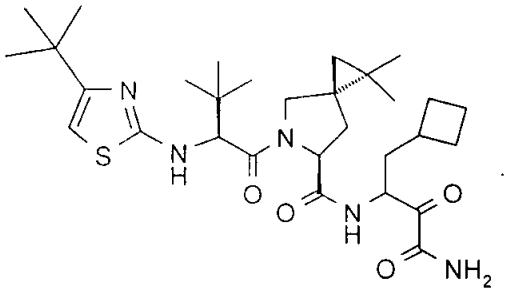
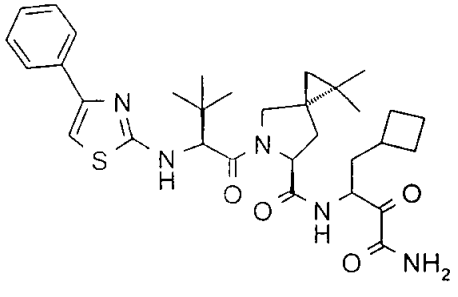
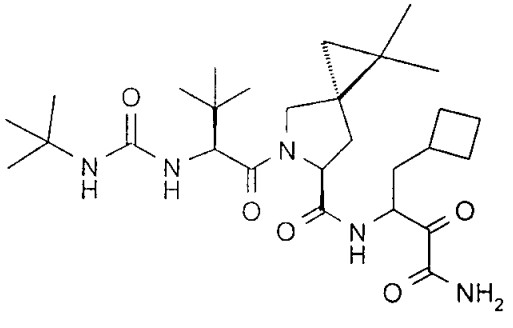
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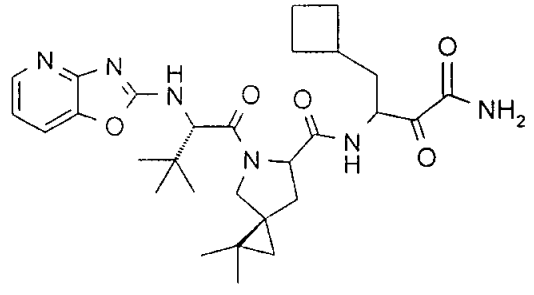
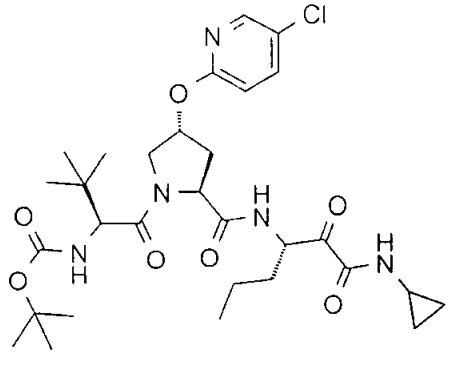
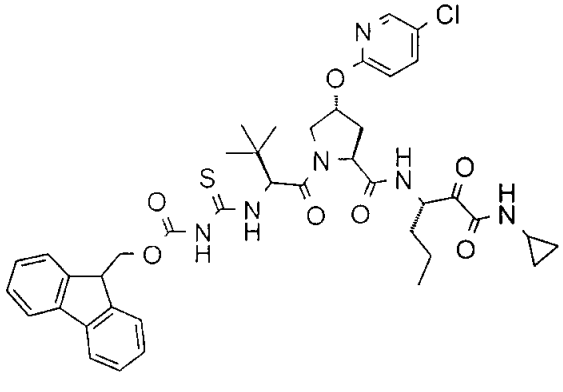
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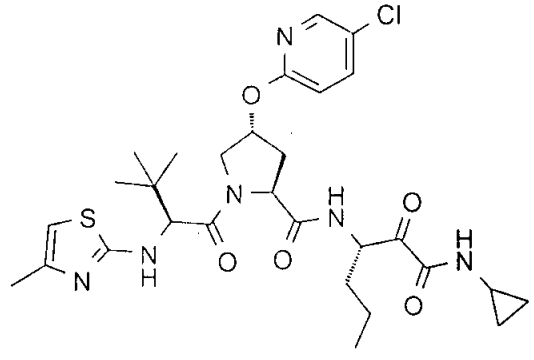
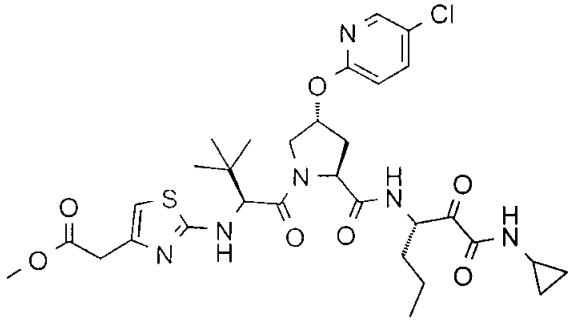
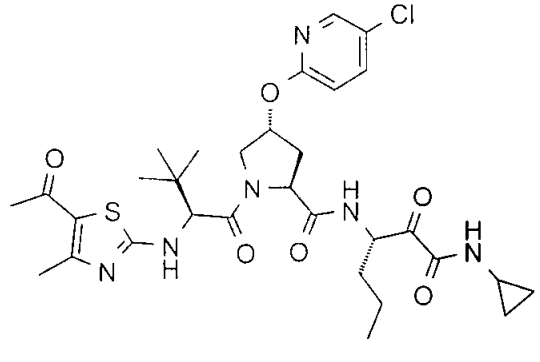
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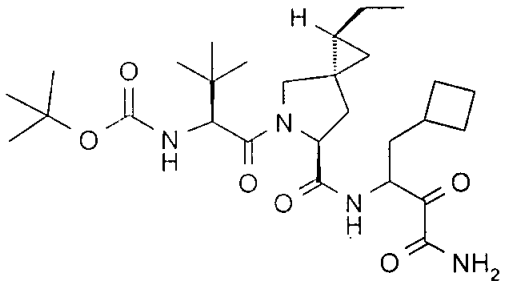
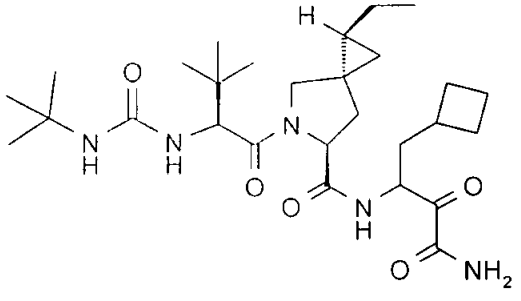
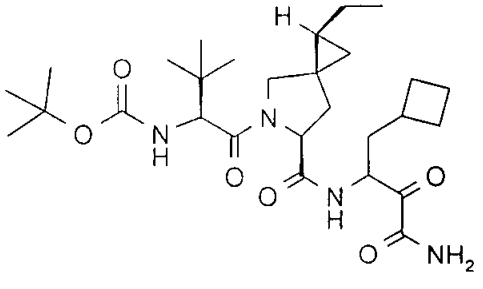
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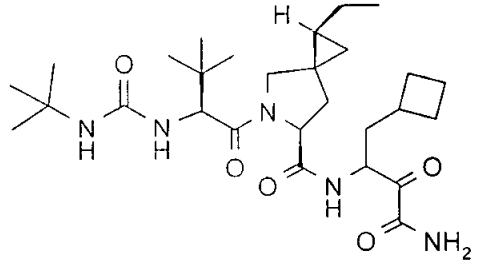
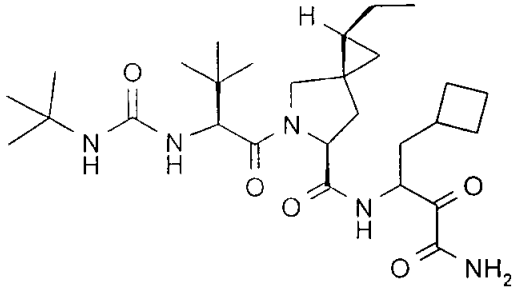
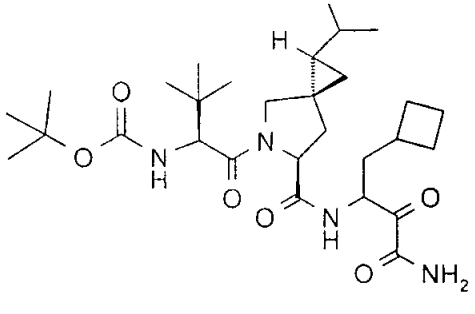
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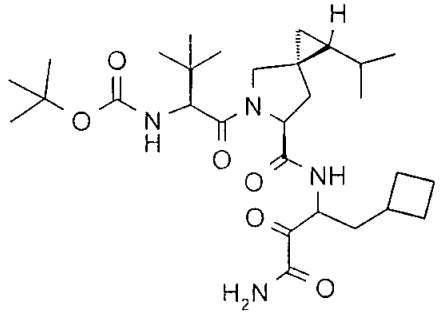
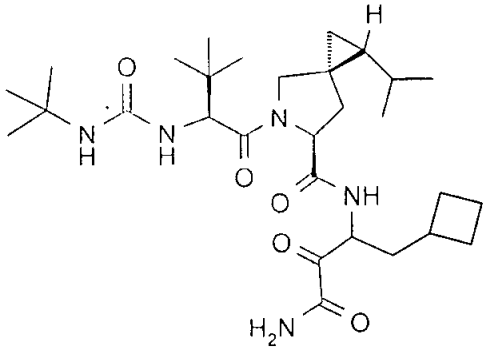
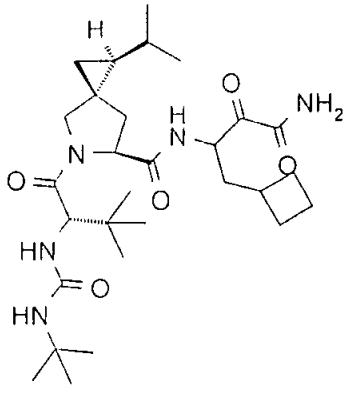
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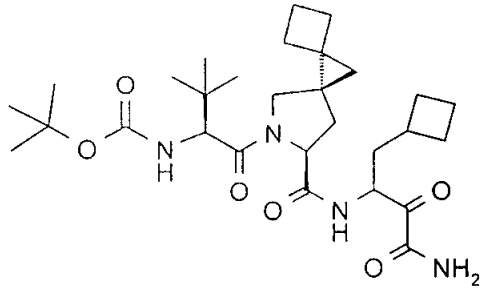
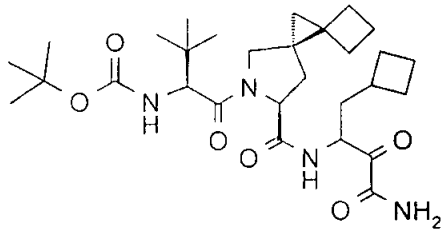
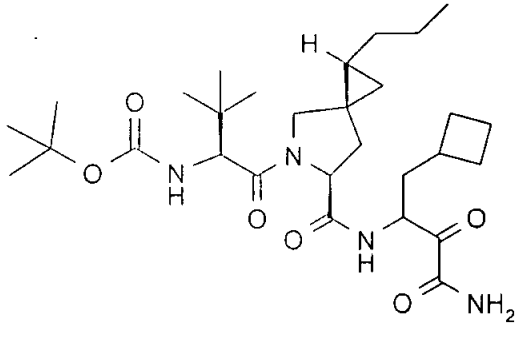
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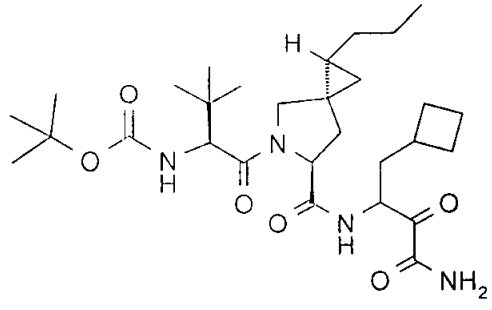
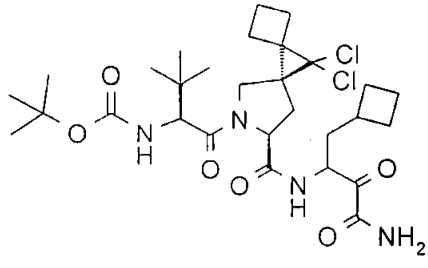
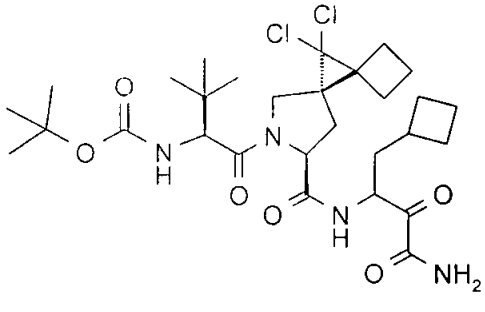
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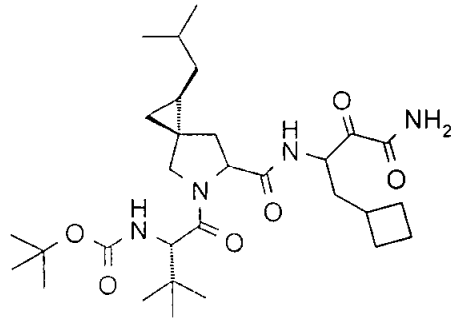
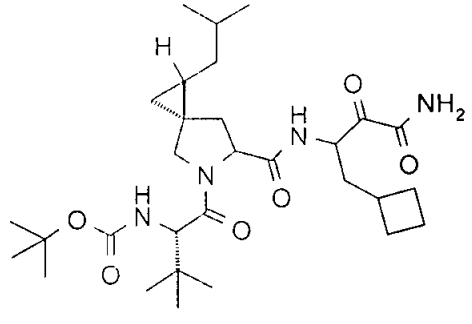
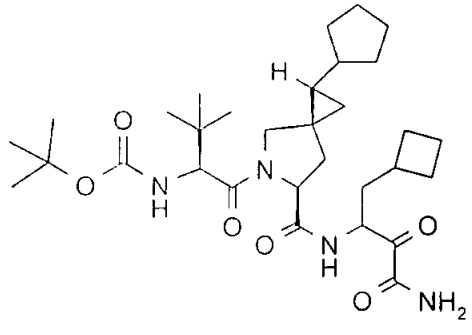
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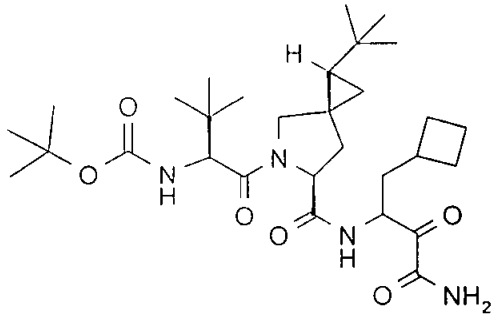
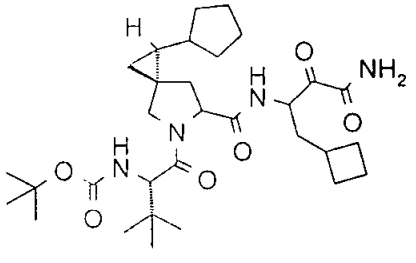
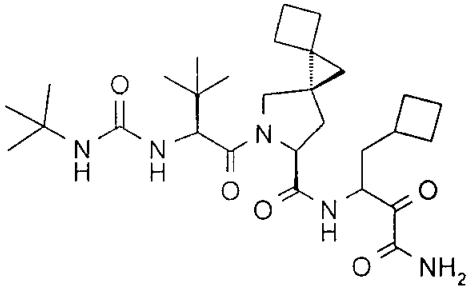
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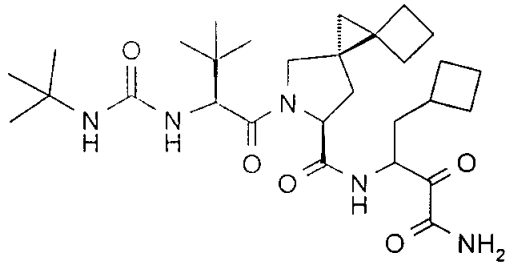
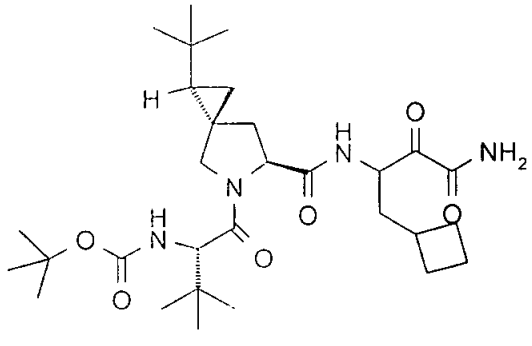
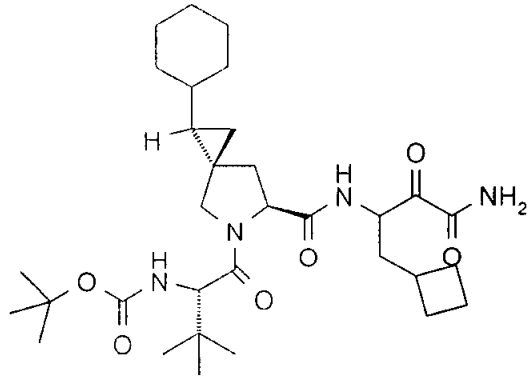
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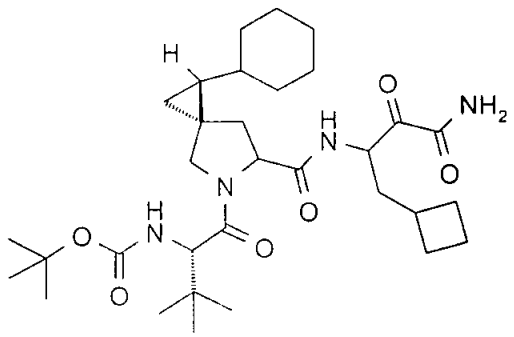
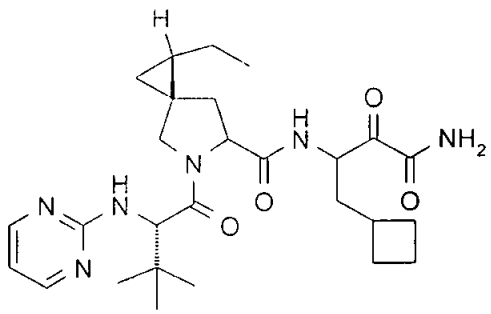
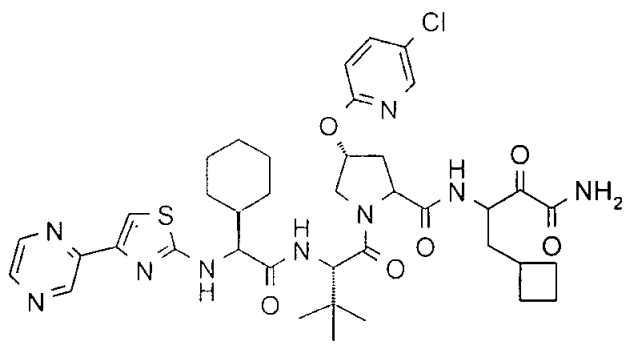
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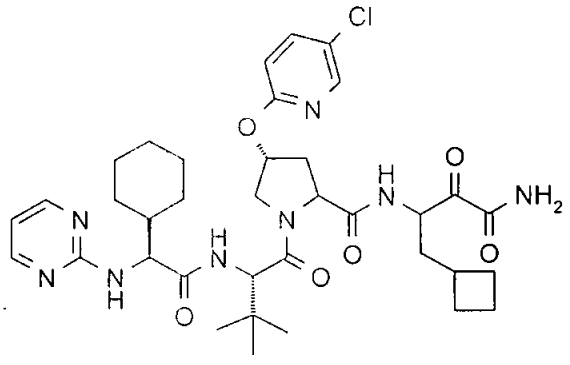
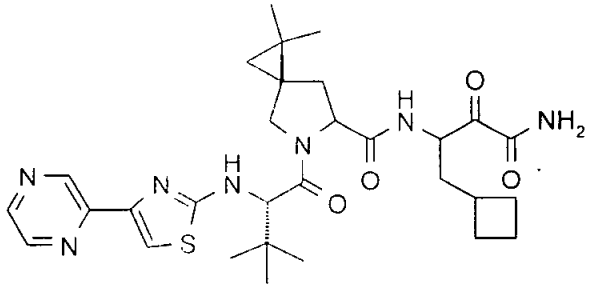
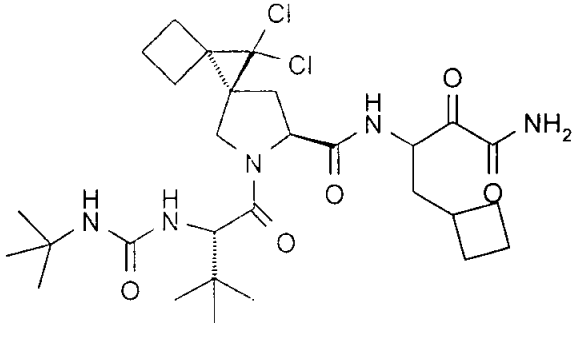
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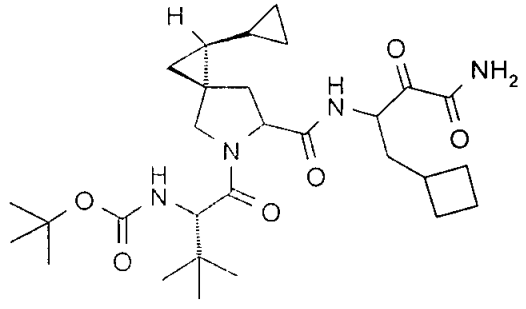
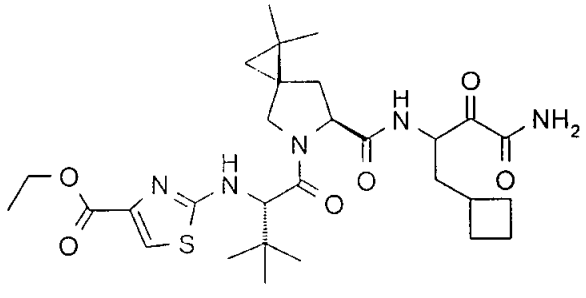
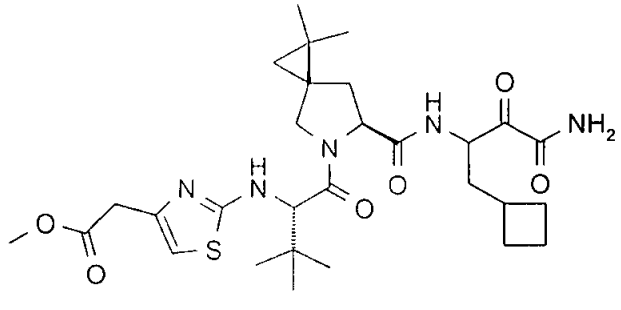
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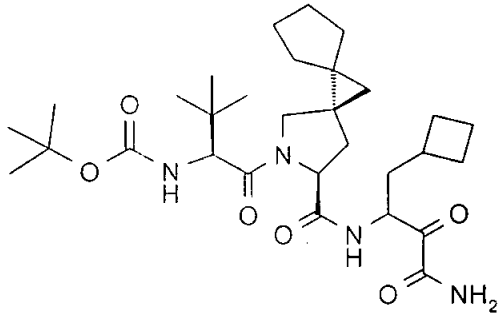
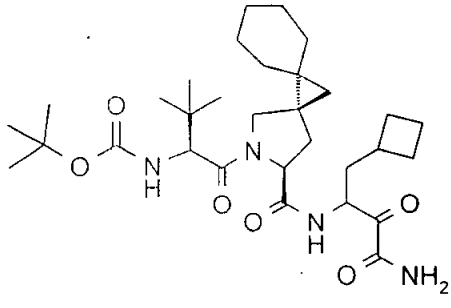
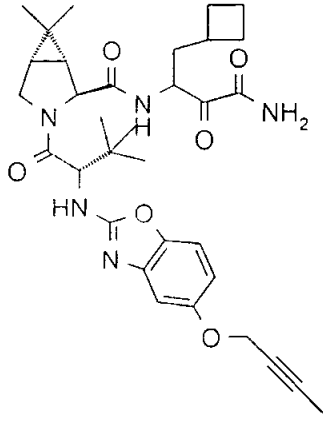
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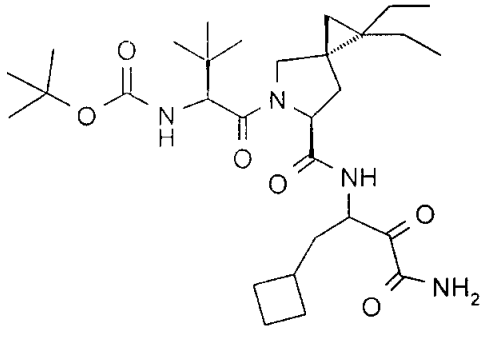
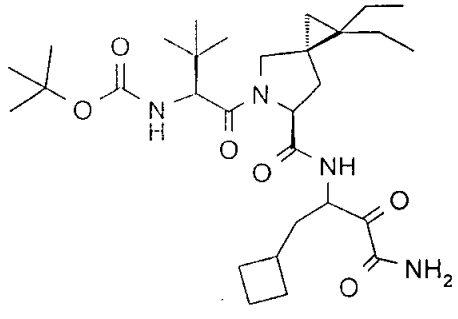
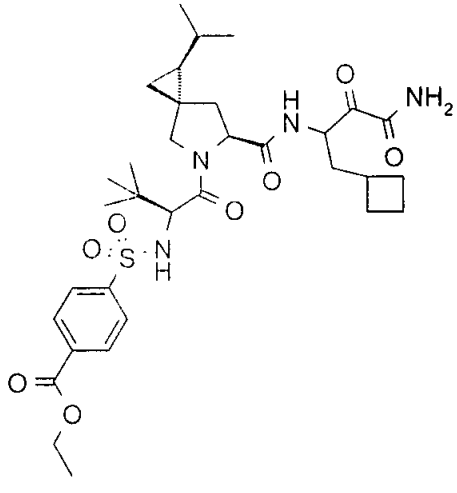
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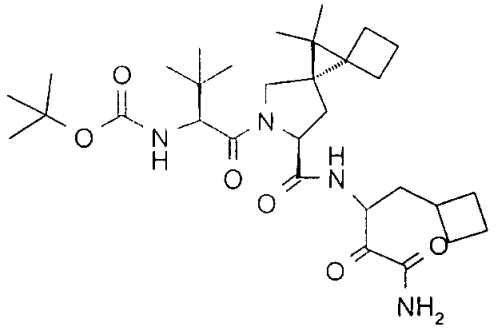
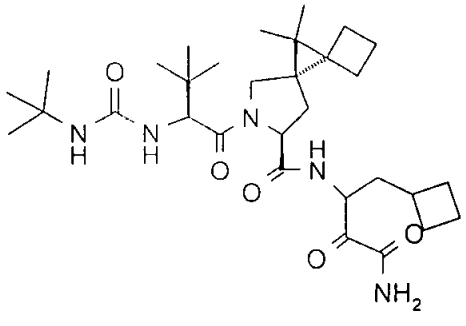
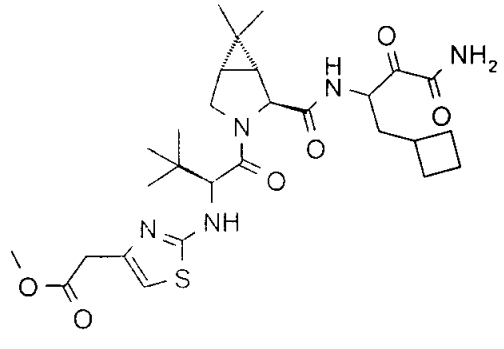
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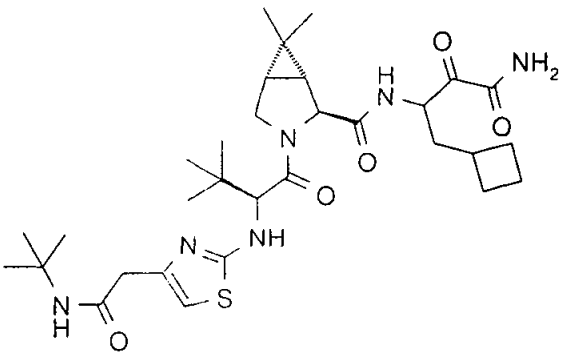
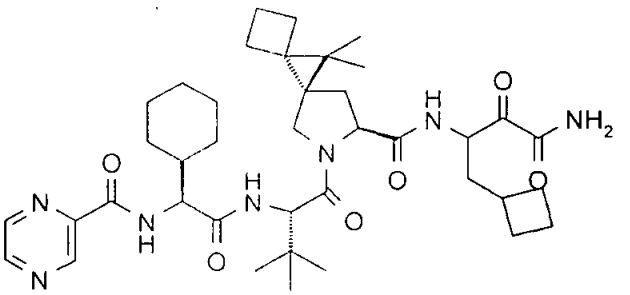
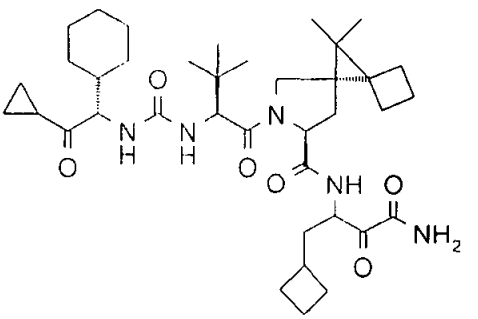
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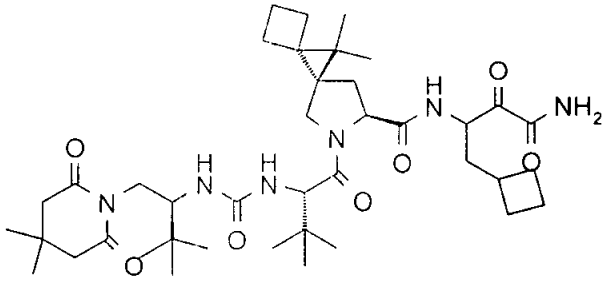
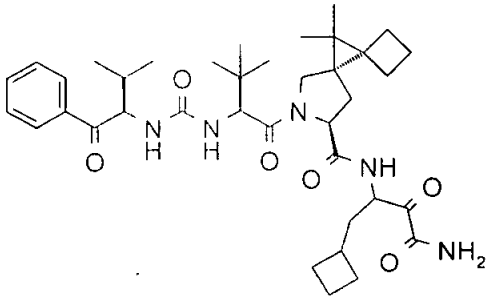
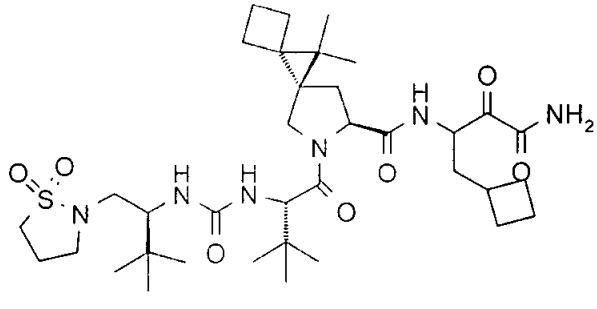
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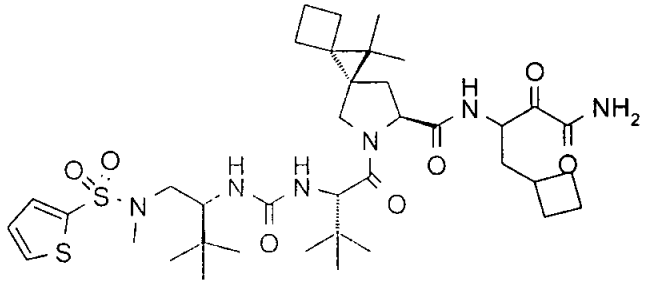
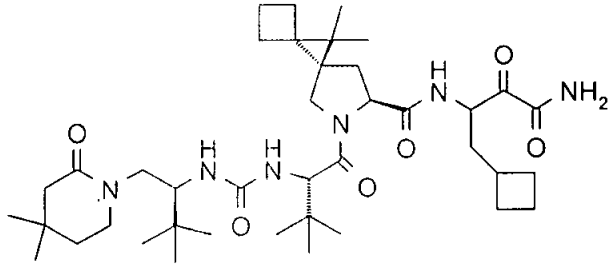
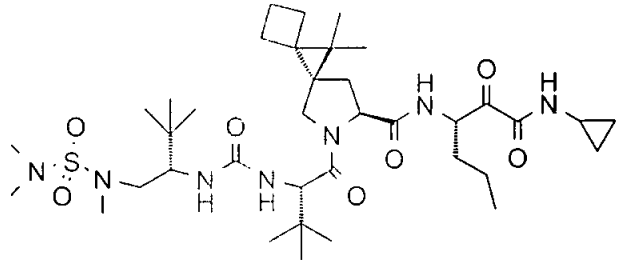
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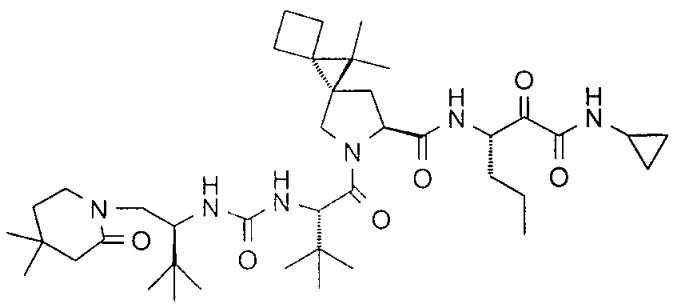
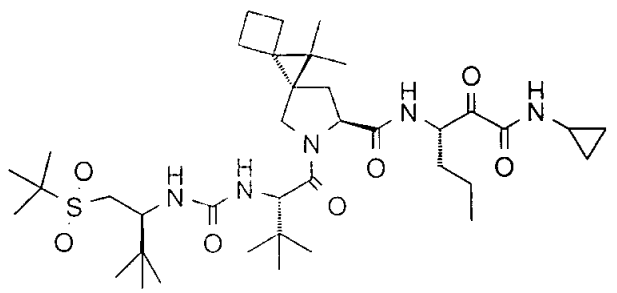
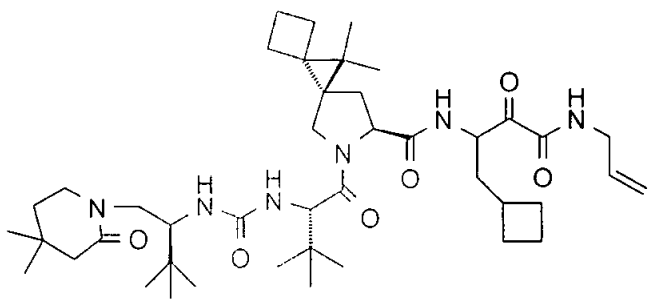
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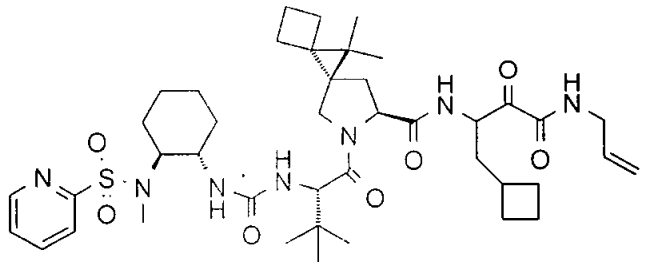
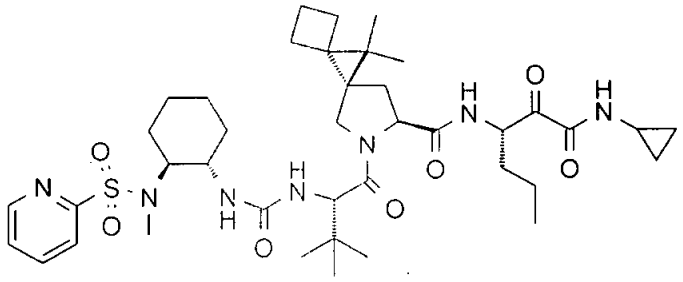
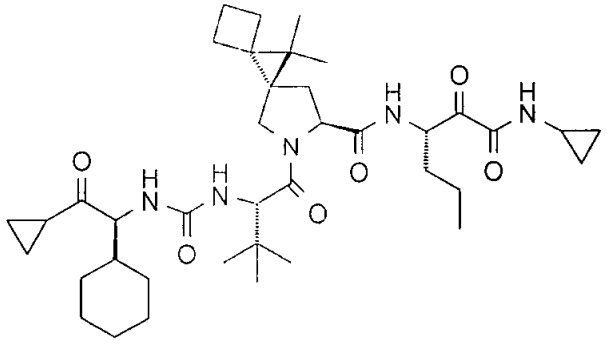
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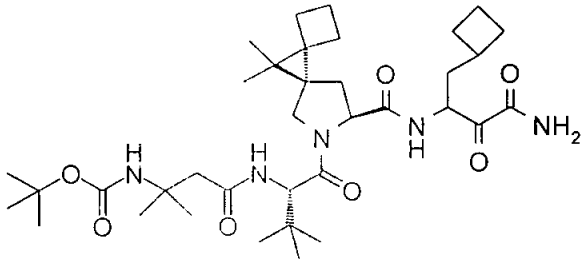
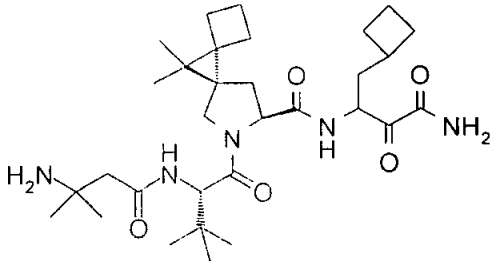
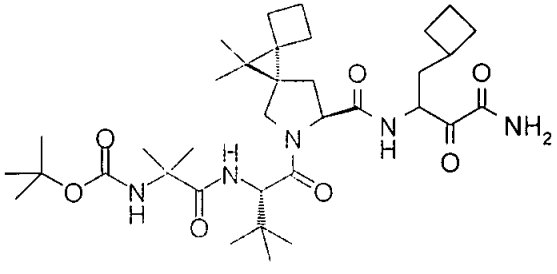
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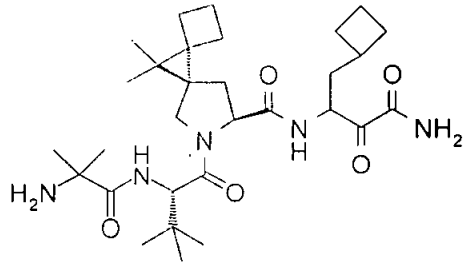
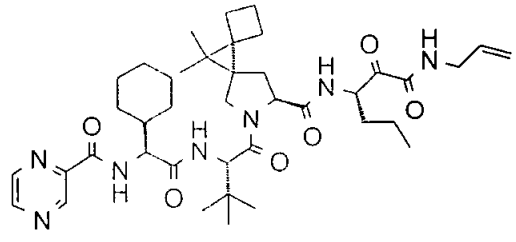
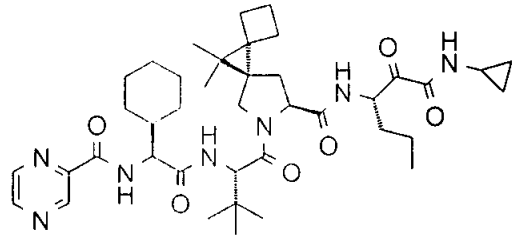
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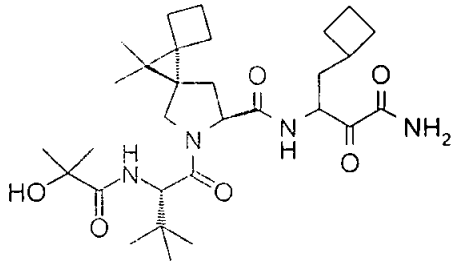
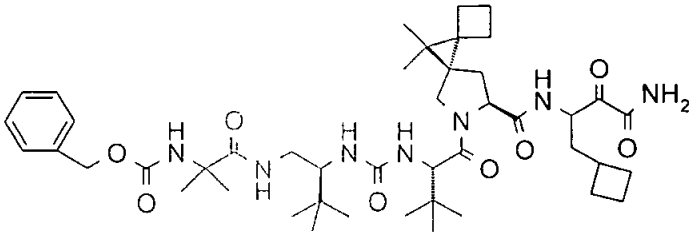
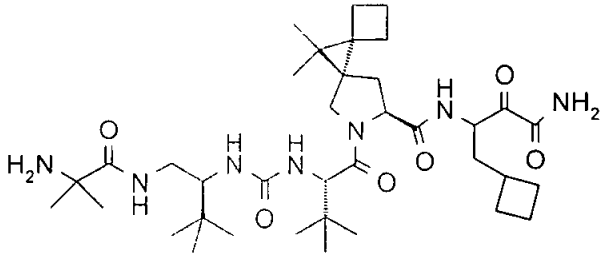
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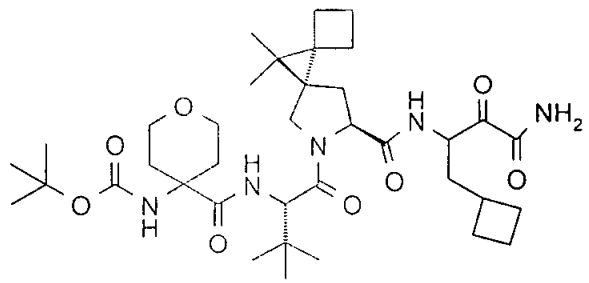
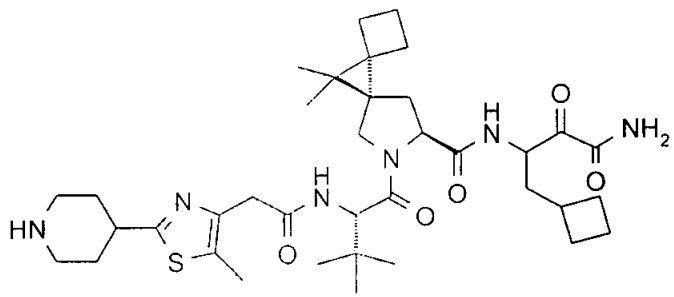
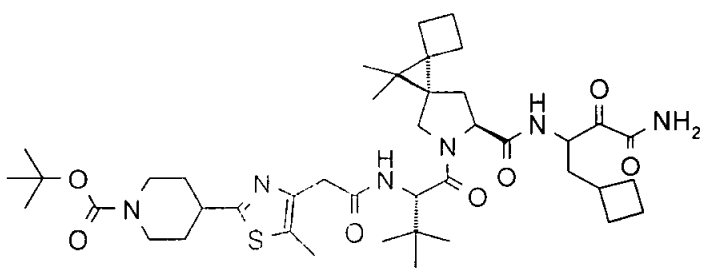
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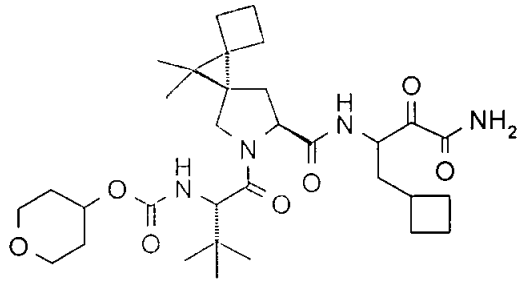
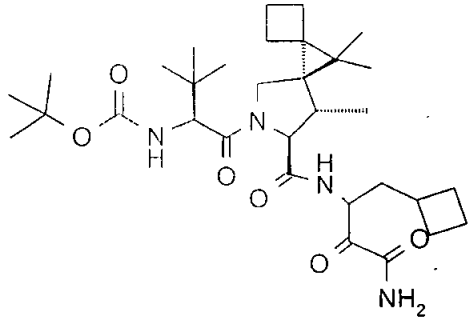
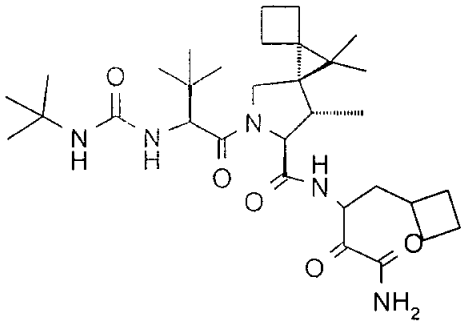
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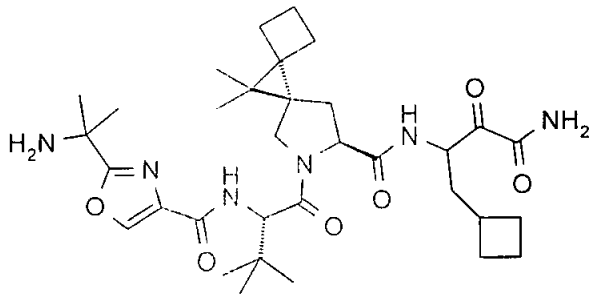
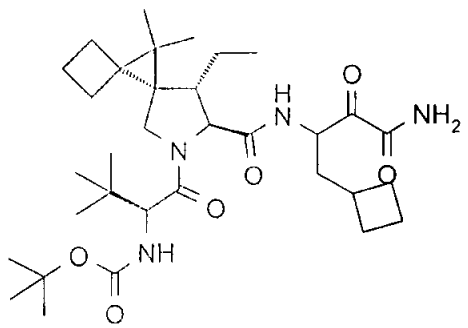
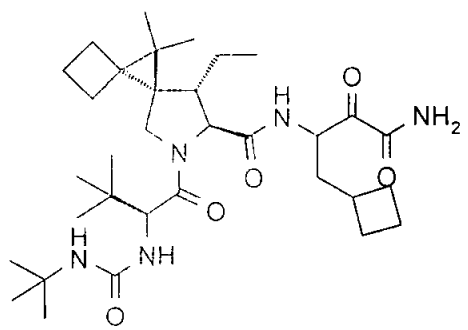
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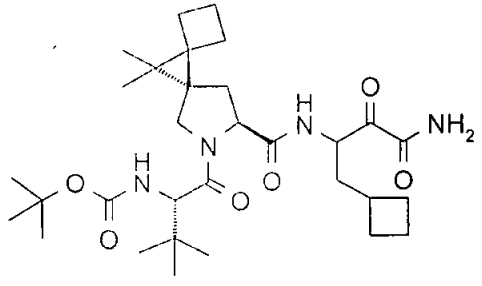
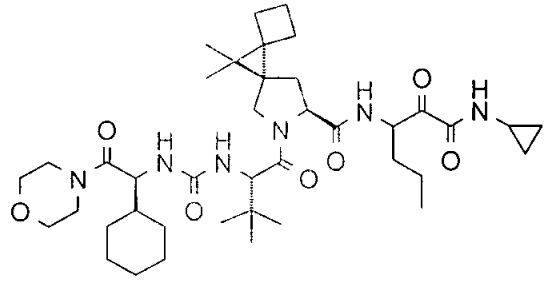
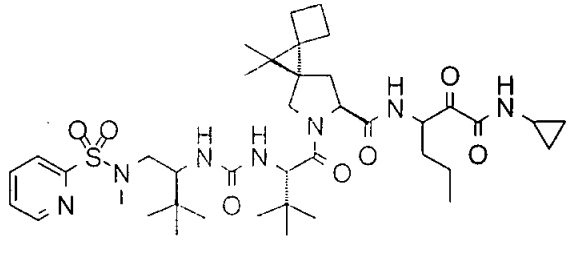
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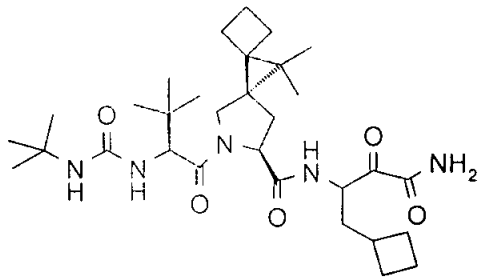
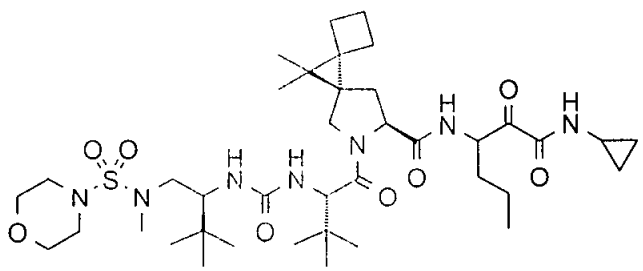
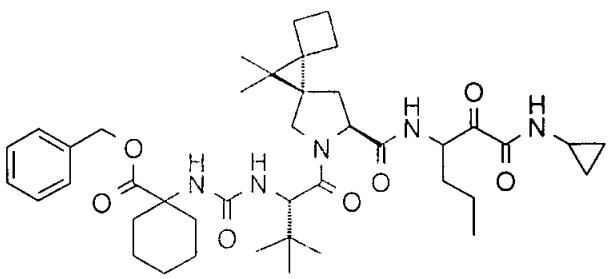
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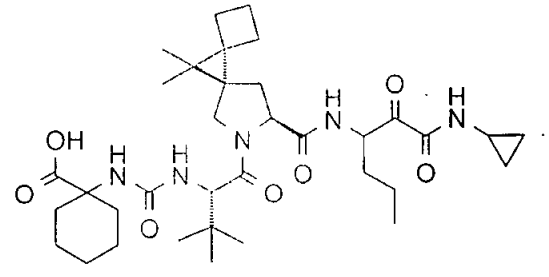
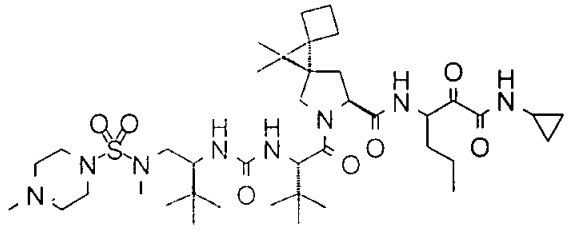
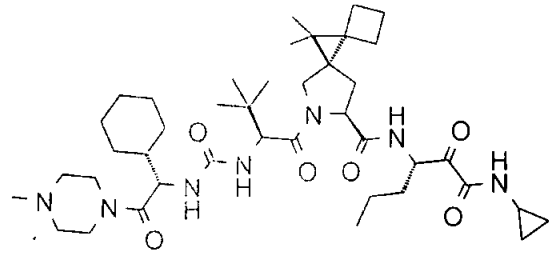
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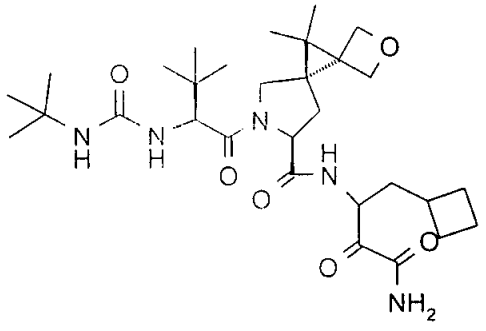
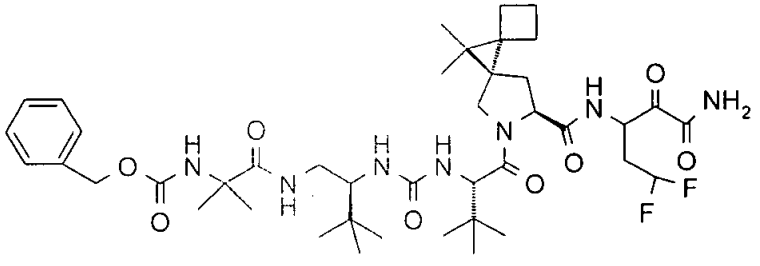
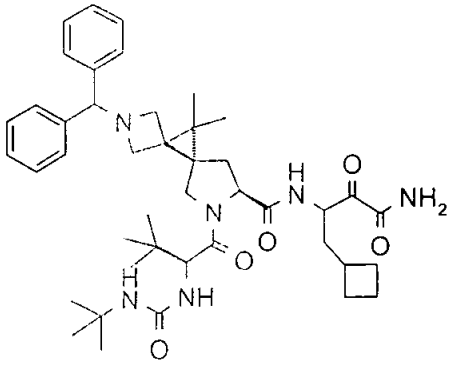
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|  | A-134 |

| Estructura | Comp. No. |
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|  | A-135 |
|  | A-136 |
|  | A-137 |

| Estructura | Comp. No. |
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|  | A-138 |
|  | A-139 |
|  | A-140 |

| Estructura | Comp. No. |
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|  | A-141 |
|  | A-142 |
|  | A-143 |

| Estructura | Comp. No. |
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|  | A-144 |
|  | A-145 |
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| Estructura | Comp. No. |
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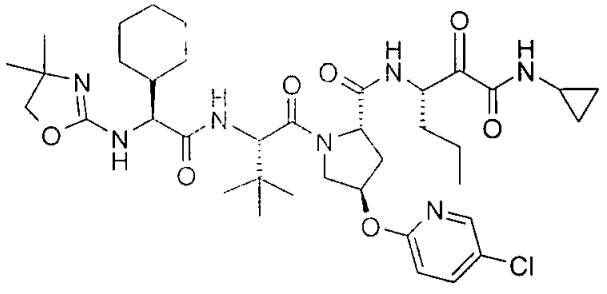
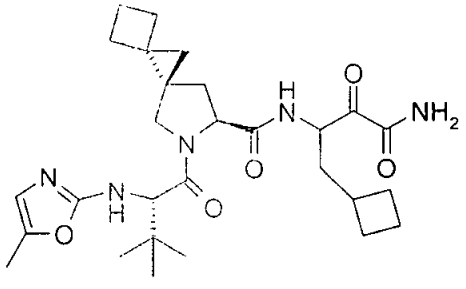
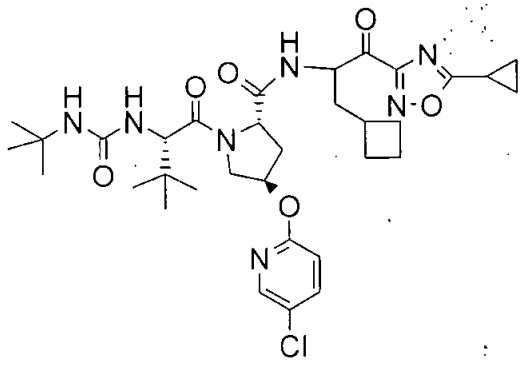
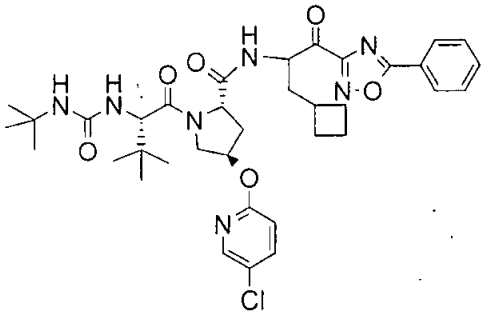
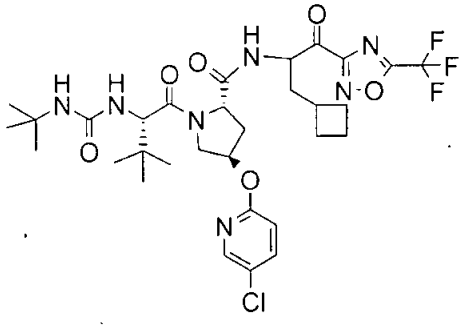
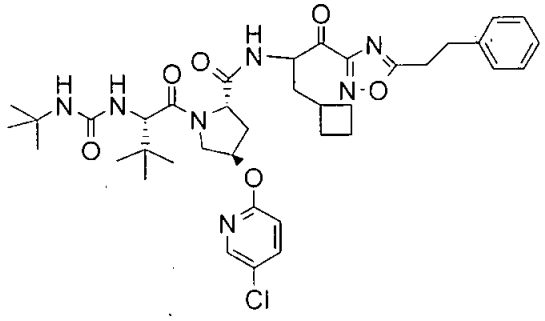
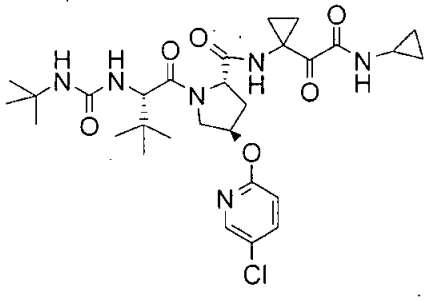
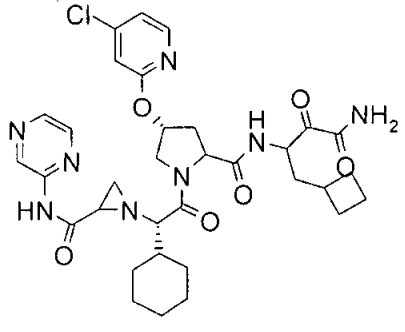
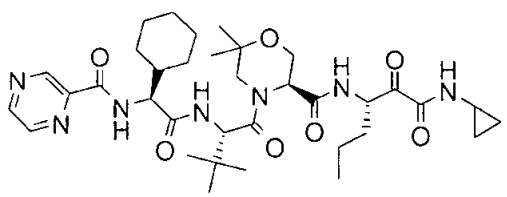
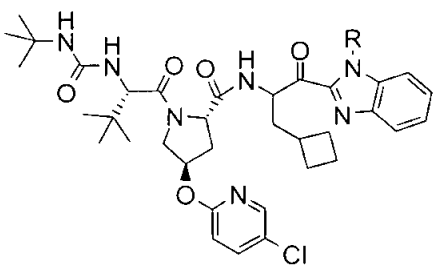
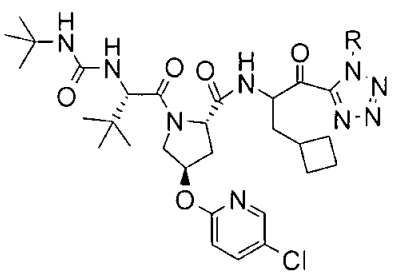
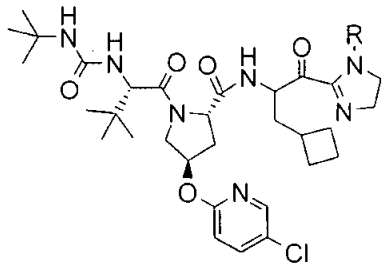
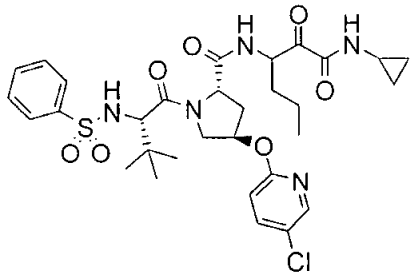
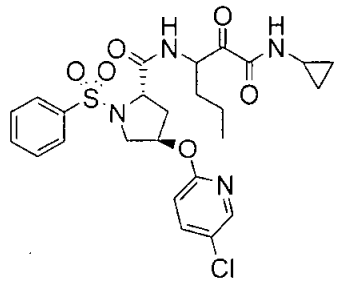
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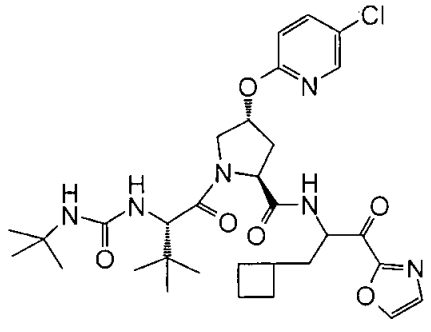
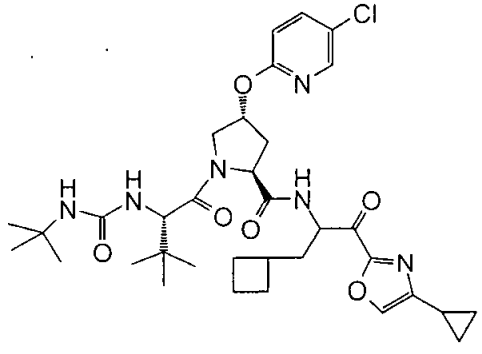
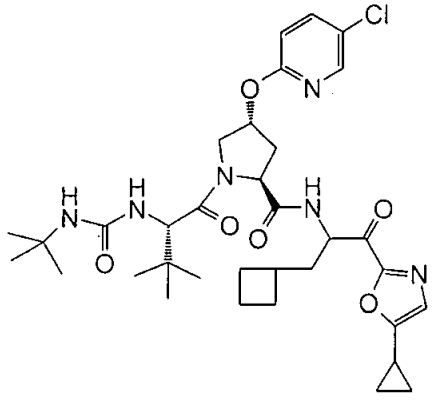
**TABLA B**

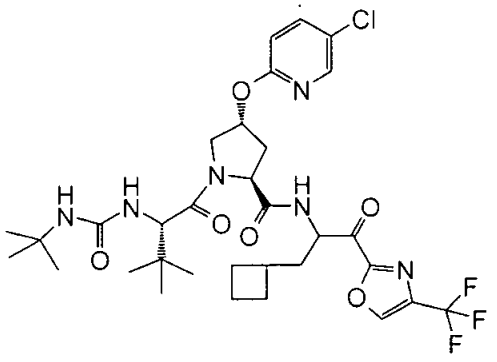
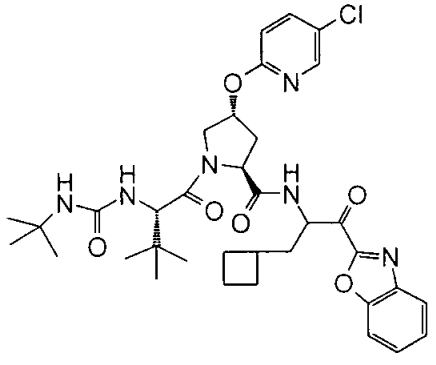
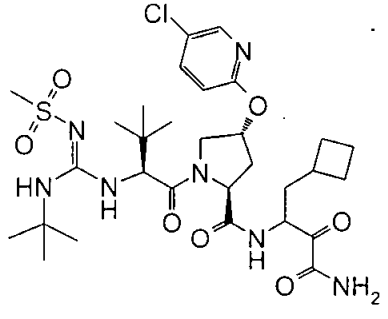
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|  | B-3 |

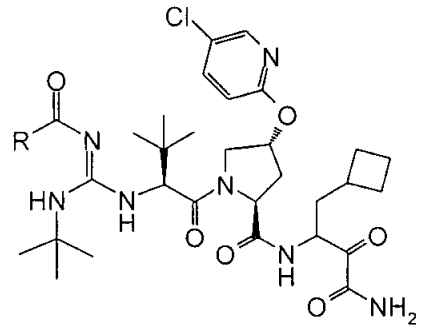
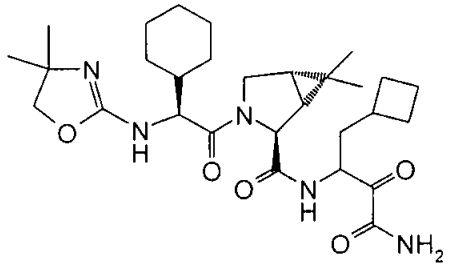
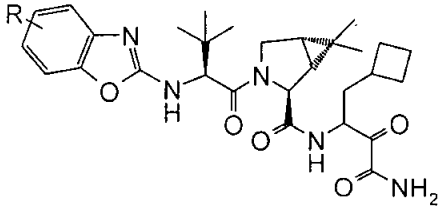
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|  | B-6 |

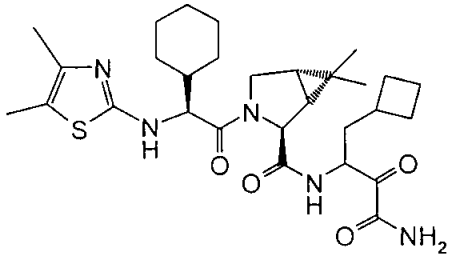
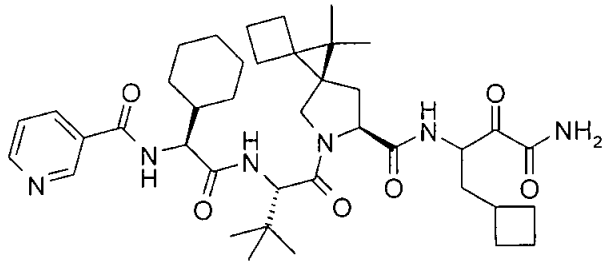
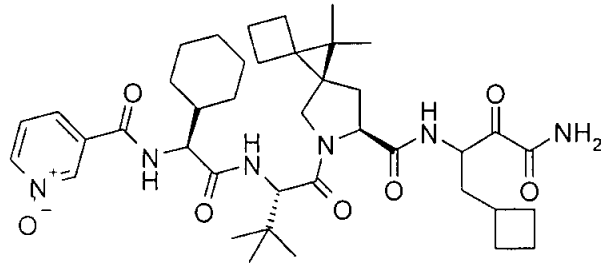
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|  | B-9 |

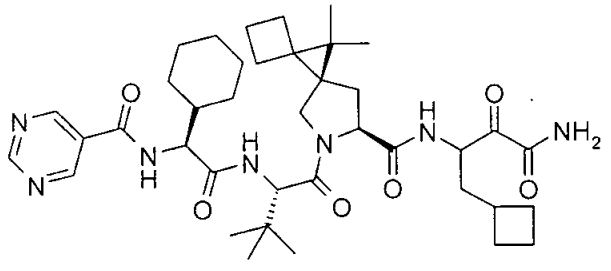
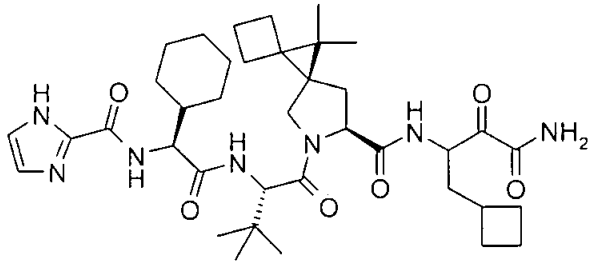
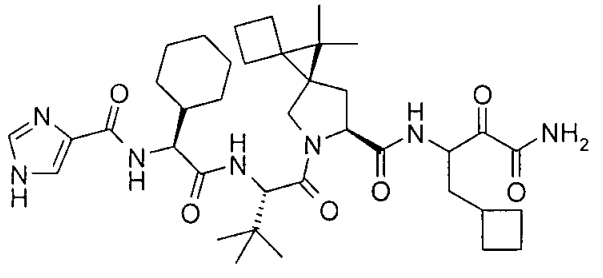
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|  | B-11 |
|  | B-12 |

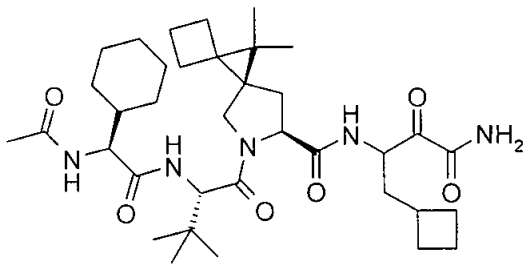
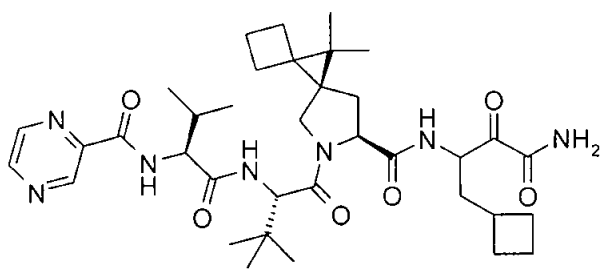
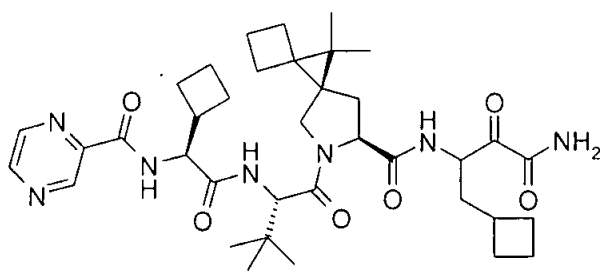
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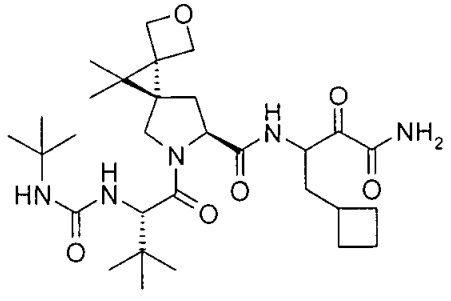
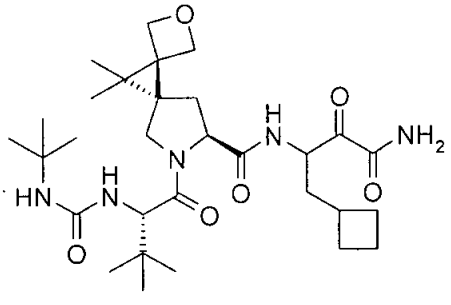
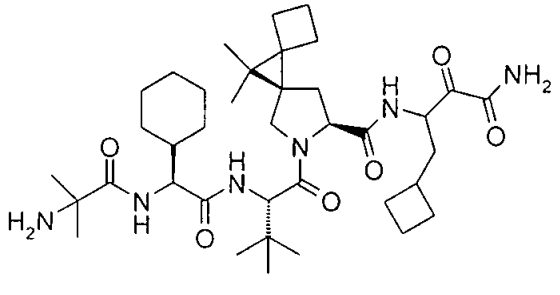
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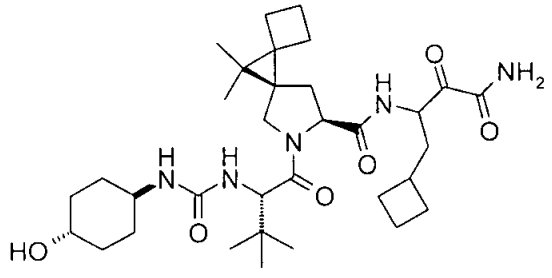
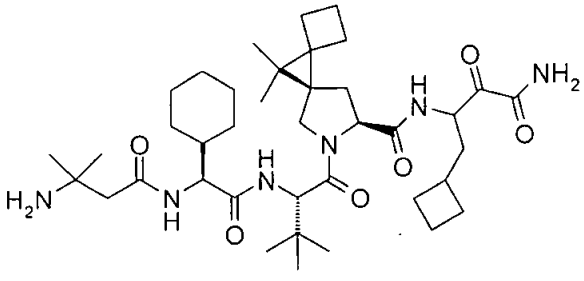
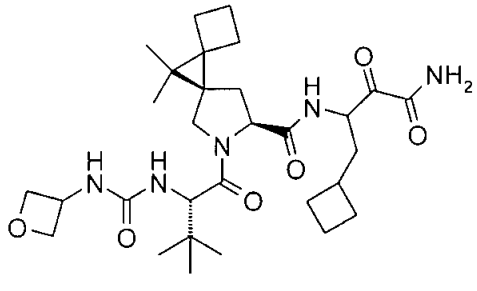
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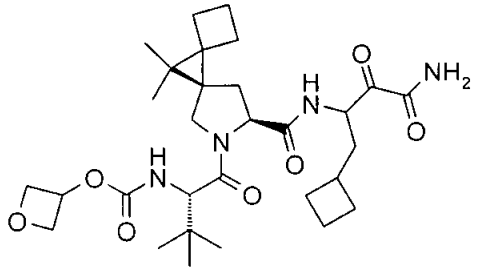
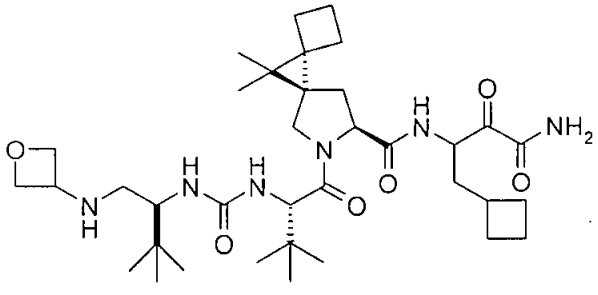
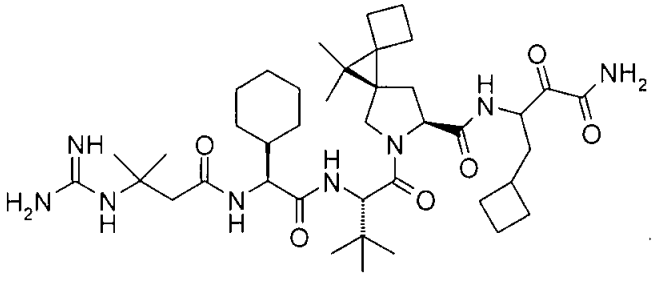
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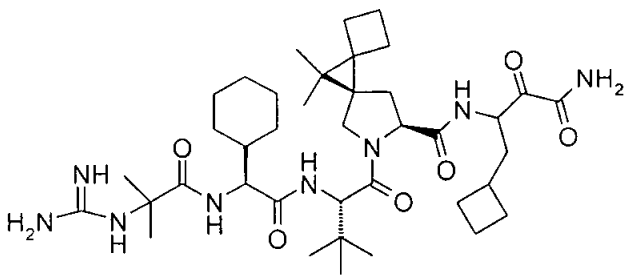
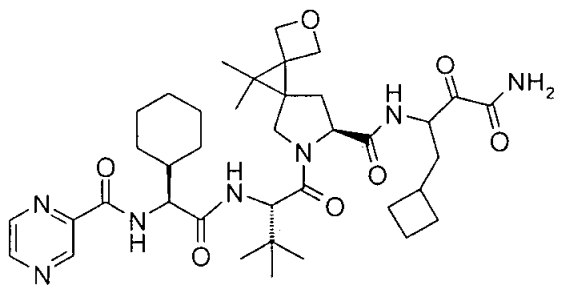
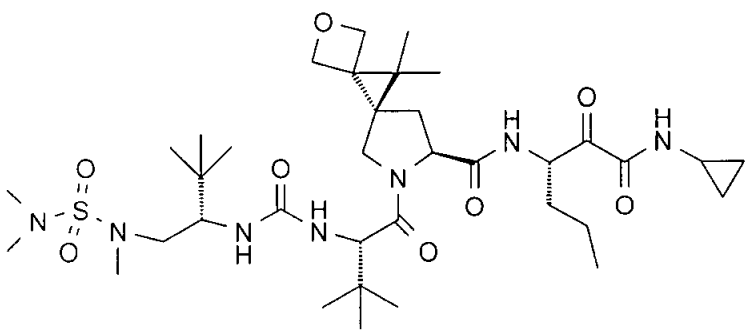
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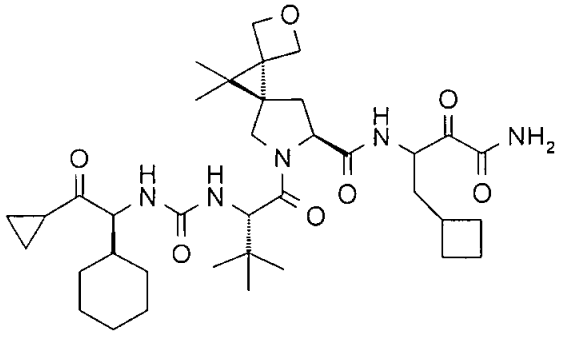
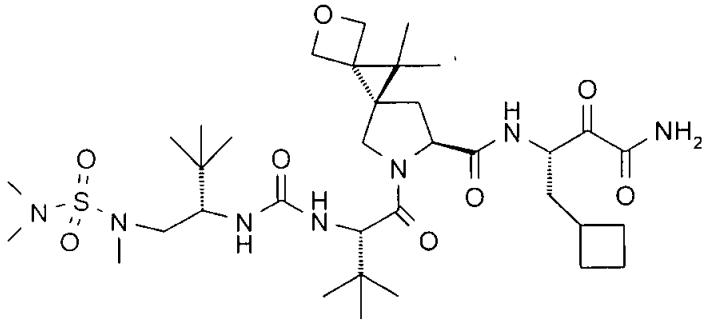
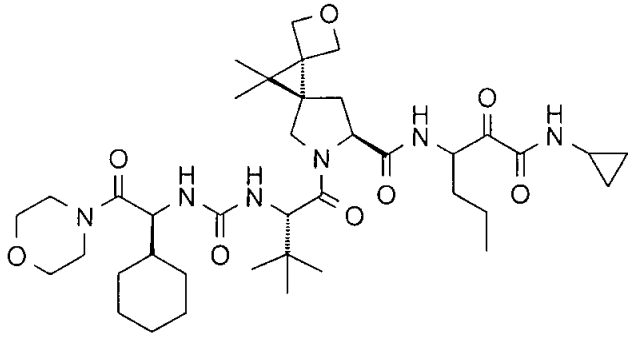
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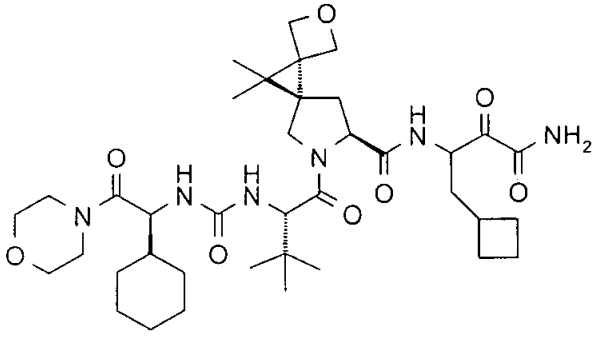
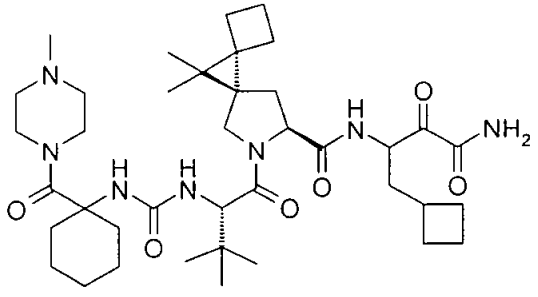
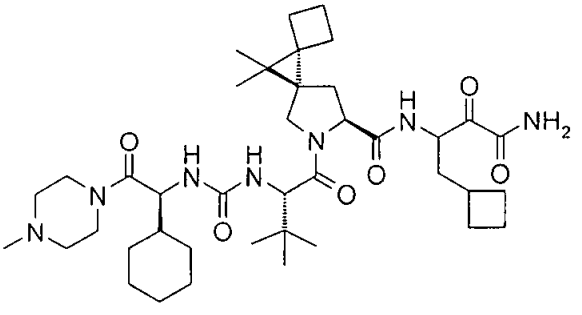
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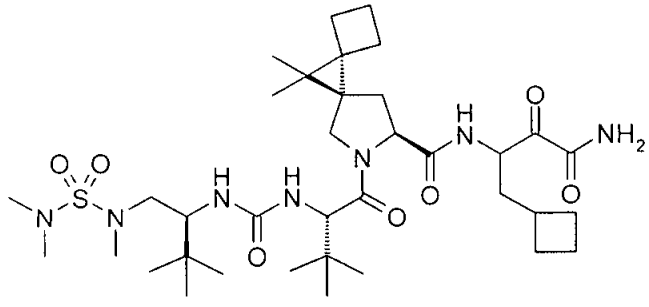
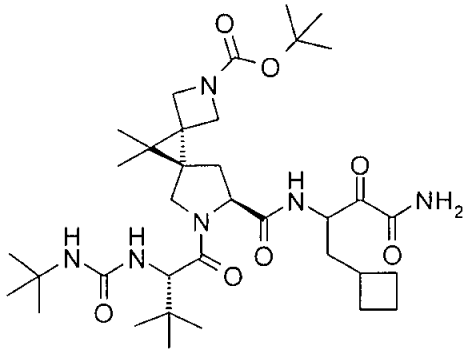
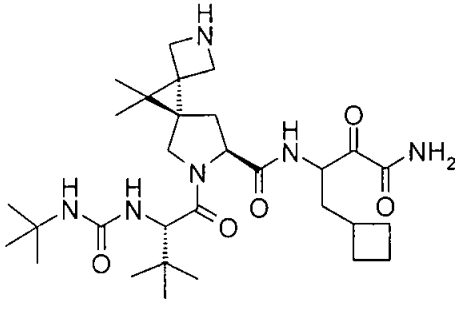
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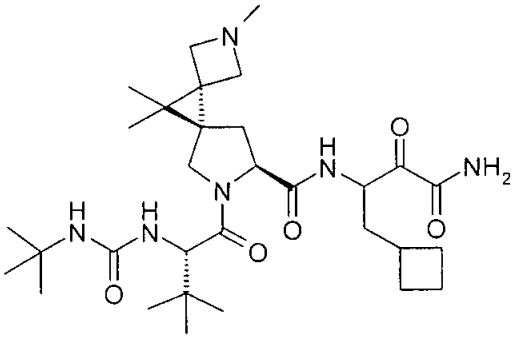
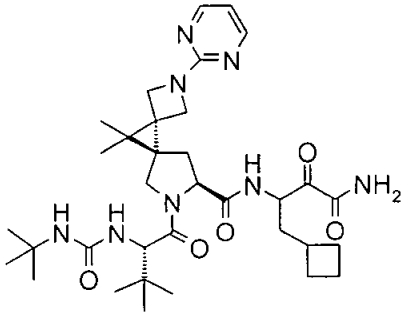
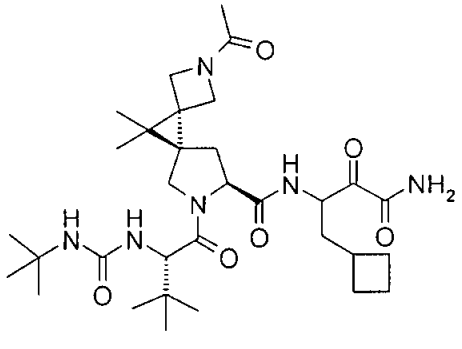
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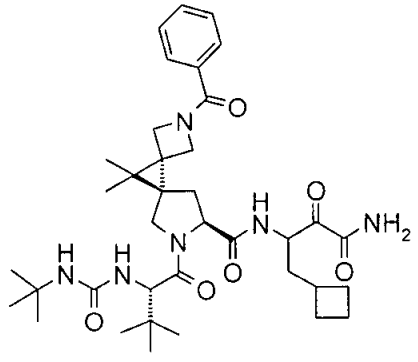
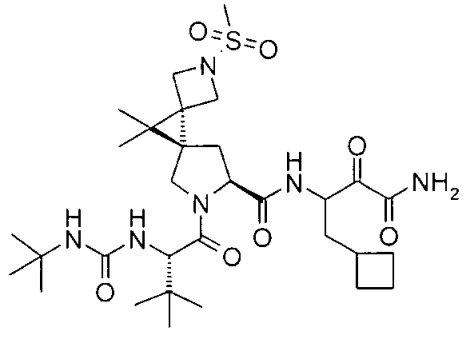
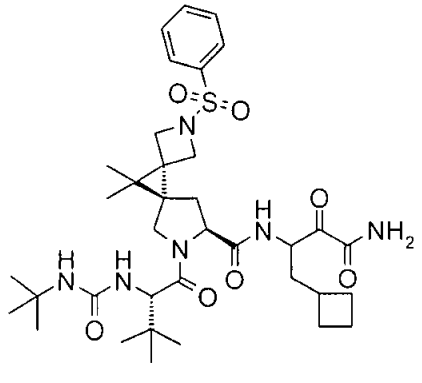
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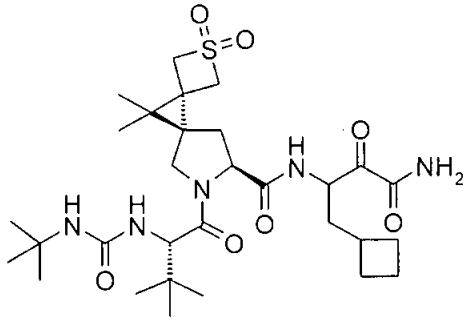
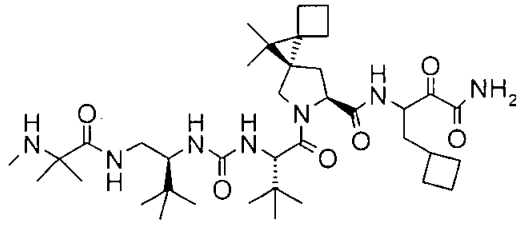
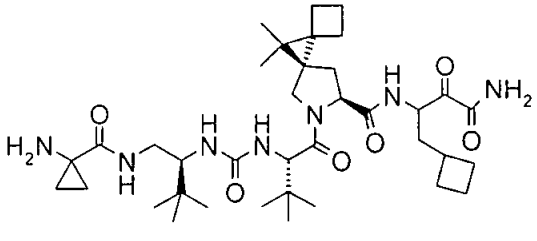
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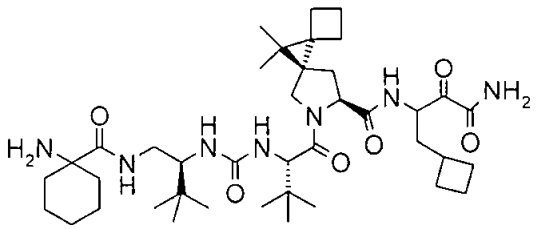
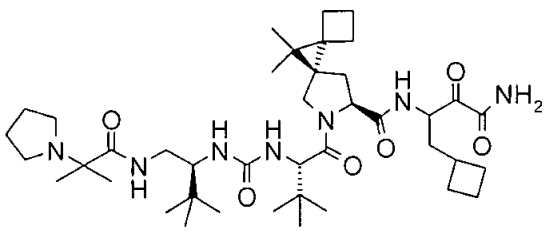
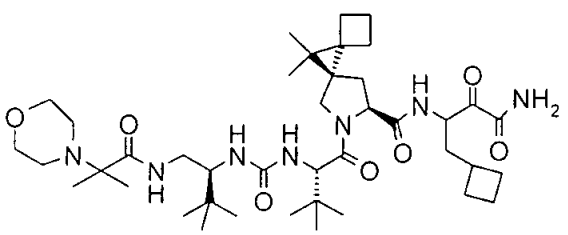
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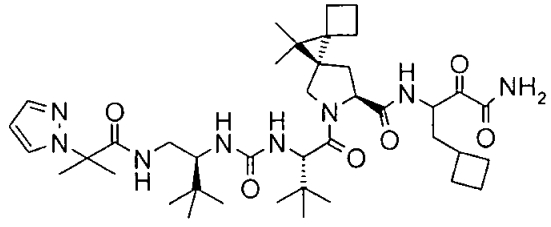
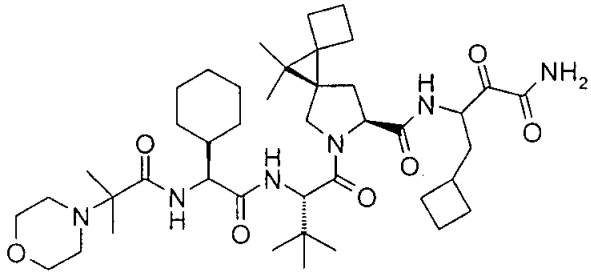
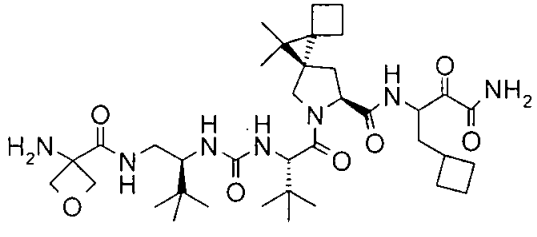
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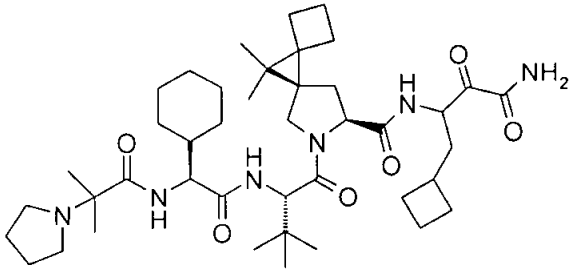
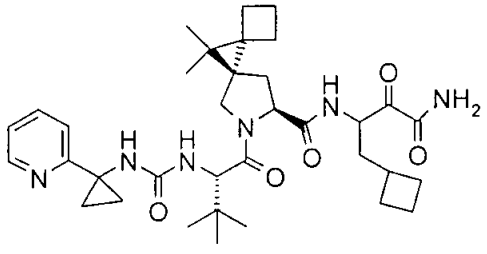
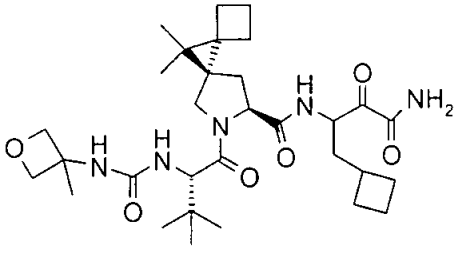
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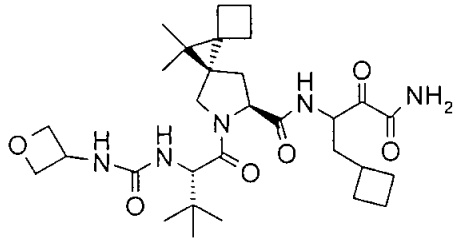
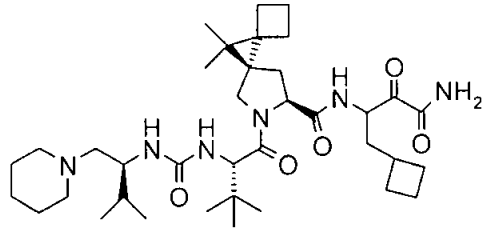
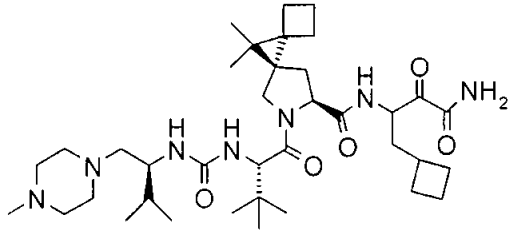
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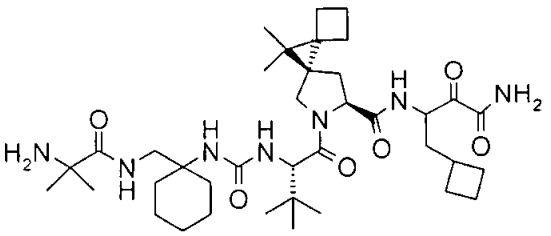
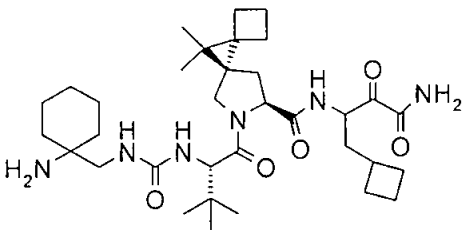
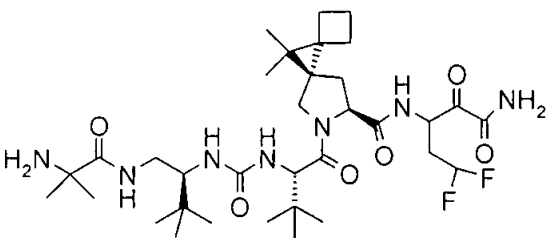
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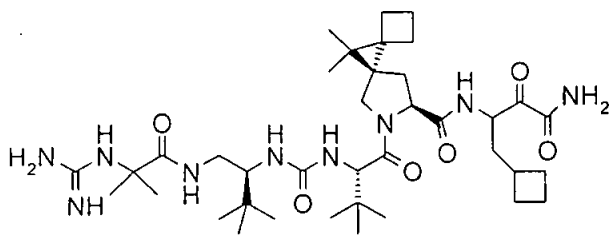
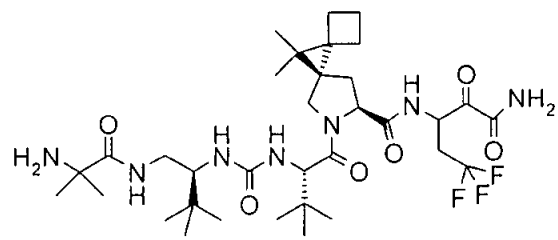
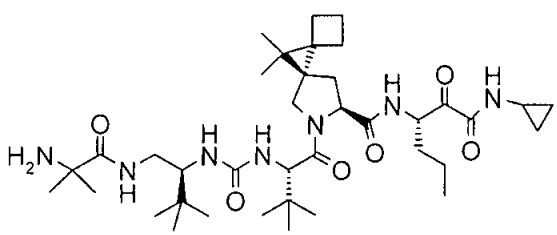
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| Estructura | Comp. No. |
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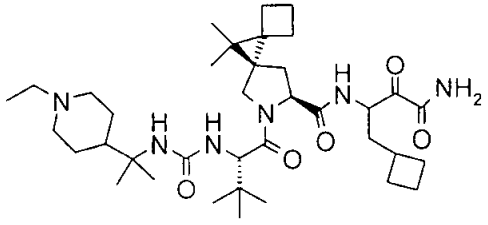
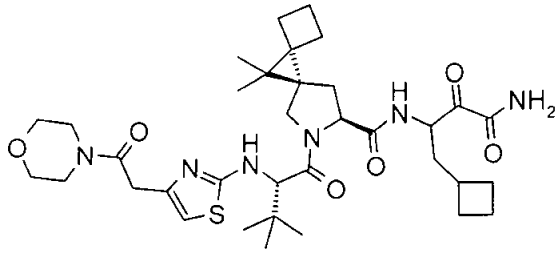
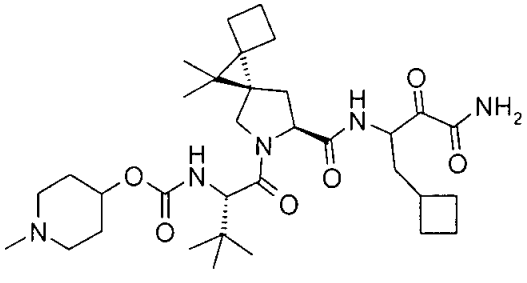
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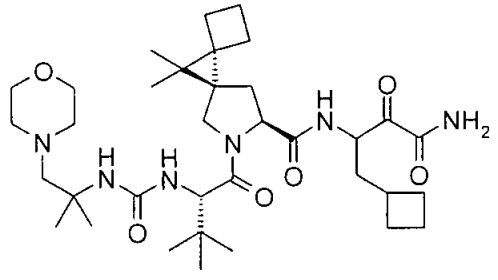
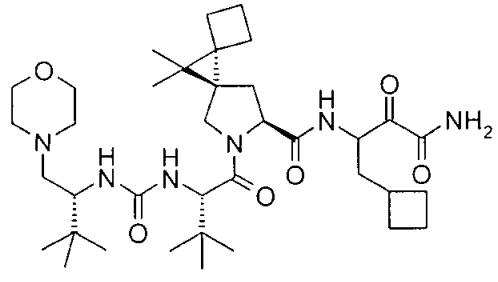
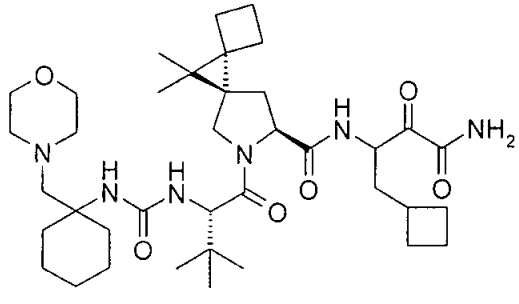
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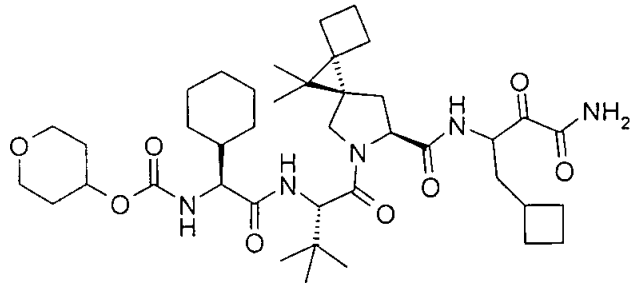
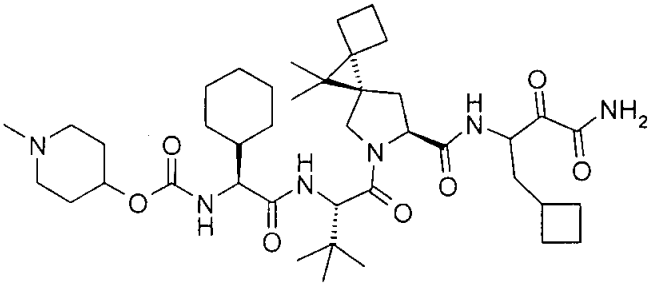
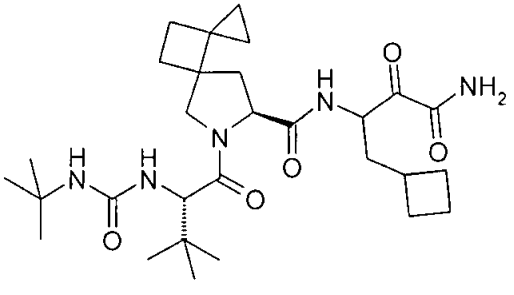
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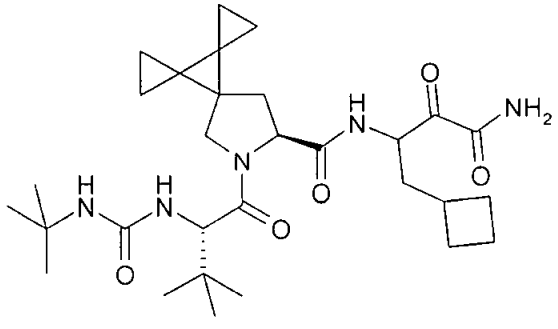
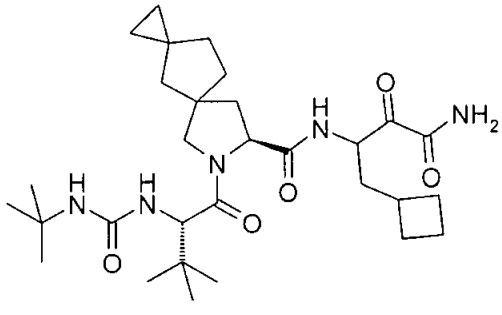
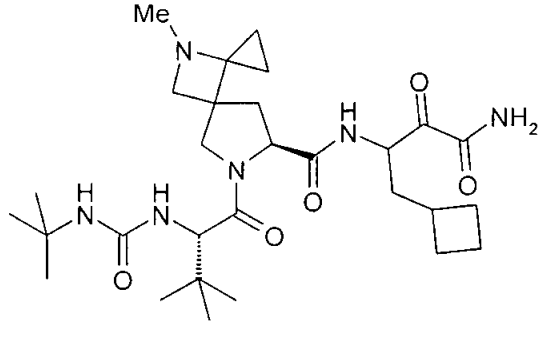
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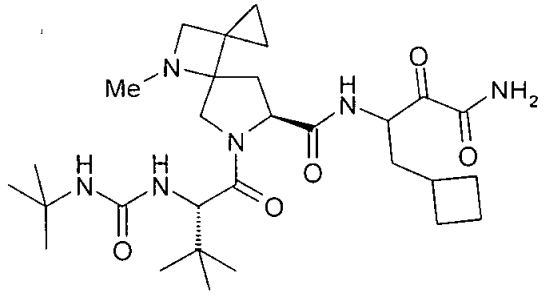
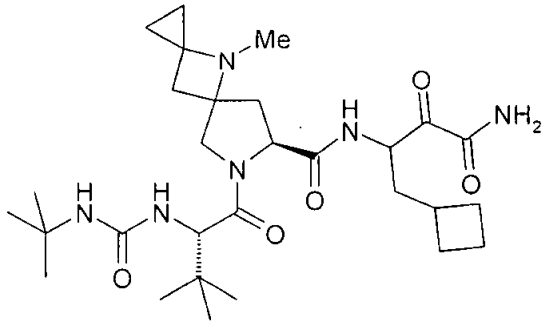
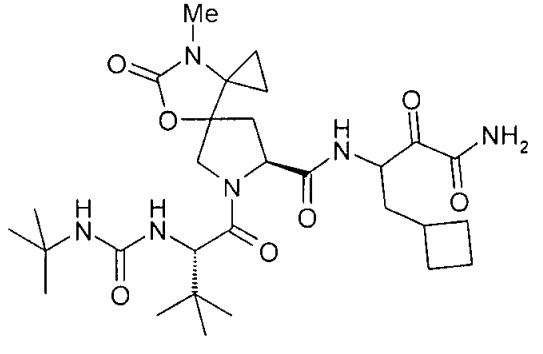
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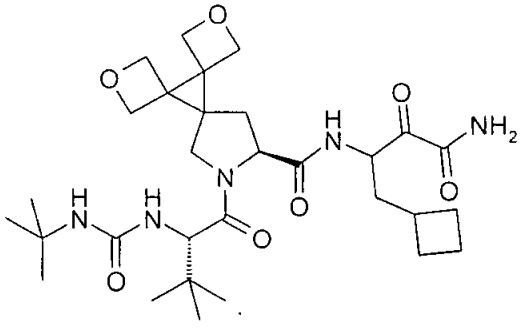
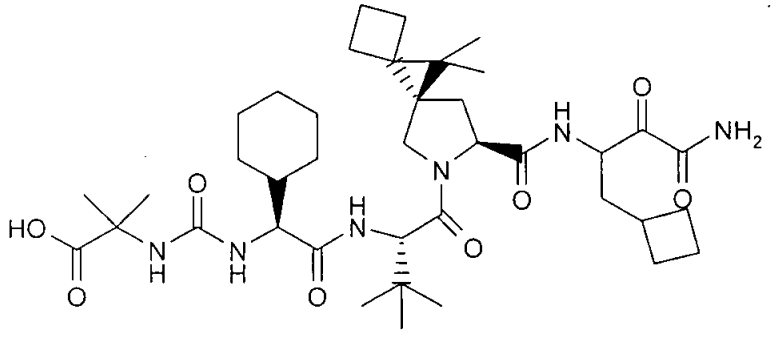
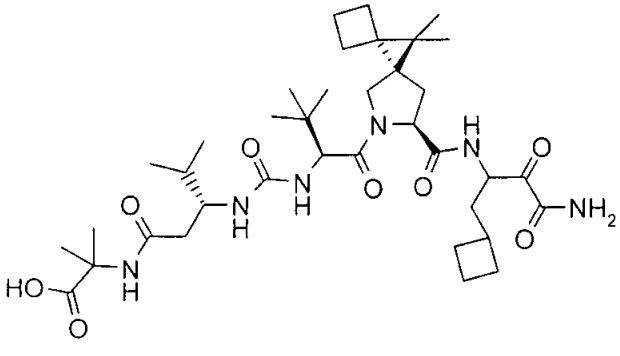
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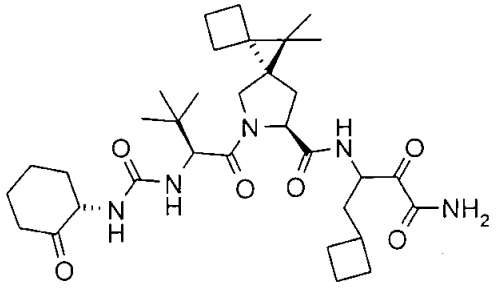
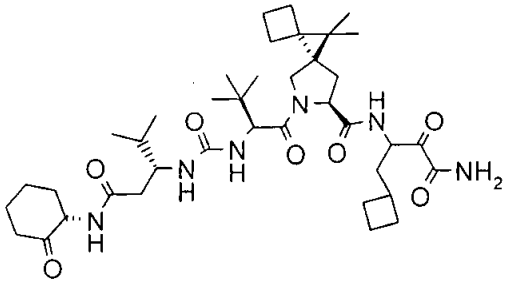
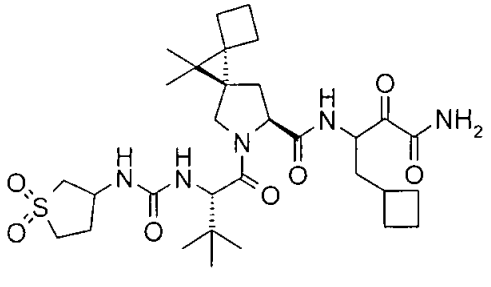
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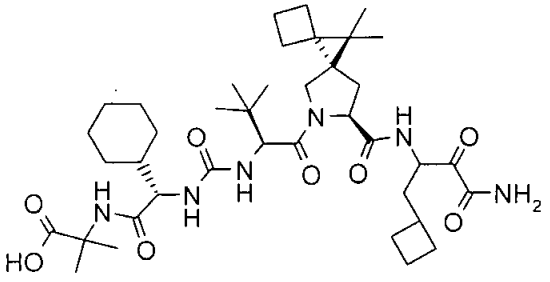
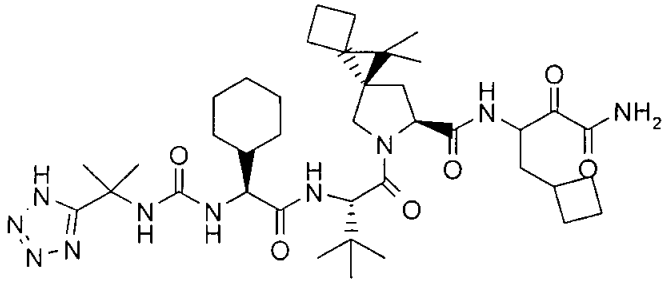
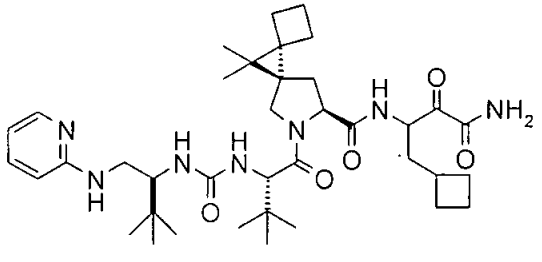
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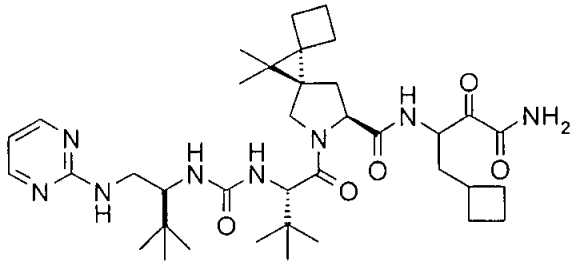
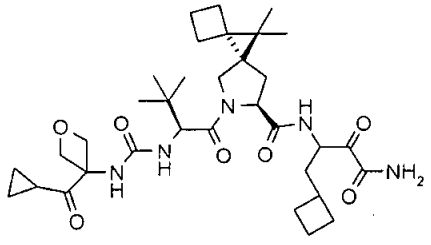
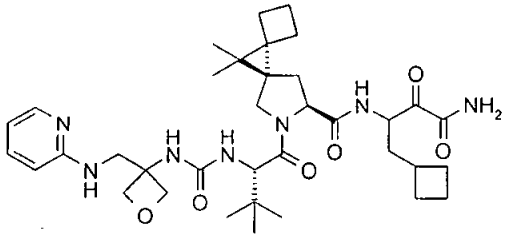
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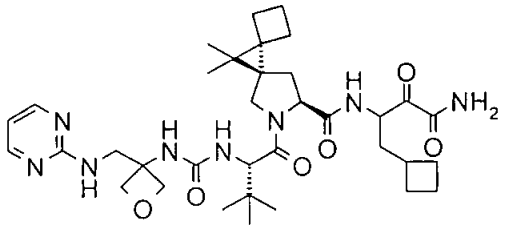
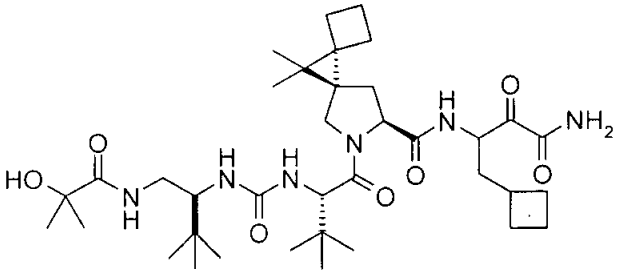
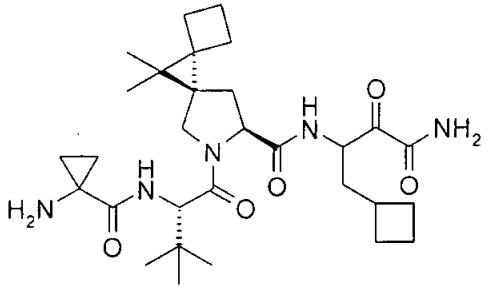
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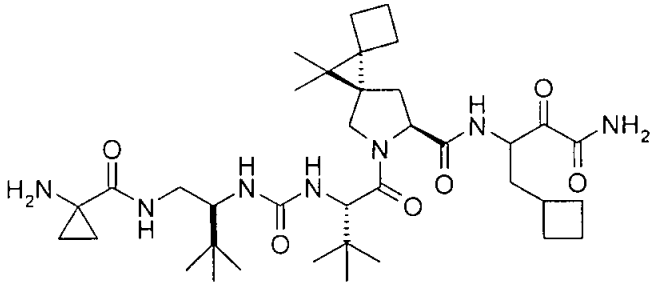
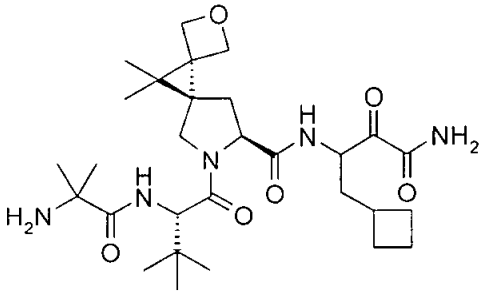
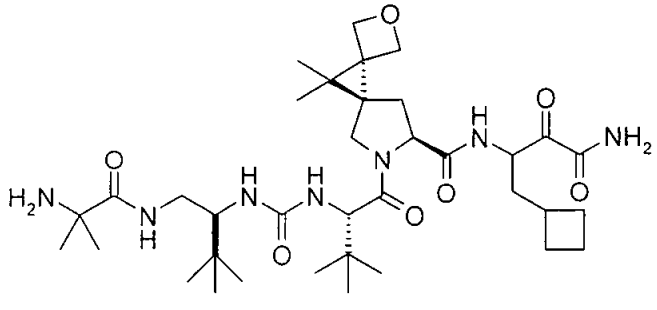
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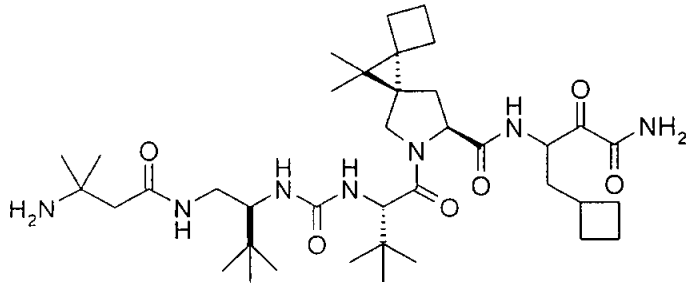
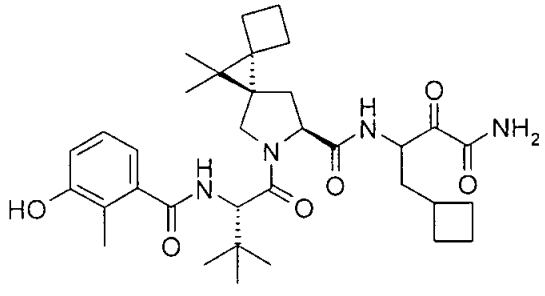
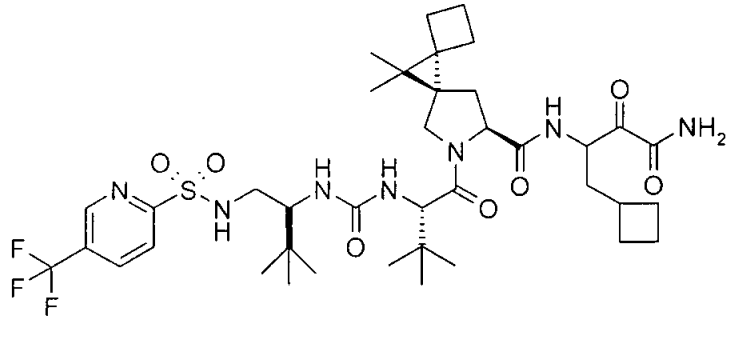
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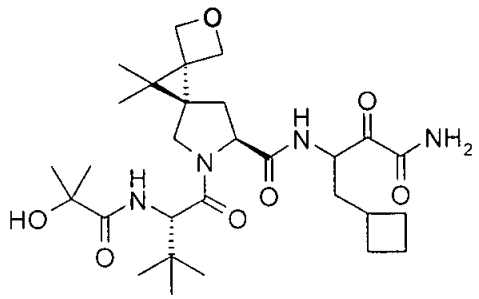
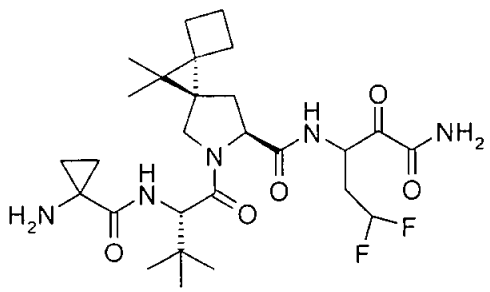
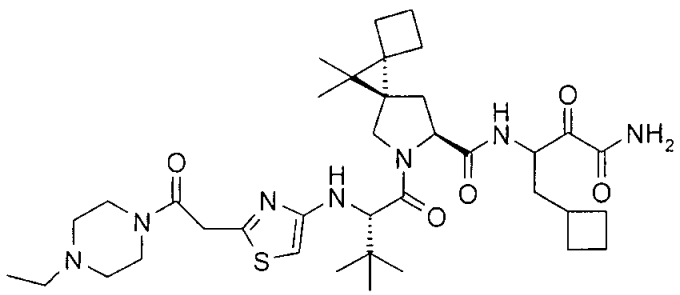
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| Estructura | Comp. No. |
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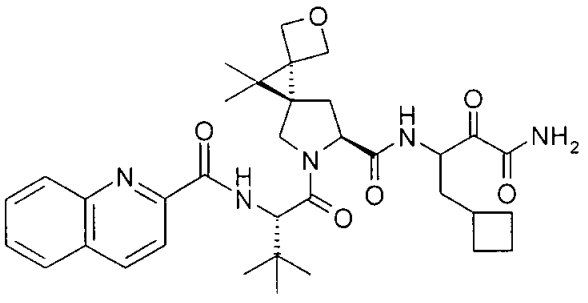
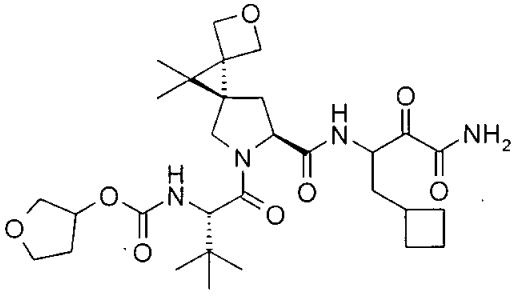
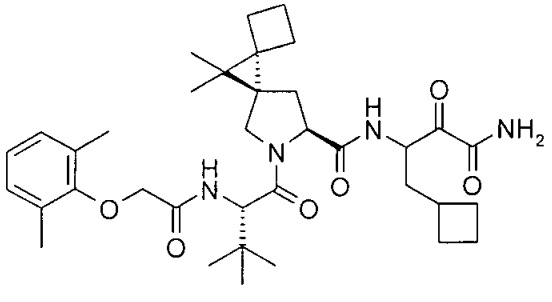
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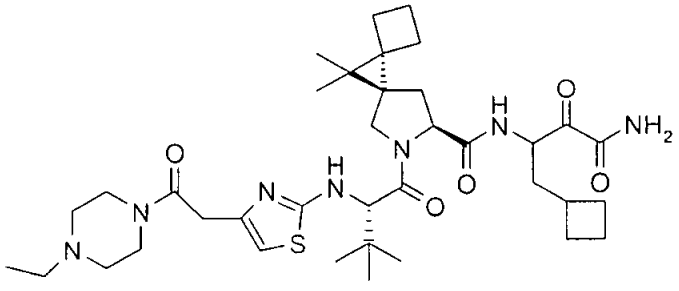
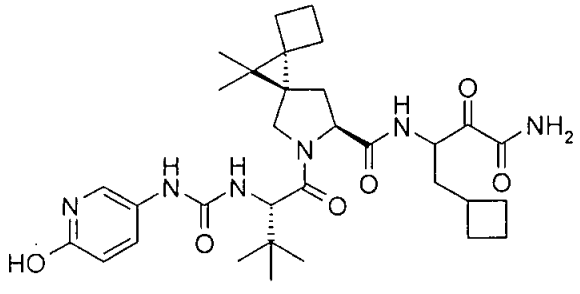
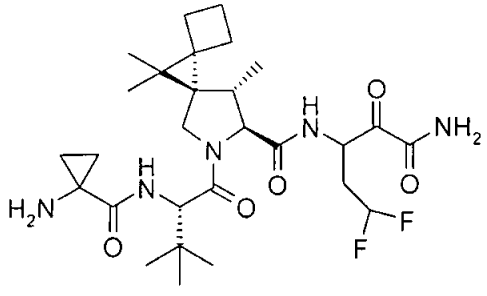
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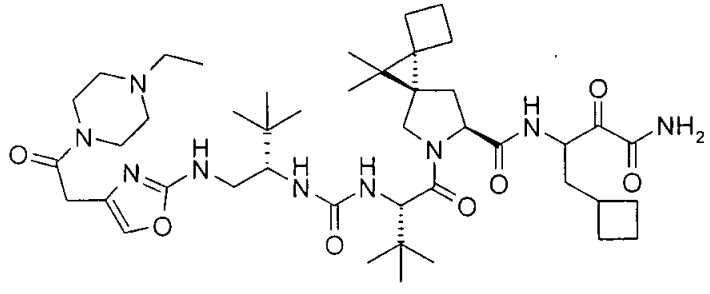
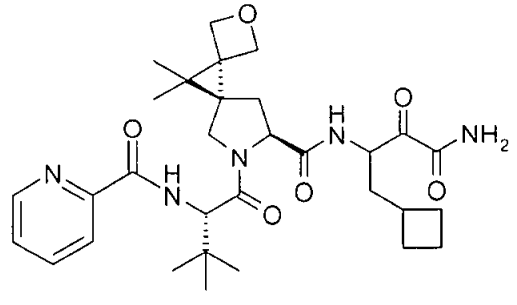
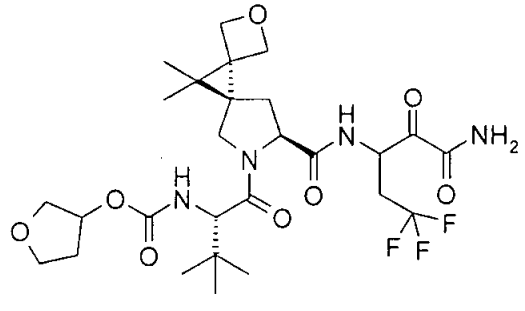
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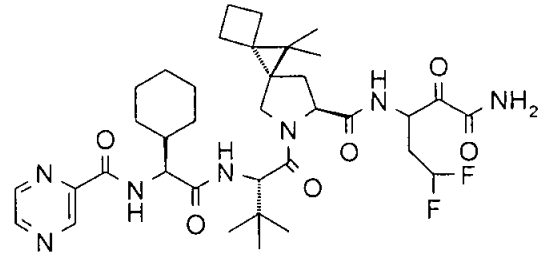
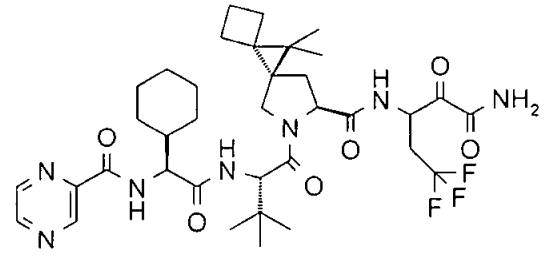
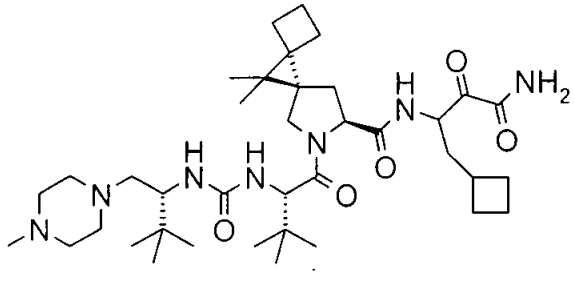
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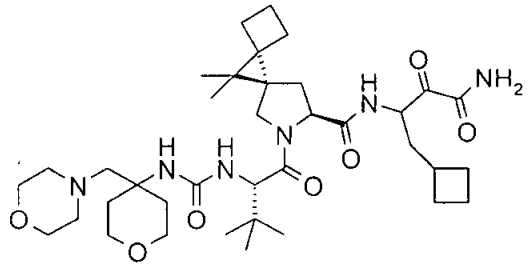
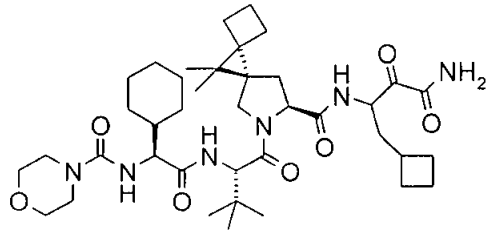
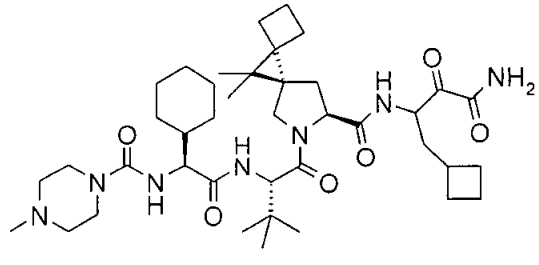
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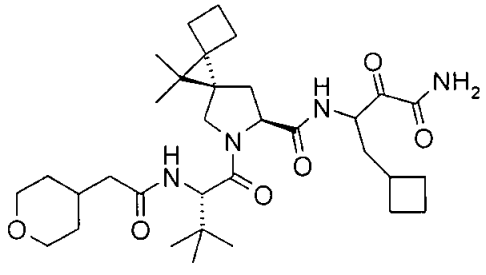
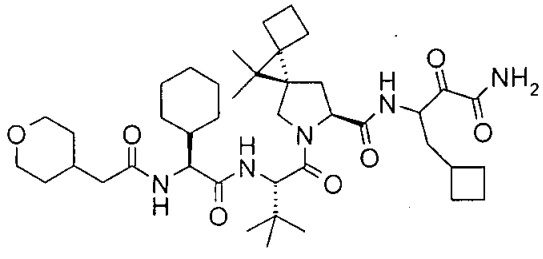
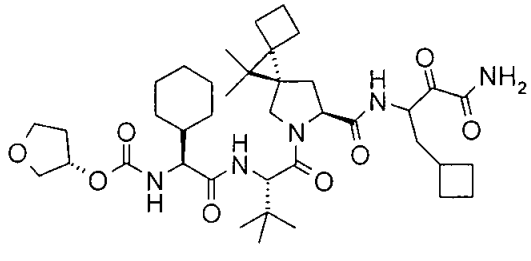
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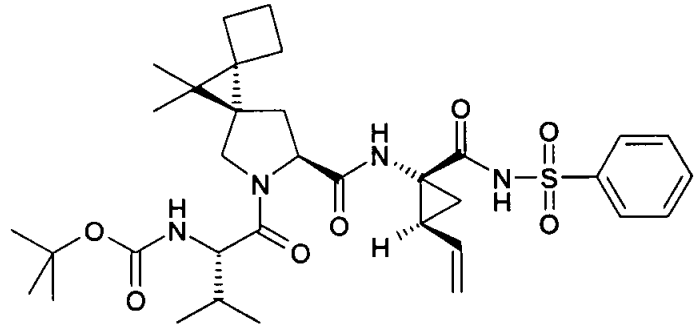
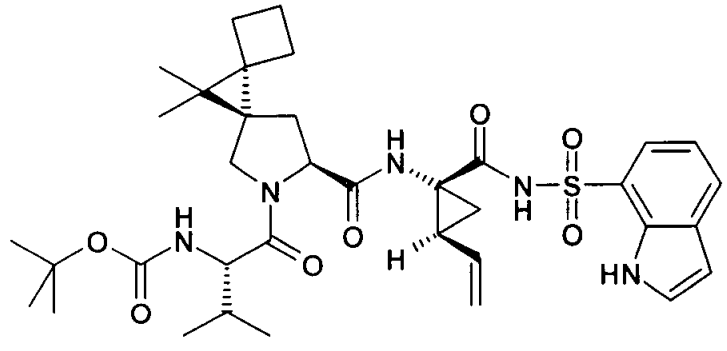
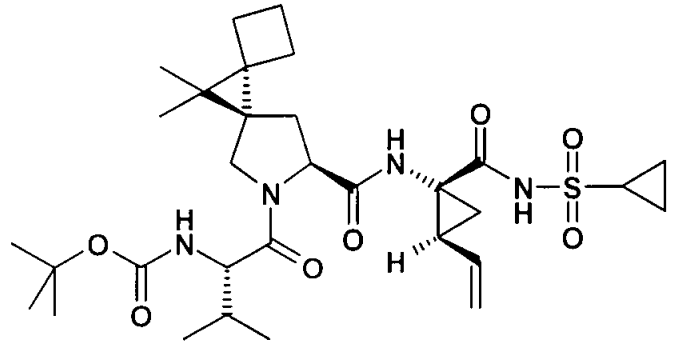
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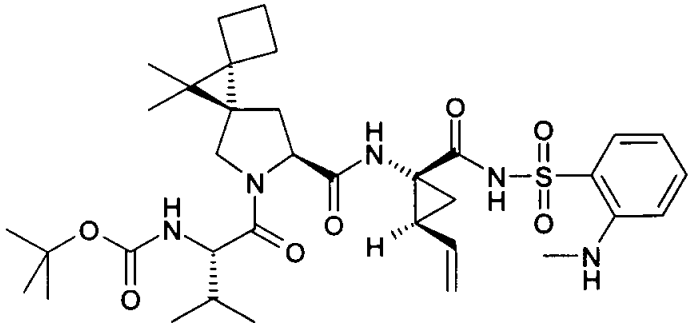
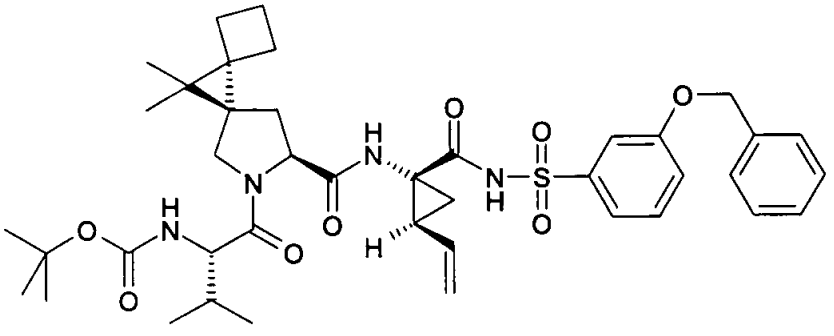
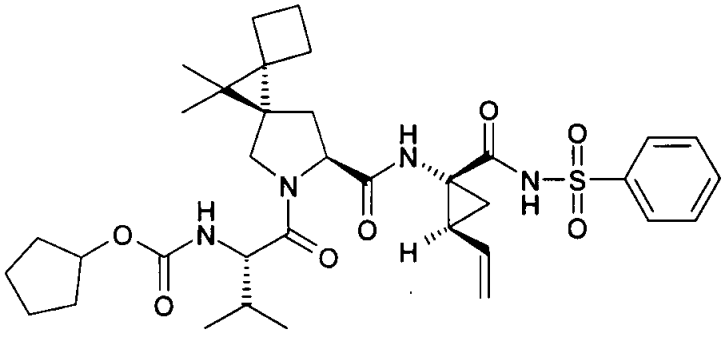
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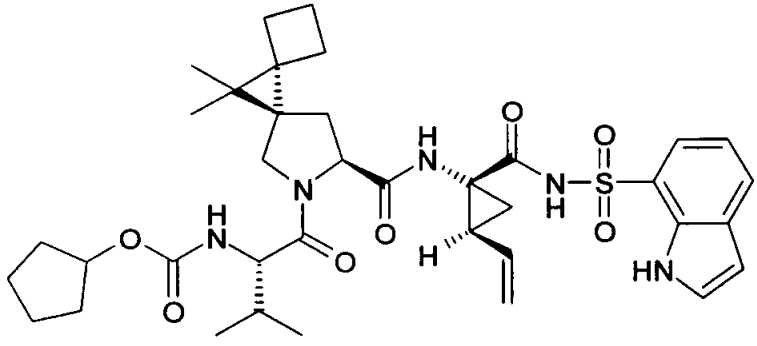
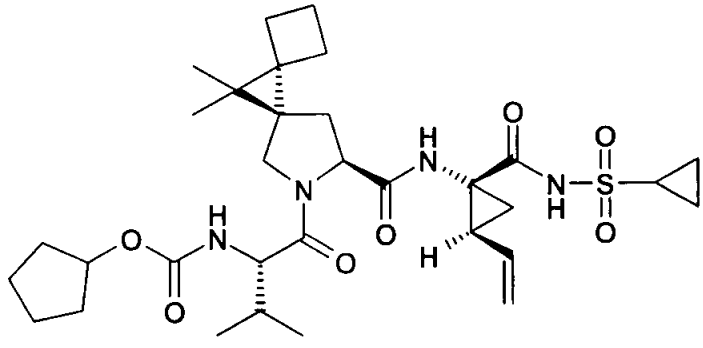
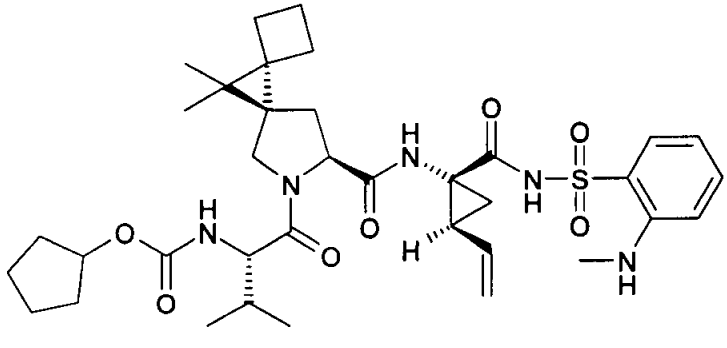
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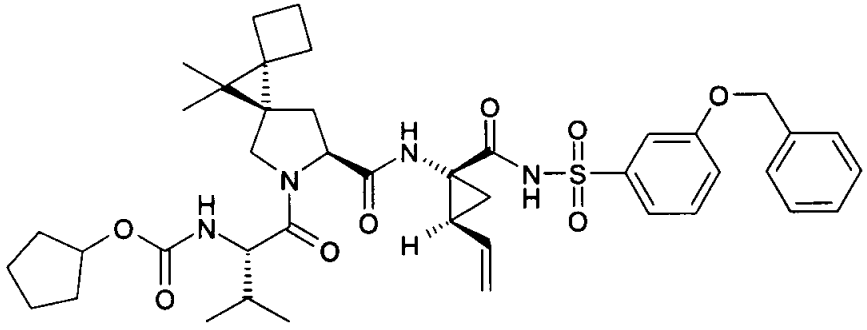
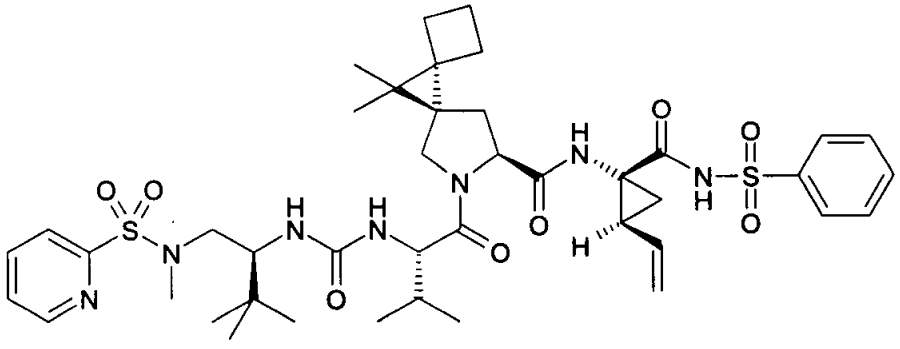
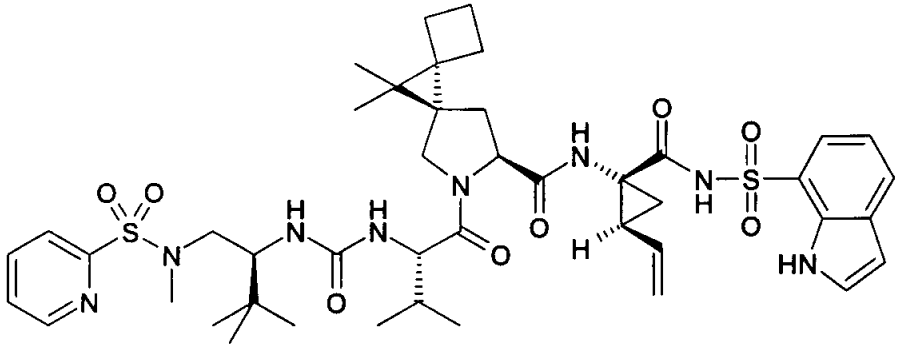
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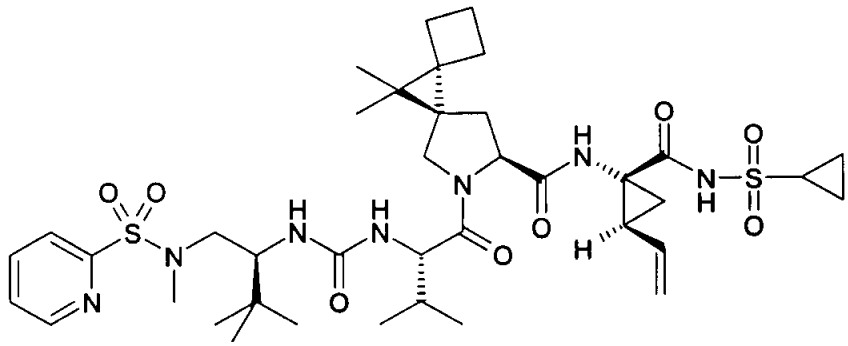
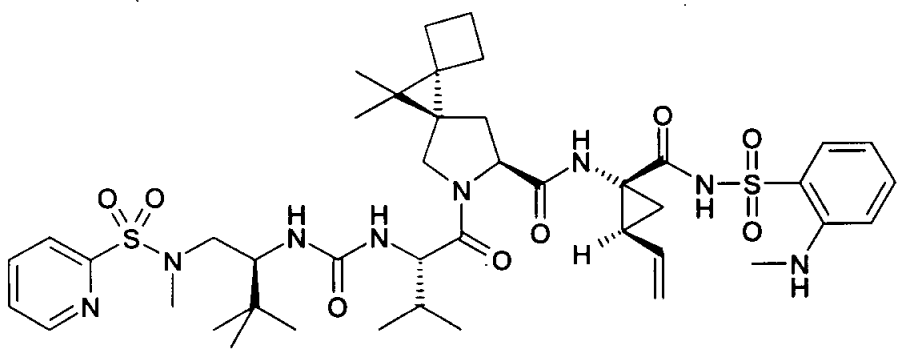
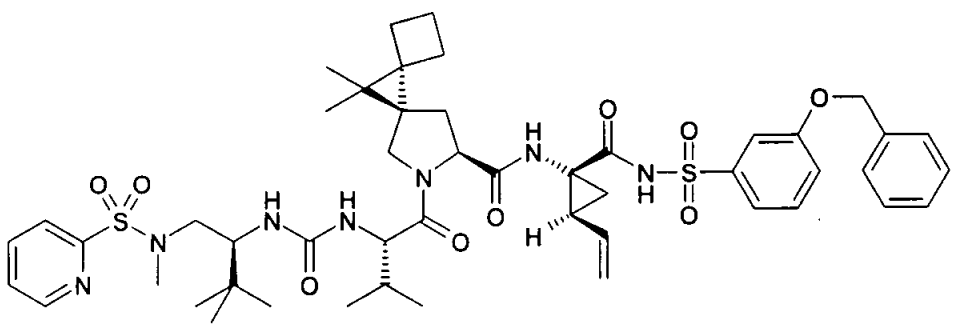
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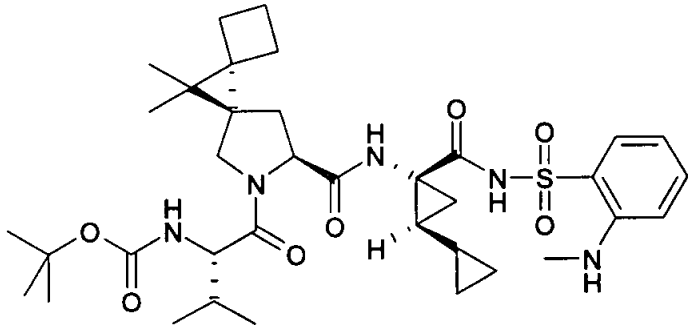
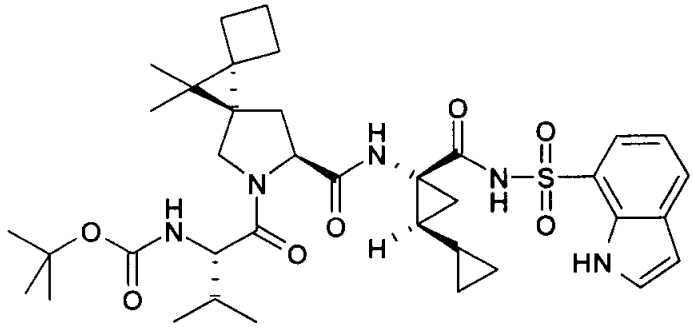
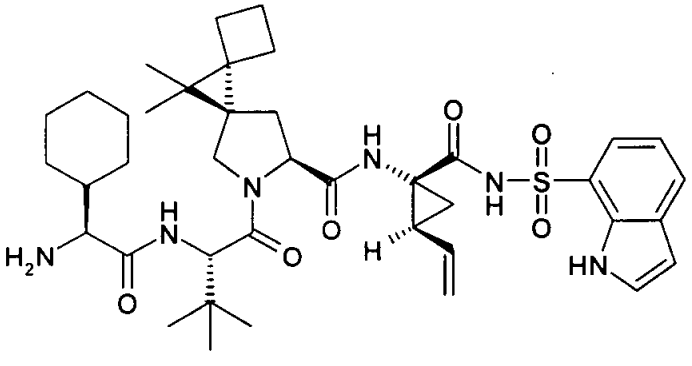
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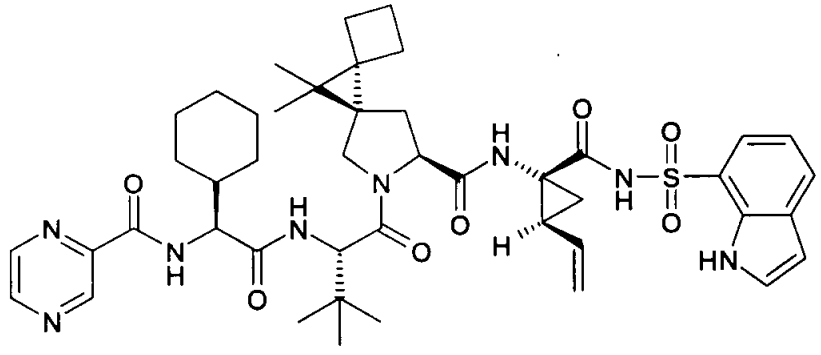
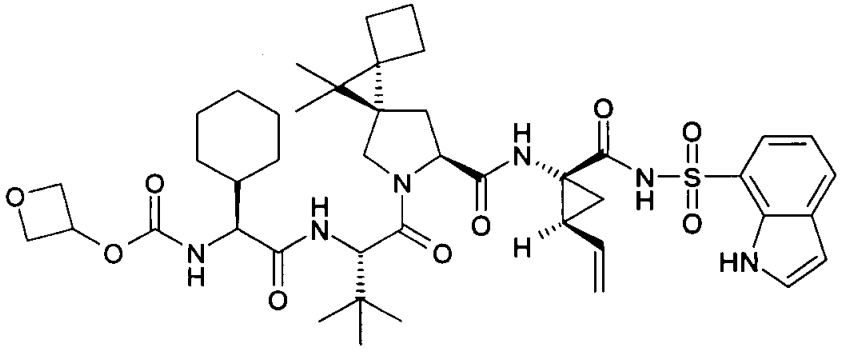
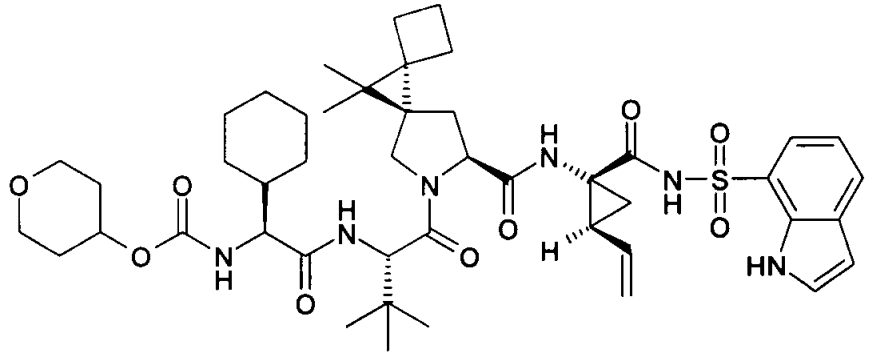
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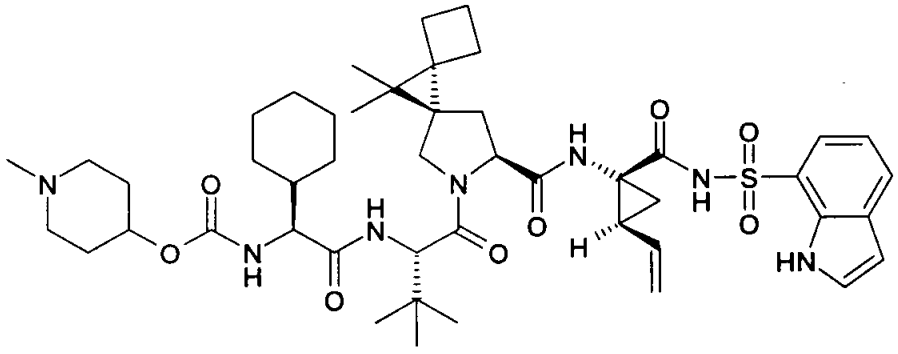
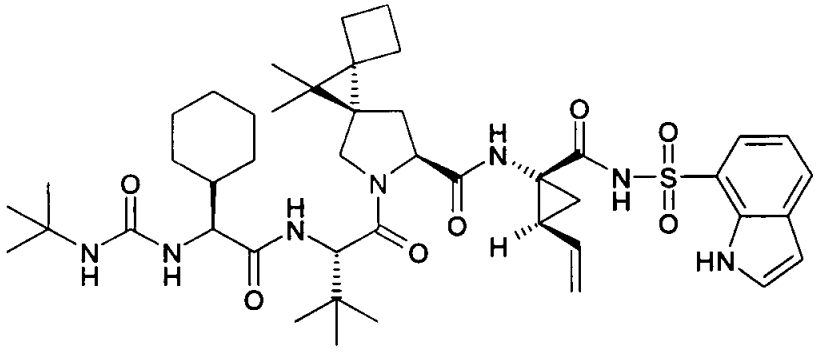
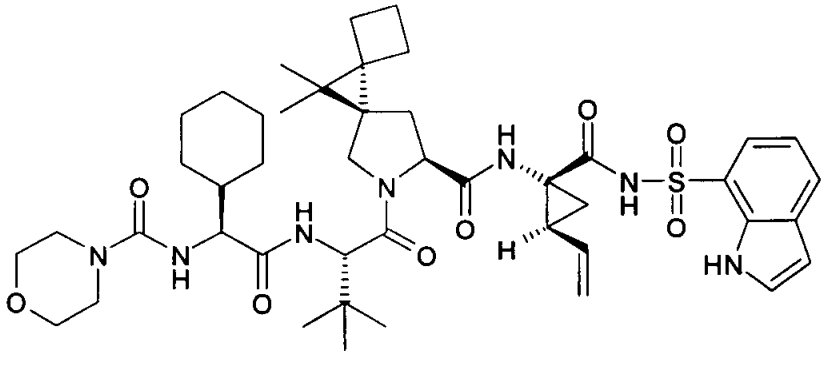
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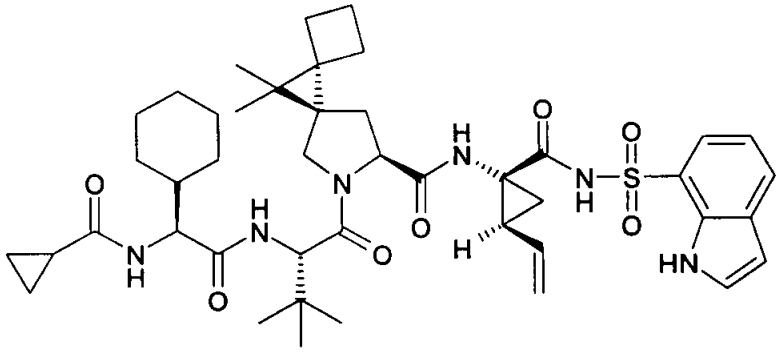
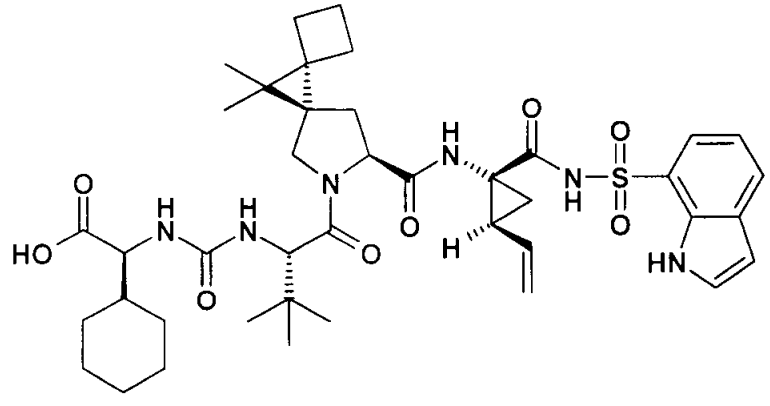
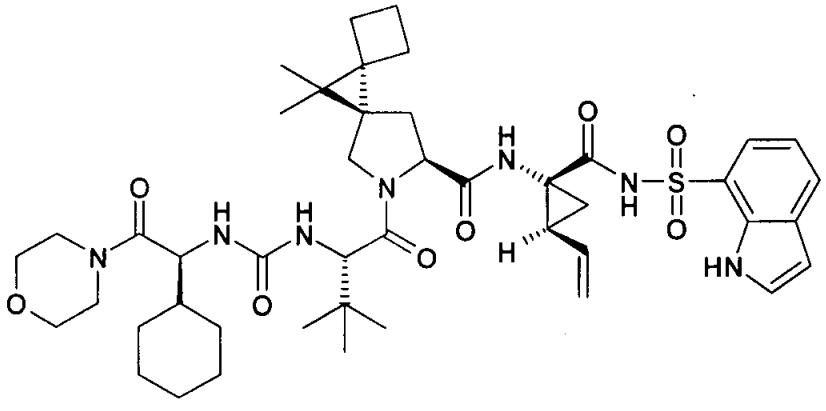
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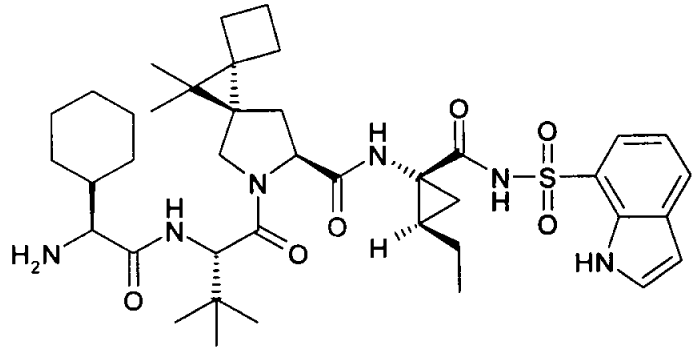
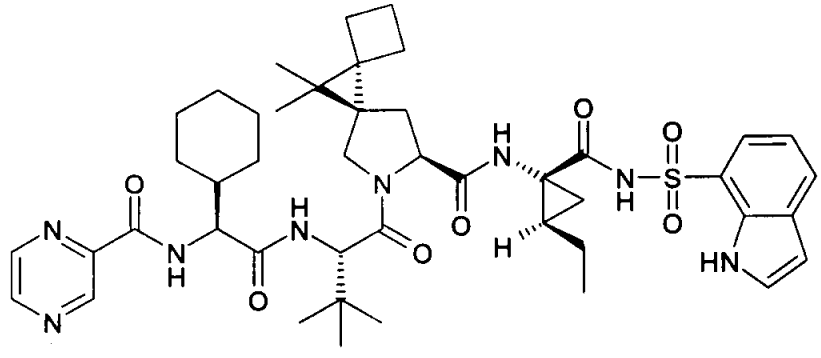
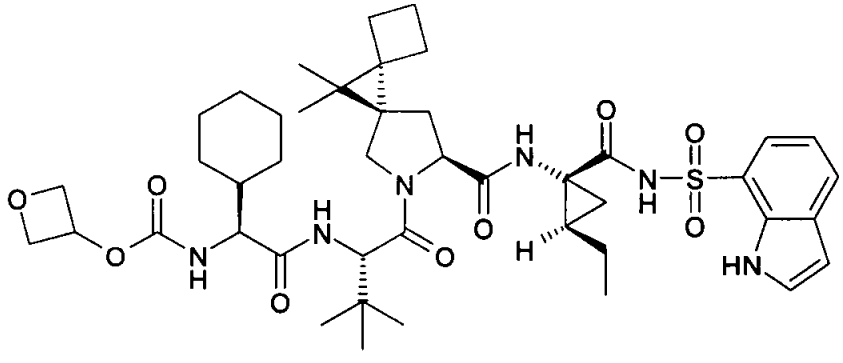
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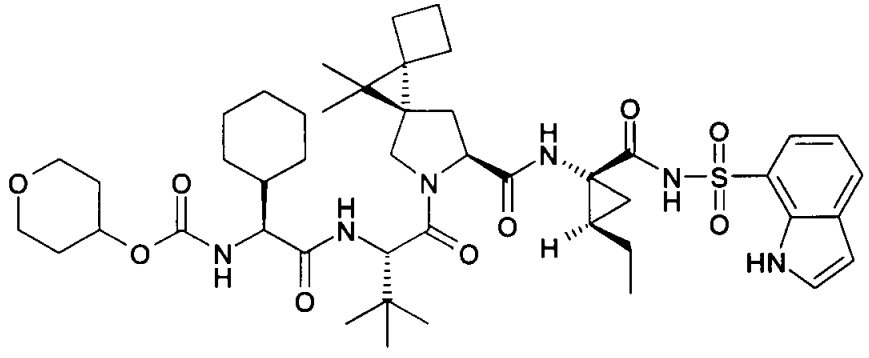
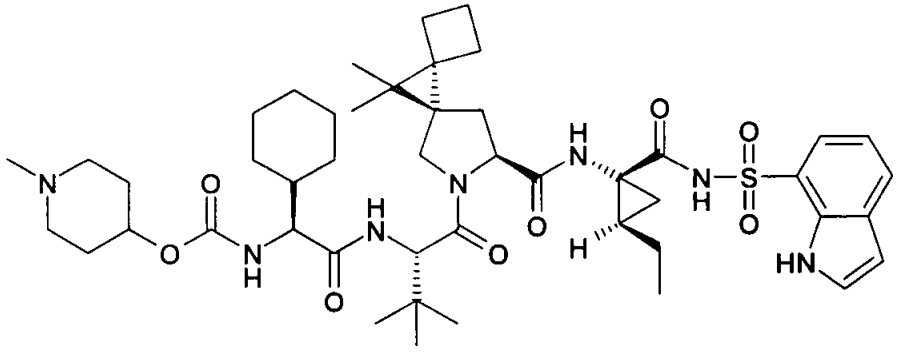
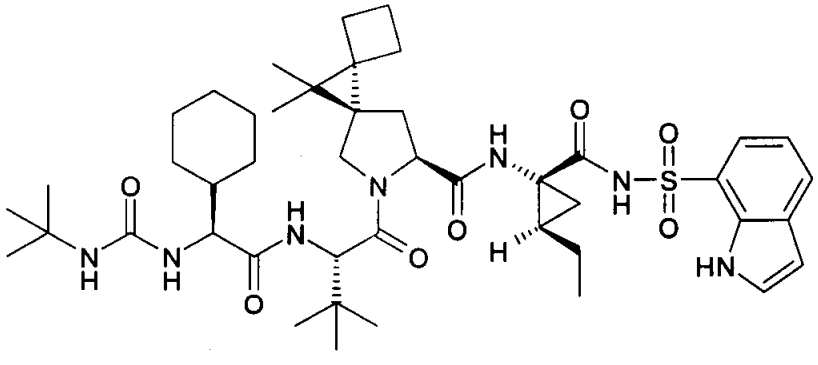
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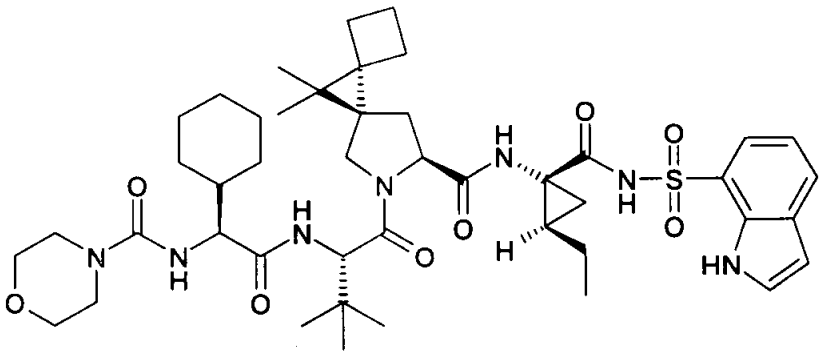
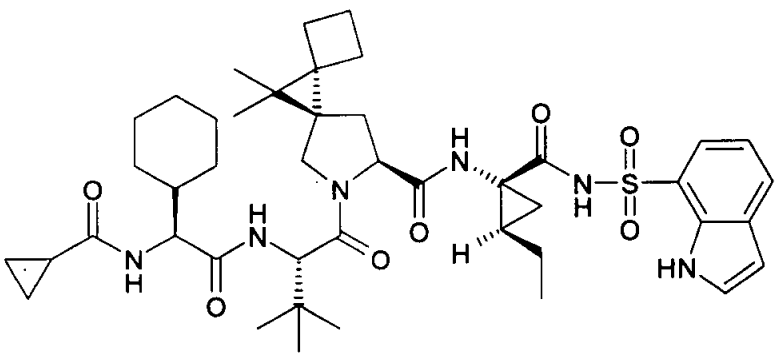
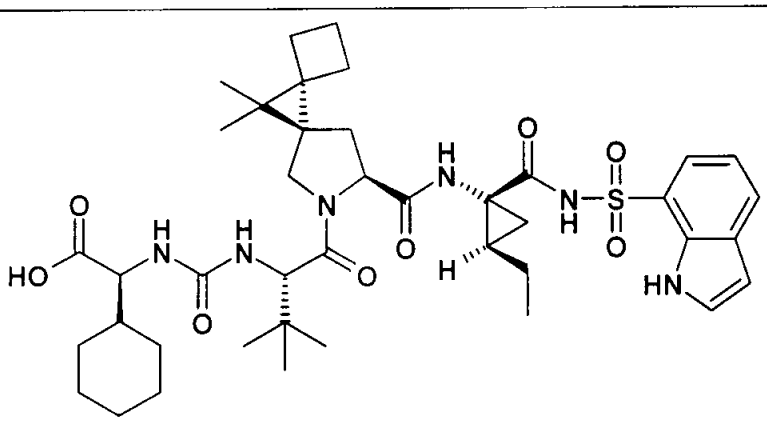
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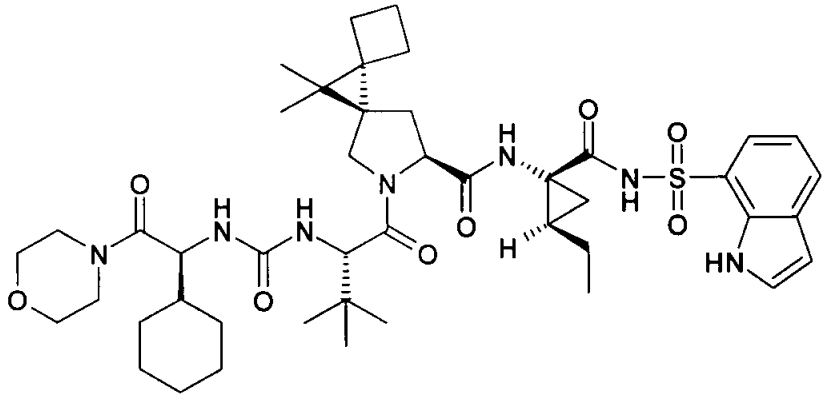
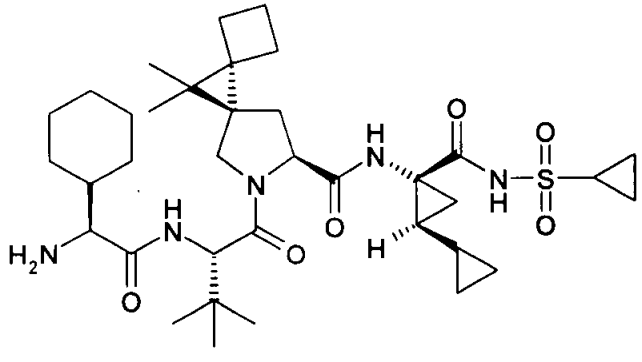
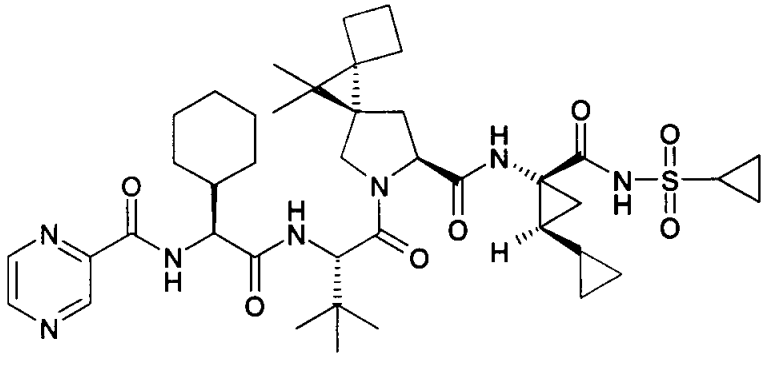
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|  | B-159 |

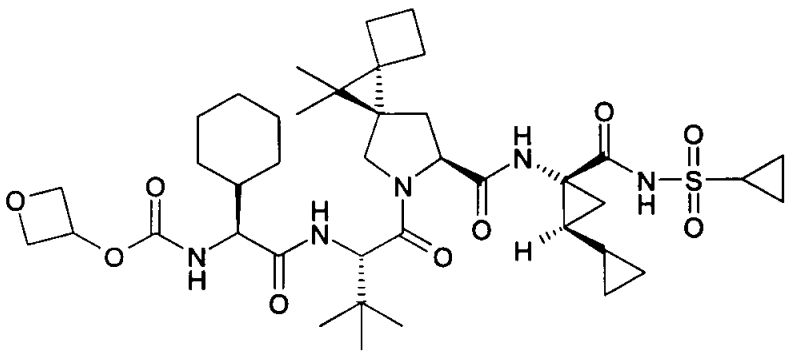
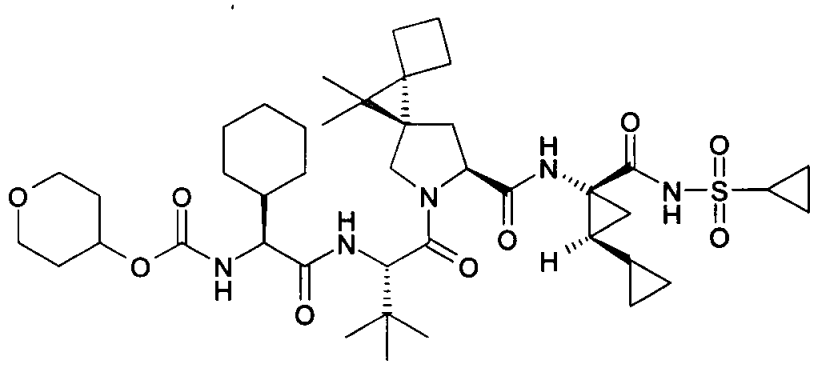
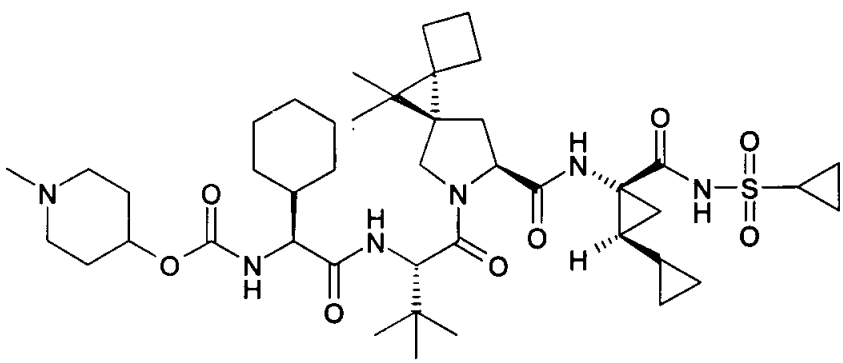
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|  | B-161 |
|  | B-162 |

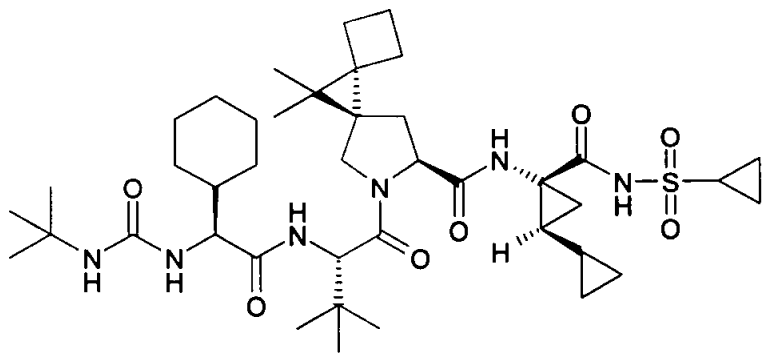
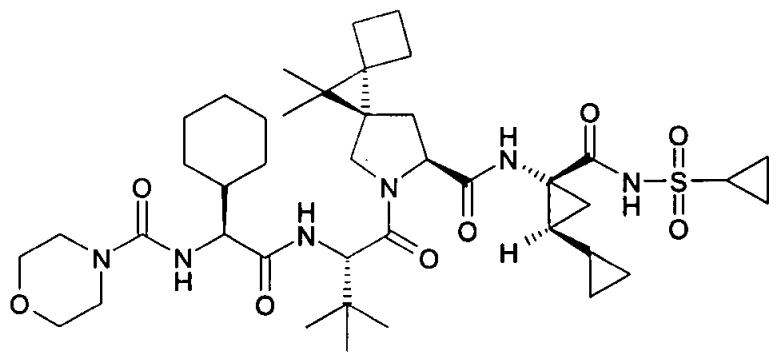
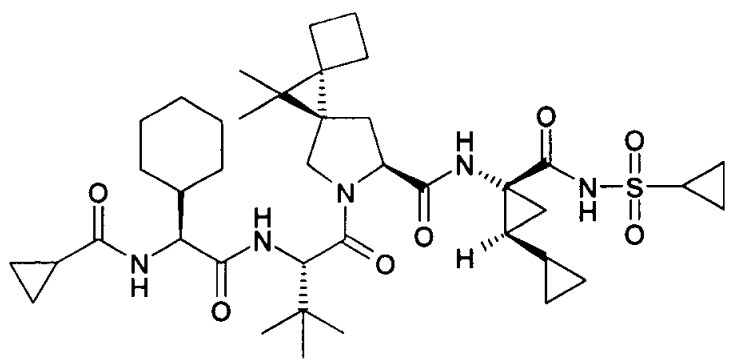
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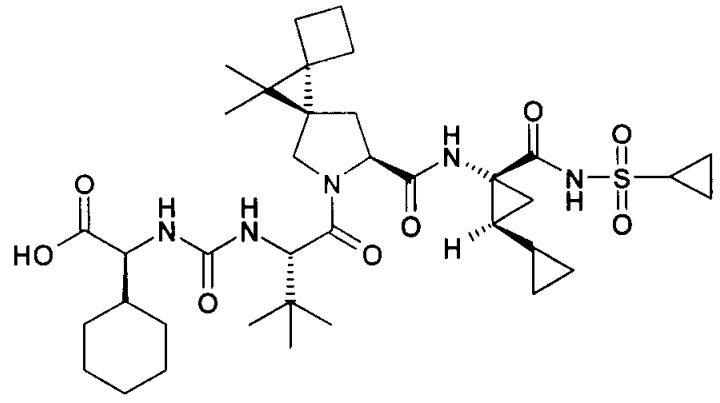
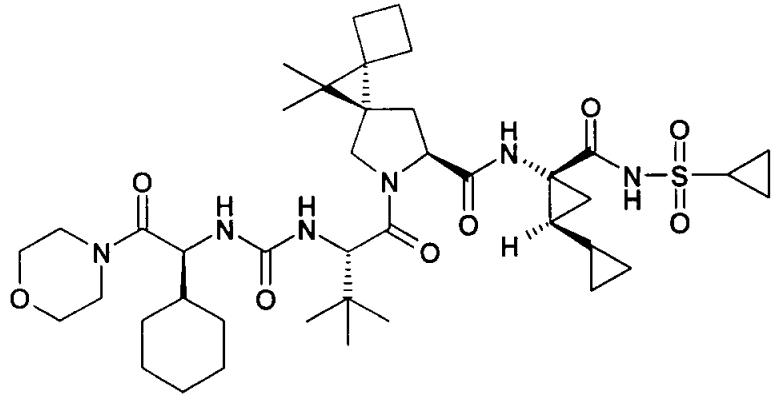
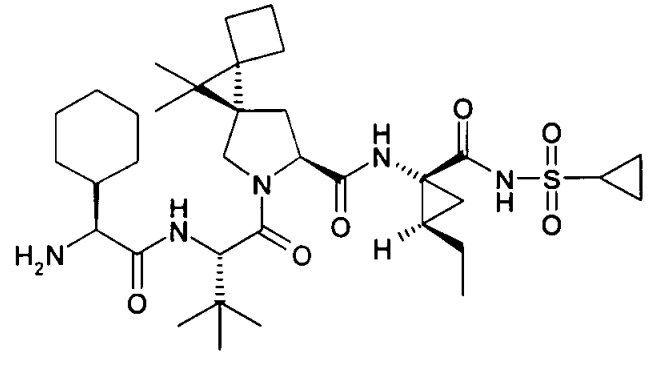
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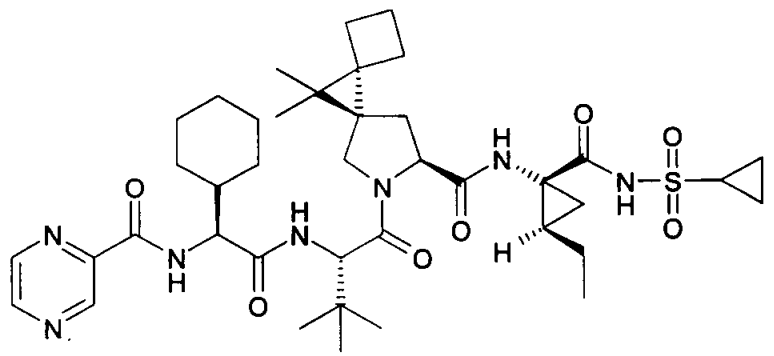
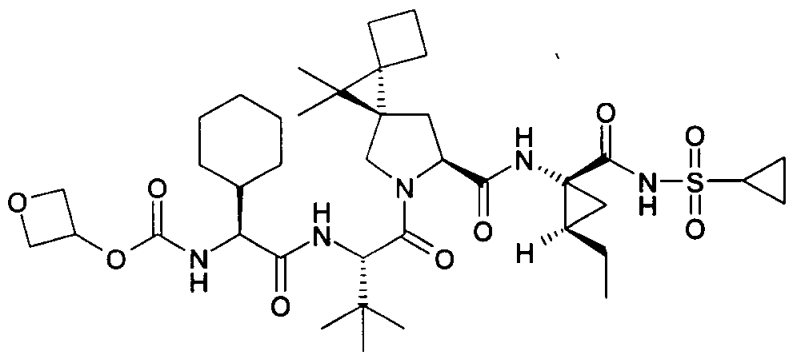
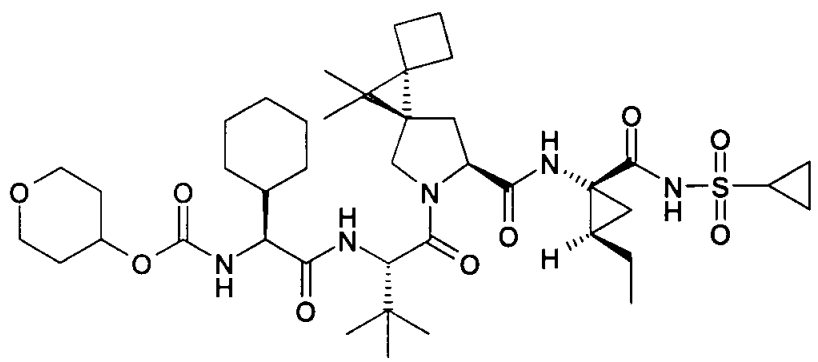
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|  | B-170 |
|  | B-171 |

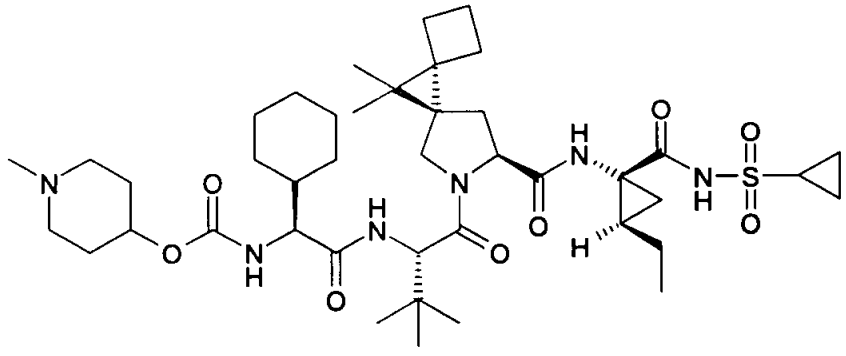
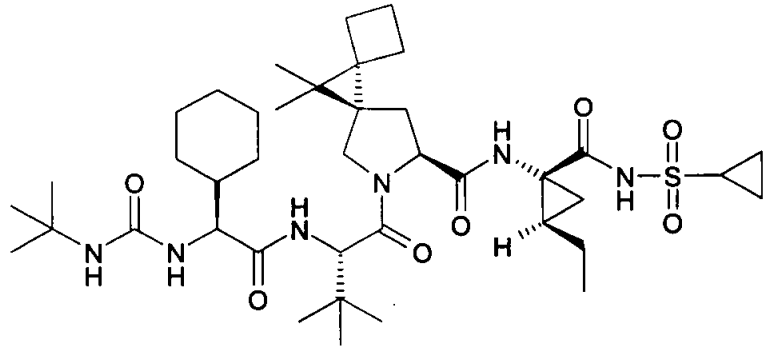
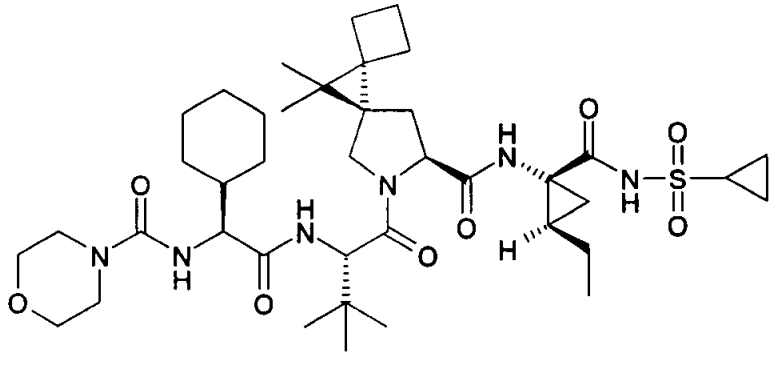
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|  | B-173 |
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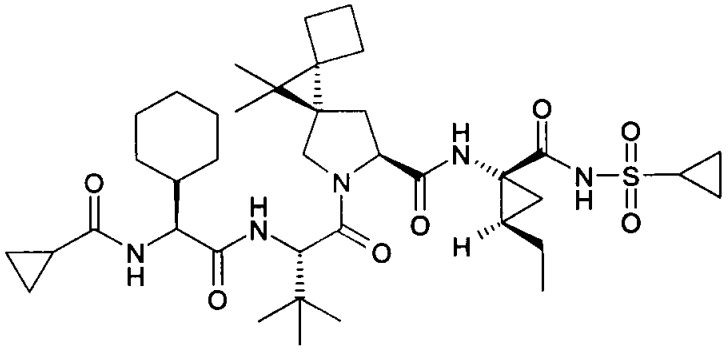
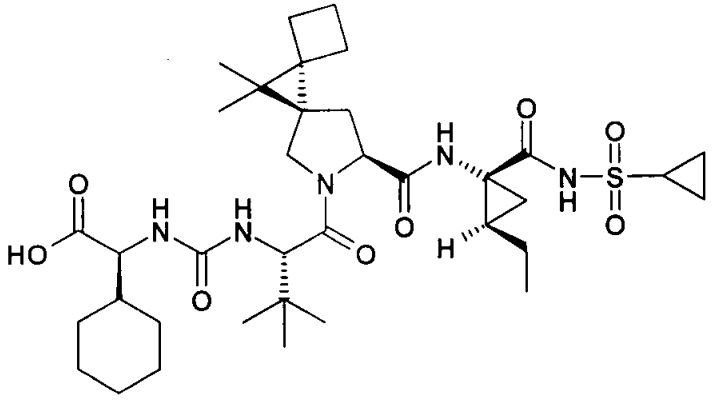
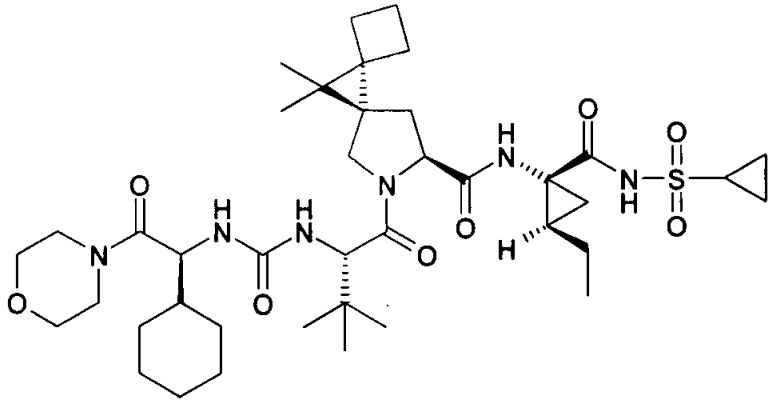
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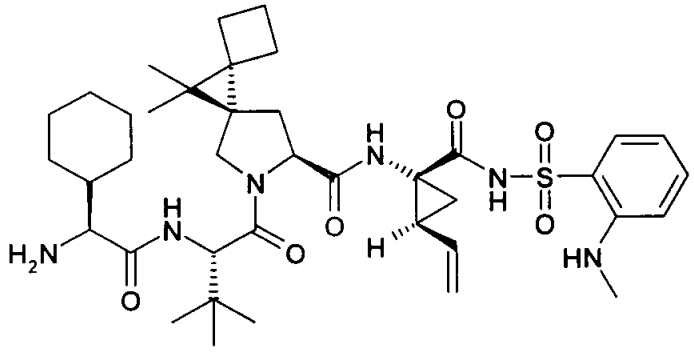
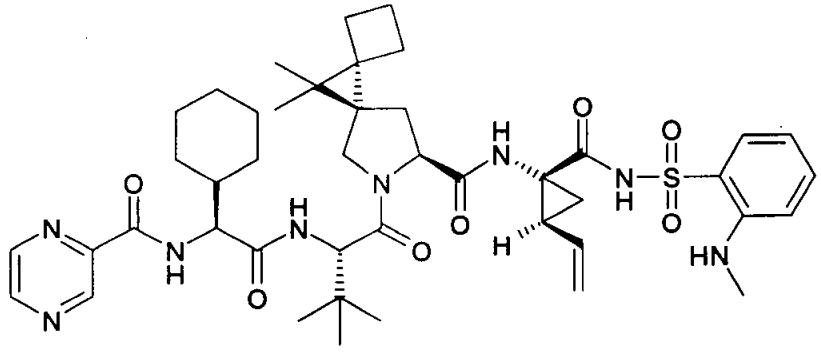
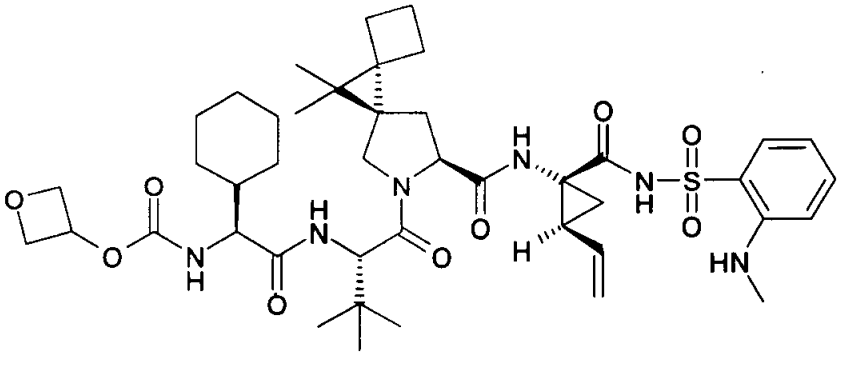
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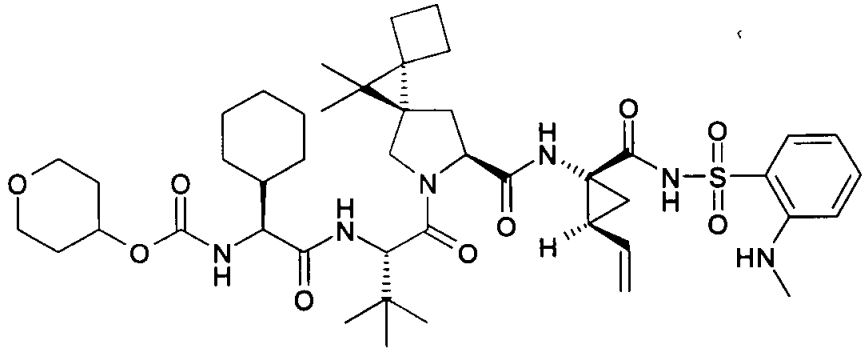
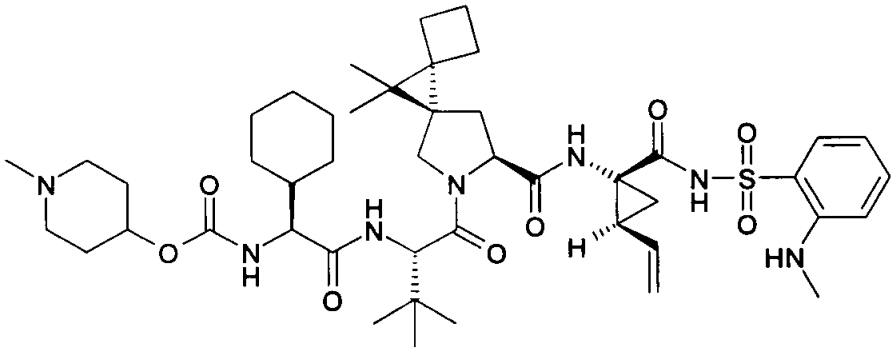
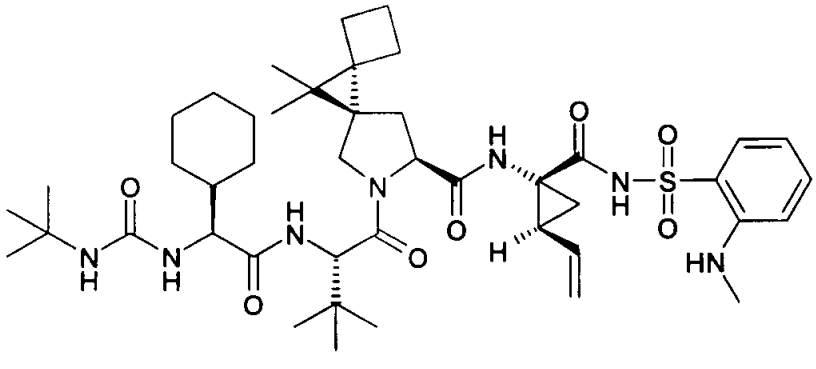
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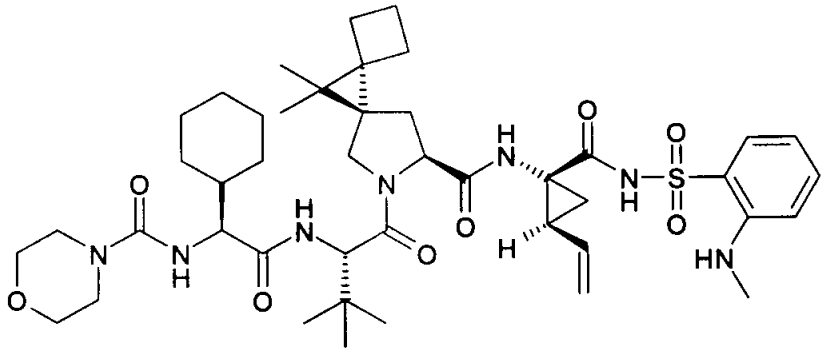
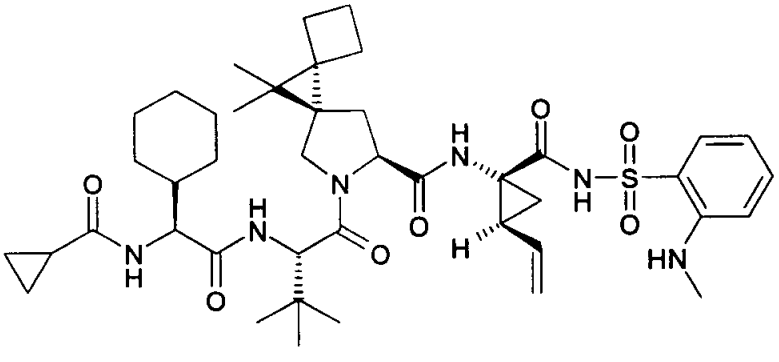
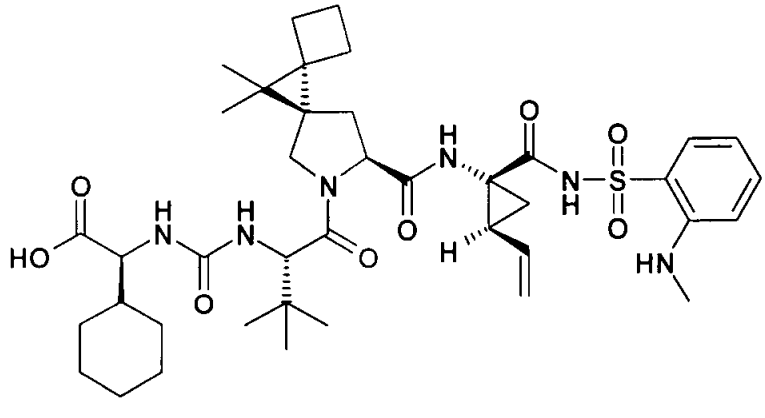
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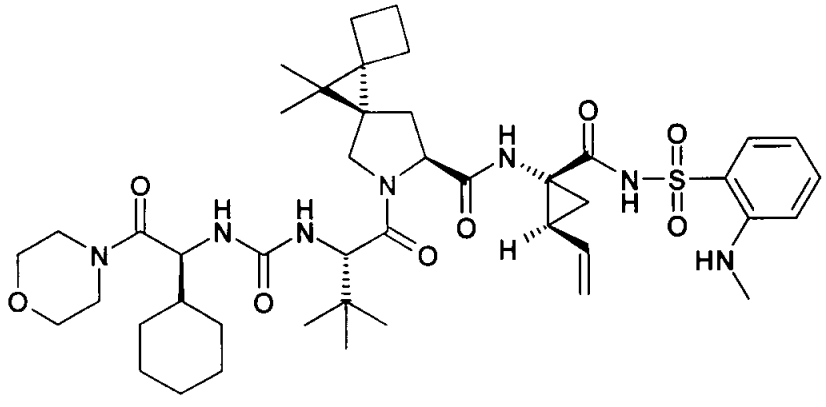
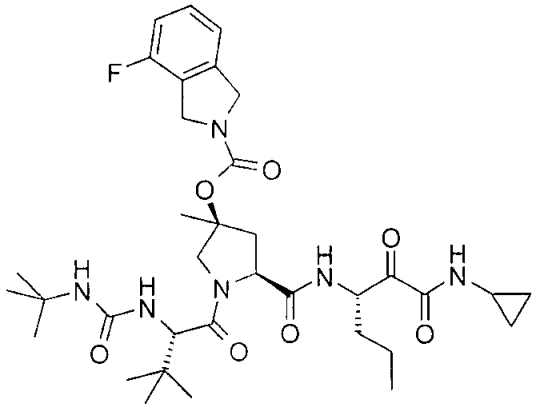
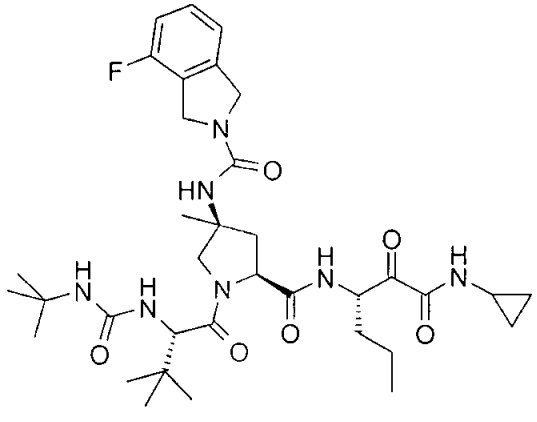
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| Estructura | Comp. No. |
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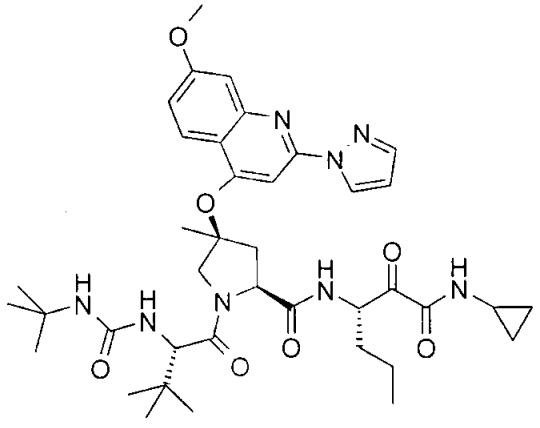
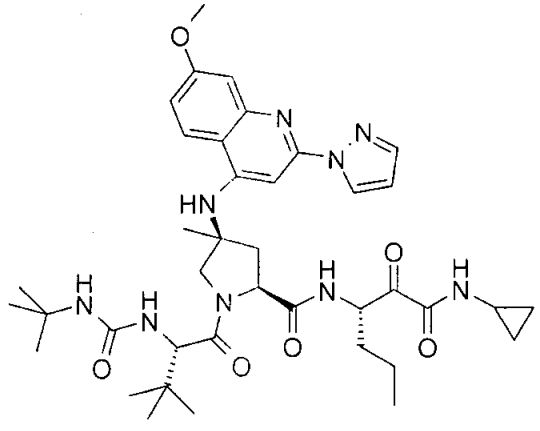
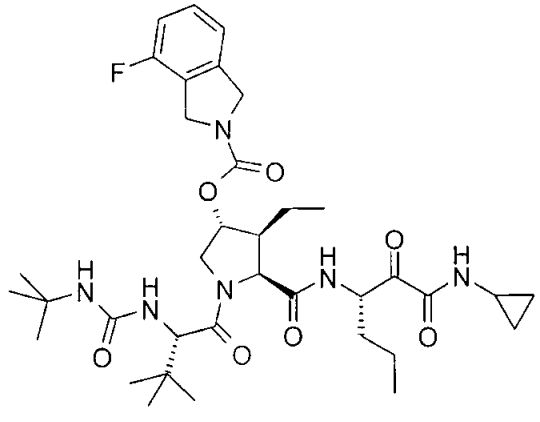
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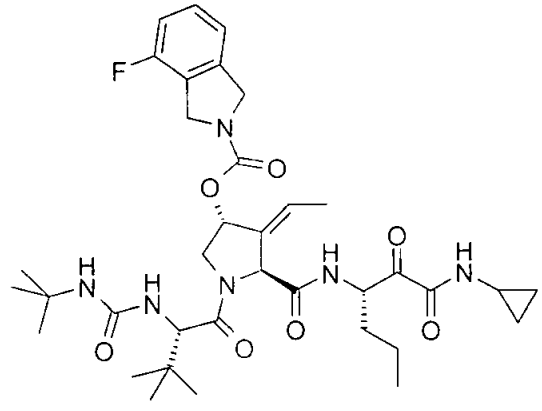
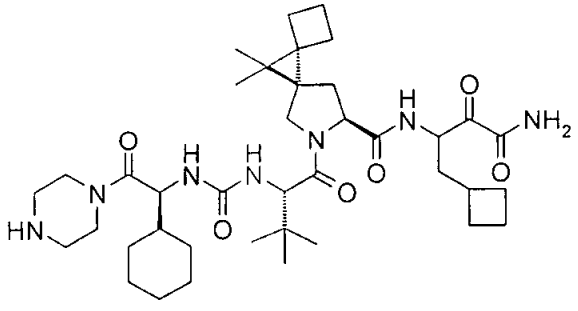
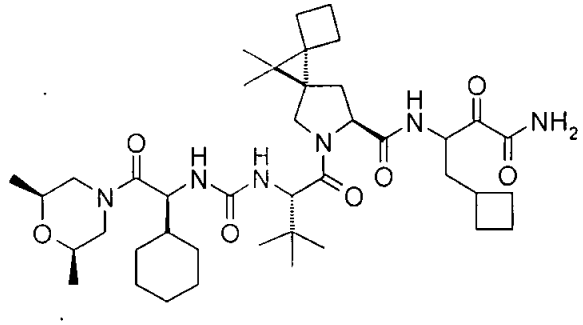
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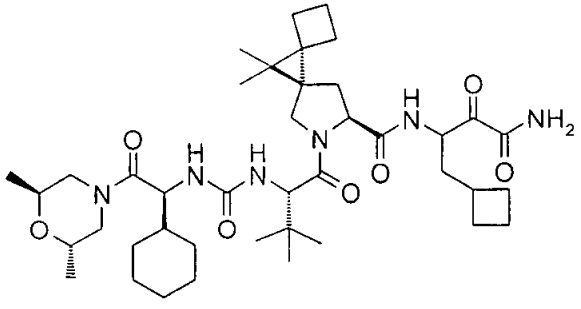
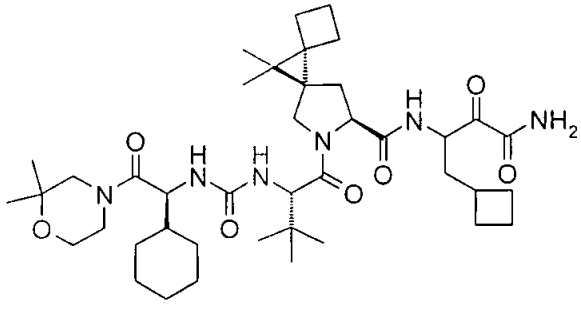
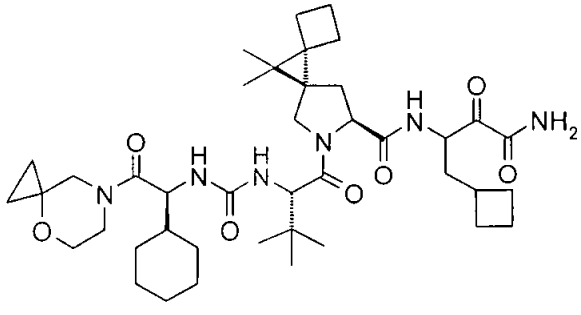
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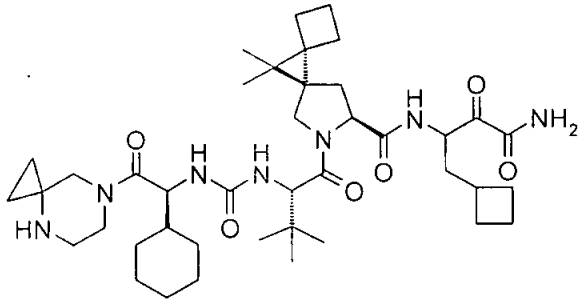
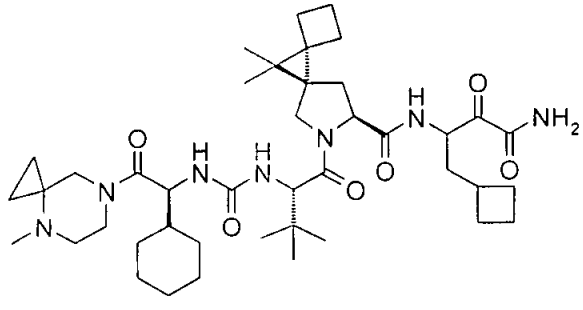
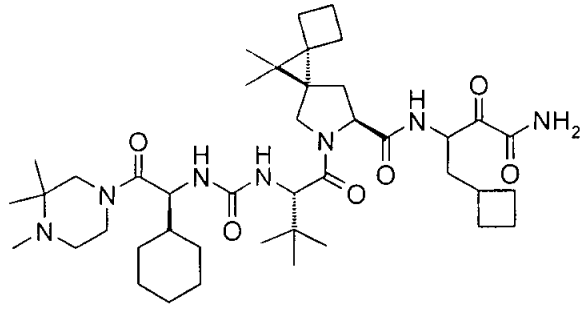
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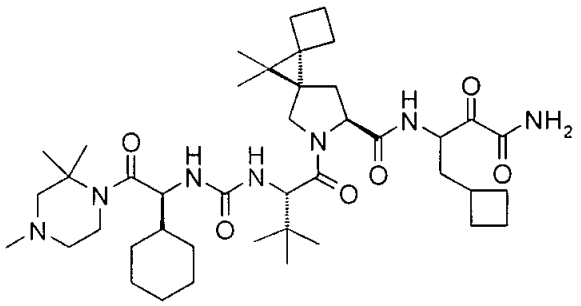
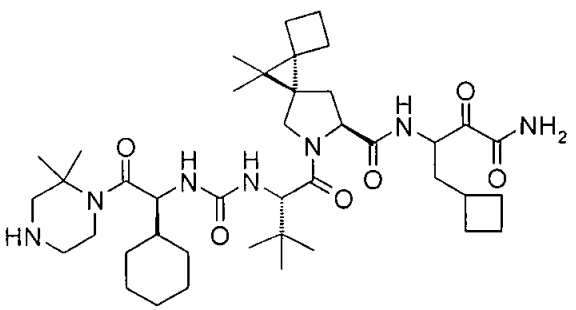
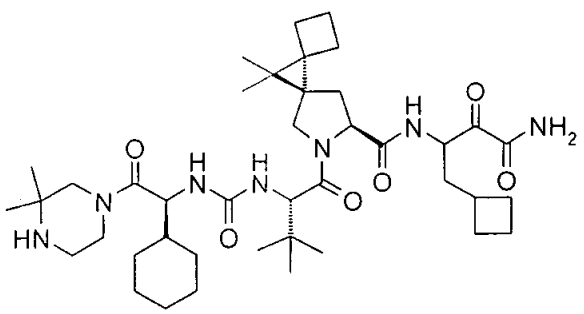
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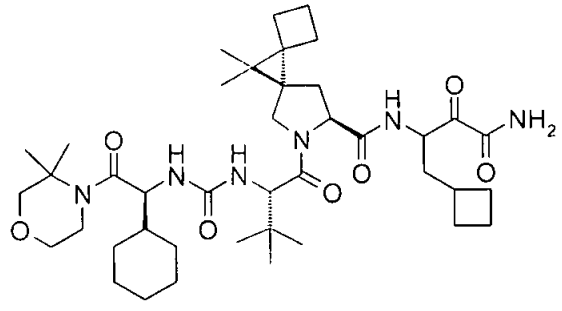
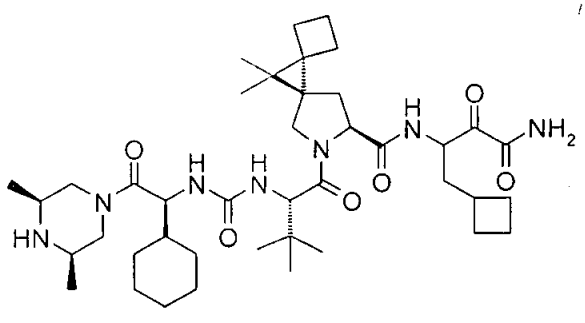
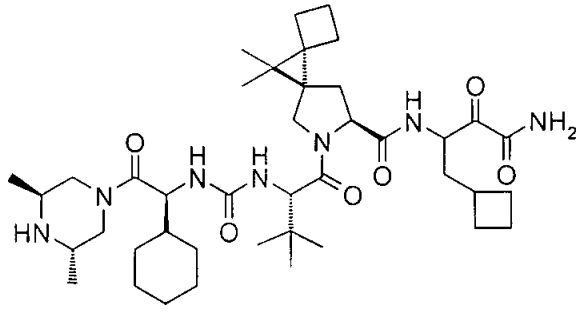
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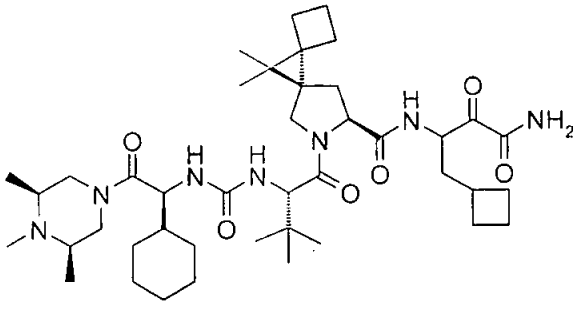
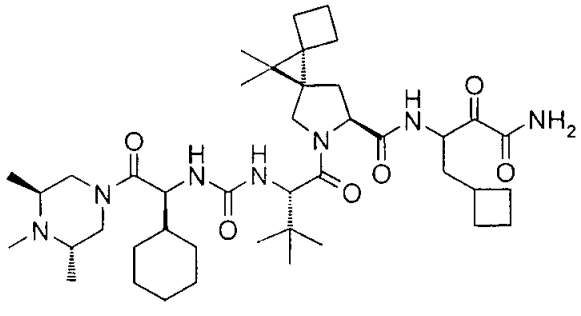
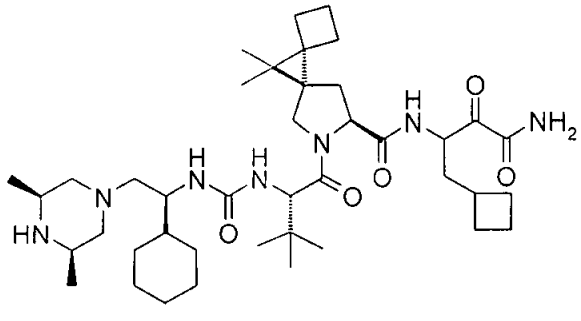
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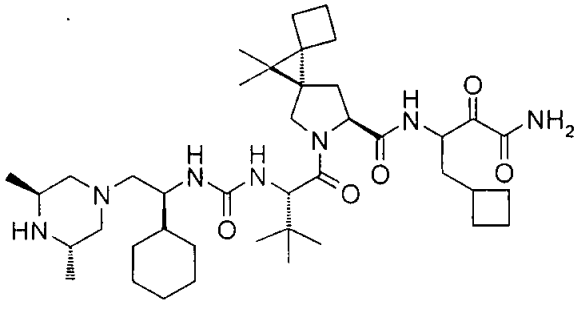
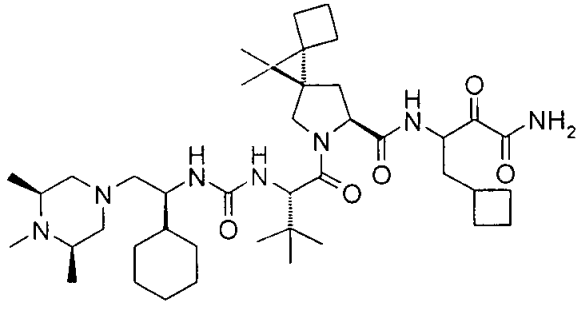
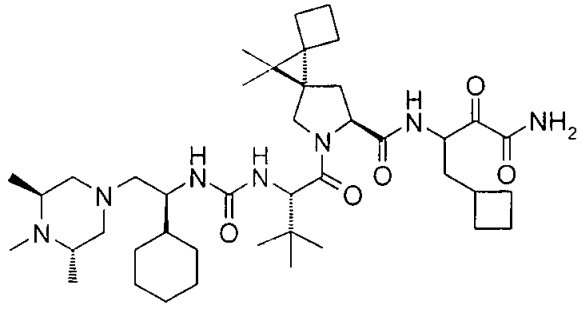
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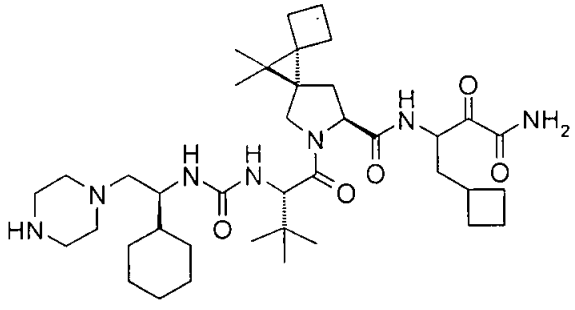
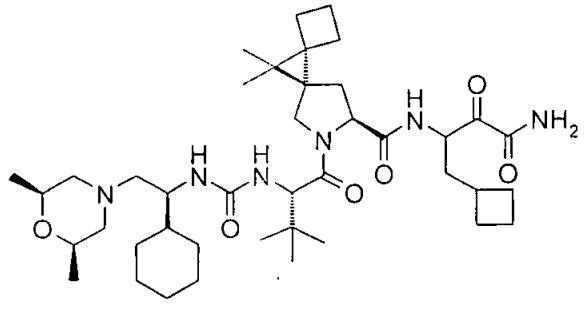
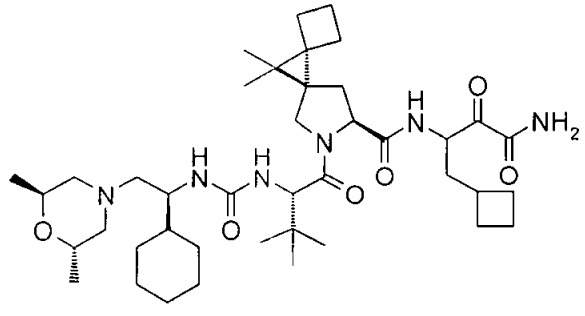
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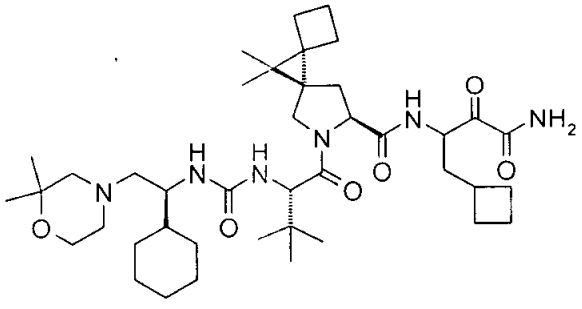
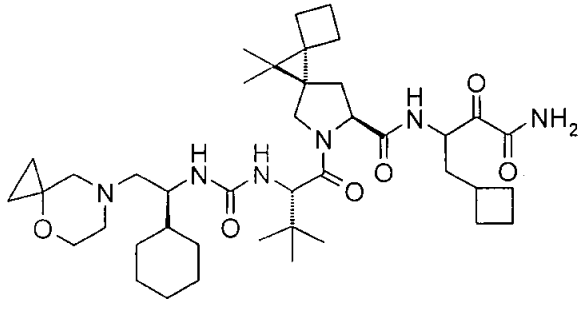
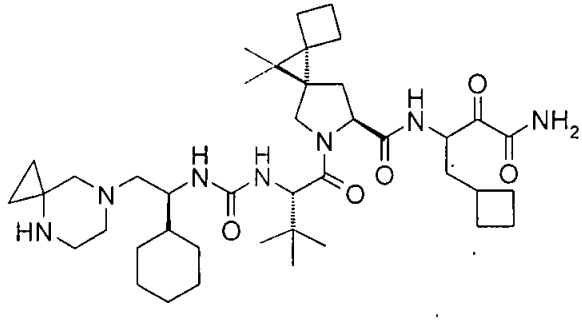
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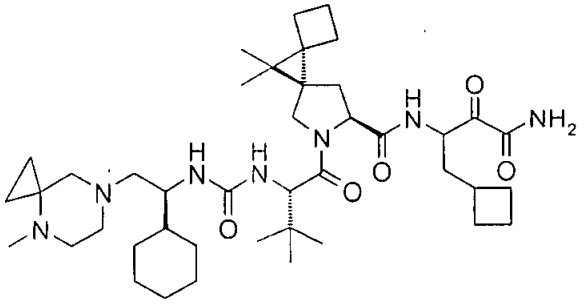
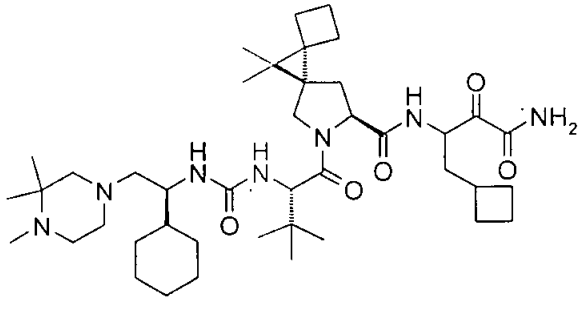
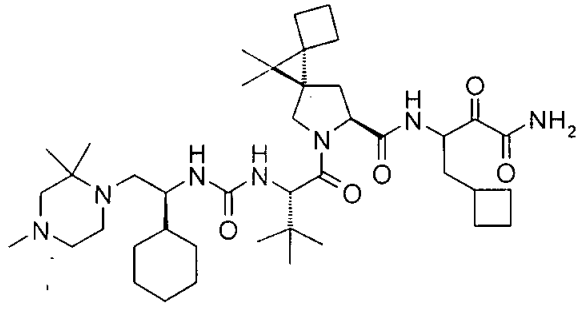
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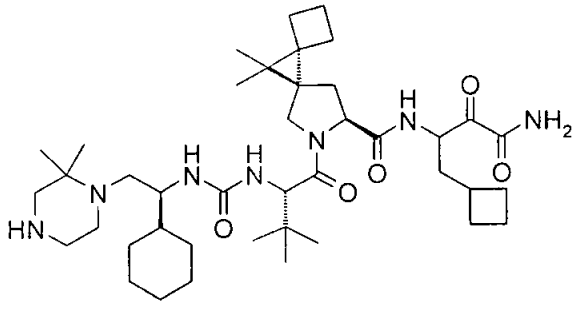
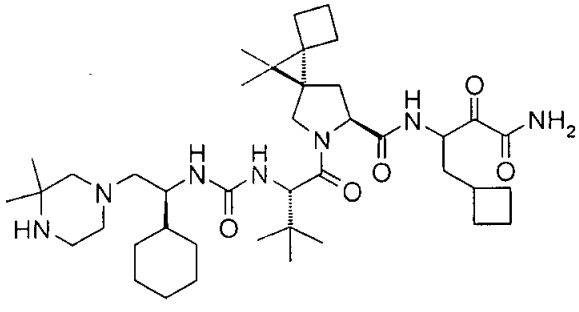
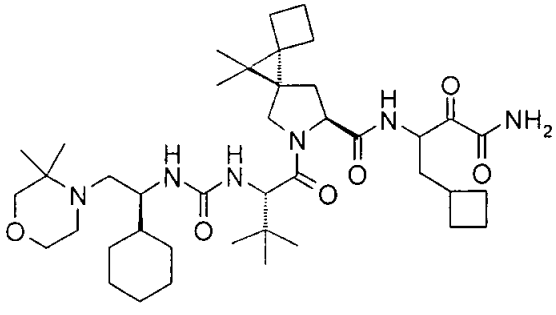
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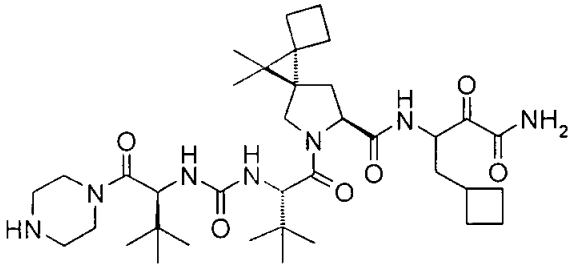
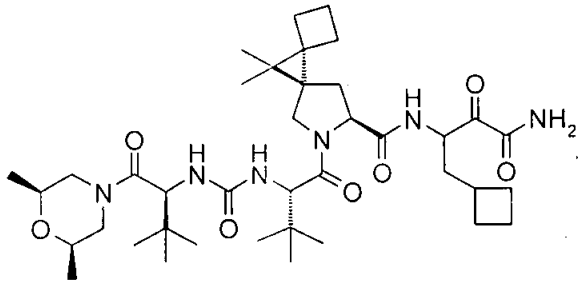
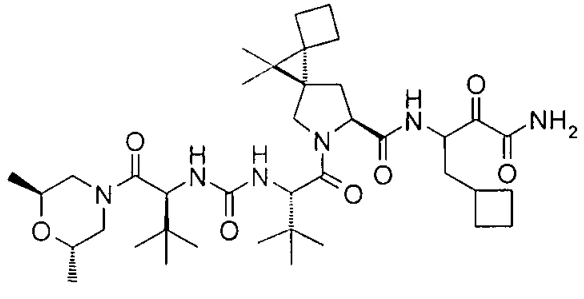
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| Estructura | Comp. No. |
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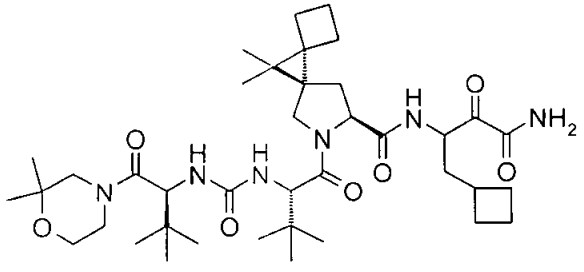
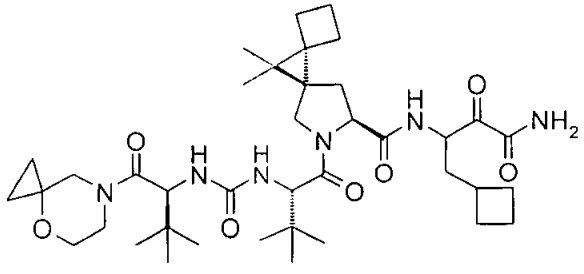
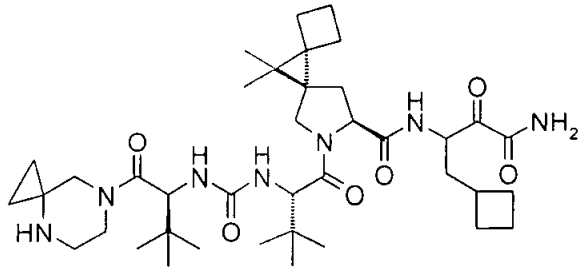
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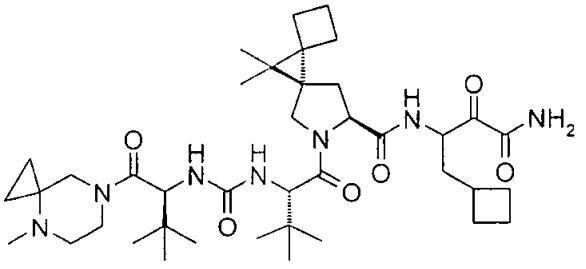
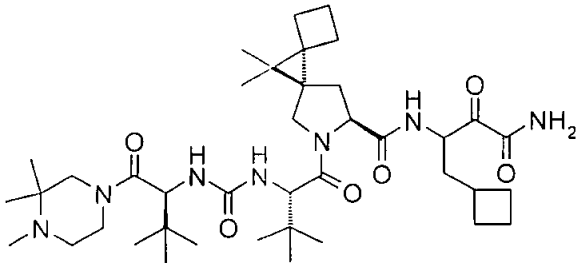
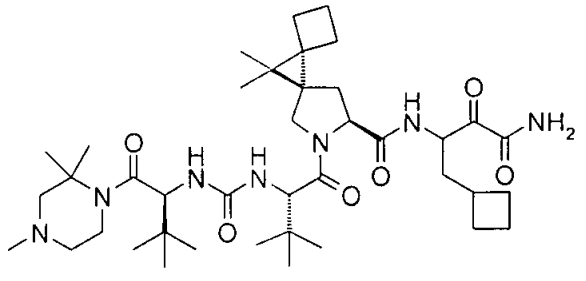
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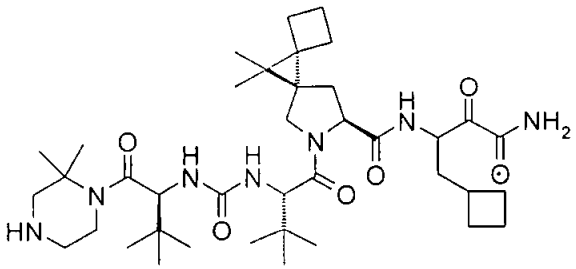
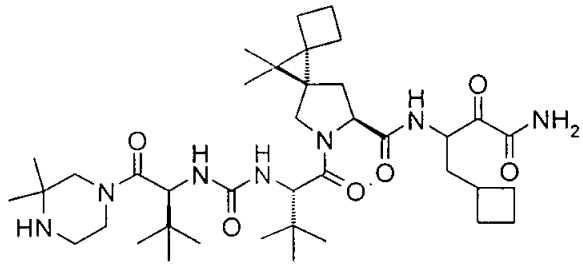
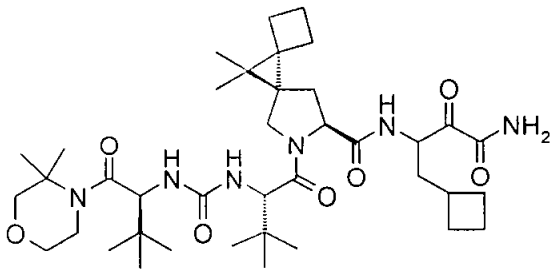
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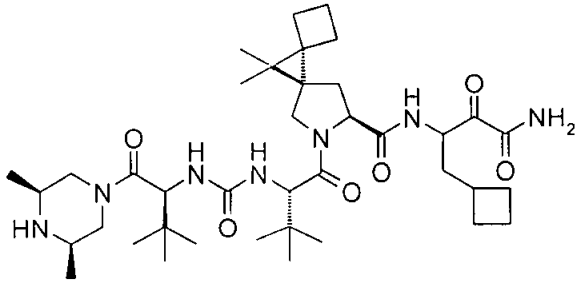
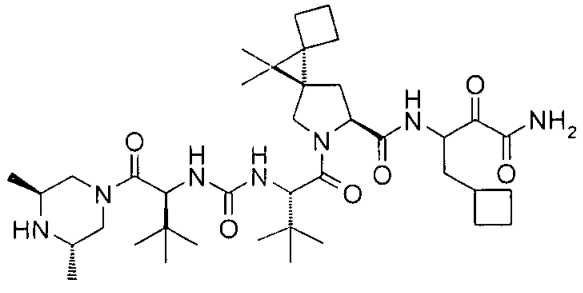
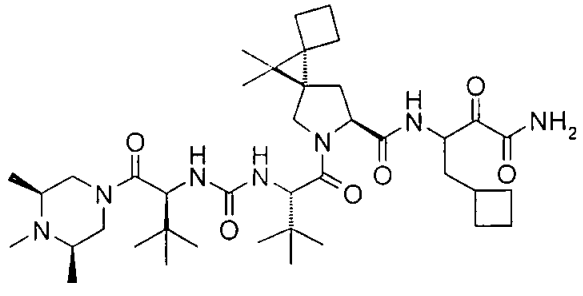
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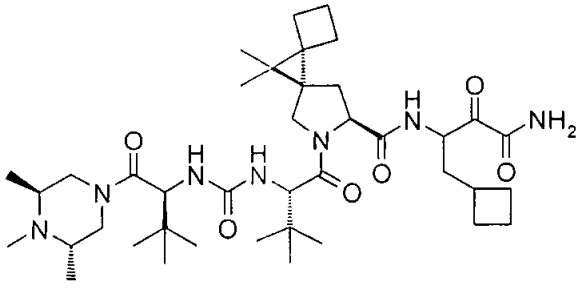
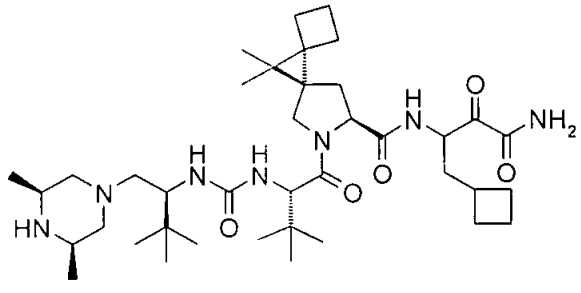
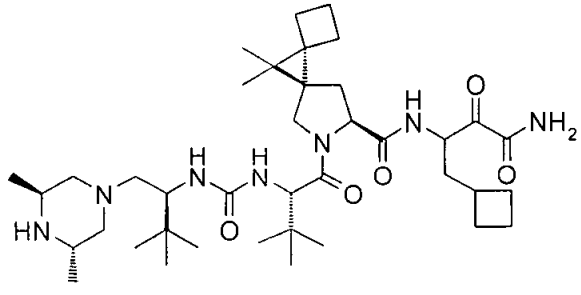
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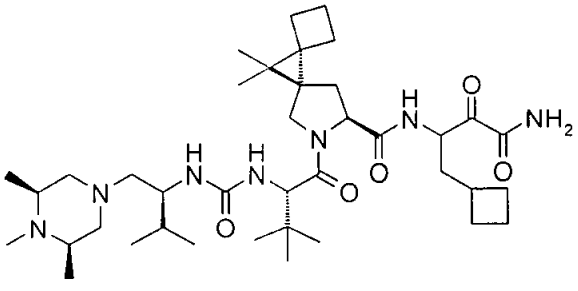
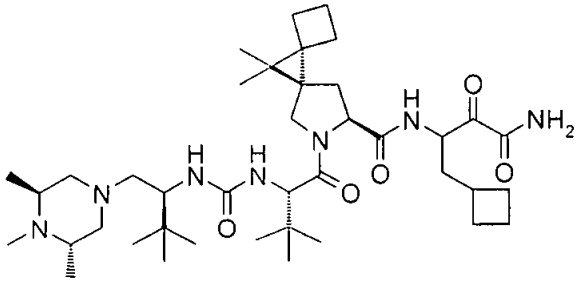
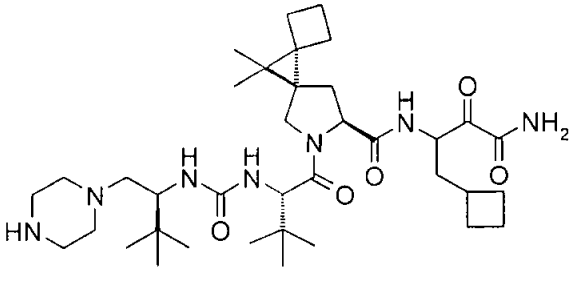
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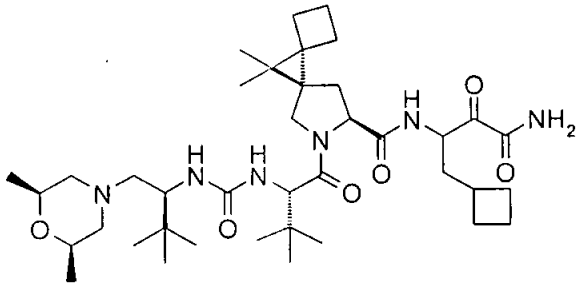
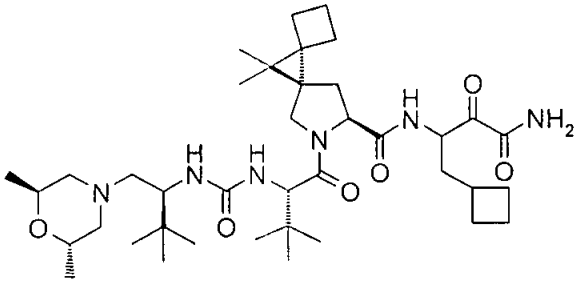
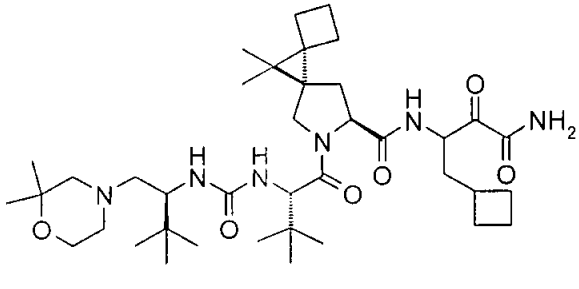
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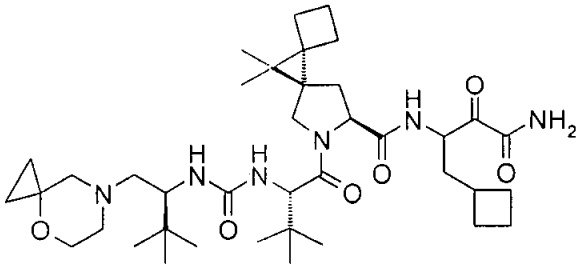
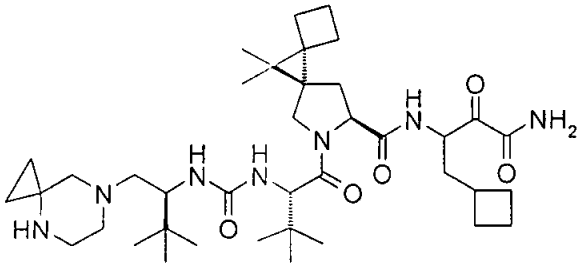
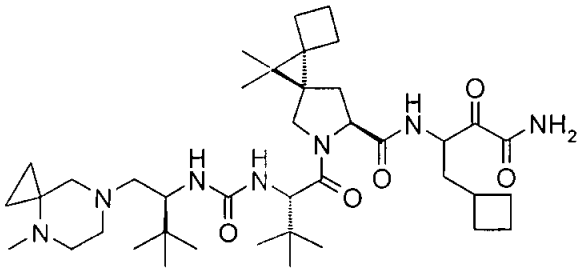
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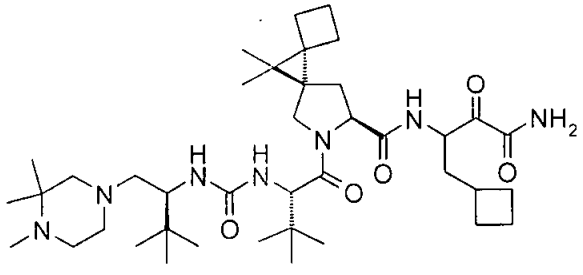
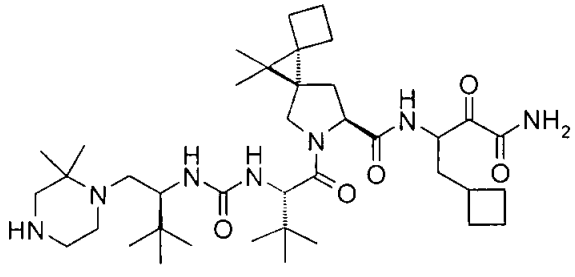
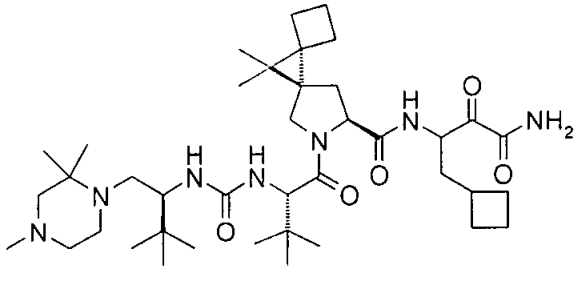
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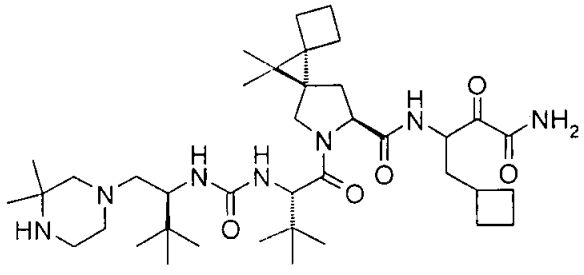
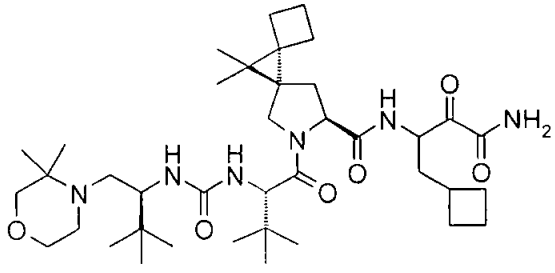
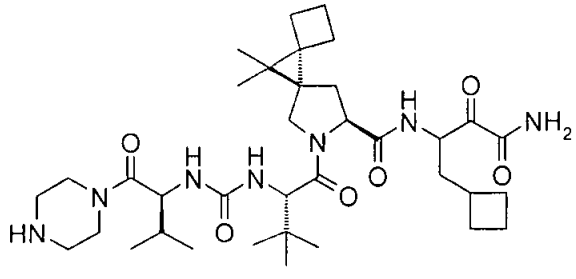
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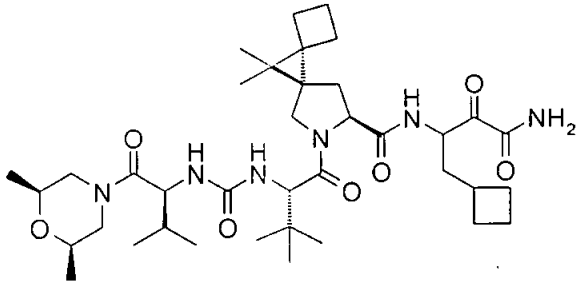
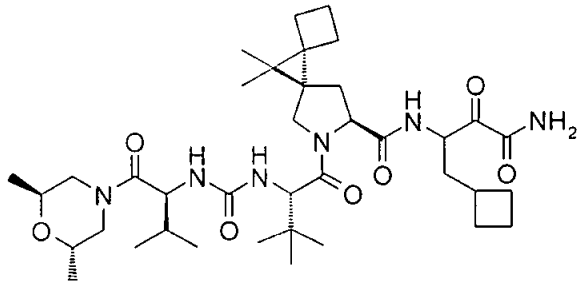
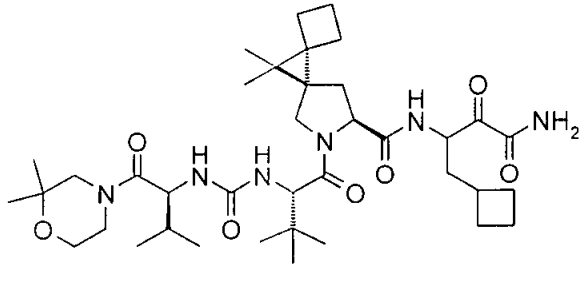
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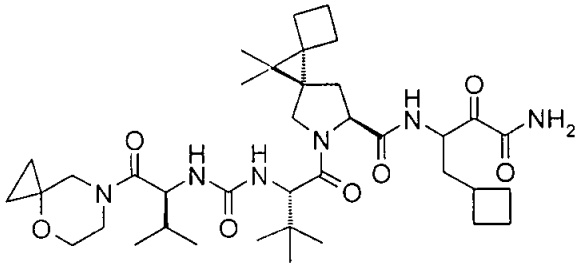
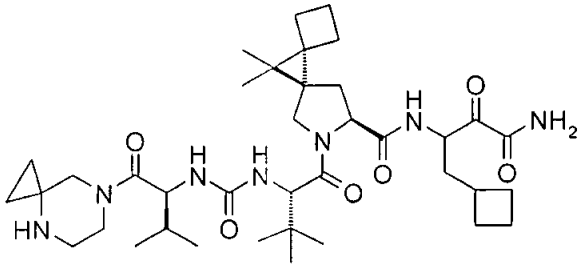
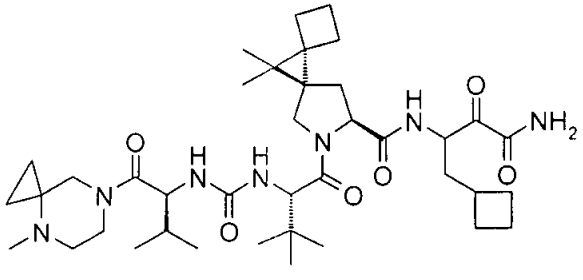
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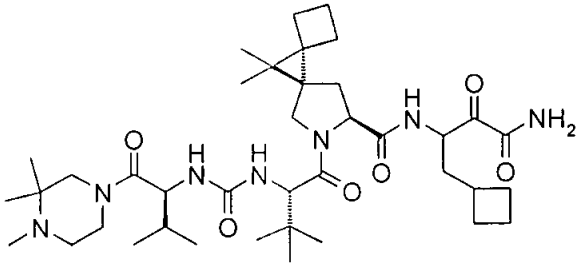
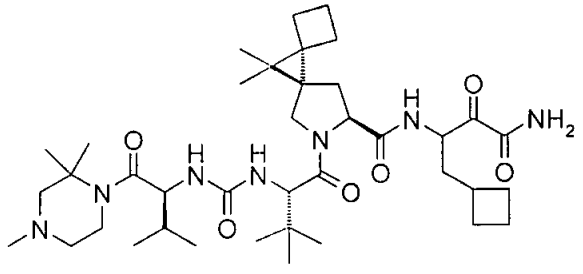
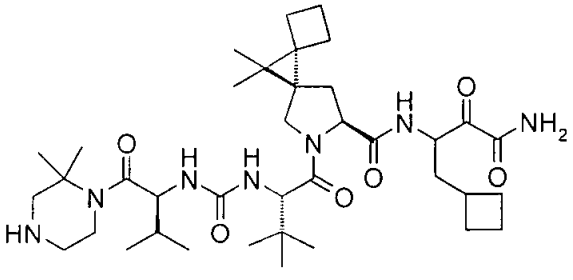
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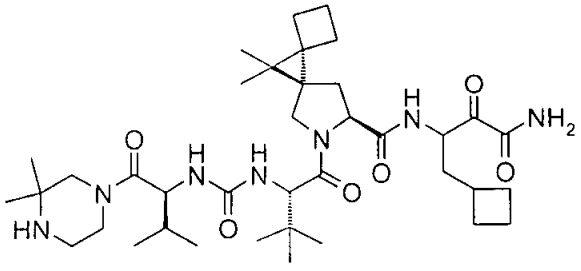
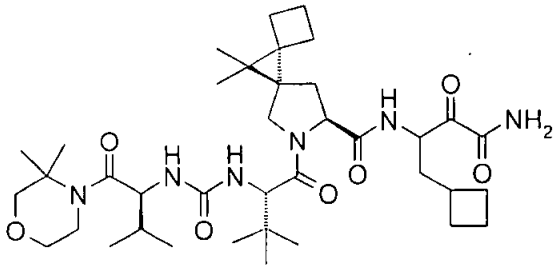
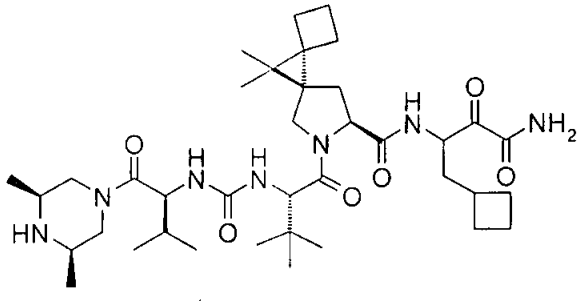
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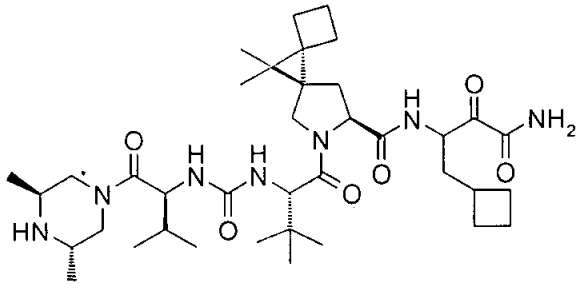
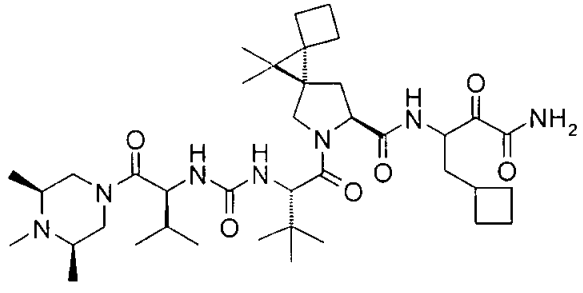
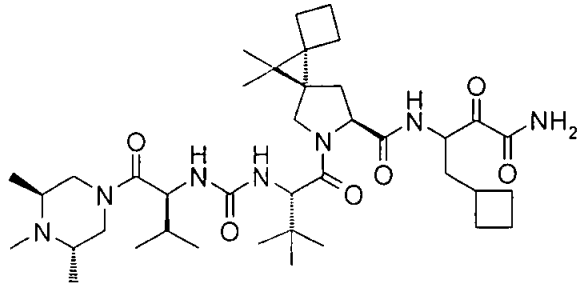
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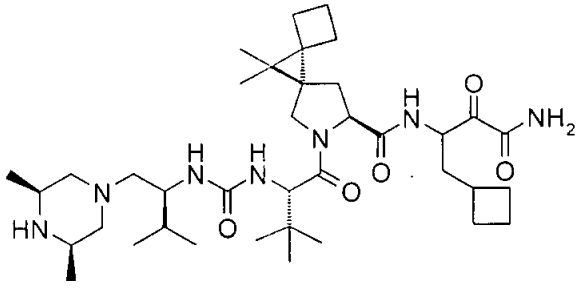
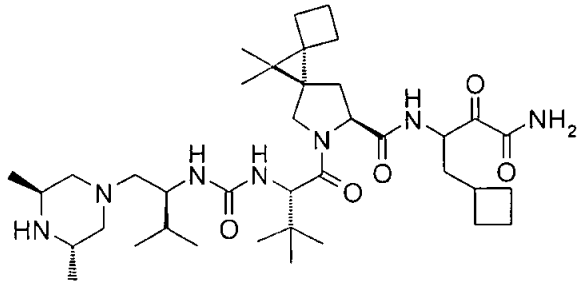
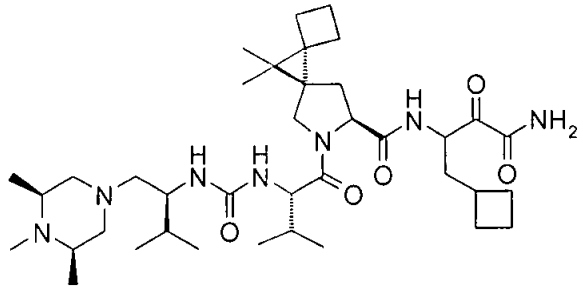
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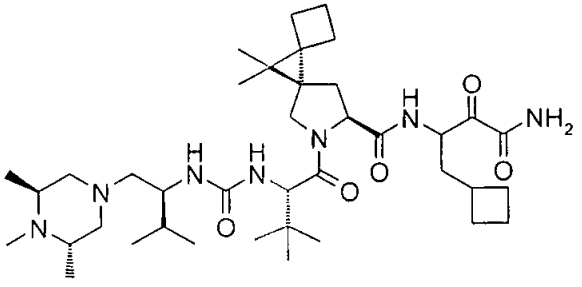
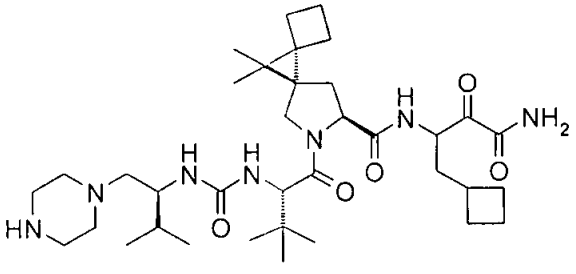
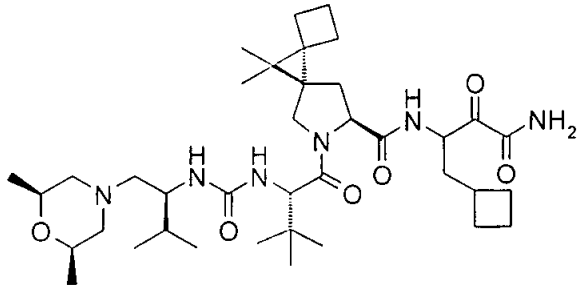
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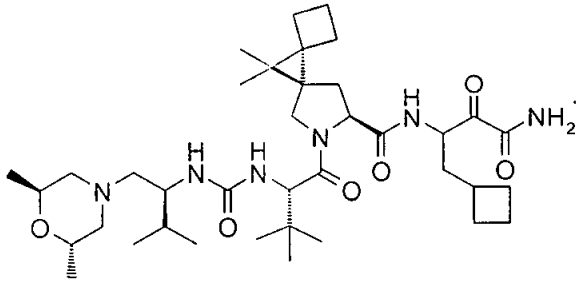
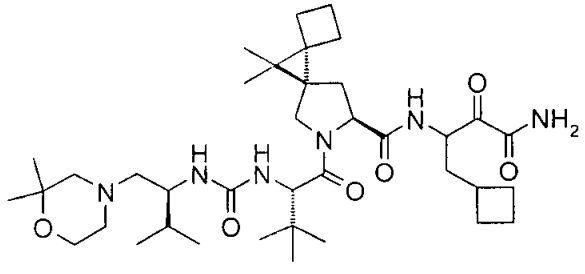
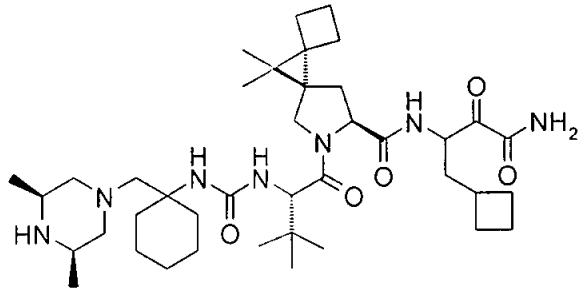
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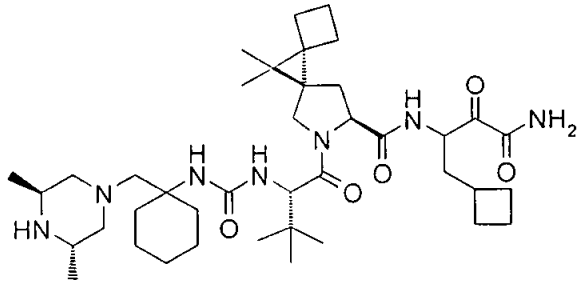
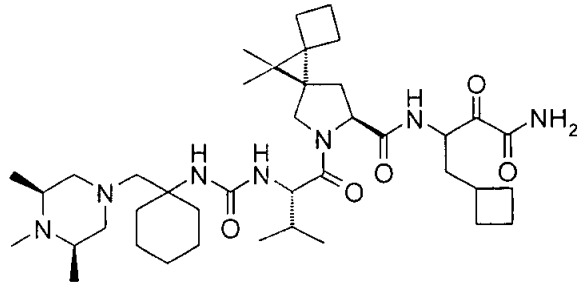
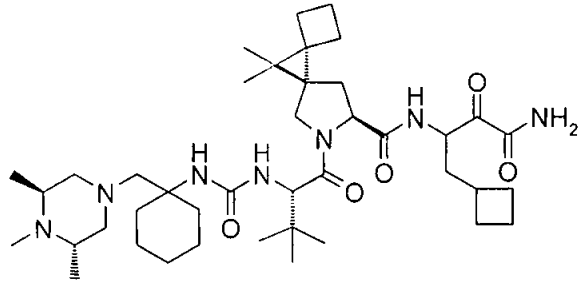
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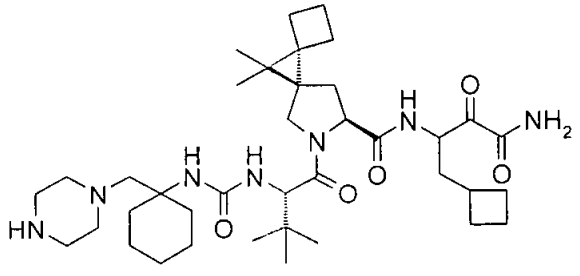
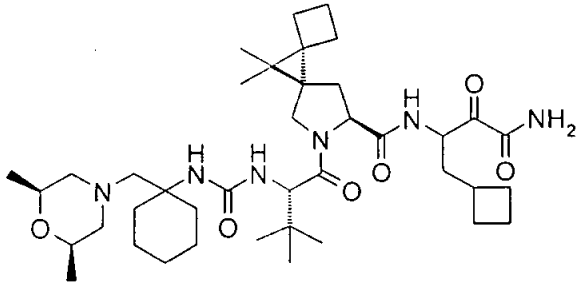
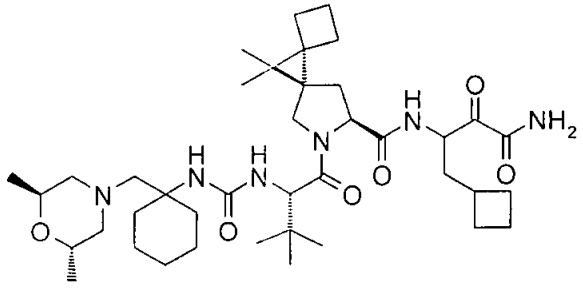
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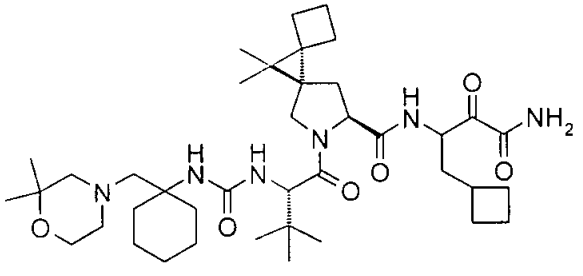
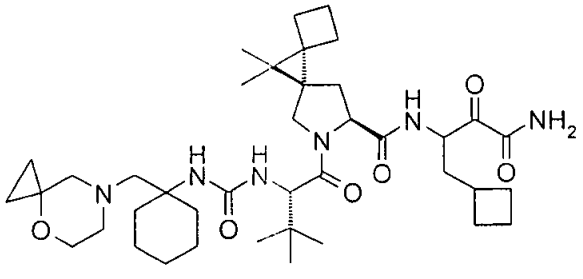
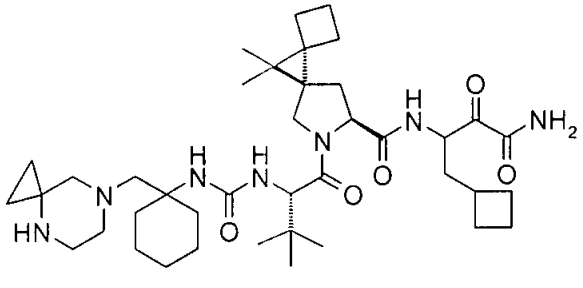
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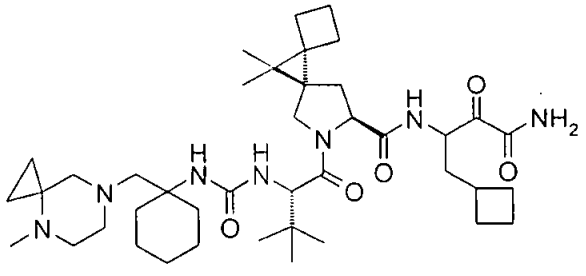
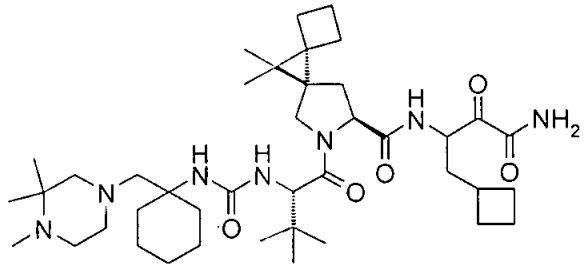
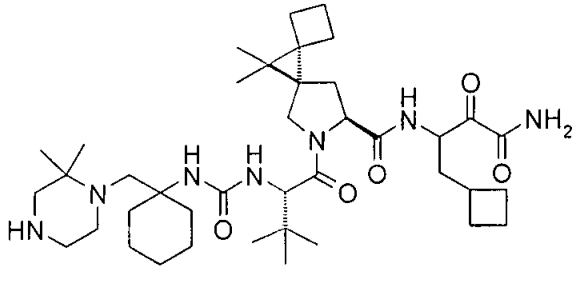
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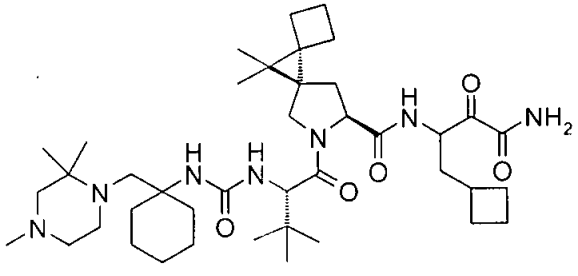
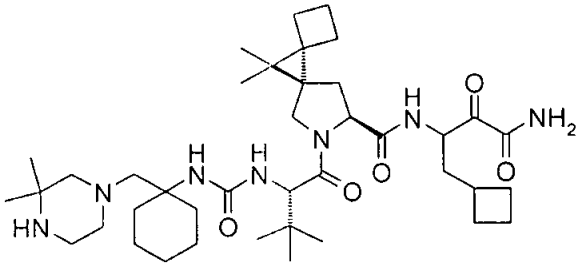
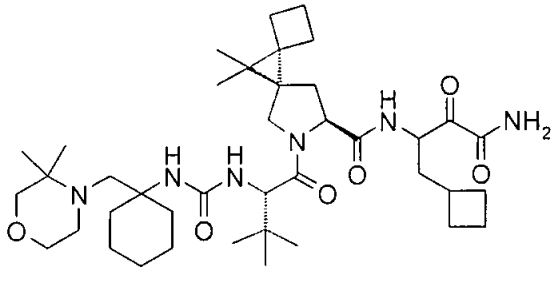
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| Estructura | Comp. No. |
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| Estructura | Comp. No. |
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Utilizando los ensayos de proteasa NS3-4A del virus de hepatitis C y del replicón de Luciferasa-HCV descritos en la sección de ejemplificación que se encuentra más adelante, se encuentra que los compuestos de la invención (incluyendo los compuestos de la Tabla A ilustrada anteriormente) muestran valores $IC_{50}$ para la inhibición del virus de hepatitis C en el intervalo desde 10 hasta más de 100 μM, ó de 0.5 a 30 μM, incluyendo, por ejemplo, el intervalo desde 0.5 hasta 10 μM ó menos.

En ciertas modalidades, un compuesto de la presente invención se caracteriza además como un modulador del virus de hepatitis C, incluyendo un virus de hepatitis C de mamífero, y en especial incluyendo un virus de hepatitis C humano. En una modalidad preferida, el compuesto de la invención es un inhibidor del virus de hepatitis C.

En ciertas modalidades, el compuesto de la invención no es VX-950 ó Sch 503034 (ver, por ejemplo, Curr. Med. Chem., 2005, 12, 2317-2342; y Antimicrob Agents Chemother., Marzo de 2006; 50(3):1013-20, ambos de los cuales se incorporan a la presente como referencia en su totalidad).

En otras modalidades, los compuestos de la invención no son las especies descritas en las Solicitudes de Patentes Internacionales Números WO 2005/058821, WO/2005/021584, WO/01/18369, WO/03/062265, WO/02/18369, WO/2003/087092 y en la Solicitud de Patente de los Estados Unidos de Norteamérica Número 2002/0032175.

Los términos "estado asociado con el virus de hepatitis C" o "trastorno asociado con el virus de hepatitis C" incluyen los trastornos y estados (por ejemplo, un estado de enfermedad) que están asociados con la actividad del virus de hepatitis C, por ejemplo infección con virus de hepatitis C en un sujeto. Los estados asociados con el virus de hepatitis C incluyen la infección con el virus de hepatitis C, cirrosis hepática, enfermedad crónica del hígado, carcinoma hepatocelular, crioglobulinemia, linfoma que no es de Hodgkin, y una respuesta inmune intracelular innata suprimida.

Los estados asociados con el virus de hepatitis C con frecuencia están asociados con la proteasa de serina NS3 del virus de hepatitis C, que es responsable de varios pasos en el procesamiento de la poliproteína del virus de hepatitis C en proteínas funcionales más pequeñas. La proteasa NS3 forma un complejo heterodimérico con la proteína NS4A, un co-factor esencial que mejora la actividad enzimática, y se cree que ayuda a anclar el virus de hepatitis C al reticulo endoplásmico. NS3 primero auto-cataliza la hidrólisis de la unión NS3-NS4A, y luego disocia la poliproteína del virus de hepatitis C intermolecularmente en las intersecciones NS4A-NS4B, NS4B-NS5A, y NS5A-NS5B. Este proceso está asociado con la réplica del virus de hepatitis C en un sujeto. La inhibición o la modulación de la actividad de una o más de las proteínas NS3, NS4A, NS4B, NS5A, y NS5B, inhibirá o modulará la réplica del virus de hepatitis C en un sujeto, previniendo o tratando de esta manera el estado asociado con el virus de hepatitis

C. En una modalidad particular, el estado asociado con el virus de hepatitis C está asociado con la actividad de la proteasa NS3. En otra modalidad particular, el estado asociado con el virus de hepatitis C está asociado con la actividad del complejo heterodimérico NS3-NS4A.

En una modalidad, los compuestos de la invención son inhibidores de la proteasa NS3/NS4A. En otra modalidad, los compuestos de la invención son inhibidores de la proteasa NS2/NS3.

Sin obligarnos por la teoría, se cree que la interrupción de las interacciones de proteína-proteína anteriores por parte de los compuestos de la invención, interferirá con el procesamiento de la poliproteína viral mediante la proteasa NS3, y por lo tanto, la réplica viral.

Los trastornos asociados con el virus de hepatitis C también incluyen las enfermedades dependientes del virus de hepatitis C. Las enfermedades dependientes del virus de hepatitis C incluyen, por ejemplo, cualquier enfermedad o trastorno que dependa de, o que esté relacionado con, la actividad o la mala regulación de cuando menos una cepa del virus de hepatitis C.

La presente invención incluye el tratamiento de los trastornos asociados con el virus de hepatitis C, como se describe anteriormente, pero no se pretende que la invención se limite a la manera mediante la cual el compuesto lleve a cabo su función pretendida de tratamiento de una enfermedad. La presente invención incluye el tratamiento de las enfermedades descritas en la presente

en cualquiera manera que permita que ocurra el tratamiento, por ejemplo la infección por el virus de hepatitis C.

En una modalidad relacionada, los compuestos de la invención pueden ser útiles para el tratamiento de las enfermedades relacionadas con VIH, así como infección por VIH y SIDA (Síndrome de Inmunodeficiencia adquirida).

En ciertas modalidades, la invención proporciona una composición farmacéutica de cualquiera de los compuestos de la presente invención. En una modalidad relacionada, la invención proporciona una composición farmacéutica de cualquiera de los compuestos de la presente invención, y un vehículo o excipiente farmacéuticamente aceptable de cualquiera de estos compuestos. En ciertas modalidades, la invención incluye los compuestos como entidades químicas novedosas.

En una modalidad, la invención incluye el tratamiento de un trastorno asociado con el virus de hepatitis C empacado. El tratamiento empacado incluye un compuesto de la invención empacado con instrucciones para utilizar una cantidad efectiva del compuesto de la invención para un uso pretendido.

Los compuestos de la presente invención son adecuados como agentes activos en composiciones farmacéuticas que son eficaces particularmente para el tratamiento de los trastornos asociados con el virus de hepatitis C. La composición farmacéutica en las diferentes modalidades, tiene una cantidad farmacéuticamente efectiva del presente agente activo, junto con otros excipientes,

vehículos, rellenos, diluyentes, y similares, farmacéuticamente aceptables. La frase "cantidad farmacéuticamente efectiva", como se utiliza en la presente, indica una cantidad necesaria para administrarse a un huésped, o a una célula, tejido, u órgano de un huésped, con el fin de lograr un resultado terapéutico, en especial un efecto contra el virus de hepatitis C, por ejemplo la inhibición de la proliferación del virus de hepatitis C, o de cualquier otra enfermedad asociada con el virus de hepatitis C.

En una modalidad, las enfermedades que van a ser tratadas por los compuestos de la invención incluyen, por ejemplo, infección por el virus de hepatitis C, cirrosis hepática, enfermedad crónica del hígado, carcinoma hepatocelular, crioglobulinemia, linfoma que no es de Hodgkin, y una respuesta inmune intracelular innata suprimida.

En otras modalidades, la presente invención proporciona un método para inhibir la actividad del virus de hepatitis C. El método incluye poner en contacto una célula con cualquiera de los compuestos de la presente invención. En una modalidad relacionada, el método dispone además que el compuesto esté presente en una cantidad efectiva para inhibir selectivamente la actividad de una o más de las proteínas NS3, NS4A, NS4B, NS5A, y NS5B. En otra modalidad relacionada, el método dispone que el compuesto esté presente en una cantidad efectiva para disminuir la carga de ARN del virus de hepatitis C en un sujeto.

En otras modalidades, la presente invención proporciona el uso de cualquiera de los compuestos de la invención para fabricar un

medicamento con el fin de tratar la infección por el virus de hepatitis C en un sujeto.

En otras modalidades, la invención proporciona un método para fabricar un medicamento, incluyendo formular cualquiera de los compuestos de la presente invención, para el tratamiento de un sujeto.

***Definiciones***

El término "tratar", "tratado", "tratando", o "tratamiento", incluye la disminución o el alivio de cuando menos un síntoma asociado o causado por el estado, trastorno, o enfermedad que se esté tratando. En ciertas modalidades, el tratamiento comprende la inducción de un estado inhibido del virus de hepatitis C, seguida por la activación del compuesto modulador del virus de hepatitis C, la cual a su vez disminuiría o aliviaría cuando menos un síntoma asociado o causado por el estado, trastorno, o enfermedad asociada con el virus de hepatitis C que se esté tratando. Por ejemplo, el tratamiento puede ser la disminución de uno o varios síntomas de un trastorno, o la erradicación completa de un trastorno.

El término "sujeto" pretende incluir organismos, por ejemplo procariotes y eucariotes, que sean capaces de sufrir de, o de ser afligidos con, un trastorno asociado con el virus de hepatitis C. Los ejemplos de los sujetos incluyen mamíferos, por ejemplo seres humanos, perros, vacas, caballos, cerdos, ovejas, cabras, gatos, ratones, conejos, ratas, y animales no humanos transgénicos. En ciertas modalidades, el sujeto es un ser humano, por ejemplo un ser

humano que sufra de, o que esté en riesgo de sufrir de, o que sea potencialmente capaz de sufrir de un trastorno asociado con el virus de hepatitis C, y para las enfermedades o condiciones descritas en la presente, por ejemplo la infección por el virus de hepatitis C. En otra modalidad, el sujeto es una célula.

El lenguaje "compuesto modulador del virus de hepatitis C", "modulador d el virus de hepatitis C", o "inhibidor del virus de hepatitis C", se refiere a los compuestos que modulan, por ejemplo inhiben, o alteran de otra manera, la actividad del virus de hepatitis C. De una manera similar, un "inhibidor de proteasa NS3/NS4A", o un "inhibidor de proteasa NS2/NS3", se refiere a un compuesto que modula, por ejemplo inhibe, o altera de otra manera, la interacción de estas proteasas unas con otras. Los ejemplos de los compuestos moduladores del virus de hepatitis C incluyen los compuestos de la Fórmula I o de la Fórmula II, así como la Tabla A y la Tabla B (incluyendo las sales farmacéuticamente aceptables de los mismos, así como los enantiómeros, estereoisómeros, rotámeros, tautómeros, diaestereómeros, o racematos de los mismos).

Adicionalmente, el método incluye administrar a un sujeto una cantidad efectiva de un compuesto modulador del virus de hepatitis C de la invención, por ejemplo los compuestos moduladores del virus de hepatitis C de la Fórmula I o de la Fórmula II, así como de la Tabla A y la Tabla B (incluyendo las sales farmacéuticamente aceptables de los mismos, así como los enantiómeros, estereoisómeros, rotámeros, tautómeros, diaestereómeros, o

racematos de los mismos).

El término "alquilo" incluye los grupos alifáticos saturados, incluyendo los grupos alquilo de cadena recta (por ejemplo, metilo, etilo, propilo, butilo, pentilo, hexilo, heptilo, octilo, nonilo, decilo, etc.), los grupos alquilo de cadena ramificada (isopropilo, butilo terciario, isobutilo, etc.), los grupos cicloalquilo (alicíclicos) (ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclo-octilo), los grupos cicloalquilo sustituido por alquilo, y los grupos alquilo sustituido por cicloalquilo. Adicionalmente, la expresión "alquilo de **x** a **y** átomos de carbono", en donde **x** es de 1 a 5, e **y** es de 2 a 10, indica un grupo alquilo particular (de cadena recta o ramificada), de un intervalo de átomos de carbono particular. Por ejemplo, la expresión "alquilo de 1 a 4 átomos de carbono" incluye, pero no se limita a, metilo, etilo, propilo, butilo, isopropilo, butilo terciario, isobutilo, y butilo secundario. Más aún, el término "cicloalquilo de 3 a 6 átomos de carbono" incluye, pero no se limita a, ciclopropilo, ciclopentilo, y ciclohexilo. Como se discute más adelante, estos grupos alquilo, así como los grupos cicloalquilo, pueden estar adicionalmente sustituidos. "Alquilo de 0 a n átomos de carbono" se refiere a un enlace covalente individual ($C_0$), o a un grupo alquilo que tiene de 1 a **n** átomos de carbono; por ejemplo, "alquilo de 0 a 4 átomos de carbono" se refiere a un enlace covalente individual o a un grupo alquilo de 1 a 4 átomos de carbono; "alquilo de 0 a 8 átomos de carbono" se refiere a un enlace covalente individual o a un grupo alquilo de 1 a 8 átomos de carbono. En algunas instancias,

se indica especificamente un sustituyente de un grupo alquilo. Por ejemplo, "hidroxi-alquilo de 1 a 4 átomos de carbono" se refiere a un grupo alquilo de 1 a 4 átomos de carbono que tiene cuando menos un sustituyente de hidroxilo.

"Alquileno" se refiere a un grupo alquilo divalente, como se define en lo anterior. Alquileno de 0 a 4 átomos de carbono es un enlace covalente individual o un grupo alquileno que tiene de 1 a 4 átomos de carbono; y alquileno de 0 a 6 átomos de carbono es un enlace covalente individual o un grupo alquileno que tiene de 1 a 6 átomos de carbono.

Un "cicloalquilo" es un grupo que comprende uno o más anillos saturados y/o parcialmente saturado, en donde todos los miembros del anillo son carbono, tales como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclo-octilo, adamantilo, decahidro-naftalenilo, octahidro-indenilo, y las variantes parcialmente saturadas de los anteriores, tales como ciclohexenilo. Los grupos cicloalquilo no comprenden un anillo aromático o un anillo heterocíclico. Ciertos grupos cicloalquilo son cicloalquilo de 3 a 8 átomos de carbono, en donde el grupo contiene un solo anillo con de 3 a 8 miembros del anillo. Un "(cicloalquilo de 3 a 8 átomos de carbono)-alquilo de 0 a 4 átomos de carbono" es un grupo cicloalquilo de 3 a 8 átomos de carbono enlazado por medio de un enlace covalente individual o un grupo alquileno de 1 a 4 átomos de carbono.

Más aún, alquilo (por ejemplo, metilo, etilo, propilo, butilo,

pentilo, hexilo, etc.) incluye tanto "alquilo insustituido" como "alquilo sustituido", el último de los cuales se refiere a las fracciones de alquilo que tienen sustituyentes reemplazando a un hidrógeno sobre uno o más átomos de carbono de la estructura base de hidrocarburo, lo cual permite que la molécula lleve a cabo su función pretendida.

El término "sustituido" pretende describir las fracciones que tienen sustituyentes reemplazando a un hidrógeno sobre uno o más átomos, por ejemplo C, O, ó N, de una molécula. Estos sustituyentes pueden incluir, por ejemplo, alquenilo, alquinilo, halógeno, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo, alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, morfolino, fenol, bencilo, fenilo, piperizina, ciclopentano, ciclohexano, piridina, 5H-tetrazol, triazol, piperidina, o una fracción aromática o hetero-aromática.

Los ejemplos adicionales de los sustituyentes de la invención, que no pretenden ser limitantes, incluyen las fracciones seleccionadas a partir de alquilo de cadena recta o ramificada (de preferencia de 1 a 5 átomos de carbono), cicloalquilo (de preferencia

de 3 a 8 átomos de carbono), alcoxilo (de preferencia de 1 a 6 átomos de carbono), tioalquilo (de preferencia de 1 a 6 átomos de carbono), alquenilo (de preferencia de 2 a 6 átomos de carbono), alquinilo (de preferencia de 2 a 6 átomos de carbono), heterociclico, carbociclico, arilo (por ejemplo fenilo), ariloxilo (por ejemplo, fenoxilo), aralquilo (por ejemplo, bencilo), ariloxi-alquilo (por ejemplo, feniloxi-alquilo), aril-acetamidoilo, alquil-arilo, hetero-aralquilo, alquil-carbonilo, y aril-carbonilo, u otro de estos grupos acilo, hetero-aril-carbonilo, o un grupo hetero-arilo, $(CR'R'')_{0-3}NR'R''$ (por ejemplo, $-NH_2$), $(CR'R'')_{0-3}CN$ (por ejemplo, -CN), $-NO_2$, halógeno (por ejemplo, -F, -Cl, -Br, ó -I), $(CR'R'')_{0-3}C(halógeno)_3$ (por ejemplo, $-CF_3$), $(CR'R'')_{0-3}CH(halógeno)_2$, $(CR'R'')_{0-3}CH_2(halógeno)$, $(CR'R'')_{0-3}CONR'R''$, $(CR'R'')_{0-3}(CNH)NR'R''$, $(CR'R'')_{0-3}S(O)_{1-2}NR'R''$, $(CR'R'')_{0-3}CHO$, $(CR'R'')_{0-3}O(CR'R'')_{0-3}H$, $(CR'R'')_{0-3}S(O)_{0-3}R'$ (por ejemplo, $-SO_3H$, $-OSO_3H$), $(CR'R'')_{0-3}O(CR'R'')_{0-3}H$ (por ejemplo, $-CH_2OCH_3$ y $-OCH_3$), $(CR'R'')_{0-3}S(CR'R'')_{0-3}H$ (por ejemplo, -SH y $-SCH_3$), $(CR'R'')_{0-3}OH$ (por ejemplo, -OH), $(CR'R'')_{0-3}COR'$, $(CR'R'')_{0-3}$(fenilo sustituido o insustituido), $(CR'R'')_{0-3}$(cicloalquilo de 3 a 8 átomos de carbono), $(CR'R'')_{0-3}CO_2R'$ (por ejemplo, $-CO_2H$), ó un grupo $(CR'R'')_{0-3}OR'$,o la cadena lateral de cualquier aminoácido que se presente naturalmente; en donde R' y R'' son cada uno independientemente hidrógeno, un grupo alquilo de 1 a 5 átomos de carbono, alquenilo de 2 a 5 átomos de carbono, alquinilo de 2 a 5 átomos de carbono, o arilo. Estos sustituyentes pueden incluir, por ejemplo, halógeno, hidroxilo, alquil-carboniloxilo,

aril-carboniloxilo, alcoxi-carboniloxilo, arilo-carbonilo, carboxilato, alquil-carbonilo, alcoxi-carbonilo, amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, oxima, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, o una fracción aromática o hetero-aromática. En ciertas modalidades, una fracción de carbonilo (C=O) puede además derivarse con una fracción de oxima, por ejemplo una fracción de aldehido se puede derivar como su análogo de oxima (-C=N=OH). Los expertos en la materia entenderán que las fracciones sustituidas sobre la cadena de hidrocarburo pueden ellas mismas estar sustituidas, si es apropiado. Los grupos cicloalquilo pueden estar adicionalmente sustituidos, por ejemplo con los sustituyentes descritos anteriormente. Una fracción de "aralquilo" es un alquilo sustituido con un arilo (por ejemplo, fenil-metilo (es decir, bencilo)).

El término "alquenilo" incluye grupos alifáticos insaturados análogos en longitud y en la posible sustitución a los alquilos descritos anteriormente, pero que contienen cuando menos un doble enlace.

Por ejemplo, el término "alquenilo" incluye los grupos alquenilo de cadena recta (por ejemplo, etenilo, propenilo, butenilo, pentenilo, hexenilo, heptenilo, octenilo, nonenilo, decenilo, etc.), los

grupos alquenilo de cadena ramificada, los grupos cicloalquenilo (alicíclicos) (ciclopropenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclo-octenilo), los grupos cicloalquenilo sustituido por alquilo o alquenilo, y los grupos alquenilo sustituido por cicloalquilo o cicloalquenilo. El término "alquenilo" incluye además los grupos alquenilo que incluyen átomos de oxígeno, nitrógeno, azufre, o fósforo reemplazando a uno o más átomos de carbono de la estructura base de hidrocarburo. En ciertas modalidades, un grupo alquenilo de cadena recta o de cadena ramificada tiene 6 ó menos átomos de carbono en su estructura base (por ejemplo, de 2 a 6 átomos de carbono para la cadena recta, y de 3 a 6 átomos de carbono para la cadena ramificada). De la misma manera, los grupos cicloalquenilo pueden tener de 3 a 8 átomos de carbono en su estructura de anillo, y más preferiblemente tienen 5 ó 6 átomos de carbono en su estructura de anillo. El término "de 2 a 6 átomos de carbono" incluye los grupos alquenilo que contienen de 2 a 6 átomos de carbono.

Más aún, el término "alquenilo" incluye tanto los "alquenilos insustituidos" como los "alquenilos sustituidos", los últimos de los cuales se refieren a las fracciones de alquenilo que tienen sustituyentes reemplazando a un hidrógeno sobre uno o más átomos de carbono de la estructura base de hidrocarburo. Estos sustituyentes pueden incluir, por ejemplo, grupos alquilo, grupos alquinilo, halógenos, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-

carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo, alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o una fracción aromática o heteroaromática.

El término "alquinilo" incluye los grupos alifáticos insaturados análogos en longitud y en posibles sustitución a los grupos alquilo descritos anteriormente, pero que contienen cuando menos un triple enlace.

Por ejemplo, el término "alquinilo" incluye los grupos alquinilo de cadena recta (por ejemplo, etinilo, propinilo, butinilo, pentinilo, hexinilo, heptinilo, octinilo, noninilo, decinilo, etc.), los grupos alquinilo de cadena ramificada, y los grupos alquinilo sustituido por cicloalquilo o cicloalquenilo. El término "alquinilo" incluye además los grupos alquinilo que incluyen átomos de oxígeno, nitrógeno, azufre, o fósforo, reemplazando a uno o más átomos de carbono de la estructura base de hidrocarburo. En ciertas modalidades, un grupo alquinilo de cadena recta o de cadena ramificada tiene 6 ó menos átomos de carbono en su estructura base (por ejemplo, de 2 a 6 átomos de carbono para la cadena recta, y de 3 a 6 átomos de carbono para la cadena ramificada). El término " de

2 a 6 átomos de carbono" incluye los grupos alquinilo que contienen de 2 a 6 átomos de carbono.

Mas aún, el término "alquinilo" incluye tanto los "alquinilos insustituidos" como los "alquinilos sustituidos", los últimos de los cuales se refieren a las fracciones de alquinilo que tienen sustituyentes reemplazando a un hidrógeno sobre uno o más átomos de carbono de la estructura base de hidrocarburo. Estos sustituyentes pueden incluir, por ejemplo, grupos alquilo, grupos alquinilo, halógenos, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo, alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), aril-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o una fracción aromática o hetero-aromática.

Se debe entender que el término "amina" o "amino" se aplica ampliamente tanto a una molécula, o una fracción o grupo funcional, como se entiende en general en la materia, y puede ser primaria, secundaria, o terciaria. El término "amina" o "amino" incluye los compuestos en donde un átomo de nitrógeno se enlaza de una manera covalente con cuando menos un átomo de carbono,

hidrógeno, o heteroátomo. Los términos incluyen, por ejemplo, pero no se limitan a, "alquil-amino", "aril-amino", "diaril-amino", "alquil-aril-amino", "alquil-amino-arilo", "aril-amino-alquilo", "alcamino-alquilo", "amida", "amido", y "amino-carbonilo". El término "alquil-amino" comprende a los grupos y compuestos en donde el átomo de nitrógeno está enlazado con cuando menos un grupo alquilo adicional. El término "dialquil-amino" incluye los grupos en donde el átomo de nitrógeno está enlazado con cuando menos dos grupos alquilo adicionales. El término "aril-amino" y "diaril-amino" incluye a los grupos en donde el átomo de nitrógeno está enlazado con cuando menos 1 ó 2 grupos arilo, respectivamente. El término "alquil-aril-amino", "alquil-amino-arilo", o "aril-amino-alquilo", se refiere a un grupo amino que está enlazado con cuando menos un grupo alquilo y cuando menos un grupo arilo. El término "alcamino-alquilo" se refiere a un grupo alquilo, alquenilo, o alquinilo enlazado con un átomo de nitrógeno que también está enlazado con un grupo alquilo.

El término "amida", "amido", o "amino-carbonilo", incluye a los compuestos o fracciones que contienen un átomo de nitrógeno que está enlazado con el átomo de carbono de un grupo carbonilo o tiocarbonilo. El término incluye a los grupos "alcamino-carbonilo", o "alquil-amino-carbonilo", los cuales incluyen a los grupos alquilo, alquenilo, arilo, o alquinilo enlazados con un grupo amino enlazado con un grupo carbonilo. Incluye a los grupos aril-amino-carbonilo y aril-carbonil-amino, los cuales incluyen a las fracciones arilo o hetero-arilo enlazadas con un grupo amino que está enlazado con el

átomo de carbono de un grupo carbonilo o tiocarbonilo. Los términos "alquil-amino-carbonilo", "alquenil-amino-carbonilo", "alquinil-amino-carbonilo", "aril-amino-carbonilo", "alquil-carbonil-amino", "alquenil-carbonil-amino", "alquinil-carbonil-amino", y "aril-carbonil-amino", están incluidos en el término "amida". Las amidas también incluyen a los grupos urea (amino-carbonil-amino) y carbamatos (oxicarbonil-amino).

El término "arilo" incluye grupos, incluyendo los grupos aromáticos de un solo anillo de 5 y 6 miembros que pueden incluir de 0 a 4 heteroátomos, por ejemplo fenilo, pirrol, furano, tiofeno, tiazol, isotiazol, imidazol, triazol, tetrazol, pirazol, oxazol, isoxazol, piridina, pirazina, piridazina, y pirimidina, y similares. Adicionalmente, el término "arilo" incluye los grupos arilo multicíclicos, por ejemplo tricíclicos, bicíclicos, por ejemplo naftaleno, benzoxazol, benzodioxazol, benzotiazol, benzoimidazol, benzotiofeno, metilendioxi-fenilo, quinolina, isoquinolina, antrilo, fenantrilo, naftiridina, indol, benzofurano, purina, deazapurina, o indolizina. Los grupos arilo que tengan heteroátomos en la estructura del anillo también pueden ser referidos como "aril-heterociclos", "heterociclos", "heteroarilos", o "heteroaromáticos". El anillo aromático puede estar sustituido en una o más posiciones del anillo con sustituyentes tales como los descritos anteriormente, como por ejemplo, alquilo, halógeno, hidroxilo, alcoxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, alquil-amino-carbonilo, aralquil-amino-carbonilo, alquenil-

amino-carbonilo, alquil-carbonilo, aril-carbonilo, aralquil-carbonilo, alquenil-carbonilo, alcoxi-carbonilo, amino-carbonilo, tioalquil-carbonilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o una fracción aromática o heteroaromática. Los grupos arilo también se pueden fusionar o puentear con anillos aliciclicos o heterocíclicos que no sean aromáticos, para formar un policiclo (por ejemplo, tetralina).

Ciertos grupos arilo mencionados en la presente son los grupos arilo de 6 a 10 átomos de carbono-alquilo de 0 a 8 átomos de carbono (es decir, los grupos en donde un grupo carbocíclico de 6 a 10 miembros que comprende cuando menos un anillo aromático está enlazado por medio de un enlace covalente individual o un grupo alquileno de 1 a 8 átomos de carbono). Estos grupos incluyen, por ejemplo, fenilo e indanilo, así como los grupos en donde cualquiera de los anteriores está enlazado por medio de alquileno de 1 a 8 átomos de carbono, de preferencia por medio de alquileno de 1 a 4 átomos de carbono. Los grupos fenilo enlazados por medio de un enlace covalente individual o un grupo alquileno de 1 a 6 átomos de carbono son designados como fenil-alquilo de 0 a 6 átomos de carbono (por ejemplo, bencilo, 1-fenil-etilo, 1-fenil-propilo, y 2-fenil-

etilo).

El término "heteroarilo", como se utiliza en la presente, representa un anillo monocíclico o bicíclico estable de hasta 7 átomos en cada anillo, en donde cuando menos un anillo es aromático y contiene de 1 a 4 heteroátomos seleccionados a partir del grupo que consiste en O, N, y S. Los grupos heteroarilo dentro del alcance de esta definición incluyen, pero no se limitan a: acridinilo, carbazolilo, cinolinilo, quinoxalinilo, pirazolilo, indolilo, benzotriazolilo, furanilo, tienilo, benzotienilo, benzofuranilo, quinolinilo, isoquinolinilo, oxazolilo, isoxazolilo, indolilo, pirazinilo, piridazinilo, piridinilo, pirimidinilo, pirrolilo, tetrahidro-quinolina. Como con la definición de heterociclo que se encuentra más adelante, se entiende también que "heteroarilo" incluye al derivado de N-óxido de cualquier heteroarilo que contenga nitrógeno. En los casos en donde el sustituyente de heteroarilo sea bicíclico, y un anillo sea no aromático o no contenga heteroátomos, se entiende que la unión es por medio del anillo aromático o por medio del anillo que contenga al heteroátomo, respectivamente.

El término "heterociclo" o "heterociclilo", como se utiliza en la presente, pretende significar un heterociclo aromático o no aromático de 5 a 10 miembros que contiene de 1 a 4 heteroátomos seleccionados a partir del grupo que consiste en O, N, y S, e incluye a los grupos bicíclicos. Por consiguiente, "heterociclilo" incluye a los heteroarilos anteriormente mencionados, así como los análogos de dihidro y tetrahidro de los mismos. Otros ejemplos de "heterociclilo"

incluyen, pero no se limitan a, los siguientes: benzoimidazolilo, benzofuranilo, benzofurazanilo, benzopirazolilo, benzotriazolilo, benzotiofenilo, benzoxazolilo, carbazolilo, carbolinilo, cinolinilo, furanilo, imidazolilo, indolinilo, indolilo, indolazinilo, indazolilo, isobenzofuranilo, isoindolilo, isoquinolilo, isotiazolilo, isoxazolilo, naftpiridinilo, oxadiazolilo, oxazolilo, oxazolina, isoxazolina, oxetanilo, piranilo, pirazinilo, pirazolilo, piridazinilo, pirido-piridinilo, piridazinilo, piridilo, pirimidilo, pirrolilo, quinazolinilo, quinolilo, quinoxalinilo, tetrahidro-piranilo, tetrazolilo, tetrazolo-piridilo, tiadiazolilo, tiazolilo, tienilo, triazolilo, azetidinilo, 1,4-dioxanilo, hexahidro-azepinilo, piperazinilo, piperidinilo, piridin-2-onilo, pirrolidinilo, morfolinilo, tiomorfolinilo, dihidro-benzo-imidazolilo, dihidro-benzo-furanilo, dihidro-benzo-tiofenilo, dihidro-benzoxazolilo, dihidro-furanilo, dihidro-imidazolilo, dihidro-indolilo, dihidro-iso-oxazolilo, dihidro-isotiazolilo, dihidro-oxadiazolilo, dihidro-oxazolilo, dihidro-pirazinilo, dihidro-pirazolilo, dihidro-piridinilo, dihidro-pirimidinilo, dihidro-pirrolilo, dihidro-quinolinilo, dihidro-tetrazolilo, dihidro-tiadiazolilo, dihidro-tiazolilo, dihidro-tienilo, dihidro-triazolilo, dihidro-azetidinilo, metilendioxi-benzoílo, tetrahidro-furanilo, y tetrahidro-tienilo, y los N-óxidos de los mismos. La unión de un sustituyente de heterociclilo se puede presentar por medio de un átomo de carbono o por medio de un heteroátomo.

Un "heterociclo-alquilo de 0 a 8 átomos de carbono" es un grupo heterocíclico enlazado por medio de un enlace covalente individual o un grupo alquileno de 1 a 8 átomos de carbono. Un

(heterociclo de 4 a 7 miembros)-alquilo de 0 a 8 átomos de carbono es un grupo heterocíclico (por ejemplo, monocíclico o bicíclico) que tiene de 4 a 7 miembros del anillo enlazados por medio de un enlace covalente individual o un grupo alquileno que tiene de 1 a 8 átomos de carbono. Un "(heteroarilo de 6 miembros)-alquilo de 0 a 6 átomos de carbono" se refiere a un grupo heteroarilo enlazado por medio de un enlace directo o un grupo alquilo de 1 a 6 átomos de carbono.

El término "acilo" incluye a los compuestos y fracciones que contienen al radical de acilo ($CH_3CO$-) o a un grupo carbonilo. El término "acilo sustituido" incluye a los grupos acilo en donde uno o más de los átomos de hidrógeno son reemplazados, por ejemplo, por grupos alquilo, grupos alquinilo, halógenos, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo, alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y dialquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o un fracción aromática o hetero-aromática.

El término "acil-amino" incluye las fracciones en donde una fracción de acilo se enlaza con un grupo amino. Por ejemplo, el

término incluye a los grupos alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido.

El término "alcoxilo" incluye a los grupos alquilo, alquenilo, y alquinilo sustituidos e insustituidos, covalentemente enlazados con un átomo de oxígeno. Los ejemplos de los grupos alcoxilo incluyen a los grupos metoxilo, etoxilo, isopropiloxilo, propoxilo, butoxilo, y pentoxilo, y pueden incluir grupos cíclicos, tales como ciclopentoxilo. Los ejemplos de los grupos alcoxilo sustituidos incluyen a los grupos alcoxilo halogenados. Los grupos alcoxilo pueden estar sustituidos con grupos tales como alquenilo, alquinilo, halógeno, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo. alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o fracciones aromáticas o hetero-aromáticas. Los ejemplos de los grupos alcoxilo sustituidos por halógeno incluyen, pero no se limitan a, fluoro-metoxilo, difluoro-metoxilo, trifluoro-metoxilo, cloro-metoxilo, dicloro-metoxilo, tricloro-metoxilo, etc.

El término "carbonilo" o "carboxilo" incluye a los compuestos

y fracciones que contienen un átomo de carbono conectado con un doble enlace a un átomo de oxígeno, y las formas tautoméricas de los mismos. Los ejemplos de las fracciones que contienen un carbonilo incluyen aldehídos, cetonas, ácidos carboxílicos, amidas, ésteres, anhídridos, etc. El término "fracción de carboxilo" o "fracción de carbonilo" se refiere a los grupos tales como los grupos "alquil-carbonilo", en donde un grupo alquilo se enlaza covalentemente a un grupo carbonilo, los grupos "alquenil-carbonilo" en donde un grupo alquenilo se enlaza covalentemente a un grupo carbonilo, los grupos "alquinil-carbonilo" en donde un grupo alquinilo se enlaza covalentemente a un grupo carbonilo, los grupos "aril-carbonilo" en donde un grupo arilo se une covalentemente al grupo carbonilo. Además, el término también se refiere a los grupos en donde uno o más heteroátomos se enlazan bivalentemente a la fracción de carbonilo. Por ejemplo, el término incluye las fracciones tales como, por ejemplo, las fracciones de amino-carbonilo (en donde un átomo de nitrógeno se enlaza al átomo de carbono del grupo carbonilo, por ejemplo una amida), fracciones de amino-carboniloxilo, en donde un átomo de oxígeno y un átomo de nitrógeno se enlazan ambos al átomo de carbono del grupo carbonilo (por ejemplo, también referido como "carbamato"). Adicionalmente, los grupos amino-carbonil-amino (por ejemplo, ureas) también se incluyen, así como otras combinaciones de grupos carbonilo enlazados con heteroátomos (por ejemplo, nitrógeno, oxígeno, azufre, etc., así como átomos de carbono). Además, el heteroátomo puede estar adicionalmente

sustituido con una o más fracciones de alquilo, alquenilo, alquinilo, arilo, aralquilo, acilo, etc.

El término "tiocarbonilo" o "tiocarboxilo" incluye a los compuestos y fracciones que contienen un átomo de carbono conectado con un doble enlace a un átomo de azufre. El término "fracción de tiocarbonilo" incluye las fracciones que son análogas a las fracciones de carbonilo. Por ejemplo, las fracciones de "tiocarbonilo" incluyen amino-tiocarbonilo, en donde un grupo amino está enlazado al átomo de carbono del grupo tiocarbonilo; además, otras fracciones de tiocarbonilo incluyen oxitiocarbonilos (oxígeno enlazado al átomo de carbono), los grupos amino-tiocarbonil-amino, etc.

El término "éter" incluye a los compuestos o fracciones que contienen un oxígeno enlazado a dos átomos de carbono o heteroátomos diferentes. Por ejemplo, el término incluye "alcoxi-alquilo", que se refiere a un grupo alquilo, alquenilo, o alquinilo covalentemente enlazado a un átomo de oxígeno que está covalentemente enlazado a otro grupo alquilo.

El término "éster" incluye a los compuestos y fracciones que contienen un átomo de carbono o un heteroátomo enlazado a un átomo de oxígeno que está enlazado al átomo de carbono de un grupo carbonilo. El término "éster" incluye a los grupos alcoxi-carboxilo, tales como metoxi-carbonilo, etoxi-carbonilo, propoxi-carbonilo, butoxi-carbonilo, pentoxi-carbonilo, etc. Los grupos alquilo, alquenilo, o alquinilo son como se definen anteriormente.

El término "tioéter" incluye a los compuestos y fracciones que contienen un átomo de azufre enlazado a dos átomos o heteroátomos diferentes. Los ejemplos de los tioéteres incluyen, pero no se limitan a, alktioalquilos, alktioalquenilos, y alktioalquinilos. El término "alktioalquilos" incluye a los compuestos con un grupo alquilo, alquenilo, o alquinilo enlazado a un átomo de azufre que está enlazado a un grupo alquilo. De una manera similar, el término "alktioalquenilos" y "alktioalquinilos" se refiere a los compuestos o fracciones en donde un grupo alquilo, alquenilo, o alquinilo está enlazado a un átomo de azufre que está covalentemente enlazado a un grupo alquinilo.

El término "hidroxi" o "hidroxilo" incluye grupos con un -OH u $-O^-$.

El término "halógeno" incluye flúor, bromo, cloro, yodo, etc. El término "perhalogenado" se refiere en general a una fracción en donde todos los hidrógenos son reemplazados por átomos de halógeno.

Los términos "policiclilo" o "radical policíclico" incluyen a las fracciones con dos o más anillos (por ejemplo, cicloalquilos, cicloalquenilos, cicloalquinilos, arilos, y/o heterociclilos) en donde dos o más átomos de carbono son comunes a dos anillos adjuntos, por ejemplo los anillos son "anillos fusionados". Los anillos que están unidos a través de átomos no adyacentes se denominan como anillos "puenteados". Cada uno de los anillos del policiclo puede estar sustituido con sustituyentes tales como los descritos

anteriormente, como por ejemplo, halógeno, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, alcoxi-carbonilo, alquil-amino-carbonilo, aralquil-amino-carbonilo, alquenil-amino-carbonilo, alquil-carbonilo, aril-carbonilo, aralquil-carbonilo, alquenil-carbonilo, amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoilo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquilo, alquil-arilo, o una fracción aromática o heteroaromática.

El término "heteroátomo" incluye a los átomos de cualquier elemento diferente de carbono o hidrógeno. Los heteroátomos preferidos son nitrógeno, oxigeno, azufre, y fósforo.

Adicionalmente, la frase "cualquier combinación de los mismos" implica que se puede combinar cualquier número de los grupos funcionales y moléculas enlistados para crear una arquitectura molecular más grande. Por ejemplo, los términos "fenilo", "carbonilo" (u "=O"), "-O-", "-OH", y $C_{1-6}$ (es decir, $-CH_3$ y $-CH_2CH_2CH_2-$), se pueden combinar para formar un sustituyente de ácido 3-metoxi-4-propoxi-benzoico. Se debe entender que, cuando se combinan grupos funcionales y moléculas para crear una arquitectura molecular más grande, se pueden remover o agregar hidrógenos,

según se requiera para satisfacer la valencia de cada átomo.

Se debe entender que todos los compuestos de la invención descritos anteriormente incluirán además enlaces entre los átomos adyacentes y/o hidrógenos, como se requiera para satisfacer la valencia de cada átomo. Es decir, se agregan enlaces y/o átomos de hidrógeno para proporcionar el siguiente número de enlaces totales para cada uno de los siguientes tipos de átomos: carbono: cuatro enlaces; nitrógeno: tres enlaces; oxígeno: dos enlaces; y azufre: dos enlaces.

Los grupos que están "opcionalmente sustituidos" están insustituidos o están sustituidos por otros diferentes de hidrógeno en una o más posiciones disponibles, típicamente 1, 2, 3, 4, ó 5 posiciones, por uno o más grupos adecuados (los cuales pueden ser iguales o diferentes). La sustitución opcional también se indica por la frase "sustituido con de 0 a X sustituyentes", en donde X es el máximo número de posibles sustituyentes. Ciertos grupos opcionalmente sustituidos están sustituidos con de 0 a 2, 3, ó 4 sustituyentes independientemente seleccionados (es decir, están insustituidos o sustituidos con hasta el número máximo mencionado de sustituyentes).

Se observará que las estructuras de algunos de los compuestos de esta invención incluyen átomos de carbono asimétricos. De conformidad con lo anterior, se debe entender que los isómeros que se presenten de esta asimetría (por ejemplo, todos los enantiómeros, estereoisómeros, rotámeros, tautómeros,

diaestereómeros, o racematos) están incluidos dentro del alcance de esta invención. Estos isómeros se pueden obtener en una forma sustancialmente pura mediante técnicas de separación clásicas y mediante síntesis estereoquímicamente controlada. Adicionalmente, las estructuras y otros compuestos y fracciones discutidos en esta solicitud también incluyen a todos los tautómeros de los mismos. Los compuestos descritos en la presente se pueden obtener a través de estrategias de síntesis reconocidas en la técnica.

También se observará que los sustituyentes de algunos de los compuestos de esta invención incluyen estructuras cíclicas isoméricas. De conformidad con lo anterior, se debe entender que los isómeros constitucionales de los sustituyentes particulares están incluidos dentro del alcance de esta invención, a menos que se indique de otra manera. Por ejemplo, el término "tetrazol" incluye tetrazol, 2H-tetrazol, 3H-tetrazol, 4H-tetrazol, y 5H-tetrazol.

***Uso en trastornos asociados con el virus de hepatitis C***

Los compuestos de la presente invención tienen valiosas propiedades farmacológicas, y son útiles en el tratamiento de enfermedades. En ciertas modalidades, los compuestos de la invención son útiles en el tratamiento de trastornos asociados con el virus de hepatitis C, por ejemplo como fármacos para tratar la infección por el virus de hepatitis C.

El término "uso" incluye a cualquiera o más de las siguientes modalidades de la invención, respectivamente: el uso en el tratamiento de trastornos asociados con el virus de hepatitis C; el

uso para la fabricación de composiciones farmacéuticas para utilizarse en el tratamiento de estas enfermedades, por ejemplo en la fabricación de un medicamento; métodos de uso de los compuestos de la invención en el tratamiento de estas enfermedades; preparaciones farmacéuticas que tienen los compuestos de la invención para el tratamiento de estas enfermedades; y compuestos de la invención para utilizarse en el tratamiento de estas enfermedades; según sea apropiado y conveniente, si no se menciona de otra manera. En particular, las enfermedades que se van a tratar, y por lo tanto las preferidas para la utilización de un compuesto de la presente invención, se seleccionan a partir de los trastornos asociados con el virus de hepatitis C, incluyendo las correspondientes a infección por el virus de hepatitis C, así como las enfermedades que dependan de la actividad de una o más de las proteínas NS3, NS4A, NS4B, NS5A y NS5B, o un complejo de NS3-NS4A, NS4A-NS4B, NS4B-NS5A ó NS5A-NS5B. El término "uso" incluye además las modalidades de las composiciones de la presente que se enlazan con una proteína del virus de hepatitis C suficientemente para servir como rastreadores o marcas, de tal manera que, cuando se acoplan con un flúor o una marca, o se hacen radioactivos, se pueden utilizar como un reactivo de investigación o como un agente de diagnóstico o de toma de imágenes.

En ciertas modalidades, se utiliza un compuesto de la presente invención para el tratamiento de enfermedades asociadas

con el virus de hepatitis C, y el uso del compuesto de la presente invención como un inhibidor de cualquiera o más virus de hepatitis C. Se prevé que un uso puede ser el tratamiento o la inhibición de una o más cepas del virus de hepatitis C.

***Ensayos***

La inhibición de la actividad del virus de hepatitis C se puede medir empleando un número de ensayos disponibles en este campo. Un ejemplo de estos ensayos se puede encontrar en Anal Biochem. 1996240(1):60-7; el cual se incorpora como referencia en su totalidad. Los ensayos para medir la actividad del virus de hepatitis C también se describen en la sección experimental que se encuentra más adelante.

***Composiciones Farmacéuticas***

El lenguaje "cantidad efectiva" del compuesto, es la cantidad necesaria o suficiente para tratar o prevenir un trastorno asociado con el virus de hepatitis C, por ejemplo prevenir los diferentes síntomas morfológicos y somáticos de un trastorno asociado con el virus de hepatitis C, y/o una enfermedad o condición descrita en la presente. En un ejemplo, una cantidad efectiva del compuesto modulador del virus de hepatitis C es la cantidad suficiente para tratar la infección por el virus de hepatitis C en un sujeto. En otro ejemplo, una cantidad efectiva del compuesto modulador del virus de hepatitis C es la cantidad suficiente para tratar la infección por el virus de hepatitis C, cirrosis hepática, enfermedad crónica del hígado, carcinoma hepatocelular,

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crioglobulinemia, linfoma que no es de Hodgkin, y una respuesta inmune intracelular innata suprimida en un sujeto. La cantidad efectiva puede variar dependiendo de factores tales como el tamaño y el peso del sujeto, el tipo de enfermedad, o el compuesto particular de la invención. Por ejemplo, la elección del compuesto de la invención puede afectar lo que constituya una "cantidad efectiva". Un experto ordinario en la materia será capaz de estudiar los factores contenidos en la presente, y de tomar la determinación con respecto a la cantidad efectiva de los compuestos de la invención sin una indebida experimentación.

El régimen de administración puede afectar lo que constituye una cantidad efectiva. El compuesto de la invención se puede administrar al sujeto ya sea antes o después del establecimiento de un estado asociado con el virus de hepatitis C. Además, se pueden administrar varias dosificaciones divididas, así como dosificaciones escalonadas, diariamente o en secuencia, o la dosis se puede infundir continuamente, o puede ser una inyección de bolo. Adicionalmente, las dosificaciones de los compuestos de la invención se pueden aumentar o reducir proporcionalmente, como sea indicado por las exigencias de la situación terapéutica o profiláctica.

Los compuestos de la invención se pueden utilizar en el tratamiento de estados, trastornos, o enfermedades descritas en la presente, o para la fabricación de composiciones farmacéuticas para utilizarse en el tratamiento de estas enfermedades. Los métodos de

uso de los compuestos de la presente invención en el tratamiento de estas enfermedades, o las preparaciones farmacéuticas que tengan los compuestos de la presente invención para el tratamiento de estas enfermedades.

El lenguaje "composición farmacéutica" incluye las preparaciones adecuadas para administrarse a mamíferos, por ejemplo seres humanos. Cuando los compuestos de la presente invención se administran como productos farmacéuticos a mamíferos, por ejemplo seres humanos, se pueden dar por sí mismos, o como una composición farmacéutica que contenga, por ejemplo, del 0.1 al 99.5 por ciento (más preferiblemente del 0.5 al 90 por ciento) de ingrediente activo, en combinación con un vehículo farmacéuticamente aceptable.

La frase "vehículo farmacéuticamente aceptable" es reconocida en la técnica, e incluye un material, composición, o vehiculo farmacéuticamente aceptable, adecuado para administrar los compuestos de la presente invención a mamíferos. Los vehículos incluyen rellenos líquidos o sólidos, diluyentes, excipientes, solventes o un material encapsulante, involucrados para portar o transportar al agente objeto desde un órgano, o porción del cuerpo, hasta otro órgano, o porción del cuerpo. Cada vehículo debe ser "aceptable" en el sentido de ser compatible con los otros ingredientes de la formulación, y no perjudicial para el paciente. Algunos ejemplos de materiales que pueden servir como vehículos farmacéuticamente aceptables incluyen: azúcares, tales como

lactosa, glucosa, y sacarosa; almidones, tales como almidón de maíz y almidón de papa; celulosa y sus derivados, tales como carboxi-metil-celulosa de sodio, etil-celulosa, y acetato de celulosa; tragacanto en polvo; malta; gelatina; talco; excipientes, tales como manteca de cacao y ceras para supositorios; aceites, tales como aceite de cacahuate, aceite de semilla de algodón, aceite de azafrán, aceite de ajonjolí, aceite de oliva, aceite de maíz, y aceite de semilla de soya; glicoles, tales como propilenglicol; polioles, tales como glicerina, sorbitol, manitol y polietilenglicol; ésteres, tales como oleato de etilo y laurato de etilo; ágar; agentes reguladores del pH, tales como hidróxido de magnesio e hidróxido de aluminio; ácido algínico; agua sin pirógeno; suero isotónico; solución de Ringer; alcohol etílico; soluciones reguladoras de fosfato; y otras sustancias compatibles no tóxicas empleadas en las formulaciones farmacéuticas.

También puede haber agentes humectantes, emulsionantes y lubricantes, tales como lauril-sulfato de sodio y estearato de magnesio, así como agentes colorantes, agentes de liberación, agentes de recubrimiento, agentes edulcorantes, saborizantes y perfumantes, conservadores y antioxidantes, presentes en las composiciones.

Los ejemplos de los antioxidantes farmacéuticamente aceptables incluyen: antioxidantes solubles en agua, tales como ácido ascórbico, clorhidrato de cisteína, bisulfato de sodio, metabisulfito de sodio, sulfito de sodio, y similares; antioxidantes

solubles en aceite, tales como palmitato de ascorbilo, hidroxi-anisol butilado (BHA), hidroxi-tolueno butilado (BHT), lecitina, galato de propilo, α-tocoferol, y similares; y agentes quelantes de metales, tales como ácido cítrico, ácido etilen-diamina-tetra-acético (EDTA), sorbitol, ácido tartárico, ácido fosfórico, y similares.

Las formulaciones de la presente invención incluyen aquéllas adecuadas para administración oral, nasal, tópica, transdérmica, bucal, sublingual, rectal, vaginal, y/o parenteral. Las formulaciones se pueden presentar de una manera conveniente en una forma de dosificación unitaria, y se pueden preparar mediante cualesquiera métodos bien conocidos en la técnica de la farmacia. La cantidad de ingrediente activo que se puede combinar con un material de vehículo para producir una sola forma de dosificación, en general será la cantidad del compuesto que produzca un efecto terapéutico. En términos generales, del 100 por ciento, esta cantidad estará en el intervalo desde aproximadamente el 1 por ciento hasta aproximadamente el 99 por ciento de ingrediente activo, de preferencia desde aproximadamente el 5 por ciento hasta aproximadamente el 70 por ciento, y más preferiblemente desde aproximadamente el 10 por ciento hasta aproximadamente el 30 por ciento.

Los métodos para la preparación de estas formulaciones o composiciones incluyen el paso de poner en asociación un compuesto de la presente invención con el vehículo, y opcionalmente, uno o más ingredientes auxiliares. En general, las

formulaciones se preparan poniendo en asociación uniforme e íntima un compuesto de la presente invención con vehículos líquidos, o con vehículos sólidos finamente divididos, o ambos, y entonces, si es necesario, se configura el producto.

Las formulaciones de la invención adecuadas para administración oral pueden estar en la forma de cápsulas, pastillas, píldoras, tabletas, grageas (utilizando una base saborizada, normalmente sacarosa y acacia o tragacanto), polvos, gránulos, o como una solución o una suspensión en un líquido o no acuoso, o como una emulsión de aceite en agua o de agua en aceite, o como un elixir o jarabe, o como pastillas (utilizando una base inerte, tal como gelatina y glicerina, o sacarosa y acacia), y/o como enjuagues bucales, y similares, cada uno conteniendo una cantidad previamente determinada de un compuesto de la presente invención como un ingrediente activo. Un compuesto de la presente invención también se puede administrar como un bolo, electuario, o pasta.

En las formas de dosificación sólida de la invención para administración oral (cápsulas, tabletas, píldoras, grageas, polvos, gránulos, y similares), el ingrediente activo se mezcla con uno o más vehículos farmacéuticamente aceptables, tales como citrato de sodio o difosfato de calcio, y/o cualquiera de los siguientes: rellenos o extensores, tales como almidones, lactosa, sacarosa, glucosa, manitol, y/o ácido silícico; aglutinantes, tales como, por ejemplo, carboxi-metil-celulosa, alginatos, gelatina, polivinil-pirrolidona, sacarosa, y/o acacia; humectantes, tales como glicerol; agentes

desintegrantes, tales como ágar-ágar, carbonato de calcio, almidón de papa o de tapioca, ácido algínico, ciertos silicatos, y carbonato de sodio; agentes retardantes de solución, tales como parafina; aceleradores de absorción, tales como compuestos de amonio cuaternario; agentes humectantes, tales como, por ejemplo, alcohol cetílico y monoestearato de glicerol; absorbentes, tales como caolín y arcilla de bentonita; lubricantes, tales como talco, estearato de calcio, estearato de magnesio, polietilenglicoles sólidos, lauril-sulfato de sodio, y mezclas de los mismos; y agentes colorantes. En el caso de las cápsulas, tabletas, y píldoras, las composiciones farmacéuticas también pueden comprender agentes reguladores del pH. También se pueden emplear composiciones sólidas de un tipo similar como rellenos en las cápsulas de gelatina rellenas blandas y duras, utilizando excipientes tales como lactosa o azúcares de leche, así como polietilenglicoles de alto peso molecular, y similares.

Una tableta se puede hacer mediante compresión o moldeo, opcionalmente con uno o más ingredientes auxiliares. Las tabletas comprimidas se pueden preparar utilizando aglutinante (por ejemplo, gelatina o hidroxi-propil-metil-celulosa), lubricante, diluyente inerte, conservador, desintegrante (por ejemplo, glicolato de almidón de sodio o carboxi-metil-celulosa de sodio reticulada), agente de actividad superficial o dispersante. Las tabletas moldeadas se pueden hacer moldeando, en una máquina adecuada, una mezcla del compuesto en polvo humedecido con un diluyente líquido inerte.

Las tabletas, y otras formas de dosificación sólida de las

composiciones farmacéuticas de la presente invención, tales como grageas, cápsulas, píldoras, y gránulos, opcionalmente se pueden marcar o preparar con recubrimientos y cubiertas, tales como recubrimientos entéricos y otros recubrimientos bien conocidos en la técnica de la formulación farmacéutica. También se pueden formular para proporcionar una liberación lenta o controlada del ingrediente activo de las mismas utilizando, por ejemplo, hidroxi-propil-metil-celulosa en diferentes proporciones, para proporcionar el perfil de liberación deseado, otras matrices poliméricas, liposomas, y/o microesferas. Se pueden esterilizar, por ejemplo, mediante filtración a través de un filtro de retención de bacterias, o mediante la incorporación de agentes esterilizantes en la forma de composiciones sólidas estériles que se puedan disolver en agua estéril, o algún otro medio inyectable estéril inmediatamente antes de usarse. Estas composiciones también pueden contener opcionalmente agentes opacificantes, y pueden ser de una composición tal que liberen los ingredientes activos solamente, o preferencialmente, en cierta porción del tracto gastrointestinal, opcionalmente de una manera demorada. Los ejemplos de las composiciones de empotramiento que se pueden utilizar incluyen sustancias poliméricas y ceras. El ingrediente activo también puede estar en una forma microencapsulada, si es apropiado, con uno o más de los excipientes anteriormente descritos.

Las formas de dosificación líquida para administración oral de los compuestos de la invención incluyen emulsiones,

microemulsiones, soluciones, suspensiones, jarabes, y elíxires farmacéuticamente aceptables. En adición al ingrediente activo, las formas de dosificación líquida pueden contener diluyentes inertes comúnmente utilizados en la técnica, tales como, por ejemplo, agua, u otros solventes, agentes solubilizantes y emulsionantes, tales como alcohol etílico, alcohol isopropílico, carbonato de etilo, acetato de etilo, alcohol bencílico, benzoato de bencilo, propilenglicol, 1,3-butilenglicol, aceites (en particular, aceites de semilla de algodón, de cacahuate, de maíz, de germen, de oliva, de ricino, y de ajonjolí), glicerol, alcohol tetrahidrofurílico, polietilenglicoles, y ésteres de ácidos grasos de sorbitán, y mezclas de los mismos.

Además de los diluyentes inertes, las composiciones orales también pueden incluir adyuvantes, tales como agentes humectantes, agentes emulsionantes y de suspensión, agentes edulcorantes, saborizantes, colorantes, perfumantes, y conservadores.

Las suspensiones, en adición a los compuestos activos, pueden contener agentes de suspensión, como por ejemplo, alcoholes isoestearílicos etoxilados, ésteres de sorbitol y de sorbitán de polioxietileno, celulosa microcristalina, metahidróxido de aluminio, bentonita, ágar-ágar y tragacanto, y mezclas de los mismos.

Las formulaciones de las composiciones farmacéuticas de la invención para administración rectal o vaginal se pueden presentar como un supositorio, el cual se puede preparar mezclando uno o más compuestos de la invención con uno o más excipientes o vehículos no irritantes que comprendan, por ejemplo, manteca de cacao,

polietilenglicol, una cera para supositorios, o un salicilato, y que sean sólidos a temperatura ambiente, pero líquidos a la temperatura corporal y que, por consiguiente, se fundan en el recto o en la cavidad vaginal y liberen el compuesto activo.

Las formulaciones de la presente invención que son adecuadas para administración vaginal también incluyen pesarios, tampones, cremas, geles, pastas, espumas, o formulaciones de rociado que contengan los vehículos conocidos en la técnica como apropiados.

Las formas de dosificación para la administración tópica o transdérmica de un compuesto de esta invención incluyen polvos, aerosoles, ungüentos, pastas, cremas, lociones, geles, soluciones, parches, e inhalantes. El compuesto activo se puede mezclar bajo condiciones estériles con un vehículo farmacéuticamente aceptable, y con cualesquiera conservadores, reguladores del pH, o propelentes que se puedan requerir.

Los ungüentos, pastas, cremas, y geles pueden contener, en adición al compuesto activo de esta invención, excipientes, tales como grasas animales y vegetales, aceites, ceras, parafinas, almidón, tragacanto, derivados de celulosa, polietilenglicoles, siliconas, bentonitas, ácido silícico, talco y óxido de zinc, o mezclas de los mismos.

Los polvos y aerosoles pueden contener, en adición a un compuesto de esta invención, excipientes tales como lactosa, talco, ácido silícico, hidróxido de aluminio, silicatos de calcio, y polvo de

poliamida, o mezclas de estas sustancias. Los aerosoles pueden contener adicionalmente los propelentes acostumbrados, tales como cloro-fluoro-hidrocarbonos y los hidrocarburos insustituidos volátiles, tales como butano y propano.

Los parches transdérmicos tienen la ventaja adicional de proporcionar el suministro controlado de un compuesto de la presente invención al cuerpo. Estas formas de dosificación se pueden hacer mediante la disolución o dispersión del compuesto en el medio apropiado. También se pueden utilizar potenciadores de absorción para aumentar el flujo del compuesto a través de la piel. La velocidad de este flujo se puede controlar ya sea proporcionando una membrana de control de velocidad, o dispersando el compuesto activo en una matriz polimérica o gel.

Las formulaciones oftálmicas, ungüentos para los ojos, polvos, soluciones, y similares, también se contemplan dentro del alcance de esta invención.

Las composiciones farmacéuticas de esta invención adecuadas para administración parenteral comprenden uno o más compuestos de la invención en combinación con una o más soluciones, dispersiones, suspensiones o emulsiones isotónicas acuosas o no acuosas estériles, farmacéuticamente aceptables, las cuales se puedan reconstituir en soluciones o dispersiones inyectables estériles justo antes de usarse, y pueden contener antioxidantes, reguladores del pH, bacteriostáticos, solutos que hagan a la formulación isotónica con la sangre del receptor

pretendido, o agentes de suspensión o espesantes.

Los ejemplos de los vehículos acuosos y no acuosos adecuados que se pueden emplear en las composiciones farmacéuticas de la invención incluyen agua, etanol, polioles (tales como glicerol, propilenglicol, polietilenglicol, y similares), y mezclas adecuadas de los mismos, aceites vegetales, tales como aceite de oliva, y ésteres orgánicos inyectables, tales como oleato de etilo. Se puede mantener la fluidez apropiada, por ejemplo, mediante el uso de materiales de recubrimiento, tales como lecitina, mediante el mantenimiento del tamaño de partículas requerido en el caso de las dispersiones, y mediante la utilización de tensoactivos.

Estas composiciones también pueden contener adyuvantes, tales como conservadores, agentes humectantes, agentes emulsionantes, y agentes de dispersión. Se puede asegurar la prevención de la acción de los microorganismos mediante la inclusión de diferentes agentes anti-bacterianos y anti-fúngicos, por ejemplo, parabeno, clorobutanol, fenol, ácido sórbico, y similares. También puede ser deseable incluir agentes isotónicos, tales como azúcares, cloruro de sodio, y similares, en las composiciones. En adición, se puede provocar una absorción prolongada de la forma farmacéutica inyectable mediante la inclusión de agentes que demoren la absorción, tales como monoestearato de aluminio y gelatina.

En algunos casos, con el objeto de prolongar el efecto de un fármaco, es deseable hacer más lenta la absorción del fármaco a

partir de la inyección subcutánea o intramuscular. Esto se puede llevar a cabo mediante el uso de una suspensión líquida de un material cristalino o amorfo que tenga una mala solubilidad en agua. La velocidad de absorción del fármaco entonces depende de su velocidad de disolución, la cual a su vez puede depender del tamaño del cristal y de la forma cristalina.

De una manera alternativa, se lleva a cabo una absorción demorada de un fármaco parenteralmente administrado mediante la disolución o suspensión del fármaco en un vehículo oleoso.

Las formas de depósito inyectables se hacen formando matrices microencapsuladas de los compuestos objeto en polímeros biodegradables, tales como polilláctido-poliglicólido. Dependiendo de la proporción del fármaco al polímero, y de la naturaleza del polímero particular empleado, se puede controlar la velocidad de liberación del fármaco. Los ejemplos de otros polímeros biodegradables incluyen poli-(*orto*-ésteres) y poli-(anhídridos). Las formulaciones inyectables de depósito también se preparan atrapando el fármaco en liposomas o en microemulsiones que sean compatibles con el tejido corporal.

Las preparaciones de la presente invención se pueden dar oralmente, parenteralmente, tópicamente, o rectalmente. Por supuesto, se dan mediante formas adecuadas para cada vía de administración. Por ejemplo, se administran en forma de tabletas o cápsulas, mediante inyección, inhalación, loción para los ojos, ungüento, supositorio, etc.; mediante administración por inyección,

infusión, o inhalación; mediante administración tópica en loción o ungüento; y mediante administración rectal en supositorios. Se prefiere la administración oral.

Las frases "administración parenteral" y "administrado parenteralmente", como se utilizan en la presente, significan los modos de administración diferentes de la administración enteral y tópica, usualmente mediante inyección, e incluyen, sin limitación, inyección e infusión intravenosa, intramuscular, intra-arterial, intratecal, intracapsular, intraorbital, intracardíaca, intradérmica, intraperitoneal, transtraqueal, subcutánea, subcuticular, intra-articular, subcapsular, subaracnoide, intraespinal, e intraesternal.

Las frases "administración sistémica", "administrado sistémicamente", "administración periférica", y "administrado periféricamente", como se utilizan en la presente, significan la administración de un compuesto, fármaco, u otro material, diferente de ser directamente en el sistema nervioso central, de tal manera que entre al sistema del paciente, y por lo tanto, esté sujeto al metabolismo y otros procesos similares, por ejemplo, la administración subcutánea.

Estos compuestos se pueden administrar a seres humanos y a otros animales para terapia mediante cualquier vía de administración adecuada, incluyendo oralmente, nasalmente, por ejemplo, como un aerosol, rectalmente, intravaginalmente, parenteralmente, intracisternalmente, y tópicamente, como polvos, ungüentos o gotas, incluyendo bucalmente y sublingualmente.

Independientemente de la vía de administración seleccionada, los compuestos de la presente invención, los cuales se pueden utilizar en una forma hidratada adecuada, y/o las composiciones farmacéuticas de la presente invención, se formulan en fórmulas de dosificación farmacéuticamente aceptables mediante métodos convencionales conocidos por los expertos en la técnica.

Los niveles de dosificación reales de los ingredientes activos en las composiciones farmacéuticas de esta invención se pueden variar para obtener una cantidad del ingrediente activo que sea efectiva para lograr la respuesta terapéutica deseada para un proceso particular, composición, y modo de administración, sin ser tóxica para el paciente.

El nivel de dosificación seleccionado dependerá de una variedad de factores, incluyendo la actividad del compuesto particular de la presente invención deseado, o del éster, sal o amida del mismo, de la vía de administración, del tiempo de administración, del índice de excreción del compuesto particular que se esté empleando, de la duración del tratamiento, de otros fármacos, compuestos y/o materiales utilizados en combinación con el compuesto particular empleado, de la edad, sexo, peso, condición, salud general, e historia médica previa del paciente que se esté tratando, y factores similares bien conocidos en la técnica médica.

Un médico o veterinario que tenga una experiencia ordinaria en la materia puede determinar fácilmente y prescribir la cantidad efectiva de la composición farmacéutica requerida. Por ejemplo, el

médico o veterinario podría iniciar con dosis de los compuestos de la invención empleados en las composiciones farmacéuticas en niveles más bajos que las requeridas con el objeto de lograr el efecto terapéutico deseado, y aumentar gradualmente la dosificación hasta que se logre el efecto deseado.

En general, una dosis diaria adecuada de un compuesto de la invención será la cantidad del compuesto que sea la dosis más baja efectiva para producir un efecto terapéutico. Esta dosis efectiva generalmente dependerá de los factores descritos anteriormente. En términos generales, las dosis intravenosas y subcutáneas de los compuestos de esta invención para un paciente, cuando se utilicen para los efectos analgésicos indicados, estará en el intervalo desde aproximadamente 0.0001 hasta aproximadamente 100 miligramos por kilogramo de peso corporal al día, más preferiblemente de aproximadamente 0.01 a aproximadamente 50 miligramos por kilogramo al día, y todavía de una manera muy preferible de aproximadamente 1.0 a aproximadamente 100 miligramos por kilogramo al día. Una cantidad efectiva es la cantidad que trate un trastorno asociado con el virus de hepatitis C.

Si se desea, la dosis diaria efectiva del compuesto activo se puede administrar como dos, tres, cuatro, cinco, seis, o más sub-dosis administradas por separado a intervalos apropiados a través de todo el día, y opcionalmente en formas de dosificación unitaria.

Aunque es posible que un compuesto de la presente invención se administre solo, es preferible administrar el compuesto

como una composición farmacéutica.

***Procedimiento Sintético***

Los compuestos de la presente invención se preparan a partir de compuestos comúnmente disponibles, empleando los procedimientos conocidos por los expertos en este campo, incluyendo cualquiera o más de las siguientes condiciones, sin limitación:

Dentro del alcance de este texto, solamente un grupo fácilmente removible que no sea un constituyente del producto final deseado particular de los compuestos de la presente invención, se designa como un "grupo protector", a menos que el contexto lo indique de otra manera. La protección de los grupos funcionales por parte de estos grupos protectores, los grupos protectores mismos, y sus reacciones de disociación, se describen, por ejemplo, en los trabajos de referencia convencionales, tales como, por ejemplo, Science of Synthesis: Houben-Weyl Methods of Molecular Transformation. Georg Thieme Verlag, Stuttgart, Alemania, 2005, 41627 pp. (URL: http://www.science-of-synthesis.com (Versión Electrónica, 48 Volúmenes)); J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, Londres y Nueva York 1973, en T. W. Greene y P. G. M. Wuts, "Protective Groups in Organic Synthesis", Tercera Edición, Wiley, Nueva York 1999, en "The Peptides"; Volumen 3 (Editores: E. Gross y J. Meienhofer), Academic Press, Londres y Nueva York 1981, en "Methoden der organischen Chemie" (*Métodos de Química Orgánica*), Houben Weyl, 4ª Edición,

Volumen 15/I, Georg Thieme Verlag, Stuttgart 1974, en H. D. Jakubke y H. Jeschkeit, "Aminosäuren, Peptide, Proteine" (*Aminoácidos, Péptidos, Proteínas*), Verlag Chemie, Weinheim, Deerfield Beach, y Basilea 1982, y en Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Química de Carbohidratos: Monosacáridos y Derivados*), Georg Thieme Verlag, Stuttgart 1974. Una característica de los grupos protectores es que se pueden remover fácilmente (es decir, sin la presentación de reacciones secundarias indeseadas), por ejemplo mediante solvólisis, reducción, fotólisis, o de una manera alternativa bajo condiciones fisiológicas (por ejemplo, mediante disociación enzimática).

Las sales de los compuestos de la presente invención que tengan cuando menos un grupo formador de sal, se pueden preparar de una manera conocida por sí misma. Por ejemplo, las sales de los compuestos de la presente invención que tengan grupos ácidos se pueden formar, por ejemplo, mediante el tratamiento de los compuestos con compuestos de metales, tales como sales de metales alcalinos de ácidos carboxílicos orgánicos adecuados, por ejemplo la sal sódica del ácido 2-etil-hexanoico, con compuestos de metales alcalinos o de metales alcalinotérreos orgánicos, tales como los hidróxidos, carbonatos, o carbonatos ácidos correspondientes, tales como hidróxido, carbonato, o carbonato ácido de sodio o de potasio, con los compuestos de calcio correspondientes, o con amoniaco o una amina orgánica adecuada, utilizándose de

preferencia cantidades estequiométricas o solamente un pequeño exceso del agente formador de sal. Las sales de adición de ácido de los compuestos de la presente invención se obtienen de la manera acostumbrada, por ejemplo mediante el tratamiento de los compuestos con un ácido o con un reactivo de intercambio de aniones adecuado. Se pueden formar las sales internas de los compuestos de la presente invención que contengan grupos formadores de sales ácidos y básicos, por ejemplo un grupo carboxilo libre y un grupo amino libre, por ejemplo, mediante la neutralización de las sales, tales como las sales de adición de ácido, hasta el punto isoeléctrico, por ejemplo con bases débiles, o mediante su tratamiento con intercambiadores de iones.

Las sales se pueden convertir de la manera acostumbrada en los compuestos libres; las sales de metal y de amonio se pueden convertir, por ejemplo, mediante su tratamiento con ácidos adecuados, y las sales de adición de ácido, por ejemplo, mediante su tratamiento con un agente básico adecuado.

Las mezclas de isómeros que se pueden obtener de acuerdo con la invención se pueden separar de una manera conocida por sí misma en los isómeros individuales; los diaestereoisómeros se pueden separar, por ejemplo, mediante división entre mezclas de solventes polifásicas, recristalización, y/o separación cromatográfica, por ejemplo sobre gel de sílice, o, por ejemplo, mediante cromatografía de líquidos a presión media sobre una columna de fase inversa, y los racematos se pueden separar, por ejemplo,

mediante la formación de sales con reactivos formadores de sales ópticamente puros y la separación de la mezcla de diaestereoisómeros que se puede obtener de esta manera, por ejemplo por medio de cristalización fraccionaria, o mediante cromatografía sobre materiales de columna ópticamente activos.

Los intermediarios y los productos finales se pueden procesar y/o purificar de acuerdo con los métodos convencionales, por ejemplo empleando métodos cromatográficos, métodos de distribución, (re-)cristalización, y similares.

**Condiciones generales del proceso**

Lo siguiente se aplica en general a todos los procesos mencionados a través de toda esta divulgación.

Los pasos del proceso para sintetizar los compuestos de la invención se pueden llevar a cabo bajo condiciones de reacción que son conocidas por sí mismas, incluyendo las mencionadas de una manera específica, en ausencia, o por costumbre en la presencia de solventes o diluyentes, incluyendo, por ejemplo, los solventes o diluyentes que sean inertes hacia los reactivos utilizados y los disuelvan, en ausencia o en la presencia de catalizadores, agentes de condensación o neutralizantes, por ejemplo intercambiadores de iones, tales como intercambiadores de cationes, por ejemplo en la forma $H^+$, dependiendo de la naturaleza de la reacción, y/o de los reactivos, a temperatura reducida, normal, o elevada, por ejemplo en un intervalo de temperatura de aproximadamente -100°C a aproximadamente 190°C, incluyendo, por ejemplo, de

aproximadamente -80°C a aproximadamente 150°C, por ejemplo de -80°C a -60°C, a temperatura ambiente, de -20°C a 40°C, o a la temperatura de reflujo, bajo presión atmosférica o en un recipiente cerrado, donde sea apropiado bajo presión, y/o en una atmósfera inerte, por ejemplo bajo una atmósfera de argón o de nitrógeno.

En todas las etapas de las reacciones, las mezclas de isómeros que se formen se pueden separar en los isómeros individuales, por ejemplo diaestereoisómeros o enantiómeros, o en cualesquiera mezclas de isómeros deseadas, por ejemplo racematos, o mezclas de diaestereoisómeros, por ejemplo de una manera análoga a los métodos descritos en Science of Synthesis: Houben-Weyl Methods of Molecular Transformation. Georg Thieme Verlag, Stuttgart, Alemania, 2005.

Los solventes a partir de los cuales se pueden seleccionar los solventes que son adecuados para cualquier reacción particular incluyen los mencionados de una manera específica, o, por ejemplo, agua, ésteres, tales como alcanoatos inferiores de alquilo inferior, por ejemplo acetato de etilo, ésteres, tales como éteres alifáticos, por ejemplo dietil-éter, o éteres cíclicos, por ejemplo tetrahidrofurano o dioxano, hidrocarburos aromáticos líquidos, tales como benceno o tolueno, alcoholes, tales como metanol, etanol, o 1- ó 2-propanol, nitrilos, tales como acetonitrilo, hidrocarburos halogenados, tales como cloruro de metileno o cloroformo, amidas de ácido, tales como dimetil-formamida o dimetil-acetamida, bases, tales como bases de nitrógeno heterocíclico, por ejemplo piridina ó N-metil-pirrolidin-2-

ona, anhídridos de ácido carboxílico, tales como anhídridos de ácido alcanoico inferior, por ejemplo anhídrido acético, hidrocarburos cíclicos, lineales o ramificados, tales como ciclohexano, hexano, o isopentano, o mezclas de estos solventes, por ejemplo soluciones acuosas, a menos que se indique de otra manera en la descripción de los procesos. Estas mezclas de solventes también se pueden utilizar en el procesamiento, por ejemplo mediante cromatografía o división.

Los compuestos, incluyendo sus sales, también se pueden obtener en la forma de hidratos, o, por ejemplo, sus cristales pueden incluir al solvente utilizado para la cristalización. Puede haber diferentes formas cristalinas presentes.

La invención se refiere también a las formas del proceso en donde un compuesto que se pueda obtener como un intermediario en cualquier etapa del proceso, se utiliza como material de partida, y se llevan a cabo los pasos restantes del proceso, o en donde se forma un material de partida bajo las condiciones de reacción, o se utiliza en la forma de un derivado, por ejemplo en una forma protegida o en la forma de una sal, o un compuesto que se pueda obtener mediante el proceso de acuerdo con la invención se produce bajo las condiciones del proceso, y se procesa adicionalmente *in situ*.

**Pro-fármacos**

La presente invención también se refiere a los pro-fármacos de un compuesto de la presente invención, que se convierten *in vivo* hasta los compuestos de la presente invención como se describe en

la presente. Cualquier referencia a un compuesto de la presente invención, por consiguiente, debe entenderse para referirse también a los pro-fármacos correspondientes del compuesto de la presente invención, según sea apropiado y conveniente.

**Combinaciones**

También se puede utilizar un compuesto de la presente invención en combinación con otros agentes, por ejemplo un compuesto modulador del virus de hepatitis C adicional que sea o no de la Fórmula I, para el tratamiento de un trastorno asociado con el virus de hepatitis C en un sujeto.

El término "combinación" significa ya sea una combinación fija en una forma unitaria de dosificación, o bien un kit de partes para la administración combinada, en donde un compuesto de la presente invención y un componente de combinación se pueden administrar de una manera independiente al mismo tiempo o por separado dentro de intervalos de tiempo que permitan especialmente que los componentes de la combinación muestren un efecto cooperativo, por ejemplo sinérgico, o cualquier combinación de los mismos.

Por ejemplo, la Publicación Internacional Número WO 2005/042020, incorporada a la presente como referencia en su totalidad, describe la combinación de diferentes inhibidores del virus de hepatitis C con un inhibidor del citocromo P450 ("CYP"). Se puede utilizar cualquier inhibidor del citocromo P450 que mejore la farmacocinética de la proteasa NS3/4A relevante en combinación con

los compuestos de esta invención. Estos inhibidores del citocromo P450 incluyen, pero no se limitan a, ritonavir (Publicación Internacional Número WO 94/14436, incorporada a la presente como referencia en su totalidad), quetoconazol, troleandomicina, 4-metil-pirazol, ciclosporina, clometiazol, cimetidina, itraconazol, fluconazol, miconazol, fluvoxamina, fluoxetina, nefazodona, sertralina, indinavir, nelfinavir, amprenavir, fosamprenavir, saquinavir, lopinavir, delavirdina, eritromicina, VX-944, y VX-497. Los inhibidores del citocromo P450 preferidos incluyen ritonavir, quetoconazol, troleandomicina, 4-metil-pirazol, ciclosporina, y clometiazol.

Los métodos para medir la capacidad de un compuesto para inhibir la actividad del citocromo P450 son conocidos (ver, por ejemplo, la Patente de los Estados Unidos de Norteamérica Número US 6,037,157 y Yun y colaboradores, *Drug Metabolism & Disposition*, Volumen 21, páginas 403-407 (1993); incorporados a la presente como referencia). Por ejemplo, un compuesto que se vaya a evaluar se puede incubar con 0.1, 0.5, y 1.0 miligramos de proteína/mililitro, u otra concentración apropiada de microsomas hepáticos humanos (por ejemplo, microsomas hepáticos caracterizados reservados, comercialmente disponibles), durante 0, 5, 10, 20, y 30 minutos, u otros tiempos apropiados, en la presencia de un sistema generador de NADPH. Se pueden llevar a cabo incubaciones de control en ausencia de los microsomas hepáticos durante 0 y 30 minutos (por triplicado). Las muestras se pueden analizar para determinar la presencia del compuesto. Se utilizarán condiciones de incubación

que produzcan un índice lineal de metabolismo del compuesto como una guía para estudios adicionales. Se pueden emplear los experimentos conocidos en este campo para determinar la cinética del metabolismo del compuesto ($K_m$ y $V_{max}$). Se puede determinar el índice de desaparición del compuesto, y se pueden analizar los datos de acuerdo con la cinética de Michaelis-Menten, empleando Lineweaver-Burk, Eadie-Hofstee, o el análisis de regresión no lineal.

Entonces se pueden llevar a cabo los experimentos de inhibición del metabolismo. Por ejemplo, se puede incubar un compuesto (una concentración, $<K_m$) con los microsomas hepáticos humanos reservados en ausencia o en la presencia de un inhibidor del citocromo P450 (tal como ritonavir), bajo las condiciones determinadas anteriormente. Como se reconocería, las incubaciones de control deben contener la misma concentración de solvente orgánico que las incubaciones con el inhibidor del citocromo P450. Las concentraciones del compuesto en las muestras se pueden cuantificar, y se puede determinar el índice de desaparición del compuesto progenitor, cuyos índices se expresan como un porcentaje de la actividad del control.

También se conocen los métodos para evaluar la influencia de la co-administración de un compuesto de la invención y un inhibidor del citocromo P450 (ver, por ejemplo, la Patente de los Estados Unidos de Norteamérica Número US2004/0028755; incorporada a la presente como referencia). Cualquiera de estos métodos se podría emplear en relación con esta invención para

determinar el impacto farmacocinético de una combinación. Entonces se podrían seleccionar los sujetos que se beneficiarían del tratamiento de acuerdo con esta invención.

De conformidad con lo anterior, una modalidad de esta invención proporciona un método para administrar un inhibidor de CYP3A4 y un compuesto de la invención. Otra modalidad de esta invención proporciona un método para administrar un inhibidor de la isozima 3A4 ("CYP3A4"), de la isozima 2C19 ("CYP2C19"), de la isozima 2D6 ("CYP2D6"), de la isozima 1A2 ("CYP1A2"), de la isozima 2C9 ("CYP2C9"), o de la isozima 2E1 ("CYP2E1"). En las modalidades en donde el inhibidor de proteasa es VX-950 (o un estereoisómero del mismo), el inhibidor de CYP de preferencia inhibe CYP3A4.

Como se apreciaría, se observa ampliamente la actividad de CYP3A4 en los seres humanos. De acuerdo con lo anterior, se esperaría que las modalidades de esta invención que involucran la inhibición de la isozima 3A4 sean aplicables a un amplio número de pacientes.

De conformidad con lo anterior, esta invención proporciona métodos en donde el inhibidor de CYP se administra junto con el compuesto de la invención en la misma forma de dosificación o en formas de dosificación separadas.

Los compuestos de la invención (por ejemplo, el compuesto de la Fórmula I ó las sub-fórmulas de la misma) se pueden administrar como el único ingrediente o en combinación o alternados

con otros agentes anti-virales, en especial agentes activos contra el virus de hepatitis C. En la terapia de combinación, se administran juntas las dosificaciones efectivas de dos o más agentes, mientras que en la terapia alternada o por pasos en secuencia, se administra una dosificación efectiva de cada agente en serie o en secuencia. En general, típicamente se prefiere la terapia de combinación sobre la terapia alternada, debido a que induce múltiples tensiones simultáneas sobre el virus. Las dosificaciones dadas dependerán del índice de absorción, inactivación y excreción del fármaco, así como de otros factores. Se debe observar que los valores de dosificación también variarán con la severidad de la condición que se vaya a aliviar. Se debe entender además que, para cualquier sujeto particular, los regímenes y programas de dosificación específicos deben ajustarse a través del tiempo de acuerdo con la necesidad individual y el juicio profesional de la persona que administre o supervise la administración de las composiciones. La eficacia de un fármaco contra la infección viral se puede prolongar, aumentar, o restablecer, mediante la administración del compuesto en combinación o alternado con un segundo, y tal vez un tercer compuesto anti-viral que induzca una mutación genética diferente de la que sea causada por el fármaco principal en un virus resistente a fármacos. De una manera alternativa, se pueden alterar los parámetros farmacocinéticos, de biodistribución, u otros parámetros mediante esta terapia de combinación o alternada.

Las dosificaciones diarias requeridas en la práctica del

método de la presente invención variarán dependiendo, por ejemplo, del compuesto de la invención empleado, del huésped, del modo de administración, y de la severidad de la condición que se esté tratando. Un intervalo de dosificación diaria preferido es de aproximadamente 1 a 50 miligramos/kilogramo al día como una sola dosis o en dosis divididas. Las dosificaciones diarias adecuadas para los pacientes son del orden, por ejemplo, de 1 a 20 miligramos/kilogramo oralmente o intravenosamente. Las formas de dosificación unitaria adecuadas para administración oral comprenden de aproximadamente 0.25 a 10 miligramos/kilogramo de ingrediente activo, por ejemplo el compuesto de la Fórmula I ó cualquier sub-fórmula de la misma, junto con uno o más diluyentes o vehículos farmacéuticamente aceptables para el mismo. La cantidad de co-agente en la forma de dosificación puede variar mucho, por ejemplo de 0.00001 a 1,000 miligramos/kilogramo de ingrediente activo.

Las dosificaciones diarias con respecto al co-agente utilizado variarán dependiendo, por ejemplo, del compuesto empleado, del huésped, del modo de administración, y de la severidad de la condición que se esté tratando. Por ejemplo, la lamivudina se puede administrar en una dosificación diaria de 100 miligramos. El interferón pegilado se puede administrar parenteralmente de 1 a 3 veces por semana, de preferencia una vez por semana, en una dosis semanal total en el intervalo de 2 a 10 millones de Unidades Internacionales, más preferiblemente de 5 a 10 millones de Unidades Internacionales, y de una manera muy

preferible de 8 a 10 millones de Unidades Internacionales. Debido a los diversos tipos de co-agente que se pueden utilizar, las cantidades pueden variar mucho, por ejemplo de 0.0001 a 5,000 miligramos/kilogramo al día.

El estándar de cuidado actual para el tratamiento de hepatitis C es la combinación del interferón-alfa pegilado con ribavirina, de los cuales las dosis recomendadas son de 0.5 microgramos/kilogramo/semana de peginterferón-alfa-2b, ó 180 microgramos/semana de peginterferón-alfa-2a, más 1,000 a 1,200 miligramos diarios de ribavirina durante 48 semanas para los pacientes con el genotipo I, u 800 miligramos diarios de ribavirina durante 24 semanas para los pacientes con el genotipo 2/3.

El compuesto de la invención (por ejemplo, el compuesto de la Fórmula I o las sub-fórmulas de la misma) y los co-agentes de la invención se pueden administrar por cualquier vía convencional, en particular enteralmente, por ejemplo oralmente, por ejemplo en la forma de soluciones para beber, tabletas o cápsulas, o parenteralmente, por ejemplo en la forma de soluciones o suspensiones inyectables. Ciertas composiciones farmacéuticas preferidas, por ejemplo, pueden ser aquéllas basadas en microemulsiones, como se describen en la Patente del Reino Unido Número UK 2,222,770 A.

El compuesto de la invención (por ejemplo, el compuesto de la Fórmula I ó las sub-fórmulas de la misma) se administra junto con otros fármacos (co-agentes), por ejemplo un fármaco que tenga una

actividad anti-viral, en especial una actividad anti-Flaviviridae, más especialmente una actividad anti-HCV, por ejemplo un interferón, por ejemplo interferón-α-2a ó interferón-α-2b, por ejemplo Intron$^{R}$ A, Roferon$^{R}$, Avonex$^{R}$, Rebif$^{R}$, ó betaferon$^{R}$, o un interferón conjugado con un polímero soluble en agua o con albúmina humana, por ejemplo albuferón, un agente anti-viral, por ejemplo ribavirina, lamivudina, los compuestos dados a conocer en la Patente de los Estados Unidos de Norteamérica Número 6,812,219 y en la Publicación Internacional Número WO 2004/002422 A2 (cuyas divulgaciones se incorporan a la presente como referencia en su totalidad), un inhibidor del virus de hepatitis C u otros factores codificados por el virus de Flaviviridae como la proteasa NS3/4A, helicasa, o polimerasa de ARN, o un pro-fármaco de este inhibidor, un agente anti-fibrótico, por ejemplo un derivado de N-fenil-2-pirimidin-amina, por ejemplo imatinib, un agente inmuno-modulador, por ejemplo ácido micofenólico, una sal o un profármaco del mismo, por ejemplo micofenolato de sodio o micofenolato-mofetil, o un agonista del receptor S1P, por ejemplo FTY720, o un análogo del mismo, opcionalmente fosforilado, por ejemplo como se da a conocer en las Patentes Números EP627406A1, EP778263A1, EP1002792A1, WO02/18395, WO02/76995, WO 02/06268, JP2002316985, WO03/29184, WO03/29205, WO03/62252 y WO03/62248, cuyas divulgaciones se incorporan a la presente como referencia en su totalidad.

Los conjugados de interferón con un polímero soluble en

agua pretenden incluir en especial los conjugados con homopolímeros de poli-óxido de alquileno, tales como polietilenglicol (PEG) o polipropilenglicoles, polioles polioxietilenados, copolímeros de los mismos y copolímeros de bloques de los mismos. Como una alternativa a los polímeros basados en poli-óxido de alquileno, se pueden utilizar efectivamente materiales no antigénicos, tales como dextrano, polivinil-pirrolidonas, poliacril-amidas, poli-alcoholes vinílicos, polímeros basados en carbohidratos, y similares. Estos conjugados de interferón-polímero se describen en las Patentes de los Estados Unidos de Norteamérica Números 4,766,106 y 4,917,888, en la Solicitud de Patente Europea Número 0,236,987, en la Solicitud de Patente Europea Número 0,510,356, y en la Publicación de Solicitud Internacional Número WO95/13090, cuyas divulgaciones se incorporan a la presente como referencia en su totalidad. Debido a que la modificación polimérica reduce suficientemente las respuestas antigénicas, el interferón extraño no necesita ser completamente autólogo. El interferón utilizado para preparar los conjugados poliméricos se puede preparar a partir de un extracto de mamífero, tal como interferón humano, de rumiante, o bovino, o se puede producir de una manera recombinante. Se prefieren los conjugados de interferón con polietilenglicol, también conocidos como interferones pegilados.

Los conjugados especialmente preferidos de interferón son los alfa-interferones pegilados, por ejemplo interferón-$\alpha$-2a pegilado, interferón-$\alpha$-2b pegilado; interferón en consenso pegilado, o el

producto de interferón-α purificado pegilado. El interferón-α-2a pegilado se describe, por ejemplo, en la Patente Europea Número 593,868 (incorporada a la presente como referencia en su totalidad), y comercialmente disponible, por ejemplo, bajo el nombre comercial de PEGASYS® (Hoffmann-La Roche). El interferón-α-2b pegilado se describe, por ejemplo, en la Patente Europea Número 975,369 (incorporada a la presente como referencia en su totalidad), y comercialmente disponible, por ejemplo, bajo el nombre comercial de PEG-INTRON A® (Schering Plough). El interferón en consenso pegilado se describe en la Publicación Internacional Número WO 96/11953 (incorporada a la presente como referencia en su totalidad). Los α-interferones pegilados preferidos son el interferón-α-2a pegilado y el interferón-α-2b pegilado. También se prefiere el interferón en consenso pegilado.

Otros co-agentes preferidos son las proteínas de fusión de un interferón, por ejemplo las proteínas de fusión del interferón-α-2a, del interferón-α-2b; del interferón en consenso, o del producto de interferón-α purificado, cada uno de los cuales se fusiona con otra proteína. Algunas proteínas de fusión preferidas comprenden un interferón (por ejemplo, interferón-α-2b) y una albúmina, como se describe en la Patente de los Estados Unidos de Norteamérica Número 6,973,322, y en las Publicaciones Internacionales Números WO02/60071, WO05/003296 y WO05/077042 (Human Genome Sciences). Un interferón preferido conjugado con una albúmina humana es el Albuferón (Human Genome Sciences).

Las ciclosporinas que se enlazan fuertemente a la ciclofilina, pero que no son inmunosupresoras, incluyen las ciclosporinas mencionadas en las Patentes de los Estados Unidos de Norteamérica Números 5,767,069 y 5,981,479, y se incorporan a la presente como referencia. La ciclosporina-Melle[4] es una ciclosporina no inmunosupresora preferida. Algunos otros derivados de ciclosporina se describen en la Publicación Internacional Número WO2006039668 (Scynexis) y en la Publicación Internacional Número WO2006038088 (Debiopharm SA), y se incorporan a la presente como referencia. Se considera que una ciclosporina es no inmunosupresora cuando tiene una actividad en la Reacción de Linfocitos Mixtos (MLR) de no más del 5 por ciento, de preferencia no más del 2 por ciento, de aquélla de la ciclosporina A. La Reacción de Linfocitos Mixtos es descrita por T. Meo en "Immunological Methods", L. Lefkovits y B. Peris, Editores, Academic Press, N. Y. páginas 227-239 (1979). Se co-incuban células de bazo ($0.5 \times 10^6$) de ratones Balb/c (hembras, de 8 a 10 semanas) durante 5 días, con $0.5 \times 10^6$ células de bazo irradiadas (2,000 rads) o tratadas con mitomicina C de ratones CBA (hembras, de 8 a 10 semanas). Las células alogeneicas irradiadas inducen una respuesta proliferativa en las células de bazo de los ratones Balb/c que se puede medir mediante la incorporación del precursor marcado en el ADN. Debido a que las células estimulantes son irradiadas (o tratadas con mitomicina C), no responden a las células de Balb/c con proliferación, pero sí retienen su antigenicidad. La $IC_{50}$ encontrada

para el compuesto de prueba en la Reacción de Linfocitos Mixtos se compara con aquélla encontrada para la ciclosporina A en un experimento paralelo. En adición, las ciclosporinas no inmunosupresoras carecen de la capacidad para inhibir CN y la senda de NF-AT corriente abajo. La ciclosporina-[Melle]$^4$ es una ciclosporina de enlace de ciclofilina no inmunosupresora preferida para utilizarse de acuerdo con la invención.

La ribavirina (1-β-D-furanosil-1-1,2,4-triazol-3-carboxamida) es un análogo de nucleósido anti-viral de amplio espectro inductor no interferón, sintético, vendido bajo el nombre comercial Virazole (The Merk Index, 11ª Edición, Editor: Budavar, S. Merck & Co., Inc., Rahway, NJ, página 1304, 1989). Las Patentes de los Estados Unidos de Norteamérica Números 3,798,209 y RE29,835 (incorporadas a la presente como referencia en su totalidad) dan a conocer y reivindican la ribavirina. La ribavirina es estructuralmente similar a la guanosina, y tiene una actividad *in vitro* contra varios virus de ADN y de ARN, incluyendo *Flaviviridae* (Gary L. Davis, Gastroenterology 118:S104-S114, 2000).

La ribavirina reduce los niveles de amino-transferasa en suero hasta lo normal en el 40 por ciento de los pacientes, pero no reduce los niveles en suero del ARN del virus de hepatitis C (Gary L. Davis, Gastroenterology 118:S104-S114, 2000). Por consiguiente, la ribavirina sola no es efectiva para reducir los niveles de ARN viral. Adicionalmente, la ribavirina tiene una toxicidad significativa, y se sabe que induce anemia. La ribavirina no está aprobada para

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monoterapia contra el virus de hepatitis C; está aprobada en combinación con el interferón-α-2a ó el interferón-α-2b para el tratamiento del virus de hepatitis C.

Una combinación preferida adicional es una combinación de un compuesto de la invención (por ejemplo, un compuesto de la Fórmula I, o cualesquiera sub-fórmulas de la misma) con una ciclosporina de enlace de ciclofilina no inmunosupresora, con ácido micofenólico, una sal o un pro-fármaco del mismo, y/o con un agonista del receptor S1P, por ejemplo FTY720.

Los ejemplos adicionales de los compuestos que se pueden utilizar en los tratamientos de combinación o alternados incluyen:

(1) Interferones, incluyendo interferón-α-2a ó 2b, e interferón-α-2a ó 2b pegilado (PEG), por ejemplo:

(a) Intron-A®, interferón-α-2b (Schering Corporation, Kenilworth, NJ);

(b) PEG-Intron®, peginterferón-α-2b (Schering Corporation, Kenilworth, NJ);

(c) Roferon®, interferón-α-2a recombinante (Hoffmann-La Roche, Nutley, NJ);

(d) Pegasys®, peginterferón-α-2a (Hoffmann-La Roche, Nutley, NJ);

(e) Berefor®, interferón-α-2 disponible (Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT);

(f) Sumiferon®, una mezcla purificada de interferones alfa naturales (Sumitomo, Japón);

(g) Wellferon®, interferón-α-n1 linfoblastoide (GlaxoSmithKline);

(h) Infergen®, interferón alfa en consenso (InterMune Pharmaceuticals, Inc., Brisbane, CA);

(i) Alferon®, una mezcla de interferones alfa naturales (Interferon Sciences, and Purdue Frederick Co., CT);

(j) Viraferon®;

(k) Interferón alfa en consenso de Amgen, Inc., Newbury Park, CA.

Otras formas de interferón incluyen: interferón beta, gamma, tau, y omega, tales como Rebif (interferón-α-1a) por Serono, Omniferon (interferón natural) por Viragen, REBIF (interferón-β-1a) por Ares-Serono, Interferón Omega por BioMedicines; Interferón-Alfa Oral por Amarillo Biosciences; un interferón conjugado con un polímero soluble en agua o con una albúmina humana, por ejemplo Albuferon (Human Genome Sciences), un agente anti-viral, un interferón en consenso, o interferón-tau ovino ó bovino.

Los conjugados de interferón con un polímero soluble en agua pretenden incluir en especial los conjugados con homopolímeros de poli-óxido de alquileno, tales como polietilenglicol (PEG) o polipropilenglicoles, polioles polioxietilenados, copolímeros de los mismos y copolímeros de bloques de los mismos. Como una alternativa para los polímeros basados en poli-óxido de alquileno, se pueden utilizar efectivamente los materiales no antigénicos, tales como dextrano, polivinil-pirrolidonas, poliacril-amidas, poli-alcoholes

vinílicos, polímeros basados en carbohidratos, y similares. Debido a que la modificación polimérica reduce suficientemente la respuesta antigénica, el interferón extraño no necesita ser completamente autólogo. El interferón utilizado para preparar los conjugados poliméricos se puede preparar a partir de un extracto de mamífero, tal como interferón humano, de rumiante, o bovino, o se puede producir de una manera recombinante. Se prefieren los conjugados de interferón con polietilenglicol, también conocidos como interferones pegilados.

(2) Ribavirina, tal como ribavirina (1-beta-D-ribofuranosil-1H-1,2,4-triazol-3-carboxamida) de Valeant Pharmaceuticals, Inc., Costa Mesa, CA); Rebetol® de Schering Corporation, Kenilworth, NJ, y Copegus® de Hoffmann-La Roche, Nutley, NJ; y los nuevos análogos de ribavirina en desarrollo, tales como Levovirina y Viramidina por Valeant,

(3) Derivados de tiazolidina, que muestran una inhibición relevante en un ensayo de HPLC de fase inversa con una proteína de fusión NS3/4A y el sustrato NS5A/5B (Sudo K. y colaboradores, *Antiviral Research*, 1996, 32, 9-18), en especial el compuesto RD-1-6250, que posee una fracción de cinamoílo fusionada sustituida con una cadena de alquilo larga, RD4 6205 y RD4 6193;

(4) Tiazolidinas y benzalidinas identificadas en Kakiuchi N. y colaboradores, *J. FEBS Letters* 421, 217-220; Takeshita N. y colaboradores, *Analytical Biochemistry,* 1997, 247, 242-246;

(5) Una fenantren-quinona que posee actividad contra la proteasa en un ensayo de SDS-PAGE y de auto-radiografía aislada del caldo de cultivo de fermentación de *Streptomyces sp.*, Sch 68631 (Chu M. y colaboradores, *Tetrahedron Letters*, 1996, 37, 7229-7232), y Sch 351633, aislado del hongo *Penicillium griseofulvum*, que demuestra actividad en un ensayo de proximidad de cintilación (Chu M. y colaboradores, *Bioorganic and Medicinal Chemistry Letters* 9, 1949-1952);

(6) Inhibidores de proteasa.

Los ejemplos incluyen los inhibidores de proteasa NS3 basados en sustrato (Attwood y colaboradores, *Antiviral peptide derivatives,* Publicación del TCP Número WO98/22496, 1998; Attwood y colaboradores, *Antiviral Chemistry and Chemotherapy* 1999, 10, 259-273; Attwood y colaboradores, *Preparation and use of amino acid derivative as anti-viral agents,* Publicación de Patente Alemana Número DE 19914474; Tung y colaboradores, *Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease;* Publicación del TCP Número WO98/17679), incluyendo alfa-quetoamidas e hidrazino-ureas, y los inhibidores que terminan en un electrófilo, tal como ácido borónico o fosfonato (Llinas-Brunet y colaboradores, *Hepatitis C inhibitor peptide analogues*, Patente del TCP Número WO99/07734), que se están investigando.

Los inhibidores de proteasa NS3 no basados en sustrato, tales como los derivados de 2,4,6-trihidroxi-3-nitro-benzamida (Sudo K. y colaboradores, *Biochemical and Biophysical Research*

*Communications*, 1997, 238 643-647; Sudo K. y colaboradores, *Antiviral Chemistry and Chemotherapy,* 1998, 9, 186), incluyendo RD3-4082 y RD3-4078, el primero sustituido sobre la amida con una cadena de 14 átomos de carbono, y el último que procesa un grupo *para*-fenoxi-fenilo, que también se están investigando.

Sch 68631, una fenantren-quinona, es un inhibidor de proteasa del virus de hepatitis C (Chu M. y colaboradores, *Tetrahedron Letters* 37:7229-7232, 1996). En otro ejemplo por los mismos autores, Sch 351633, aislado del hongo *Penicillium griseofulvum*, se identificó como un inhibidor de proteasa (Chu M. y colaboradores, *Bioorganic and Medicinal Chemistry Letters* 9:1949-1952). Se ha alcanzado una potencia nanomolar contra la enzima proteasa NS3 del virus de hepatitis C mediante el diseño de inhibidores selectivos basados en la macromolécula eglina c. La eglina c, aislada de la sanguijuela, es un potente inhibidor de varias proteasas de serina, tales como las proteasas A y B de *S. griseus*, ∀-quimiotripsina, quimasa, y subtilisina. Qasim M. A. y colaboradores, *Biochemistry* 36:1598-1607, 1997.

Las patentes de los Estados Unidos de Norteamérica que dan a conocer proteasa para el tratamiento del virus de hepatitis C incluyen, por ejemplo, la Patente de los Estados Unidos de Norteamérica Número 6,004,933 a Spruce y colaboradores (incorporada a la presente como referencia en su totalidad), que da a conocer una clase de inhibidores de proteasa de cisteína para inhibir la endopeptidasa 2 del virus de hepatitis C; la Patente de los

Estados Unidos de Norteamérica Número 5,990,276 a Zhang y colaboradores (incorporada a la presente como referencia en su totalidad), que da a conocer inhibidores sintéticos de la proteasa NS3 del virus de hepatitis; la Patente de los Estados Unidos de Norteamérica Número 5,538,865 a Reyes y colaboradores (incorporada a la presente como referencia en su totalidad). Los péptidos como inhibidores de proteasa de serina NS3 del virus de hepatitis C se dan a conocer en la Publicación Internacional Número WO 02/008251 a Corvas International, Inc., y en las Publicaciones Internacionales Números WO 02/08187 y WO 02/008256 a Schering Corporation (incorporadas a la presente como referencia en su totalidad). Los tripéptidos inhibidores del virus de hepatitis C se dan a conocer en las Patentes de los Estados Unidos de Norteamérica Números 6,534,523, 6,410,531 y 6,420,380 a Boehringer Ingelheim, y en la Publicación Internacional Número WO 02/060926 a Bristol Myers Squibb (incorporadas a la presente como referencia en su totalidad). Los péptidos de diarilo como inhibidores de proteasa de serina NS3 del virus de hepatitis C se dan a conocer en la Publicación Internacional Número WO 02/48172 a Schering Corporation (incorporada a la presente como referencia). Las imidazolidinonas como inhibidores de la proteasa de serina NS3 del virus de hepatitis C, se dan a conocer en la Publicación Internacional Número WO 02/18198 a Schering Corporation, y en la Publicación Internacional Número WO 02/48157 a Bristol Myers Squibb (incorporadas a la presente como referencia en su totalidad). La

Publicación Internacional Número WO 98/17679 a Vertex Pharmaceuticals, y la Publicación Internacional Número WO 02/48116 a Bristol Myers Squibb, también dan a conocer inhibidores de proteasa del virus de hepatitis C (incorporadas a la presente como referencia en su totalidad).

Los inhibidores de proteasa de serina HCV NS3-4A, incluyendo BILN 2061 por Boehringer Ingelheim, VX-950 por Vertex, SCH 6/7 por Schering-Plough, y otros compuestos que están actualmente en desarrollo pre-clínico;

Los inhibidores de proteasa NS3 basados en sustrato, incluyendo alfa-quetoamidas e hidrazino-ureas, y los inhibidores que terminan en un electrófilo, tal como un ácido borónico o fosfonato; los inhibidores de proteasa NS3 no basados en sustrato, tales como los derivados de 2,4,6-trihidroxi-3-nitro-benzamida, incluyendo RD3-4082 y RD3-4078, el primero sustituido sobre la amida con una cadena de 14 átomos de carbono, y el último que procesa un grupo *para*-fenoxi-fenilo, y Sch68631, una fenantren-quinona, un inhibidor de proteasa del virus de hepatitis C.

Sch 351633, aislado del hongo *Penicillium griseofulvum*, se identificó como un inhibidor de proteasa. Eglina c, aislada de la sanguijuela, es un potente inhibidor de varias proteasas de serina, tales como las proteasas A y B de *S. griseus*, a-quimiotripsina, quimasa, y subtilisina.

La Patente de los Estados Unidos de Norteamérica Número 6004933 (incorporada a la presente como referencia en su totalidad)

da a conocer una clase de inhibidores de proteasa de cisteína que inhiben la endopeptidasa 2 del virus de hepatitis C; los inhibidores sintéticos de la proteasa NS3 del virus de hepatitis C (pat), los tripéptidos inhibidores del virus de hepatitis C (pat), los péptidos de diarilo, tales como los inhibidores de proteasa de serina NS3 del virus de hepatitis C (pat), las imidazolindionas como inhibidores de proteasa de serina NS3 del virus de hepatitis C (pat).

Tiazolidinas y benzanilidas (ref). Los derivados de tiazolidina que muestran una inhibición relevante en un ensayo de HPLC de fase inversa con una proteína de fusión NS3/4A y el sustrato NS5A/5B, en especial el compuesto RD-16250, que posee una fracción de cinamoílo fusionada sustituida con una cadena de alquilo larga, RD4 6205 y RD4 6193.

La fenantren-quinona que posee actividad contra la proteasa en un ensayo de SDS-PAGE y de auto-radiografía aislada a partir del caldo de cultivo de fermentación de *Streptomyces sp.*, Sch68631 y Sch351633, aislados del hongo *Penicillium griseofulvum*, que demuestra actividad en un ensayo de proximidad de cintilación.

(7) Los inhibidores de nucleósido y no de nucleósido de la polimerasa de ARN dependiente del ARN de NS5B del virus de hepatitis C, tales como la ribofuranosil-citidina del éster de 2'-C-metil-3'-O-L-valina (Idenix), como se da a conocer en la Publicación Internacional Número WO 2004/002422 A2 (incorporada a la presente como referencia en su totalidad), R803 (Rigel), JTK-003 (Japan Tabacco), HCV-806 (ViroPharma/Wyeth), y otros compuestos

que están actualmente en desarrollo pre-clínico;

Gliotoxina (ref), y el producto natural cerulenina;

2'-fluoro-nucleósidos;

Otros análogos de nucleósidos, como se dan a conocer en las Publicaciones Internacionales Números WO 02/057287 A2, WO 02/057425 A2, WO 01/90121, WO 01/92282, y en la Patente de los Estados Unidos de Norteamérica Número 6,812,219, cuyas divulgaciones se incorporan a la presente como referencia en su totalidad.

Idenix Pharmaceuticals da a conocer el uso de nucleósidos ramificados en el tratamiento de flavivirus (incluyendo el virus de hepatitis C) y pestivirus, en las Publicaciones Internacionales Números WO 01/90121 y WO 01/92282 (incorporadas a la presente como referencia en su totalidad). De una manera específica, un método para el tratamiento de infección por hepatitis C (y flavivirus y pestivirus) en seres humanos y en otros animales huéspedes, se da a conocer en las publicaciones de Idenix, que incluye administrar una cantidad efectiva de un nucleósido B-D ó B-L 1', 2', 3', ó 4'-ramificado biológicamente activo, o una sal farmacéuticamente aceptable o pro-fármaco del mismo, administrado ya sea solo o en combinación con otro agente anti-viral, opcionalmente en un vehículo farmacéuticamente aceptable. Algunos nucleósidos B-D ó B-L 1', 2', 3', ó 4'-ramificados biológicamente activos preferidos, incluyendo Telbivudina, se describen en las Patentes de los Estados Unidos de Norteamérica Números 6,395,716 y 6,875,751, cada una de las

cuales se incorpora a la presente como referencia.

Otras solicitudes de patente que dan a conocer el uso de ciertos análogos de nucleósido para tratar el virus de hepatitis C incluyen: PCT/CA00/01316 (WO 01/32153; presentada el 3 de noviembre de 2000), y PCT/CA01/00197 (WO 01/60315; presentada el 19 de febrero de 2001), presentadas por BioChem Pharma, Inc. (ahora Shire Biochem, Inc.); PCT/US02/01531 (WO 02/057425; presentada el 18 de enero de 2002), y PCT/US02/03086 (WO 02/057287; presentada el 18 de enero de 2002), presentadas por Merck & Co., Inc., PCT/EP01/09633 (WO 02/18404; publicada el 21 de agosto de 2001), presentada por Roche, y las Publicaciones del TCP Números WO 01/79246 (presentada el 13 de abril de 2001), WO 02/32920 (presentada el 18 de octubre de 2001), y WO 02/48165 por Pharmasset, Ltd. (las divulgaciones de las cuales se incorporan a la presente como referencia en su totalidad).

La Publicación del TCP Número WO 99/43691 a Emory University (incorporada a la presente como referencia en su totalidad), titulada como "2'-fluoro-nucleósidos", da a conocer el uso de ciertos 2'-fluoro-nucleósidos para tratar el virus de hepatitis C.

Eldrup y colaboradores (Oral Session V, Hepatitis C Virus, Flaviviridae; 16$^{th}$ International Conferencia on Antiviral Research (27 de abril de 2003, Savannah, GA)), describieron la relación de actividad-estructura de los nucleósidos 2'-modificados para la inhibición del virus de hepatitis C.

Bhat y colaboradores (Oral Session V, Hepatitis C Virus,

Flaviviridae, 2003 (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International conference on Antiviral Research (27 de abril de 2003, Savannah, Ga); p A75) describe la síntesis y las propiedades farmacocinéticas de los análogos de nucleósido como posibles inhibidores de la réplica del ARN del virus de hepatitis C. Los autores reportan que los nucleósidos 2'-modificados demuestran una potente actividad inhibidora en los ensayos de replicones basados en células.

Olsen y colaboradores (Oral Session V, Hepatitis C Virus, Flaviviridae; 16th International Conference on Antiviral Research (27 de abril de 2003, Savannah, Ga) p A76), también describieron los efectos de los nucleósidos 2'-modificados sobre la réplica del ARN del virus de hepatitis C.

(8) Inhibidores de polimerasa de nucleótidos y gliotoxina (Ferrari R. y colaboradores, *Journal of Virology*, 1999, 73, 1649-1654), y el producto natural cerulenina (Lohmann V. y colaboradores, *Virology*, 1998, 249, 108-118);

(9) Inhibidores de helicasa NS3 del virus de hepatitis C, tales como VP_50406 por ViroPhama, y los compuestos de Vertex. Otros inhibidores de helicasa (Diana G. D. y colaboradores, *Compounds, compositions and methods for treatment of hepatitis C*, Patente de los Estados Unidos de Norteamérica Número 5,633,358 (incorporada a la presente como referencia en su totalidad); Diana G. D. y colaboradores, *Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis C*,

Publicación del TCP Número WO 97/36554);

(10) Oligodesoxi-nucleótidos de fosforotioato anti-sentido (S-ODN) complementarios para los estiramientos de secuencia en la región no codificante 5' (NCR) del virus (Alt M. y colaboradores, *Hepatology*, 1995, 22, 707-717), o los nucleótidos 326-348 que comprenden el extremo 3' de la región no codificante, y los nucleótidos 371-388 localizados en la región codificante del núcleo del ARN del virus de hepatitis C (Alt M. y colaboradores, *Archives of Virology*, 1997, 142, 589-599; Galderisi U. y colaboradores, *Journal of Cellular Physiology*, 199, 181, 251-257); tales como ISIS 14803 por Isis Pharm/Elan, anti-sentido por Hybridon, anti-sentido por AVI BioPharma,

(11) Inhibidores de la traducción dependiente de IRES (Ikeda N. y colaboradores, *Agent for the prevention and treatment of hepatitis C,* Publicación de Patente Japonesa Número JP-08268890; Kai Y. y colaboradores, *Prevention and treatment of viral diseases*, Publicación de Patente Japonesa Número JP-10101591), tales como ISIS 14803 por Isis Pharm/Elan, el inhibidor IRES por Anadys, los inhibidores IRES por Immusol, la química de ARN dirigida por PCT Therapeutics.

(12) Ribozimas, tales como las ribozimas resistentes a nucleasa (Maccjak, D. J. y colaboradores, *Hepatology* 1999, 30, extracto 995), y aquéllas mencionadas en la Patente de los Estados Unidos de Norteamérica Número 6,043,077 a Barber y colaboradores, y en las Patentes de los Estados Unidos de

Norteamérica Números 5,869,253 y 5,610,054 a Draper y colaboradores (incorporadas a la presente como referencia en su totalidad), por ejemplo HEPTAZYME por RPI;

(13) El ARNsi dirigido contra el genoma del virus de hepatitis C;

(14) El inhibidor de la réplica del virus de hepatitis C de cualesquiera otros mecanismos, tales como mediante VP50406ViroPharma/Wyeth, inhibidores de Achillion, Arrow;

(15) Un inhibidor de otros objetivos en el ciclo de vida del virus de hepatitis C, incluyendo la entrada viral, el ensamble, y la maduración;

(16) Un agente inmuno-modulador, tal como un inhibidor de IMPDH, ácido micofenólico, una sal o un pro-fármaco del mismo, micofenolato de sodio o micofenolato-mofetil, o Merimebodid (VX-497); timosin-alfa-1 (Zadaxin, por SciClone); o un agonista del receptor S1P, por ejemplo FTY720, o un análogo del mismo, opcionalmente fosforilado;

(17) Un agente anti-fibrótico, tal como un derivado de N-fenil-2-pirimidin-amina, imatinib (Gleevac), IP-501 por Indevus, e interferón gamma 1b de InterMune;

(18) Una vacuna terapéutica por Intercell, Epimmune/Genecor, Merix, Tripep (Chron-VacC), inmunoterapia (Therapore) por Avant, terapia de células-T por CellExSys, anticuerpo monoclonal XTL-002 por STL, ANA 246 y ANA 246 by Anadys;

(19) Otros compuestos varios, incluyendo 1-amino-alquil-ciclohexanos (Patente de los Estados Unidos de Norteamérica Número 6,034,134 a Gold y colaboradores), lípidos de alquilo (Patente de los Estados Unidos de Norteamérica Número 5,922,757 a Chojkier y colaboradores), vitamina E y otros antioxidantes (Patente de los Estados Unidos de Norteamérica Número 5,922,757 a Chojkier y colaboradores), amantadina, ácidos biliares (Patente de los Estados Unidos de Norteamérica Número 5,846,99964 a Ozeki y colaboradores), ácido N-(fosfono-acetil)-L-aspártico, (Patente de los Estados Unidos de Norteamérica Número 5,830,905 a Diana y colaboradores), bencen-dicarboxamidas (Patente de los Estados Unidos de Norteamérica Número 5,633,388 a Diane y colaboradores), derivados de poli-ácido adenílico (Patente de los Estados Unidos de Norteamérica Número 5,496,546 a Wang y colaboradores), 2',3'-didesoxi-inosina (Patente de los Estados Unidos de Norteamérica Número 5,026,687 a Yarchoan y colaboradores), bencimidazoles (Patente de los Estados Unidos de Norteamérica Número 5,891,874 a Colacino y colaboradores), extractos de plantas (Patente de los Estados Unidos de Norteamérica Número 5,837,257 a Tsai y colaboradores, Patente de los Estados Unidos de Norteamérica Número 5,725,859 a Omer y colaboradores, y Patente de los Estados Unidos de Norteamérica Número 6,056,961), y piperidinas (Patente de los Estados Unidos de Norteamérica Número 5,830,905 a Diana y colaboradores); las divulgaciones de las cuales se incorporan a la presente como referencia en su totalidad. También, escualeno,

telbivudina, ácido N-(fosfono-acetil)-L-aspártico, bencen-dicarboxamidas, derivados de poli-ácido adenílico, inhibidores de glicosilación, y agentes citoprotectores no específicos que bloquean la lesión celular causada por infección por virus.

(20) Cualquier otro compuesto actualmente en desarrollo pre-clínico o clínico para el tratamiento del virus de hepatitis C, incluyendo Interleucina-10 (Schering-Plough), AMANTADINE (Symmetrel) por Endo Labs Solvay, inhibidor de caspasa IDN-6556 por Idun Pharma, HCV/MF59 por Chiron, CIVACIR (Inmunoglobulina de Hepatitis C) por NABI, CEPLENE (dicloruro de histamina) por Maxim, IDN-6556 por Idum PHARM, T67, un inhibidor de beta-tubulina, por Tularik, una vacuna terapéutica dirigida a E2 por Innogenetics, FK788 por Fujisawa Helathcare, IdB1016 (Siliphos, fitosoma de silibin-fosfatidil-colina oral), inhibidor de fusión por Trimeris, Dication por Immtech, hemopurificador por Aethlon Medical, UT 231B por United Therapeutics.

(21) Antagonistas de análogos de nucleósido de purina de TIR7 (receptores tipo toll) desarrollados por Anadys, por ejemplo Isotorabina (ANA245) y su pro-fármaco (ANA975), los cuales se describen en las Solicitudes Europeas Números EP348446 y EP636372, en las Publicaciones Internacionales Números WO2004/108687, WO2005/12288, y WO2006/076529, y en la Patente de los Estados Unidos de Norteamérica Número 6/973322, cada una de las cuales se incorpora como referencia.

(22) Inhibidores no de nucleósidos desarrollados por

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Genelabs, y descritos en las Publicaciones Internacionales Números WO2004/108687, WO2005/12288, y WO2006/076529, cada una de las cuales se incorpora como referencia.

(23) Otros co-agentes (por ejemplo, compuestos no inmunomoduladores o inmunomoduladores) que se pueden utilizar en combinación con un compuesto de esta invención incluyen, pero no se limitan a, los especificados en la Publicación Internacional Número WO 02/18369, la cual se incorpora a la presente como referencia.

Los métodos de esta invención también pueden involucrar la administración de otro componente que comprenda un agente adicional seleccionado a partir de un agente inmunomodulador; un agente anti-viral; un inhibidor de la proteasa del virus de hepatitis C; un inhibidor de otro objetivo en el ciclo de vida del virus de hepatitis C; un inhibidor del citocromo P450; o combinaciones de los mismos.

De conformidad con lo anterior, en otra modalidad, esta invención proporciona un método que comprende administrar un compuesto de la invención y otro agente anti-viral, de preferencia un agente contra el virus de hepatitis C. Estos agentes anti-virales incluyen, pero no se limitan a, agentes inmunomoduladores, tales como los interferones $\alpha$, $\beta$, y $\delta$, compuestos de interferón-a derivados pegilados, y timosina; otros agentes anti-virales, tales como ribavirina, amantadina, y telbivudina; otros inhibidores de proteasas de hepatitis C (inhibidores de NS2-NS3 e inhibidores de NS3-NS4A); inhibidores de otros objetivos en el ciclo de vida del virus de

hepatitis C, incluyendo inhibidores de helicasa, polimerasa, y metaloproteasa; inhibidores de la entrada del ribosoma interno; inhibidores virales de amplio espectro, tales como inhibidores de IMPDH (por ejemplo, los compuestos de las Patentes de los Estados Unidos de Norteamérica Números 5,807,876; 6,498,178; 6,344,465; 6,054,472; las Publicaciones Internacionales Números WO 97/40028, WO 98/40381, WO 00/56331, y el ácido micofenólico y sus derivados, e incluyendo, pero no limitándose a, VX-497, VX-148, y/o VX-944), o combinaciones de cualquiera de los anteriores.

De conformidad con lo anterior, la presente invención proporciona, en un aspecto todavía adicional:

• Una combinación farmacéutica que comprende: a) un primer agente que es un compuesto de la invención, por ejemplo un compuesto de la Fórmula I ó cualesquiera sub-fórmulas de la misma, y b) un co-agente, por ejemplo un segundo agente de fármaco como se define anteriormente.

• Un método como se define anteriormente, el cual comprende la co-administración, por ejemplo de una manera concomitante o en secuencia, de una cantidad terapéuticamente efectiva de un compuesto de la invención, por ejemplo un compuesto de la Fórmula I ó cualesquiera sub-fórmulas de la misma, y un co-agente, por ejemplo un segundo agente de fármaco como se define anteriormente.

Los términos "co-administración" o "administración combinada", o similares, como se utilizan en la presente, pretenden

abarcar la administración de agentes terapéuticos seleccionados a un solo paciente, y pretenden incluir regímenes de tratamiento en donde los agentes no necesariamente se administran por la misma vía de administración o al mismo tiempo. Las combinaciones fijas también están dentro del alcance de la presente invención. La administración de una combinación farmacéutica de la invención da como resultado un efecto benéfico, por ejemplo un efecto terapéutico sinérgico, comparándose con una monoterapia aplicando solamente uno de sus ingredientes farmacéuticamente activos.

Cada componente de una combinación de acuerdo con esta invención se puede administrar por separado, junto, o en cualquier combinación del mismo. Como es reconocido por los practicantes expertos, las dosificaciones del interferón típicamente se miden en Unidades Internacionales (por ejemplo, de aproximadamente 4 millones de Unidades Internacionales a aproximadamente 12 millones de Unidades Internacionales).

Si se selecciona un agente adicional a partir de otro inhibidor del citocromo P450, por consiguiente, el método emplearía dos o más inhibidores del citocromo P450. Cada componente se puede administrar en una o más formas de dosificación. Cada forma de dosificación se puede administrar al paciente en cualquier orden.

El compuesto de la invención y cualquier agente adicional se pueden formular en formas de dosificación separadas. De una manera alternativa, para reducir el número de formas de dosificación administradas a un paciente, el compuesto de la invención y

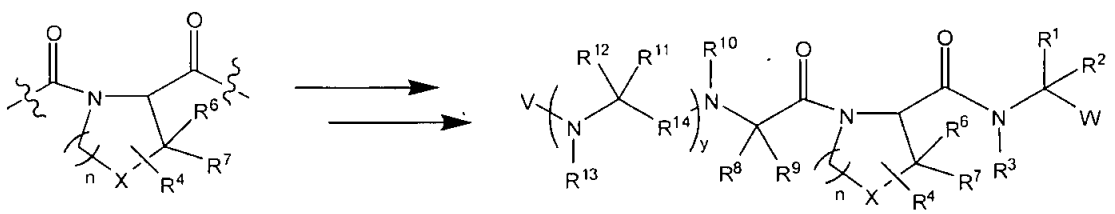
cualquier agente adicional se pueden formular juntos en cualquier combinación. Por ejemplo, el compuesto del inhibidor de la invención se puede formular en una forma de dosificación, y el agente adicional se puede formular junto en otra forma de dosificación. Cualesquiera formas de dosificación separadas se pueden administrar al mismo tiempo o en diferentes tiempos.

De una manera alternativa, una composición de esta invención comprende un agente adicional como se describe en la presente. Cada componente puede estar presente en composiciones individuales, composiciones de combinación, o en una sola composición.

### *Ejemplificación de la Invención*

La invención se ilustra adicionalmente mediante los siguientes Ejemplos, los cuales no deben interpretarse como una limitación adicional. Los ensayos utilizados a través de todos los Ejemplos están aceptados. La demostración de eficacia en estos ensayos es predictiva de la eficacia en los sujetos.

### MÉTODOS GENERALES DE SÍNTESIS



Todos los materiales de partida, bloques de construcción, reactivos, ácidos, bases, agentes deshidratantes, solventes, y catalizadores utilizados para la síntesis de los compuestos de la presente invención, están comercialmente disponibles, o se pueden

producir mediante los métodos de síntesis orgánica conocidos por un experto ordinario en este campo (Houben-Weyl, 4ª Edición, 1952, Methods of Organic Synthesis, Thieme, Volumen 21). Además, los compuestos de la presente invención se pueden producir mediante los métodos de síntesis orgánica conocidos por un experto ordinario en la materia, como se muestra en los siguientes Ejemplos.

**LISTA DE ABREVIATURAS**

| | |
|---|---|
| Ac | Acetilo. |
| ACN | Acetonitrilo. |
| AcOEt / EtOAc | Acetato de etilo. |
| AcOH | Ácido acético. |
| ac | Acuoso. |
| Ar | Arilo. |
| Bn | Bencilo. |
| Bu | Butilo (nBu = n-butilo, tBu = terbutilo). |
| CDI | Carbonil-di-imidazol. |
| $CH_3CN$ | Acetonitrilo. |
| DBU | 1,8-diazabiciclo-[5.4.0]-undec-7-eno. |
| DCE | 1,2-dicloro-etano. |
| DCM | Dicloro-metano. |
| DIPEA | N-etil-di-isopropil-amina. |
| DMAP | Dimetil-amino-piridina. |
| DMF | N,N'-dimetil-formamida. |
| DMSO | Sulfóxido de dimetilo. |
| EI | Ionización por electropulverización. |

| | |
|---|---|
| $Et_2O$ | Dietil-éter. |
| $Et_3N$ | Trietil-amina. |
| Éter | Dietil-éter. |
| EtOH | Etanol. |
| FC | Cromatografía por evaporación instantánea. |
| h | Hora(s). |
| HATU | Hexafluorofosfato de O-(7-azabenzo-triazol-1-il)-N,N,N'N'-tetrametil-uronio. |
| HBTU | Hexafluorofosfato de O-(benzotriazol-1-il)-N,N,N',N'-tetrametil-uronio. |
| HCl | Ácido clorhídrico. |
| HOBt | 1-hidroxi-benzotriazol. |
| HPLC | Cromatografía de líquidos de alto rendimiento |
| $H_2O$ | Agua. |
| L | Litro(s). |
| LC-MS | Cromatografía de líquidos-espectrometría de masas. |
| Me | Metilo. |
| MeI | Yodo-metano. |
| MeOH | Metanol. |
| mg | Miligramos. |
| min | Minuto(s). |
| mL | Mililitros. |

| | |
|---|---|
| MS | Espectrometría de masas. |
| Pd/C | Paladio sobre carbón. |
| PG | Grupo protector. |
| Ph | Fenilo. |
| Prep | Preparación. |
| Rf | Proporción de frentes. |
| RP | Fase inversa. |
| Rt | Tiempo de retención. |
| rt | Temperatura ambiente. |
| $SiO_2$ | Gel de sílice. |
| TBAF | Fluoruro de tetrabutil-amonio. |
| TEA | Trietil-amina. |
| TFA | Ácido trifluoro-acético. |
| THF | Tetrahidrofurano. |
| TLC | Cromatografía de capa delgada. |

**Métodos de HPLC:**

**Método A**

HPLC

Instrumento: Sistema Agilent.

Columna: Waters Symmetry C18, 3.5 micras, 2.1 x 50 milímetros, flujo de 0.6 mililitros/minuto.

Solvente: $CH_3CN$ (0.1% $CF_3CO_2H$); $H_2O$ (0.1% $CF_3CO_2H$).

Gradiente: 0-3.5 minutos: del 20 al 95 por ciento de $CH_3CN$, 3.5-5 minutos: 95 por ciento de $CH_3CN$, 5.5-5.55

minutos: del 95 por ciento al 20 por ciento de $CH_3CN$

**Método B:**

Sistema cromatográfico Agilent 1100 LC con detección de Micromass ZMD MS. Un gradiente binario compuesto de A (agua conteniendo el 5 por ciento de acetonitrilo y el 0.05 por ciento de ácido trifluoro-acético), y B (acetonitrilo conteniendo el 0.045 por ciento de ácido trifluoro-acético) se utiliza como una fase móvil sobre una columna Waters X Terra$^{MR}$ C-18 (30 x 3 milímetros, tamaño de partículas de 2.5 micras) como una fase estacionaria.

Se aplica el siguiente perfil de elución: Un gradiente lineal de 3.5 minutos a una velocidad de flujo de 0.6 mililitros/minuto, desde el 5 por ciento de B hasta el 95 por ciento de B, seguido por una elución isocrática de 0.5 minutos a una velocidad de flujo de 0.7 mililitros/minuto, del 95 por ciento de B, seguida por una elución isocrática de 0.5 minutos a una velocidad de flujo de 0.8 mililitros/minuto del 95 por ciento de B, seguida por un gradiente lineal de 0.2 minutos a una velocidad de flujo de 0.8 mililitros/minuto desde el 95 por ciento hasta el 5 por ciento de B, seguido por una elución isocrática de 0.2 minutos a una velocidad de flujo de 0.7 mililitros/minuto del 5 por ciento de B.

**Método C:**

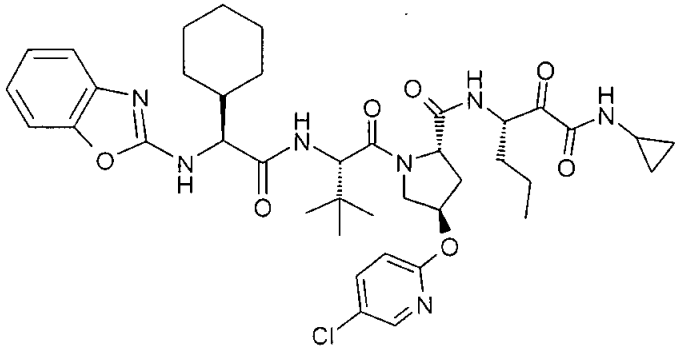
HPLC

Instrumento: Kontron, Kroma-System.

Columna: Macherey-Nagel, Lichrosphere 100-5 RP 18.

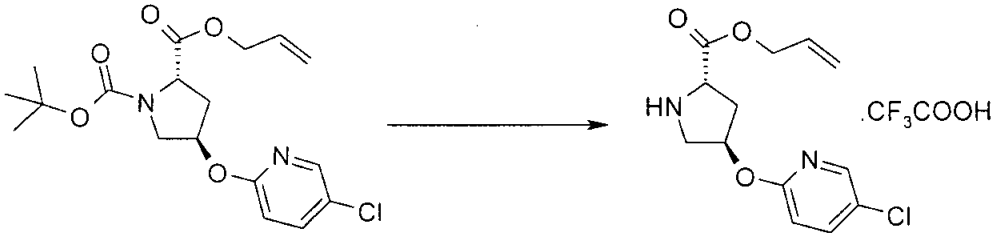
Solvente: $CH_3CN$ (0.1% $CF_3CO_2H$); $H_2O$ (0.1% $CF_3CO_2H$).

**Ejemplo 1:**



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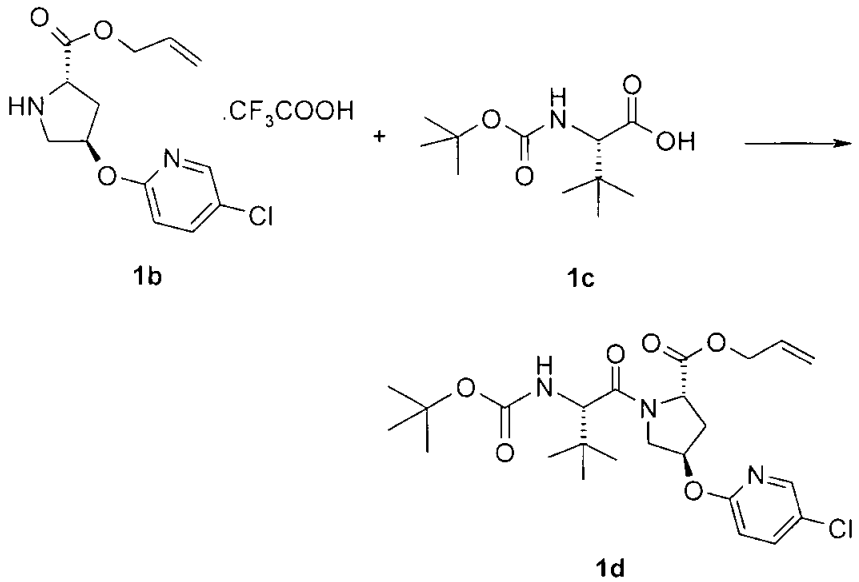
**Paso 1-A:**



1a 1b

A una solución del 1a (3.0 gramos, 7.84 milimoles) en dicloro-metano (20 mililitros) a temperatura ambiente, se le agrega ácido trifluoro-acético (20 mililitros). La mezcla se agita durante 3 horas, después de lo cual el solvente se evapora al vacío, para dar el producto deseado (4.5 gramos). m/z encontrada ES+ = 283 y ES- = 281.

**Paso 1-B:**



1b 1c

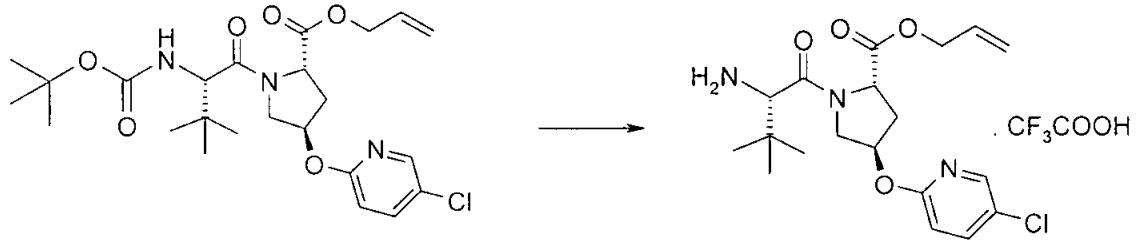


1d

Una solución del 1c (2.18 gramos, 9.45 milimoles) en dicloro-metano anhidro (57 mililitros) y N,N'-dimetil-formamida anhidra (57 mililitros), se agita a 0 °C, y se agrega hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.4 equivalentes, 5.0 gramos, 13.23 milimoles). El 1b (1.2 equivalentes, 4.50 gramos, 11.34 milimoles) se agrega en pequeñas porciones. Entonces, se agrega por goteo N-metil-morfolina (4.0 equivalentes, 3.82 gramos, 37.8 milimoles). La mezcla de reacción se calienta gradualmente a temperatura ambiente y se agita durante la noche. Todos los volátiles se remueven al vacío y el residuo se disuelve en acetato de etilo. La capa orgánica se lava con agua, solución acuosa de HCl 1.0N, solución acuosa saturada de $NaHCO_3$, y salmuera. La capa orgánica se seca sobre $Na_2SO_4$, se filtra y se concentra al vacío. El residuo se pasa por cromatografía sobre gel de sílice (gradiente: acetona/hexano; 2:8 a 1:1) para proporcionar el

1d (3.11 gramos). m/z encontrada ES+ = 496.

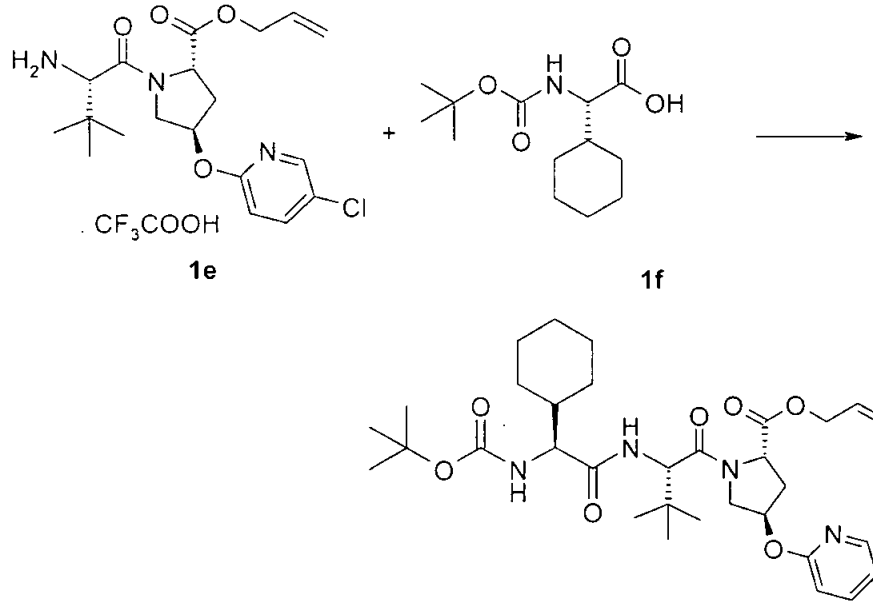
**Paso 1-C:**



**1d** **1e**

A una solución del 1d (3.1 gramos, 6.25 milimoles) en dicloro-metano (15 mililitros) a temperatura ambiente, se le agrega ácido trifluoro-acético (15 mililitros). La mezcla se agita durante 3 horas, después de lo cual el solvente se evapora al vacío para dar 4.7 gramos del 1e. m/z encontrada ES+ = 396.

**Paso 1-D:**

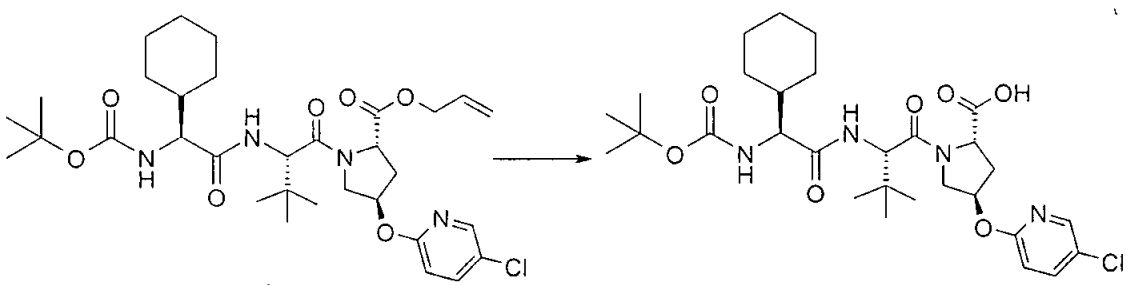


**1e** **1f** **1g**

Una solución de la Boc-L-2-ciclohexil-glicina 1f (2.0 gramos, 7.79 milimoles) en dicloro-metano anhidro (40 mililitros) y N,N'-

dimetil-formamida anhidra (40 mililitros) se agita a 0 °C y se trata con hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.4 equivalentes, 4.14 gramos, 10.90 milimoles). El 1e (1.2 equivalentes, 4.77 gramos, 9.35 milimoles) se agrega en pequeñas porciones. Entonces, se agrega por goteo N-metil-morfolina (4.0 equivalentes, 3.15 gramos, 31.16 milimoles). La mezcla de reacción se calienta gradualmente a temperatura ambiente y se agita durante la noche. Todos los volátiles se remueven al vacío y el residuo se disuelve en acetato de etilo. La capa orgánica se lava con agua, solución acuosa de HCl 1.0N, solución acuosa saturada de $NaHCO_3$, y salmuera. La capa orgánica se seca sobre $Na_2SO_4$, se filtra y se concentra al vacío. El residuo se pasa por cromatografía sobre gel de sílice (gradiente: acetona/hexano; 2:8 a 1:1) para proporcionar 3.0 gramos del 1g. m/z encontrada ES+ = 635.

**Paso 1-E:**

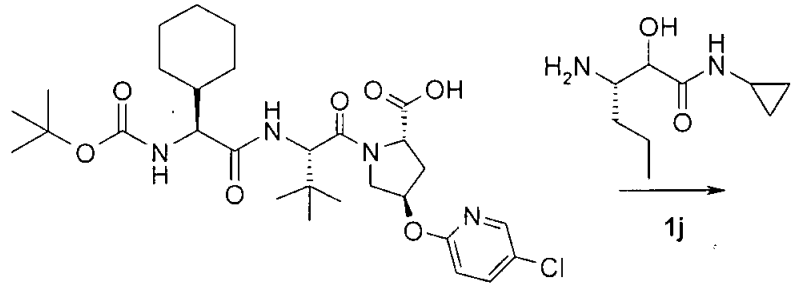


1g 1h

A una solución del 1g (3.0 gramos, 4.72 milimoles) en 45 mililitros de una mezcla de 1:1:1 de tetrahidrofurano/MeOH/agua, se le agrega monohidrato de hidróxido de litio (2 equivalentes, 394 miligramos). La mezcla se agita durante la noche. Todos los

volátiles se evaporan al vacío y al residuo se le agrega diclorometano (100 mililitros). El pH de la capa acuosa se ajusta a un pH de 5 con la adición por goteo de una solución acuosa de HCl 1.0N. Las capas se separan, y la capa acuosa se extrae con diclorometano. Las capas orgánicas combinadas se secan ($Na_2SO_4$), se filtran, y se concentran, para proporcionar 1.87 gramos del 1h (1.87 gramos). m/z encontrada ES+ = 595 y ES- = 593

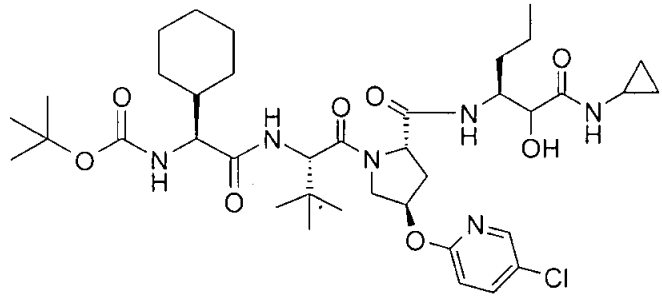
**Paso 1-F:**



1i



1j

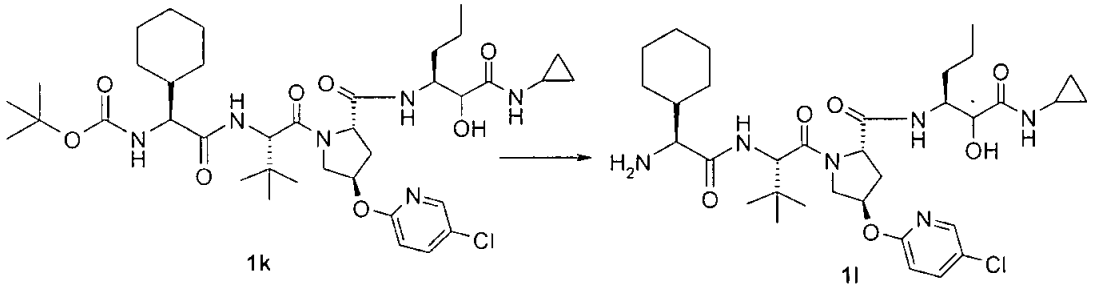


1k

Una solución del 1i (2.80 gramos, 4.7 milimoles) en diclorometano anhidro (24 mililitros) y N,N'-dimetil-formamida anhidra (24 mililitros) se agita a 0 °C, y se trata con hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.4 equivalentes, 2.5 gramos, 6.58 milimoles). La hidroxi-quetoamida-amina 1j (1.2

equivalentes, 1.05 gramos, 5.66 milimoles) se agrega en pequeñas porciones. Entonces, se agrega por goteo N-metil-morfolina (4.0 equivalentes, 1.90 gramos, 18.80 milimoles). La mezcla de reacción se calienta gradualmente a temperatura ambiente y se agita durante la noche. Todos los volátiles se remueven al vacío y el residuo se disuelve en acetato de etilo. La capa orgánica se lava con agua, solución acuosa de HCl 1.0N, solución acuosa saturada de $NaHCO_3$, y salmuera. La capa orgánica se seca sobre $Na_2SO_4$, se filtra y se concentra al vacío. El residuo se pasa por cromatografía sobre gel de sílice (gradiente: acetona/hexano; 2:8 a 1:1) para proporcionar 3.0 gramos del 1k. m/z encontrada ES+ = 763 y ES- = 761.

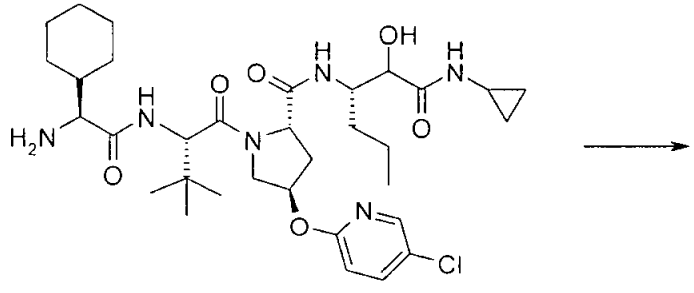
**Paso 1-G:**



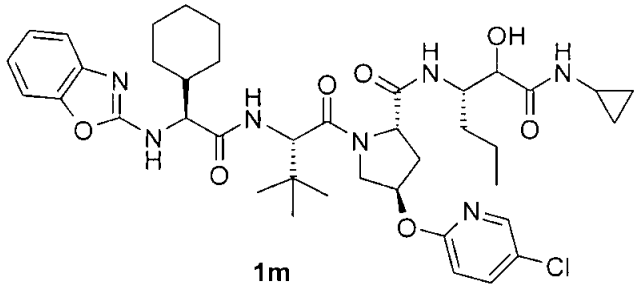

A una solución del 1k (4.0 gramos, 5.24 milimoles) en dicloro-metano (26 mililitros) a temperatura ambiente, se le agrega ácido trifluoro-acético (26 mililitros). La mezcla se agita durante 3 horas, después de lo cual el solvente se evapora al vacío, y al residuo se le agrega dicloro-metano (100 mililitros). The pH se ajusta a 8 mediante la adición por goteo de una solución acuosa saturada de $NaHCO_3$. Las capas se separan. La capa orgánica se lava con salmuera, se seca sobre $Na_2SO_4$, se filtra y se concentra,

para dar 4.0 gramos del 1l (4.0 gramos). m/z encontrada ES+ = 663 y ES- = 661.

**Paso 1-H:**



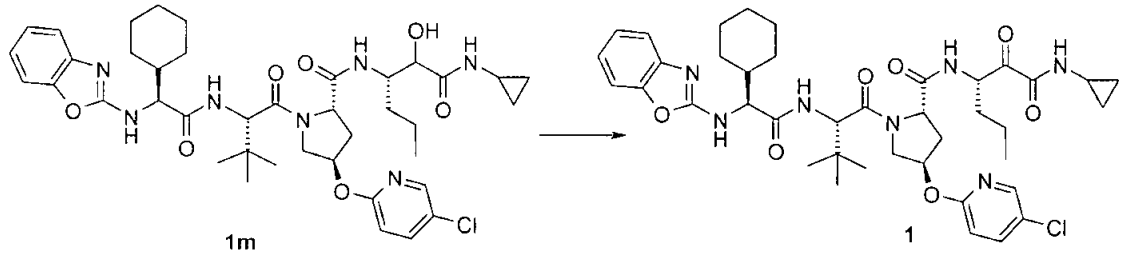
1l



1m

A una solución del 1l (350 miligramos, 0.53 milimoles) en dioxano (1.0 mililitros) a temperatura ambiente, se le agregan 2-cloro-benzoxazol (122 miligramos, 0.79 milimoles) y $NaHCO_3$ (89 miligramos, 1.1 milimoles). Las mezclas se agitan a 65 °C durante 6 horas. Entonces la mezcla se carga directamente en una columna de gel de sílice, y se eluye con hexano/EtOH (de 95/5 a 85/15) para dar 360 miligramos del 1m. m/z encontrada ES+ = 780 y ES- = 778.

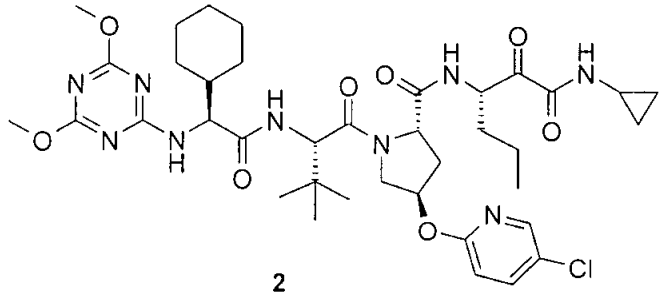
**Paso 1-I:**



1m 1

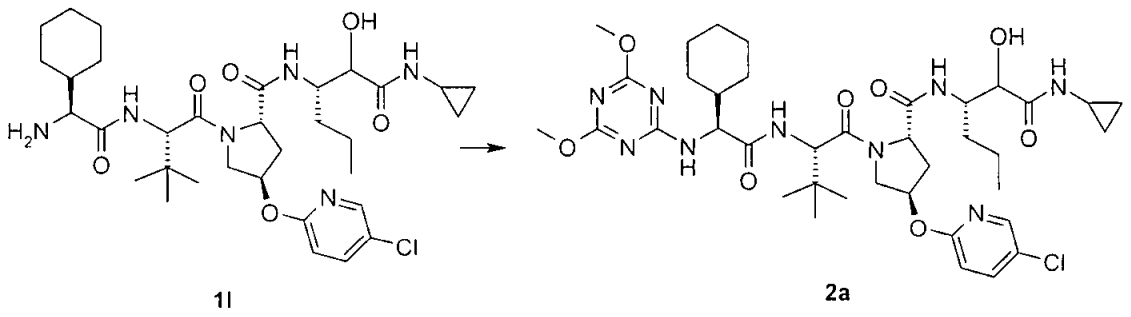
A una solución del 1m (253 miligramos, 0.32 milimoles) en $CH_2Cl_2$ (1.6 mililitros) a 0 °C, se le agrega N-etil-di-isopropil-amina (1.3 milimoles, 168 miligramos) seguida por una solución de sulfóxido de piridina (0.65 milimoles, 103 miligramos) en sulfóxido de dimetilo (1.6 mililitros). La solución se agita a 0 °C durante 10 minutos. A la solución se le agrega EtOAc y una solución acuosa saturada de $NH_4Cl$. Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/Acetona, 1/1), para dar 245 miligramos del 1. m/z encontrada en ES+ 778, m/z en ES- = 776.

**Ejemplo 2:**



2

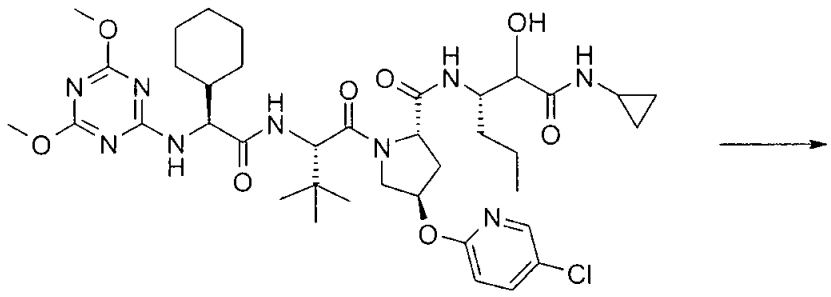
**Paso 2-A:**



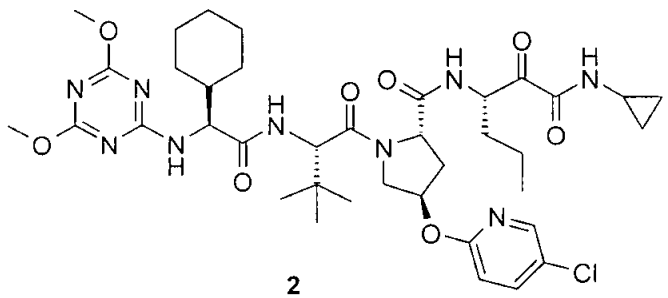
1l 2a

A una solución de la amina 1l (50 miligramos, 0.07 milimoles) en dioxano (350 mililitros) a temperatura ambiente, se le agregan 2-cloro-4,6-dimetoxi-triazina (20 miligramos, 0.11 milimoles) y $NaHCO_3$ (13 miligramos, 0.16 milimoles). Las mezclas se agitan a 80 °C durante 2 horas. La mezcla de reacción se concentra al vacío y al residuo se agrega acetato de etilo (30 mililitros). La capa orgánica se lava con solución acuosa de HCl 1.0N, solución acuosa saturada de $NaHCO_3$ y salmuera. Entonces la solución orgánica se seca sobre sulfato de sodio y se concentra. La purificación empleando cromatografía de capa delgada de preparación (eluyente: Acetona/hexano, 1:1) proporciona 48 miligramos del 2a. m/z encontrada ES+ = 802 y ES- = 800.

**Paso 2-B:**



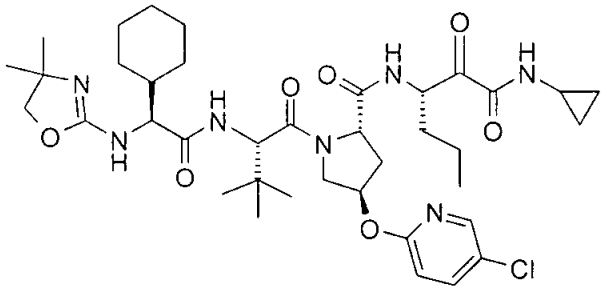
2a



2

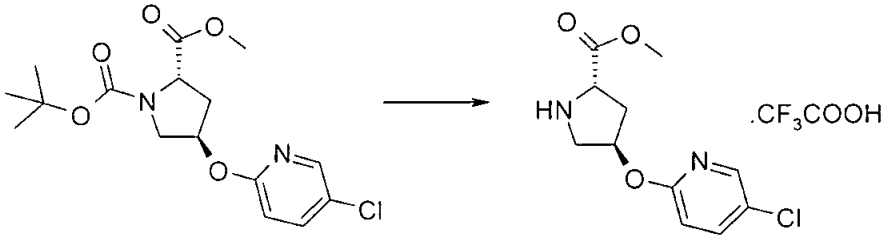
Una solución del 2a (48 miligramos, 0.06 milimoles) en dicloro-metano anhidro (0.6 mililitros) se trata con DMP (2.0 equivalentes, 51 miligramos). La mezcla de reacción se agita a temperatura ambiente durante 30 minutos. A la mezcla se le agrega una solución acuosa de tiosulfato de sodio 1.0 M (2 mililitros) y las mezclas resultantes se agitan durante 5 minutos. Se agrega una solución acuosa saturada de bicarbonato de sodio (2 mililitros) y se continúa la agitación durante otros 10 minutos. Las fases se separan y la capa acuosa se extrae con dicloro-metano. La capa orgánica combinada se seca sobre sulfato de sodio, se filtra y se concentra. El residuo se pasa por cromatografía empleando cromatografía de capa delgada de preparación en gel de sílice (Eluyente: acetona/hexanos, 4:6) para proporcionar 36 miligramos del 2. m/z encontrada ES+ = 800.

**Ejemplo 3:**



3

**Paso 3-A:**

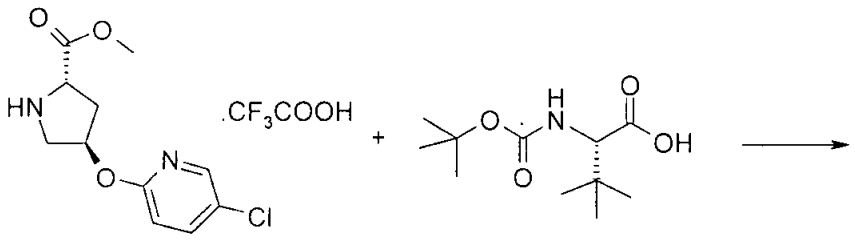


3a 3b

A una solución del 3a (2.5 gramos, 7.0 milimoles) en dicloro-metano (6.0 mililitros) a temperatura ambiente, se le agrega ácido trifluoro-acético (6 mililitros). La mezcla se agita durante 3 horas, después de lo cual el solvente se evapora al vacío para dar 4.0 gramos del 3b. m/z encontrada ES+ = 257.

**Paso 3-B:**

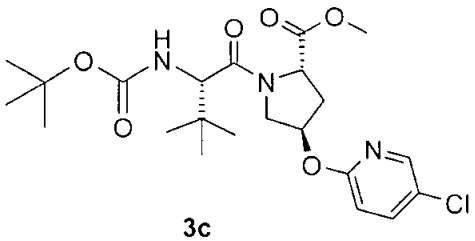
661



3b



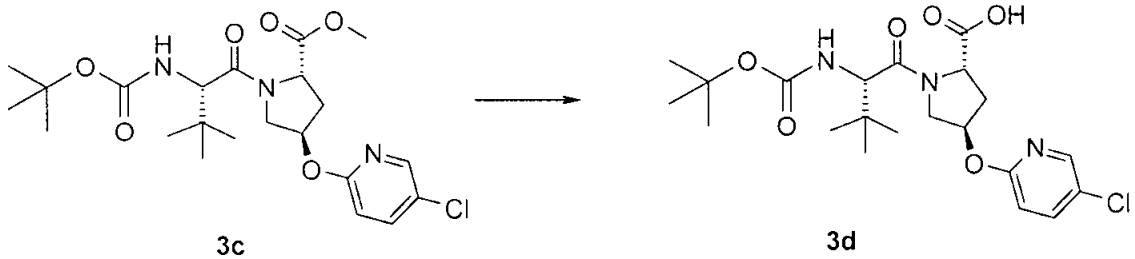
1c



3c

Una solución del 1c (219 miligramos, 2.68 milimoles) en dicloro-metano anhidro (13 mililitros) y N,N'-dimetil-formamida anhidra (13 mililitros) se agita a 0 °C y se trata con hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.4 equivalentes, 1.42 gramos, 3.75 milimoles). Se agrega el 3b (1.0 equivalentes, 0.99 gramos, 2.67 milimoles) en pequeñas porciones. Entonces, se agrega por goteo N-metil-morfolina (4.0 equivalentes, 1.08 gramos, 10.7 milimoles). La mezcla de reacción se calienta gradualmente a temperatura ambiente y se agita durante la noche. Todos los volátiles se remueven al vacío y el residuo se disuelve en acetato de etilo. La capa orgánica se lava con agua, solución acuosa de HCl 1.0N, solución acuosa saturada de bicarbonato de sodio, y salmuera. La capa orgánica se seca sobre $Na_2SO_4$, se filtra y se concentra al vacío. El residuo se pasa por cromatografía sobre gel de sílice (gradiente: EtOAc/Hexano, 1:1)) para proporcionar el 1.3 gramos del 3c. m/z encontrada ES+ = 470.

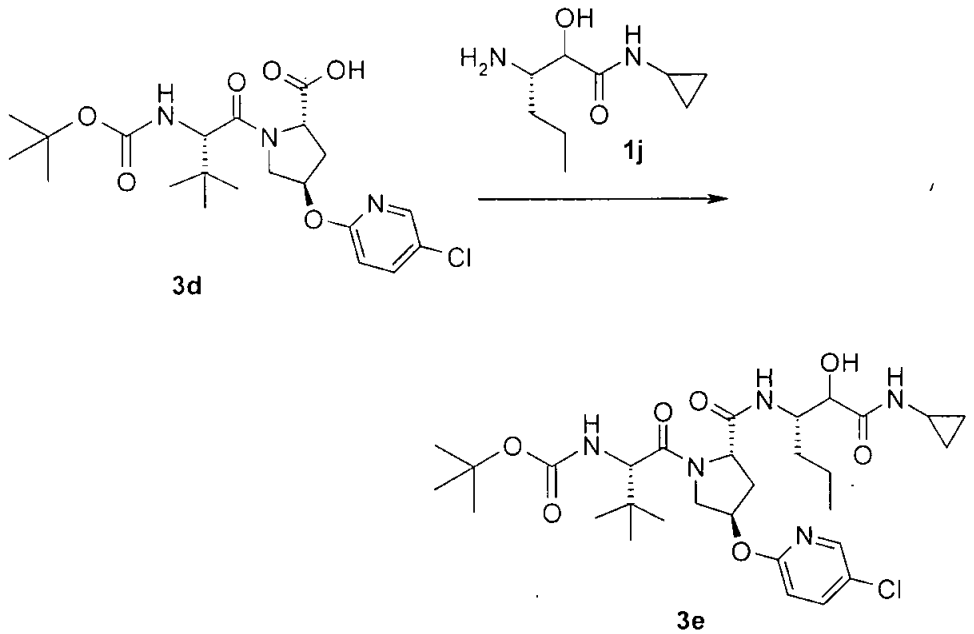
**Paso 3-C:**



3c 3d

A una solución del 3c (1.2 gramos, 2.55 milimoles) en 12 mililitros de una mezcla de 1:1:1 de tetrahidrofurano/MeOH/agua, se le agrega monohidrato de hidróxido de litio (2.0 equivalentes, 214 miligramos). La mezcla se agita durante la noche. Todos los volátiles se evaporan al vacío y al residuo se le agrega dicloro-metano. El pH de la capa acuosa se ajusta a 5 con la adición por goteo de solución acuosa de HCl 1.0N y se separan las capas. La capa acuosa se extrae con dicloro-metano. Las capas orgánicas combinadas se secan sobre sulfato de sodio, se filtran, y se concentran, para proporcionar 822 miligramos del 3d. m/z encontrada ES+ = 456 y ES- = 454.

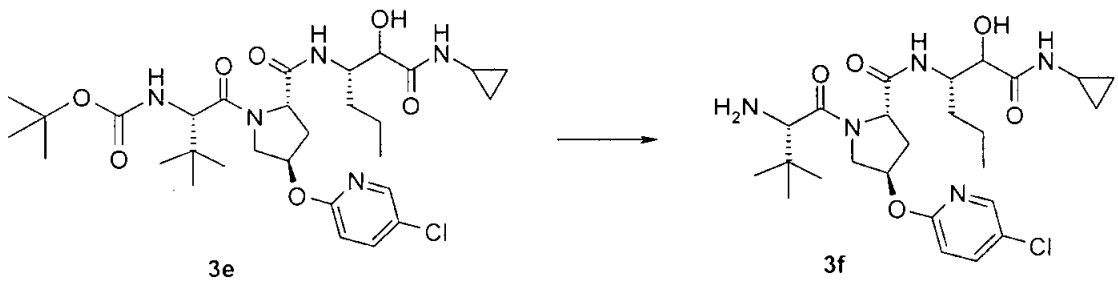
**Paso 3-D:**




Una solución del 3d (822 miligramos, 1.8 milimoles) en dicloro-metano anhidro (4.5 mililitros) y N,N'-dimetil-formamida anhidra (4.5 mililitros) se agita a 0 °C y se trata con hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.4 equivalentes, 962 miligramos, 2.53 milimoles). Se agrega el 1j (1.0 equivalentes, 335 miligramos, 1.8 milimoles) en pequeñas porciones. Entonces, se agrega por goteo N-metil-morfolina (4.0 equivalentes, 731 miligramos, 7.23 milimoles). La mezcla de reacción se calienta gradualmente a temperatura ambiente y se agita durante la noche. Todos los volátiles se remueven al vacío y el residuo se disuelve en acetato de etilo. La capa orgánica se lava con agua, solución acuosa de HCl 1.0N, solución acuosa saturada de bicarbonato de sodio, y salmuera. La capa orgánica se seca sobre $Na_2SO_4$, se filtra y se concentra al vacío. El residuo se pasa por cromatografía sobre gel de sílice (gradiente: acetona/Hexanos, 3:7) para proporcionar

800 miligramos del 3e. m/z encontrada ES+ = 624.

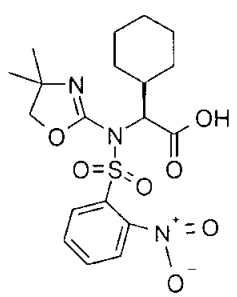
**Paso 3-E:**



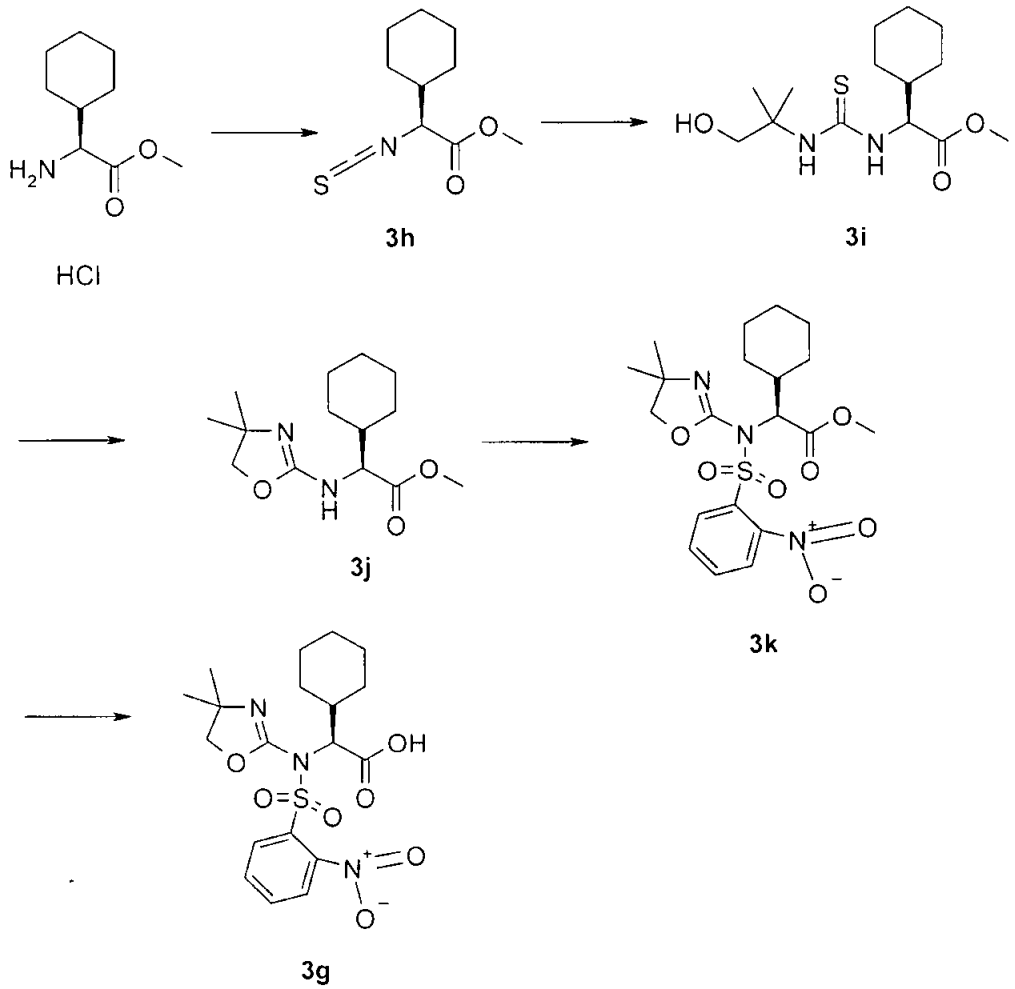
3e 3f

A una solución del 3e (800 miligramos, 1.28 milimoles) en dicloro-metano (3.5 mililitros) a temperatura ambiente, se le agrega ácido trifluoro-acético (3.5 mililitros). La mezcla se agita durante 3 horas, después de lo cual el solvente se evapora al vacío y al residuo se le agrega dicloro-metano. The pH se ajusta a 8 mediante la adición por goteo de una solución acuosa saturada de bicarbonato de sodio. Las capas se separan. La capa orgánica se lava con salmuera, se seca sobre $Na_2SO_4$, y se concentra para dar el 3f. m/z encontrada ES+ = 524.

**Paso 3-F:**



3g




A mezclas de H-ciclohexil-gly-OMe•HCl (2.07 gramos, 10 milimoles) en $CH_2Cl_2$ (100 mililitros) y una solución acuosa saturada de $NaHCO_3$ (100 mililitros) a temperatura ambiente, se les agrega $CSCl_2$ (0.804 mililitros, 10 milimoles). La mezcla se agita a temperatura ambiente durante 30 minutos. Las dos fases se separan, y la capa acuosa se extrae con $CH_2Cl_2$. Las capas orgánicas se combinan, se secan sobre $Na_2SO_4$ y se concentran, para dar 2.1 gramos del 3h, el cual se continúa hasta el siguiente paso sin mayor purificación.

A una solución del 2-amino-2-metil-1-propanol (178

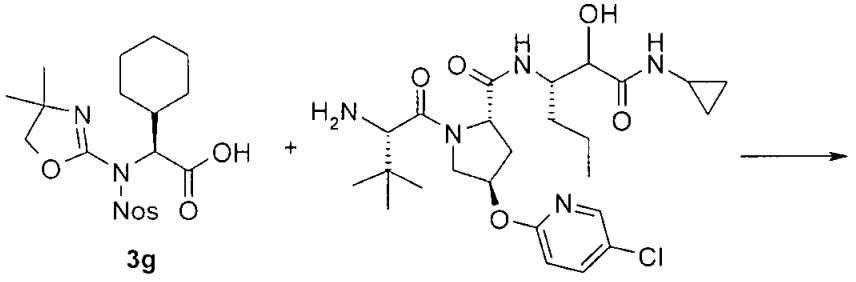
miligramos, 2.0 milimoles) en tetrahidrofurano (2.0 mililitros) se le agrega el 3h (426 miligramos, 2.0 milimoles). La solución se agita a temperatura ambiente durante 12 horas, después de lo cual, se evapora el solvente. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOAc, 2/1) para dar 438 miligramos del 3i. m/z encontrada en ES+ = 303, m/z en ES- = 301.

A una solución del 3i (60 miligramos, 0.2 milimoles) en $CH_3CN$ (2.0 mililitros) a 0 °C se le agrega una solución del tetra-fluoro-borato de 2-cloro-3-etil-benzoxazolio (81 miligramos, 0.3 milimoles, 1.5 equivalentes) en $CH_3CN$ (1.0 mililitros). La solución se agita a temperatura ambiente durante 30 minutos, después de lo cual, se agrega trietil-amina (0.139 mililitros, 1.0 milimoles, 5.0 equivalentes), y la solución se agita a temperatura ambiente durante otros 30 minutos. Entonces se evapora el solvente, y el residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOAc, 4/1 a 0/1) para dar 40 miligramos del 3j. m/z encontrada en ES+ = 269.

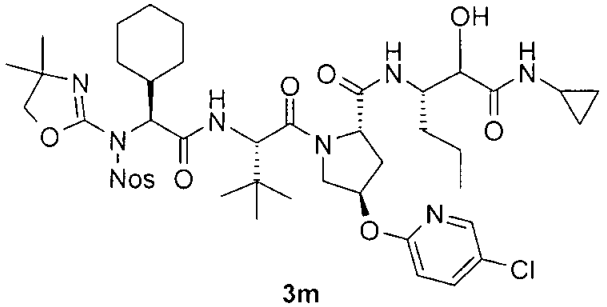
A una solución del 3j (57 miligramos, 0.2 milimoles) en $CH_2Cl_2$ (0.2 mililitros) se le agregan trietil-amina (0.056 mililitros, 0.4 milimoles, 2.0 equivalentes), cloruro de 2-nitro-bencen-sulfonilo (66 miligramos, 0.3 milimoles, 1.5 equivalentes) y dimetil-amino-piridina (10 miligramos). La solución se agita a temperatura ambiente durante 4 horas. Las mezclas se cargan entonces directamente a una columna de gel de sílice, y se inundan con hexano/EtOAc (9/1 a 1/1) para dar 67 miligramos del 3k. m/z encontrada en ES+ = 454.

A una solución del 3k (40 miligramos) en tetrahidrofurano (0.3 mililitros), y MeOH (0.3 mililitros) a 0 °C, se le agrega una solución de $LiOH \cdot H_2O$ (12 miligramos) en agua (0.3 mililitros). La solución se agita a temperatura ambiente durante 8 horas, después de lo cual, se agrega una solución acuosa de HCl 1.0N. Las mezclas se extraen con $CH_2Cl_2$. La capa orgánica combinada se seca sobre $Na_2SO_4$ y se concentra para dar el 3g. m/z encontrada en ES+ = 440, m/z en ES- = 438.

**Paso 3-G:**



3g + 3l

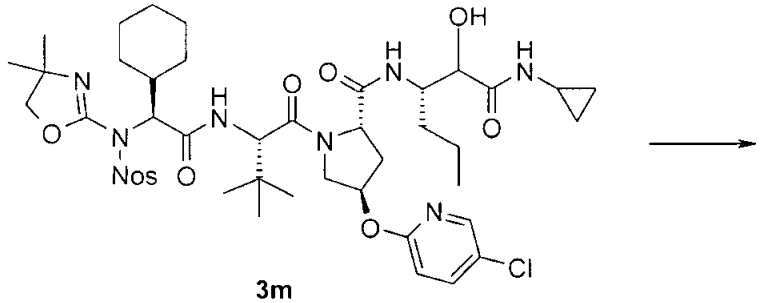


3m

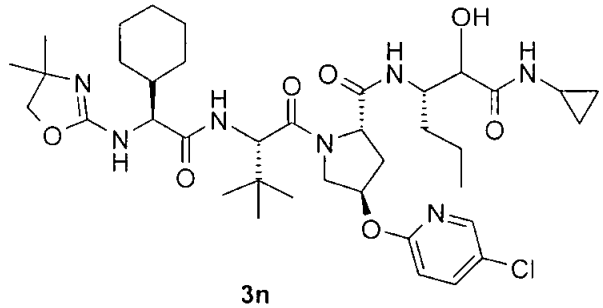
Una solución del ácido 3g (47 miligramos, 0.11 milimoles) en dicloro-metano anhidro (0.5 mililitros) y N,N'-dimetil-formamida anhidra (0.5 mililitros) se agita a 0 °C y se trata con hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.4 equivalentes, 57 miligramos, 0.15 milimoles). A la solución, se le

agrega el 3f (1.2 equivalentes, 62 miligramos, 0.12 milimoles) en pequeñas porciones. Entonces, se agrega por goteo N-metil-morfolina (4.0 equivalentes, 0.047 mililitros, 0.43 milimoles). La mezcla de reacción se calienta gradualmente a temperatura ambiente y se agita durante la noche. Todos los volátiles se remueven al vacío y el residuo se disuelve en acetato de etilo. La capa orgánica se lava con agua, solución acuosa de HCl 1.0N, solución acuosa saturada de bicarbonato de sodio, y salmuera. La capa orgánica se seca sobre $Na_2SO_4$, se filtra y se concentra al vacío. El residuo se pasa por cromatografía sobre gel de sílice (eluyente: acetona/hexano; 1:1) para proporcionar el producto deseado 3m. m/z encontrada ES+ = 945.

**Paso 3-H:**




**3m**

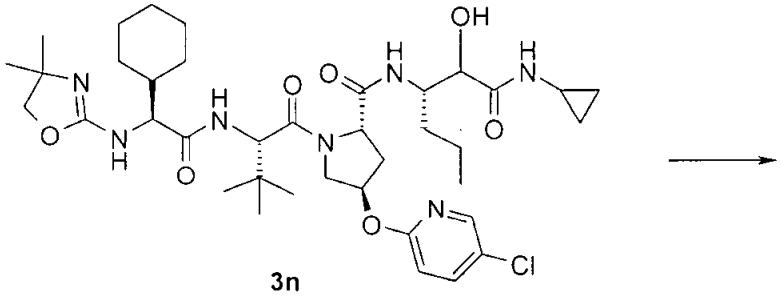



**3n**

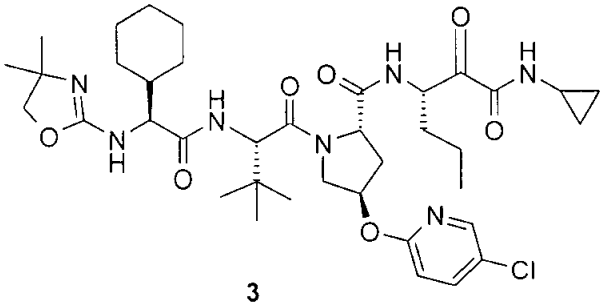
A una solución del 3m (50 miligramos, 0.05 milimoles) en

N,N'-dimetil-formamida (0.5 mililitros) se le agrega ácido mercapto-acético (19 miligramos, 0.21 milimoles) y monohidrato de hidróxido de litio (18 miligramos, 0.42 milimoles) a temperatura ambiente. La mezcla de reacción se agita durante 3 horas, después de lo cual, se agrega una solución acuosa saturada de bicarbonato de sodio. Las fases se separan y la capa acuosa se extrae con acetato de etilo. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre sulfato de sodio, y se concentran, para dar el producto deseado 3n. m/z encontrada ES+ = 760.

**Paso 3-l:**



3n

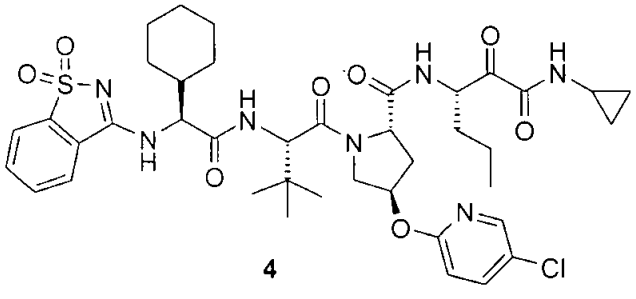


3

A una solución del 3n (35 miligramos, 0.05 milimoles) en dicloro-metano anhidro (0.5 mililitros), se le agrega peryodinano Dess-Martin (2.0 equivalentes, 39 miligramos) y las mezclas se agitan a temperatura ambiente durante 30 minutos. A las mezclas de reacción se les agrega una solución acuosa de tiosulfato de sodio

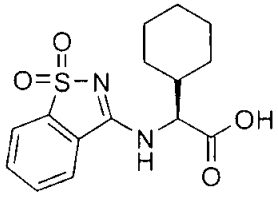
1.0 M (1 mililitros) y se agitan durante 5 minutos. Se agrega una solución acuosa saturada de bicarbonato de sodio (2 mililitros), y se continúa la agitación durante otros 10 minutos. Las mezclas se extraen con dicloro-metano. Las capas orgánicas combinadas se secan sobre sulfato de sodio, y se concentran. El residuo se purifica empleando cromatografía de capa delgada de preparación en una placa de gel de sílice (Eluyente: acetona/hexanos, 1:1) para proporcionar el producto deseado 3. m/z encontrada ES+ = 758

**Ejemplo 4:**

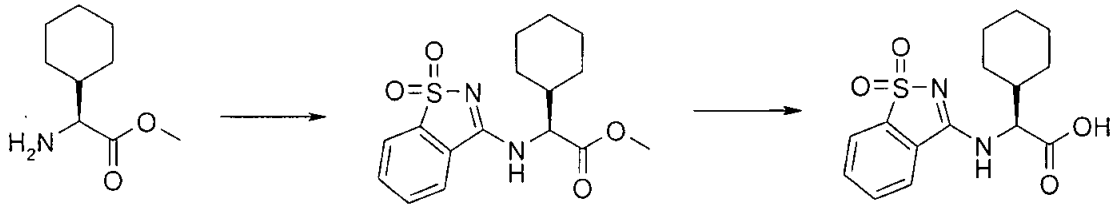


**4**

**Paso 4-A:**



**4a**

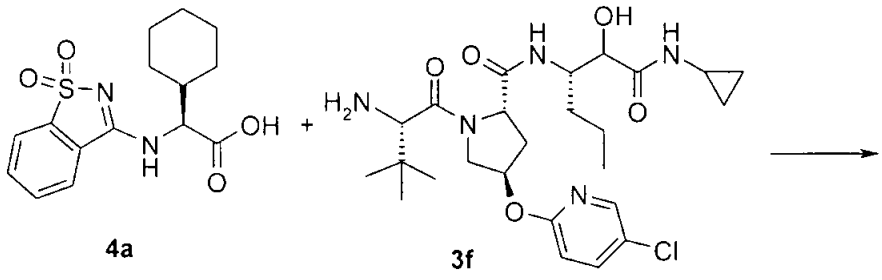


HCl **4b** **4a**

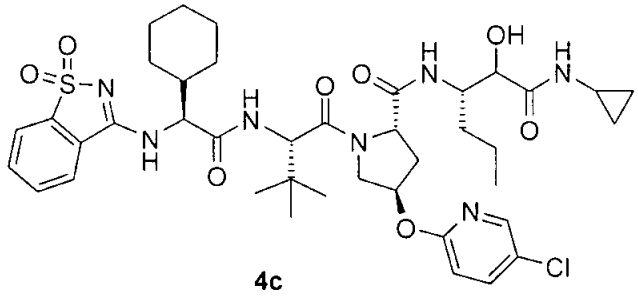
A una solución de H-ciclohexil-gly-OMe•HCl en agua (1.0 mililitros) y dioxano (1.0 mililitros), se le agregan NaOH (60 miligramos, 1.5 milimoles, 3.0 equivalentes) y 1,1-dióxido de 3-cloro-benzo-isotiazol (220 miligramos, 1.0 milimoles, 1.0 equivalentes). La solución se agita a temperatura ambiente durante 1 hora, después de lo cual, el pH de la solución se ajusta a 5 mediante la adición de una solución acuosa de HCl 1.0N. Las dos fases se separan, y la fase acuosa se extrae con $CH_2Cl_2$. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$, y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOAc, 1/1), para dar 150 miligramos del 4b. m/z encontrada en ES+ = 337, m/z en ES- = 335.

A una solución del metil-éster 4b (100 miligramos) en tetrahidrofurano (0.3 mililitros) y MeOH (0.3 mililitros) a 0 °C, se le agrega una solución de $LiOH•H_2O$ (25 miligramos) en agua (0.3 mililitros). La solución se agita a temperatura ambiente durante 3 horas. El pH de la solución se ajusta entonces a 6 mediante la adición de una solución acuosa de HCl 1.0N. Luego se agrega $CH_2Cl_2$, y se separan las dos fases. La capa acuosa se extrae con $CH_2Cl_2$. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$, y se concentran, para dar 75 miligramos del 4a. m/z encontrada en ES+ = 323, m/z en ES- = 321.

**Paso 4-B:**



4a 3f

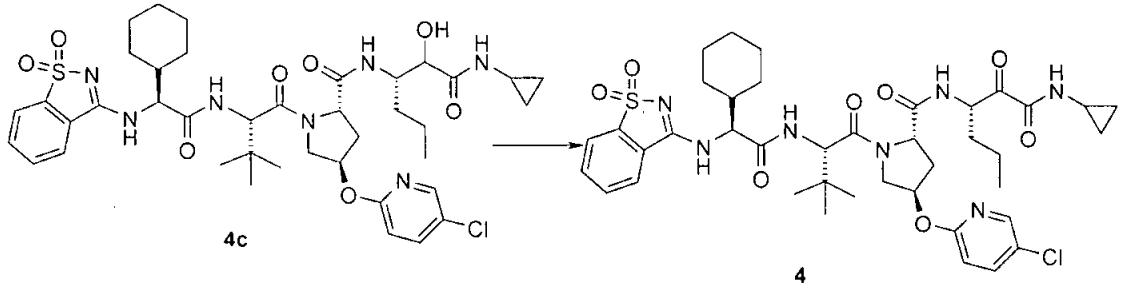


4c

Una solución del 4a (74 miligramos, 0.23 milimoles) en dicloro-metano anhidro (1.0 mililitros) y N,N'-dimetil-formamida anhidra (1.0 mililitros), se agita a 0 °C, y se trata con hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.4 equivalentes, 105 miligramos, 0.27 milimoles). A esta solución se le agrega el 3f (1 equivalente, 120 miligramos, 0.23 milimoles) en pequeñas porciones. Entonces, se agrega por goteo N-metil-morfolina (4.0 equivalentes, 0.101 mililitros, 0.92 milimoles). La mezcla de reacción se calienta gradualmente a temperatura ambiente y se agita durante la noche. Todos los volátiles se remueven al vacío, y el residuo se disuelve en acetato de etilo. La capa orgánica se lava con agua, solución acuosa de HCl 1.0N, solución acuosa saturada de bicarbonato de sodio, y salmuera. La capa orgánica se seca sobre $Na_2SO_4$ y se concentra al vacío. El residuo se pasa por cromatografía sobre gel de sílice (eluyente: acetona/hexano; 1:1)

para proporcionar el producto deseado 4c. m/z encontrada ES+ = 828.

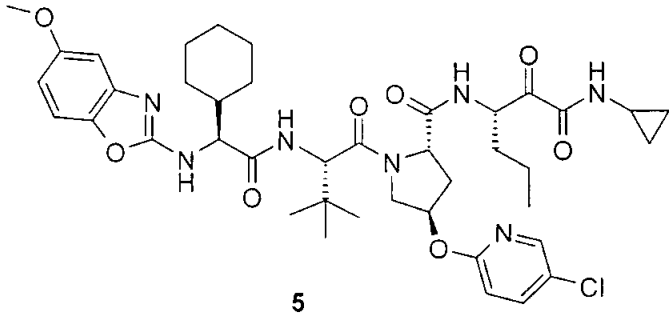
**Paso 4-C:**



4c 4

Una solución del 4c (41 miligramos, 0.05 milimoles) en dicloro-metano anhidro (3 mililitros) se trata con peryodinano Dess-Martin (3.0 equivalentes, 63 miligramos) y las mezclas de reacción se agitan a temperatura ambiente durante 30 minutos. A la mezcla se le agrega una solución acuosa de tiosulfato de sodio 1.0 M (2 mililitros) y se agita durante 5 minutos. Se agrega una solución acuosa saturada de bicarbonato de sodio (2 mililitros), y se continúa la agitación durante otros 10 minutos. La mezcla se extrae con dicloro-metano. Las capas orgánicas combinadas se secan sobre sulfato de sodio, se filtran y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (acetona/hexanos, 1:1) para proporcionar el producto deseado 4. m/z encontrada ES+ = 826 y m/z ES- = 824.

**Ejemplo 5:**



**5**

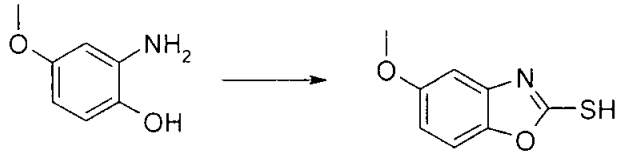
**Paso 5-A:**



**5a** **5b**

A una solución del 5a (5.0 gramos, 29.56 milimoles) en etanol (60 mililitros), se le agrega Pd/C (20 por ciento, 1.0 gramos). La mezcla de reacción se agita entonces bajo 1.0 atmósfera de un globo de $H_2$ durante 12 horas. La mezcla de reacción se filtra entonces a través de Celite 545 y el filtrado se concentra para dar 3.6 gramos del 5b.

**Paso 5-B:**

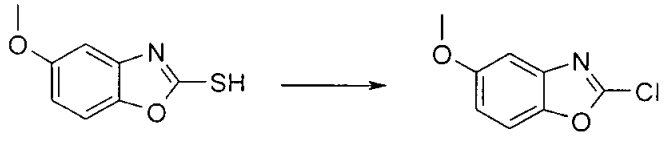


**5b** **5c**

Las mezclas del 5b (1.2 gramos, 8.62 milimoles), hidróxido

de potasio (581 miligramos, 10.34 milimoles) y disulfuro de carbono (10 mililitros, 173 milimoles) en etanol (17 mililitros), se calientan a reflujo durante la noche. Entonces se evapora el solvente. Al residuo se le agregan solución acuosa de HCl 1.0 N (10 mililitros) y acetato de etilo (100 mililitros. Las fases se separan. La capa orgánica se lava con agua, salmuera, se seca sobre sulfato de sodio, y se concentra, para dar 1.2 gramos del 5c.

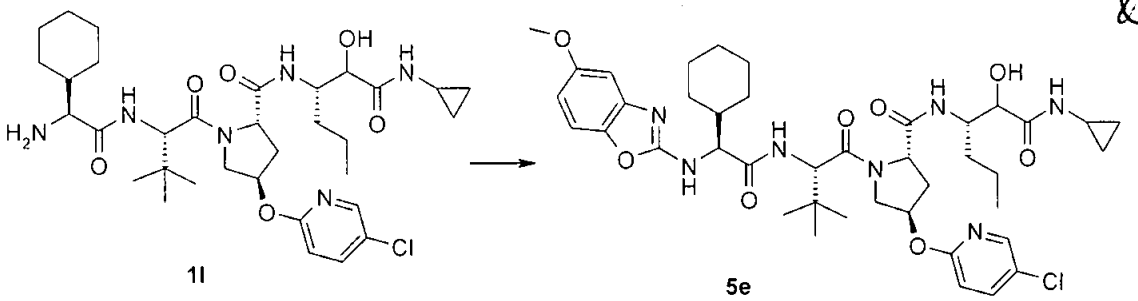
**Paso 5-C:**




**5c** **5d**

Al 5c (1.0 gramos, 5.5 milimoles) y cloruro de tionilo (6 mililitros, 66 milimoles), se les agregan , N,N'-dimetil-formamida y las mezclas resultantes se calientan a 70 °C durante 30 minutos. La solución se enfría entonces a temperatura ambiente, y se diluye con dicloro-metano. Entonces se evapora el solvente. Al residuo se le agregan otros 10 mililitros de dicloro-metano, y la solución se concentra. El residuo se disuelve en hexanos calientes, y luego se filtra. El filtrado se concentra para dar 1.0 gramos del 5d.

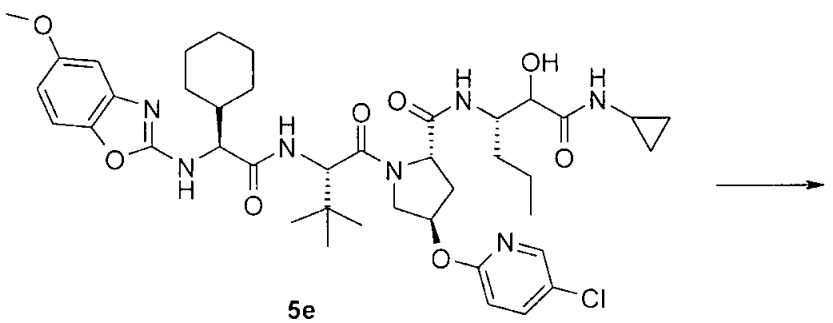
**Paso 5-D:**



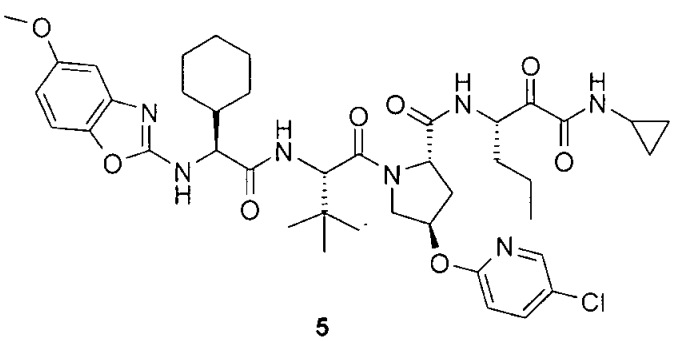
1l 5e

A una solución del 1l (75 miligramos, 0.11 milimoles) en dioxano (0.4 mililitros) a temperatura ambiente, se le agregan el 5d (31 miligramos, 0.17 milimoles) y bicarbonato de sodio (19 miligramos, 0.23 milimoles). Las mezclas se agitan a 65 °C durante 12 horas. Las mezclas se cargan directamente en una columna de gel de sílice, y se eluyen con hexano/EtOH (de 95/5 a 85/15), para dar el 5e. m/z encontrada ES+ = 810 y ES- = 808.

**Paso 5-E:**



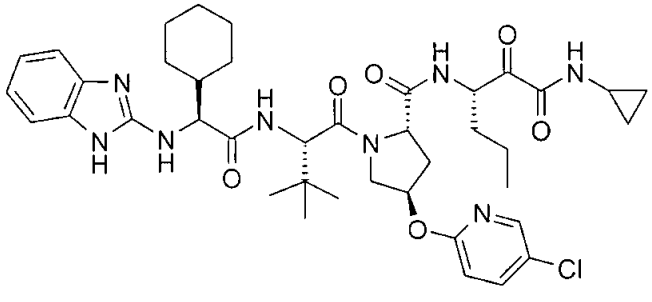
5e



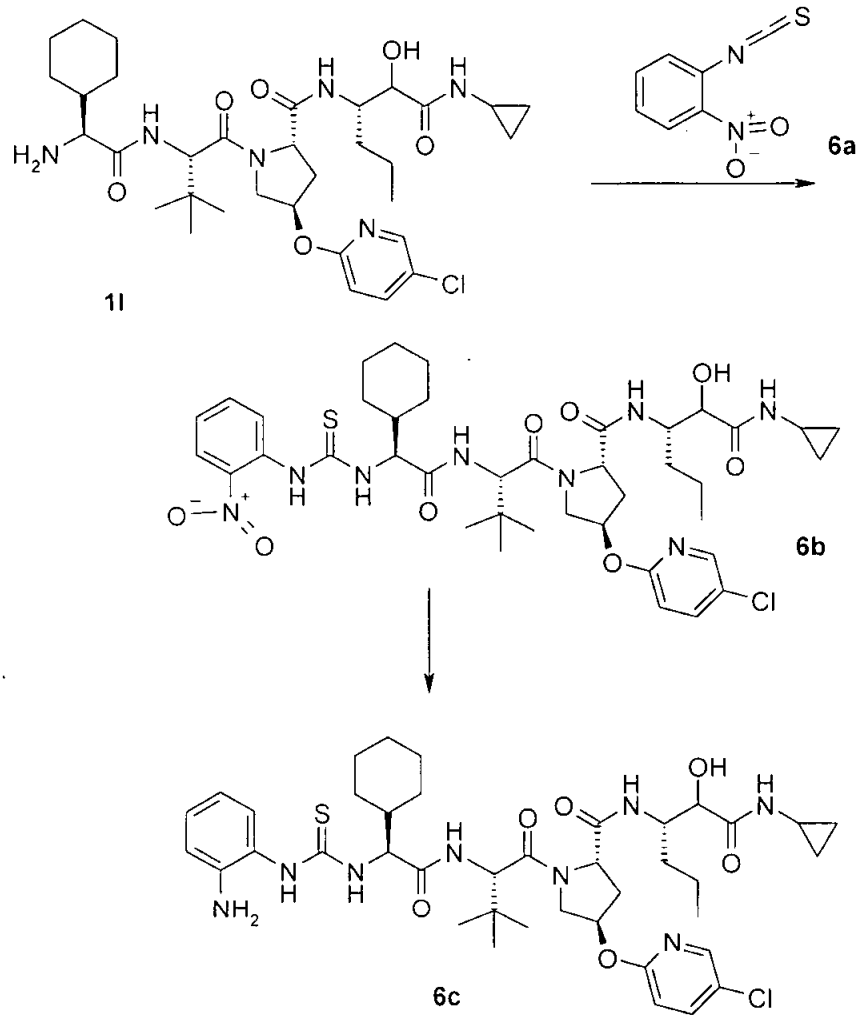
5

A una solución del 5e (62 miligramos, 0.08 milimoles) en dicloro-metano anhidro (0.80 mililitros), se le agrega peryodinano Dess-Martin (2.0 equivalentes, 65 miligramos). La mezcla de reacción se agita a temperatura ambiente durante 30 minutos. A la mezcla se le agrega una solución acuosa de tiosulfato de sodio 1.0 M (2 mililitros) y se agita durante 5 minutos. Se agrega una solución acuosa saturada de bicarbonato de sodio (2 mililitros, y se continúa la agitación durante otros 10 minutos. La mezcla se extrae con dicloro-metano. Las capas orgánicas combinadas se secan sobre sulfato de sodio, se filtran y se concentran. El residuo se purifica empleando cromatografía de capa delgada de preparación en gel de sílice (gradiente: acetona/hexanos, 3:7 a 1:1), para proporcionar el producto deseado 5. m/z encontrada ES+ = 808 y ES- = 806.

**Ejemplo 6:**



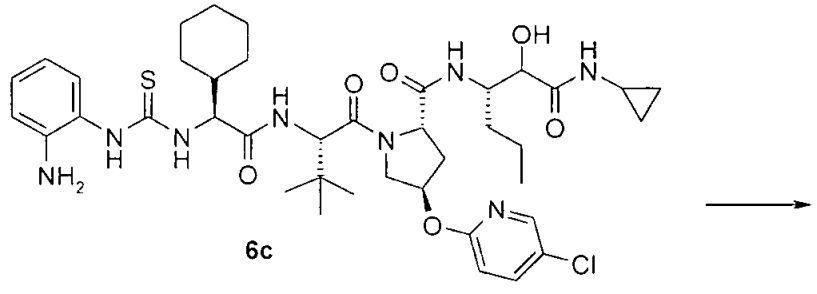
6



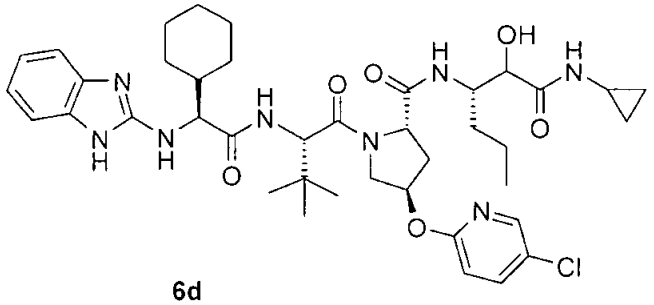

Una solución del 1l (100 miligramos, 0.15 milimoles, 1.0 equivalentes) y el 6a (27 miligramos, 0.15 milimoles, 1.0 equivalentes) en EtOH (0.5 mililitros), se agita a temperatura ambiente durante 1 hora. m/z encontrada para el 6b ES+ = 843, m/z en ES- = 841.

A la solución anterior se le agrega $SnCl_2$ (142 miligramos, 0.75 milimoles), y las mezclas se calientan a 70 °C durante 30 minutos. La solución se enfría entonces a 0 °C. Se agrega hielo,

seguido por $NaHCO_3$ acuoso saturado y EtOAc. Las fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$, y se concentran, para dar el producto crudo 6c, el cual se continúa hasta el siguiente paso sin mayor purificación. m/z encontrada en ES+ = 813, m/z en ES- = 811.

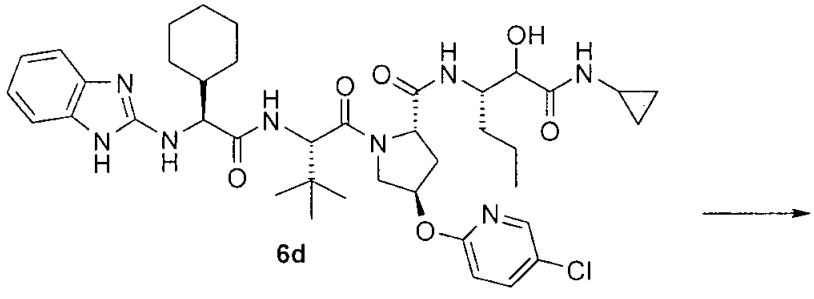


6c

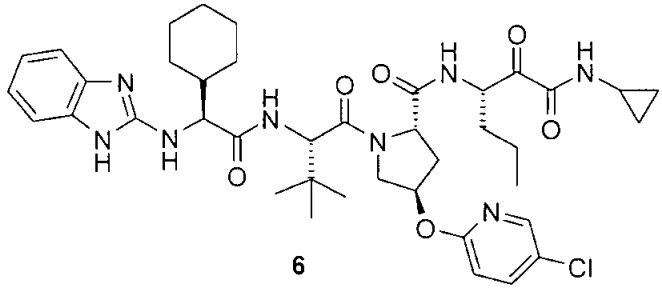


6d

A una solución del 6c (120 miligramos, 0.15 milimoles) en tolueno (0.6 mililitros), se le agrega HgO (64.8 miligramos, 0.3 milimoles, 2.0 equivalentes) y azufre (4.8 miligramos, 0.15 milimoles, 1.0 equivalentes), y las mezclas se agitan a 90 °C durante 1 hora. Las mezclas se filtran, se lavan con $CH_2Cl_2$ y la solución se concentra. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOH = 4/1) para dar el producto deseado 6d (54 miligramos). m/z encontrada en ES+ = 779.



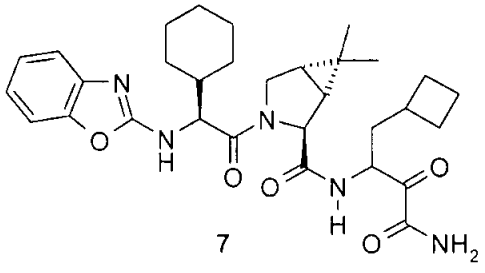
6d



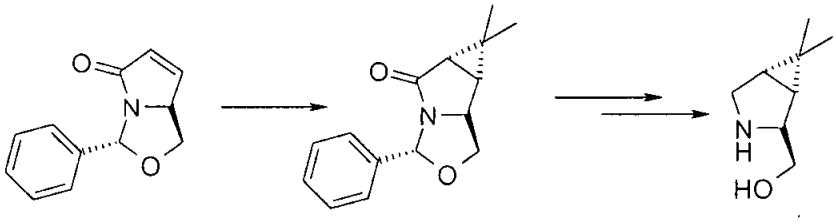
6

A una solución del alcohol 6d (54 miligramos, 0.069 milimoles) en $CH_2Cl_2$ (1.0 mililitros) a 0 °C, se le agrega DMP (58.7 miligramos, 0.138 milimoles, 2.0 equivalentes). La solución se agita a temperatura ambiente durante 4 horas. A la solución se le agregan entonces $NaHCO_3$ acuoso saturado y una solución acuosa de $Na_2S_2O_3$ 1.0 M. Las fases se separan, y la capa acuosa se extrae con $CH_2Cl_2$. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/acetona 1/1) para dar el producto 6. m/z encontrada en ES+ = 777.

**Ejemplo 7:**



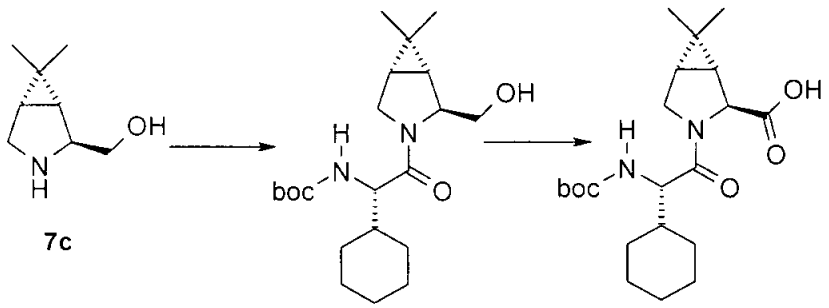
7



7a 7b 7c

A una solución de tetra-fluoro-borato de isopropil-difenil-sulfonio (ref. Matsuyama, H. *y colaboradores, J. Org. Chem.* 2000, *65*, 4796.) (13.4 gramos, 42.5 milimoles, 1.7 equivalentes) en tetrahidrofurano a -78 °C, se le agrega *t*-BuLi (22.0 mililitros, 37.5 milimoles, 1.70 M en pentano, 1.5 equivalentes), y la solución se agita a esta temperatura durante 30 minutos. A la solución se le agrega entonces una solución del 7a (5.0 gramos, 25 milimoles, 1.0 equivalentes) en tetrahidrofurano (20 mililitros). La solución se agita a -78 °C durante 1 hora. La reacción se apaga mediante la adición de $NaHCO_3$ acuoso saturado. La solución se calienta a temperatura ambiente y se diluye con EtOAc. Las dos fases se separan, y la capa orgánica se lava con salmuera, se seca sobre $Na_2SO_4$ y se concentra. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOAc, 9/1 a 3/1) para dar 5.1 gramos del 7b. El 7b se convierte hasta el amino-alcohol 7c de acuerdo con la

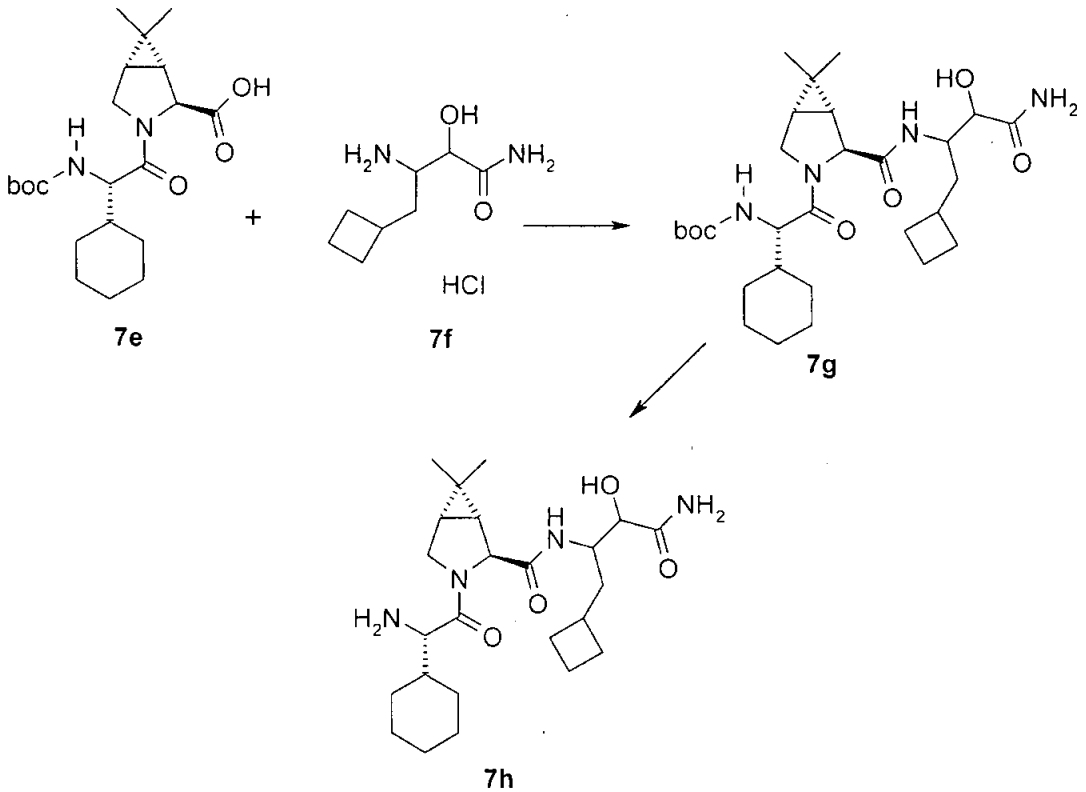
referencia: *J. Org. Chem.* 1999, *64*, 330.




A una solución de Boc-L-ciclohexil-gly-OH (2.57 gramos, 10 milimoles, 1.0 equivalentes) en $CH_3CN$ (60.0 mililitros) a 0 °C, se le agrega hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (3.878 gramos, 10.2 milimoles, 1.02 equivalentes), HOAT (1.38 gramos, 10.2 milimoles, 1.02 equivalentes), seguido por el 7c (1.39 gramos, 10 milimoles, 1.0 equivalentes) y N-etil-di-isopropil-amina (6.95 mililitros, 40 milimoles, 4.0 equivalentes). La solución se agita a temperatura ambiente durante 12 horas, después de lo cual se evapora el solvente. El residuo se divide entre EtOAc y agua. Las fases se separan y la capa orgánica se lava con $NaHCO_3$ acuoso saturado, salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOAc, 1/1) para dar el producto 7d (3.43 gramos).

A una solución del 7d (2.4 gramos, 6.5 milimoles) en acetona (40.0 mililitros) a -5 °C, se le agrega una solución del reactivo de Jones (3.0 M, 10.7 mililitros). La mezcla se calienta a 0°C y se agita a esta temperatura durante 2 horas. La reacción se apaga entonces mediante la adición lenta de *i*-PrOH (10 mililitros), y

la mezcla entonces se filtra. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan ($Na_2SO_4$), y se concentran, para dar el producto deseado 7e, 2.35 gramos. El material se continúa hasta el siguiente paso sin mayor purificación. m/z encontrada en ES+ = 395, m/z en ES- = 393.

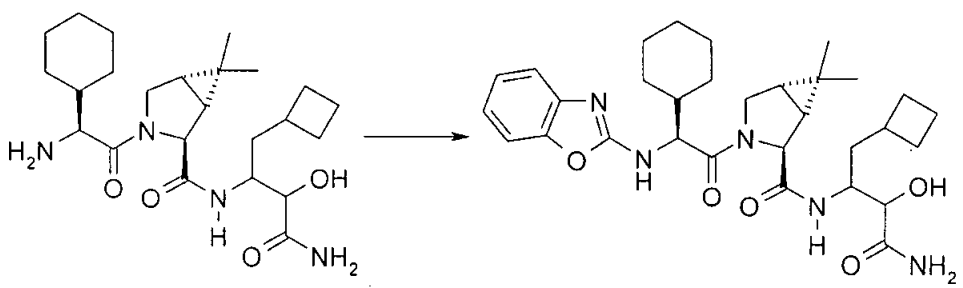



**7e** **7f** **7g** **7h**

A una solución del 7e (1.0 gramos, 2.5 milimoles) en N,N'-dimetil-formamida (5.0 mililitros) y $CH_2Cl_2$ (5.0 mililitros) a 0 °C, se le agregan hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.05 gramos, 2.75 milimoles, 1.1 equivalentes), el 7f (0.53 gramos, 2.5 milimoles, 1.0 equivalentes), y N-metil-morfolina (0.825 mililitros, 7.5 milimoles, 3.0 equivalentes). La solución se agita a 0 °C durante 30 minutos, y luego a temperatura ambiente

durante 6 horas. A la mezcla de reacción se le agrega una solución acuosa saturada de $NaHCO_3$ y EtOAc. Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$, y se concentran. El material crudo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOH, 9/1) para dar el producto 7g (950 miligramos). m/z encontrada en ES+ = 549.

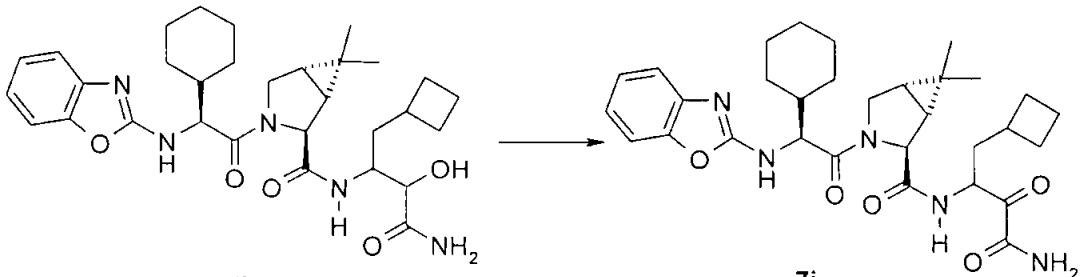
A una solución del 7g (110 miligramos) en $CH_2Cl_2$ (2.0 mililitros), se le agrega ácido trifluoro-acético (2.0 mililitros), y la solución se agita a temperatura ambiente durante 1 hora. Entonces se evapora el solvente. Al residuo se le agrega una solución acuosa saturada de $NaHCO_3$ y EtOAc. Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se secan sobre $Na_2SO_4$ y se concentran, para dar el producto deseado 7h (67 miligramos). m/z encontrada en ES+ = 449.



**7h** **7i**

A una solución del 7h (150 miligramos, 0.33 milimoles) en dioxano (1.0 mililitros) a temperatura ambiente, se le agregan 2-cloro-benzoxazol (76 miligramos, 0.50 milimoles, 1.5 equivalentes) y $NaHCO_3$ (84 miligramos, 1.0 milimoles, 3.0 equivalentes). La mezcla se agita a 60 °C durante 6 horas. La mezcla se carga entonces

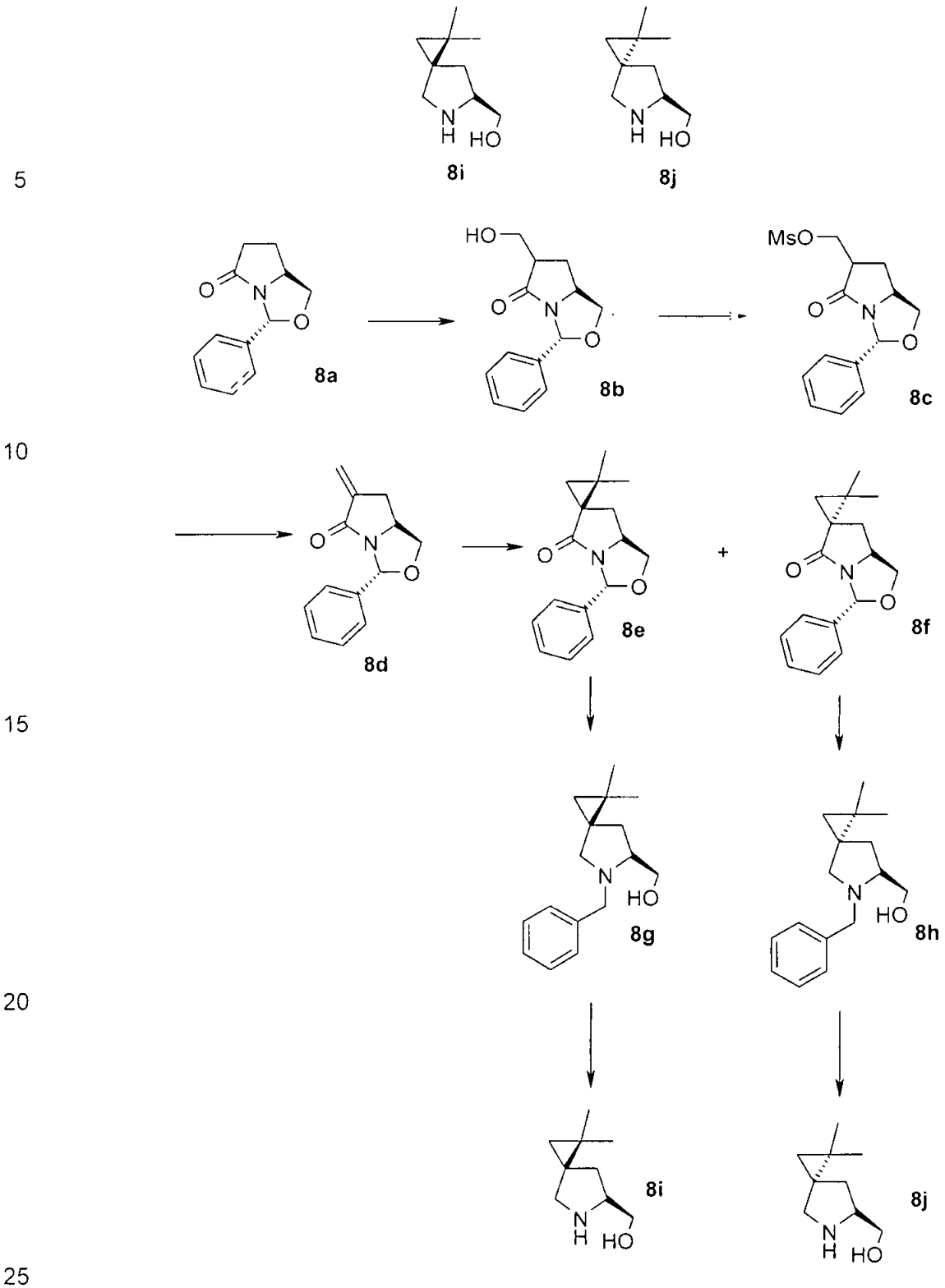
directamente en una columna de gel de sílice, y se eluye con hexano/acetona (2/1), para dar el producto deseado 7i (145 miligramos). m/z encontrada en ES+ = 566, m/z en ES- = 564.



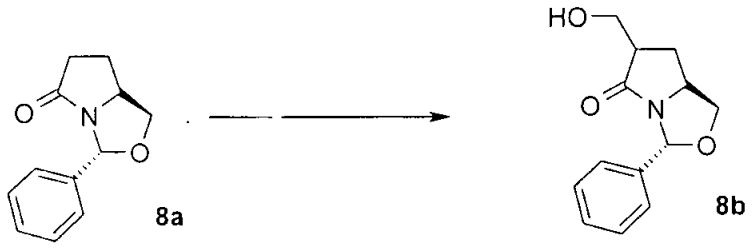
7i 7j

A una solución del 7i (120 miligramos, 0.21 milimoles) en $CH_2Cl_2$ (2.0 mililitros) a 0 °C, se le agrega N-etil-di-isopropil-amina (0.148 mililitros, 0.848 milimoles, 4.0 equivalentes) seguida por una solución del $Py{\bullet}SO_3$ (67.6 miligramos, 0.424 milimoles, 2.0 equivalentes) en sulfóxido de dimetilo (2.0 mililitros). La solución se agita entonces a 0 °C durante 10 minutos. A la solución se le agrega EtOAc y una solución acuosa saturada de $NaHCO_3$. Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/Acetona, 1/1) para dar el producto 7j (108 miligramos). m/z encontrada en ES+ = 564, m/z en ES- = 562.

**Ejemplo 8:**

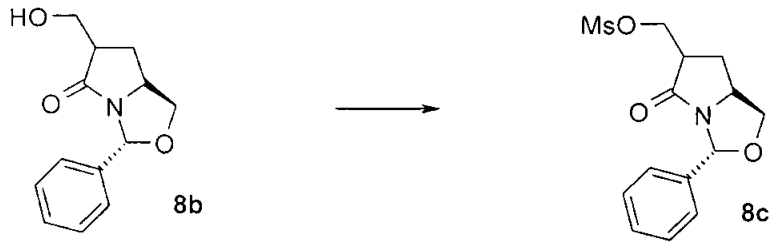


**Paso 8-A:**



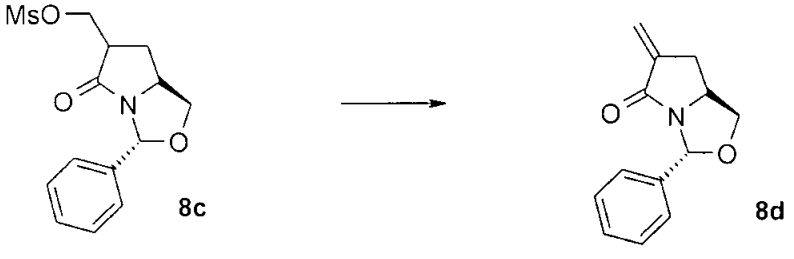

A una solución de DIPA (12.4 mililitros, 88.6 milimoles, 1.2 equivalentes) en tetrahidrofurano (400 mililitros) a -30 °C, se le agrega *n*-BuLi (50 mililitros, 1.60 M en hexano, 81.0 milimoles, 1.10 equivalentes). La solución se agita a esta temperatura durante 30 minutos. Subsecuentemente se agrega una solución del 8a (el 8a se prepara de acuerdo con *J. Org. Chem.* 1986, *51*, 3140.) (15.0 gramos, 73.8 milimoles, 1.0 equivalentes) a la solución, la cual se agita entonces a -30 °C durante 30 minutos. Se burbujea una corriente de HCHO (22.0 gramos, 738 milimoles, 10 equivalentes) y gas de $N_2$ a través de esta solución durante 10 minutos. La mezcla de reacción se calienta hasta 0 °C durante 30 minutos, y se apaga mediante la adición de una solución de HCl 2.0 N hasta un pH=3. Se agrega EtOAc, y las fases se separan. La capa acuosa se extrae con EtOAc tres veces. La capa orgánica combinada se lava con salmuera, se seca sobre $Na_2SO_4$ y se concentra para dar el 8b, el cual se utiliza en el siguiente paso sin purificación.

**Paso 8-B:**




A una solución del 8b en $CH_2Cl_2$ (200 mililitros) a 0 °C, se le agregan trietil-amina (30.9 mililitros, 222 milimoles, 3.0 equivalentes), dimetil-amino-piridina (902 miligramos, 7.4 milimoles, 0.1 equivalentes) y MsCl (11.5 mililitros, 148 milimoles, 2.0 equivalentes). La temperatura de reacción se mantiene a <5 °C. La solución se agita a temperatura ambiente durante 2 horas. Entonces se agrega una solución acuosa saturada de $NH_4Cl$, seguida por una mezcla de 1/1 de EtOAc/TBME. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan con $Na_2SO_4$ y se concentran, para proporcionar el 8c, el cual se continúa hasta el siguiente paso sin purificación.

**Paso 8-C:**

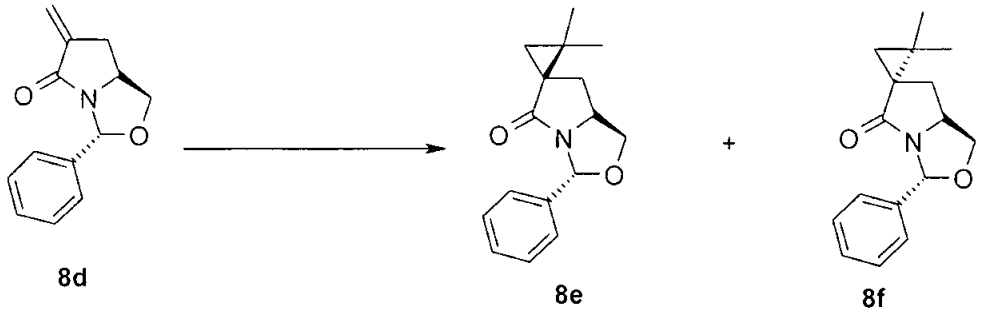



El residuo 8c del paso anterior se disuelve en $CH_2Cl_2$/tolueno (20 mililitros/20 mililitros). A 0 °C, se agregan 15

mililitros de 1,8-diaza-biciclo-[5.4.0]-undec-7-eno. La temperatura interna se mantiene debajo de 20 °C. La solución se agita a temperatura ambiente durante 2 horas. La mezcla se carga directamente en una columna de gel de sílice, y se inunda con hexano/EtOAc (2/1 a 1/1) para dar el producto 5 (7.4 gramos). El producto 8d se lleva adelante hasta el siguiente paso inmediatamente.

M/z encontrada en ES+ = 216; LC-MS (método A) $t_R$ = 0.86 minutos.

**Paso 8-D:**



**8d** **8e** **8f**

dr **8e/8f** = 1/2

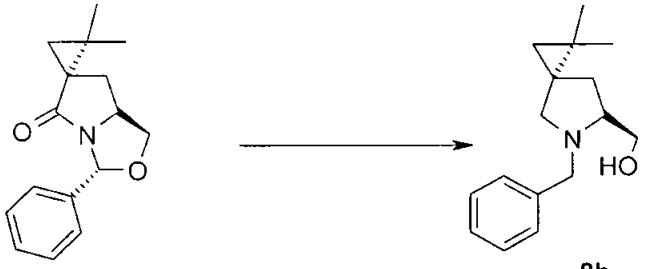
A una solución de yoduro de isopropil-trifenil-fosfina (10.4 gramos, 24.1 milimoles, 1.4 equivalentes) en tetrahidrofurano (70 mililitros) a -30 °C, se le agrega *n*-BuLi (1.60 M, 13.9 mililitros, 22.4 milimoles). La solución se agita a 0 °C durante 30 minutos, luego se enfría a -30 °C. A la solución anterior se le agrega una solución del 8d (3.7 gramos, 17.2 milimoles, 1.0 equivalentes). La mezcla de reacción resultante se calienta a temperatura ambiente durante 1 hora, y se agita a temperatura ambiente durante 3 horas. La reacción se apaga mediante la adición de una solución acuosa saturada de $NaHCO_3$. Después de que se diluye con EtOAc, la

mezcla se filtra. Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOAc 3/1 a 2/1) para dar los productos 8e (1.1 gramos), y 8f (2.3 gramos).

TLC, Rf (EtOAc/heptano 1:2) = 0.53 (8e) y 0.46 (8f)

**Paso 8-E:**

**Procedimiento para la síntesis del 8j.**




8f 8h

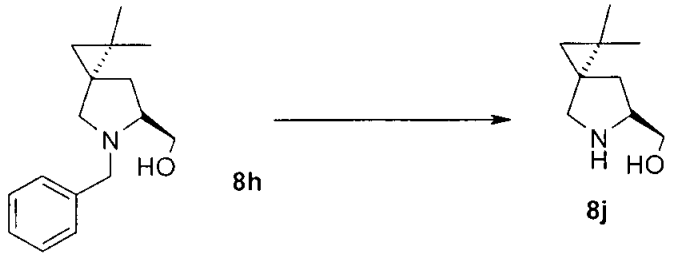
A una solución del 8f (5.0 gramos, 19.5 milimoles) en tetrahidrofurano (75 mililitros) a 0 °C, se le agrega $LiAlH_4$ (2.2 gramos, 58.4 milimoles, 3. equivalentes). La solución se calienta a reflujo durante 5 horas. Después de enfriarse a 0 °C, la solución de la reacción se agrega lentamente a 5.0 mililitros de una solución acuosa saturada de $Na_2SO_4$. Las mezclas se diluyen con EtOAc y se agitan a temperatura ambiente durante 30 minutos. La mezcla se filtra y la solución se concentra para dar el producto 8h (aproximadamente 5.0 gramos).

HPLC (método B) $t_R$ = 2.64 minutos.

TLC, Rf ($CH_2Cl_2$/MeOH 9:1) = 0.48.

MS (método C): 246 [M+H].

**Paso 8-F:**



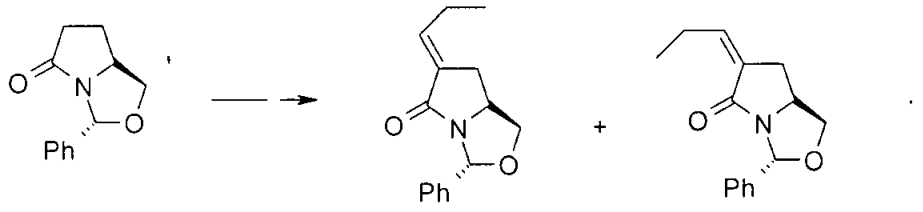

A una solución del 8h (3.0 gramos) en EtOAc/HOAc (40 mililitros/40 mililitros) a temperatura ambiente, se le agrega Pd (al 10 por ciento sobre carbón), 2.0 gramos. La mezcla se coloca bajo 2.8 $kg/cm^2$ de $H_2$ en un agitador Parr durante 3 horas. La mezcla se diluye con $CH_2Cl_2$ y se filtra. La solución se concentra. La mayor parte del HOAc se remueve al vacío a 30 Torr, 40 °C. La solución se basifica a un pH = 13 con una solución acuosa de NaOH 6.0 M. Después de diluirse con $CH_2Cl_2$, la solución se filtra. Las dos fases se separan, y la capa acuosa se extrae con $CH_2Cl_2$. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$, $K_2CO_3$, y se concentran, para dar el producto 8j (1.8 gramos).

TLC, $R_f$ ($CH_2Cl_2$/MeOH 4:1) = 0.29.

MS (método C): 156 [M+H].

El Compuesto 8i se prepara a partir del 8g mediante un procedimiento análogo al empleado para convertir el 8h hasta el 8j.

**Paso 9-A:**



**8a** **9a** **9b**

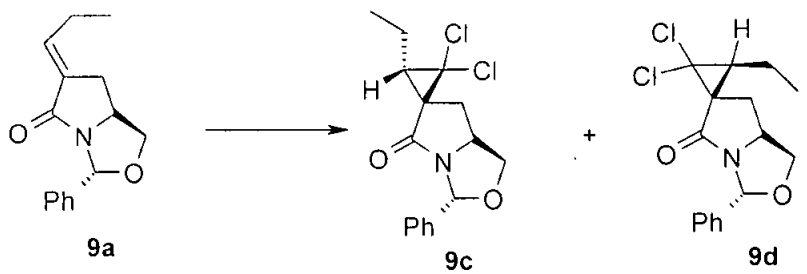
A una solución de DIPA (6.6 mililitros, 47.3 milimoles, 1.2 equivalentes) en tetrahidrofurano (200 mililitros) a -30 °C, se le agrega *n*-BuLi (27 mililitros, 1.60 M en hexano, 43.3 milimoles, 1.10 equivalentes). La solución se agita a esta temperatura durante 30 minutos. Luego se agrega a la reacción, una solución del 8a (15.0 gramos, 73.8 milimoles, 1.0 equivalentes), que se prepara de acuerdo con *J. Org. Chem.* 1986, *51*, 3140, y la solución se agita a -78 °C durante 30 minutos. A esta solución se le agrega propanal (3.4 mililitros, 47.3 milimoles, 1.2 equivalentes). Después de 1.5 horas, la reacción se apaga mediante la adición de una solución acuosa de HCl 4.0 N, hasta un pH=3. Se agrega EtOAc y las fases se separan. La capa acuosa se extrae con EtOAc tres veces. La capa orgánica combinada se lava con salmuera, se seca sobre $Na_2SO_4$ y se concentra. El residuo se continúa hasta el siguiente paso sin mayor purificación.

El producto obtenido del paso anterior se disuelve en $CH_2Cl_2$ (40 mililitros). A esta solución a 0 °C, se le agregan trietil-amina (10.9 mililitros, 78.8 milimoles, 2.0 equivalentes), dimetil-amino-piridina (950 miligramos, 7.8 milimoles, 0.2 equivalentes), seguida por la adición lenta de MsCl (4.6 mililitros, 59.1 milimoles,

1.5 equivalentes). La temperatura de reacción se mantiene a <5 °C. La solución se agita a temperatura ambiente durante 2 horas. Entonces se agrega una solución acuosa saturada de $NH_4Cl$, seguida por una mezcla de 1/1 de EtOAc/dietil-éter. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan con $Na_2SO_4$ y se concentran.

El residuo del paso anterior se disuelve en $CH_2Cl_2$ (30.0 mililitros). A 0 °C, se agregan 10 mililitros de 1,8-diaza-biciclo-[5.4.0]-undec-7-eno. La temperatura interna se mantiene debajo de 20 °C. La solución se agita a temperatura ambiente durante 2 horas. La mezcla se carga directamente en una columna de gel de sílice, y se inunda con hexano/EtOAc (2/1 a 1/1) para dar los productos 9a (3.7 gramos) y 9b (4.2 gramos).

**Paso 9-B:**

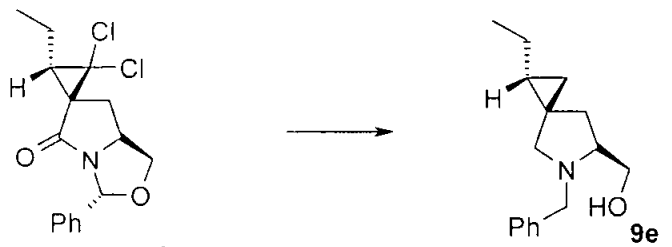



**9a** **9c** **9d**

A una solución del 9a (1.7 gramos) en $CHCl_3$ (10 mililitros) a temperatura ambiente, se le agrega una solución acuosa de NaOH (12 gramos, mezcla de 1/1) y cloruro de bencil-trietil-amonio (227 miligramos). La solución se agita a temperatura ambiente durante 12 horas. Entonces las mezclas se dividen entre EtOAc y agua. La

capa acuosa se separa y se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía por evaporación instantánea (9/1 heptano/EtOAc hasta 2/2 heptano/ EtOAc) para dar los productos 9c y 9d.

**Paso 9-C:**



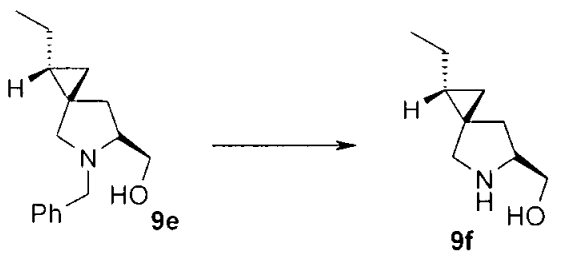

**9c** **9e**

A una solución del 9c (1.8 gramos, 5.5 milimoles) en tetrahidrofurano (30 mililitros) a 0 °C, se le agrega lentamente $LiAlH_4$ (1.05 gramos, 27.6 milimoles, 5.0 equivalentes). La solución se calienta a reflujo durante 5 horas. Después de enfriarse a 0 °C, la solución de la reacción se agrega lentamente a 2.5 mililitros de una solución acuosa saturada de $Na_2SO_4$. La mezcla se diluye con EtOAc y se agita a temperatura ambiente durante 30 minutos. La mezcla se filtra y la solución se concentra. El residuo se utiliza en el siguiente paso sin mayor purificación.

El material aislado (1.0 gramos) del paso anterior se disuelve en 18 mililitros de tetrahidrofurano y 5.0 gramos de *t*-BuOH. A la solución se le agregan pequeños pedazos de sodio (1.6 gramos, 71 milimoles, 20 equivalentes). La mezcla se calienta a reflujo durante aproximadamente 6 horas. Se saca el sodio, y se apaga con

EtOH. A la solución se le agregan 5 mililitros de EtOH, y se agita a temperatura ambiente hasta que ya no queda sodio. A la mezcla se le agrega hielo, y se diluye con EtOAc. Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan y se lavan con salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en gel de sílice (heptano/EtOAc, 1/1) para dar el producto 9e.

**Paso 9-D:**

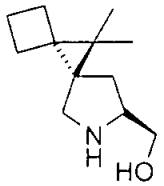



Se agrega paladio sobre carbón (10 por ciento; 300 miligramos) a una solución del 9e (500 miligramos) en EtOAc/HOAc (4.0 mililitros/3.0 mililitros) a temperatura ambiente. La mezcla se coloca bajo 2.8 kg/cm$^2$ de $H_2$ (2.7 x 10$^5$ Pa) en un agitador Parr durante 3 horas. La mezcla se diluye con $CH_2Cl_2$ y se filtra. La solución se concentra. La mayor parte del HOAc se remueve al vacío a 30 Torr, 40 °C. La solución se basifica a un pH = 13 con una solución acuosa de NaOH 6.0 M. Después de diluirse con $CH_2Cl_2$, la solución se filtra. Las dos fases se separan, y la capa acuosa se extrae con $CH_2Cl_2$. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$, $K_2CO_3$ y se concentran, para dar el producto 9f.

El Compuesto 9g se prepara a partir del 9b mediante un

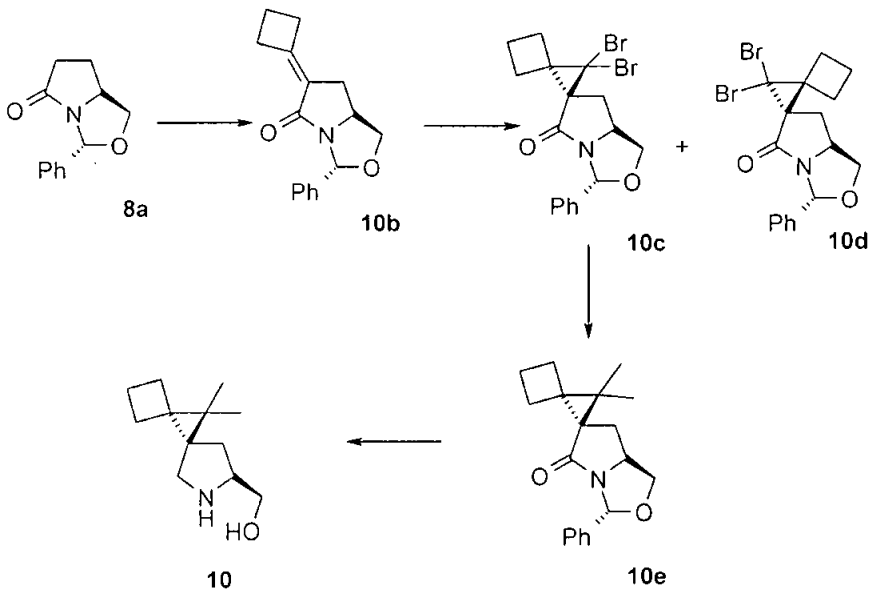
procedimiento análogo al empleado para convertir el 9a hasta el 9f.

**Ejemplo 10:**

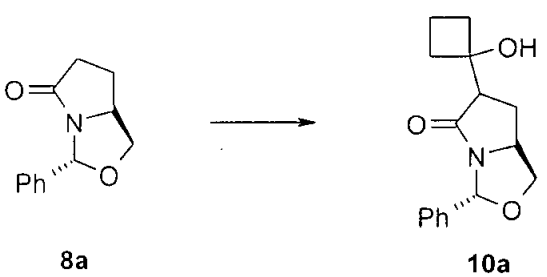


**10**

**Esquema:**




**Paso 10-A:**



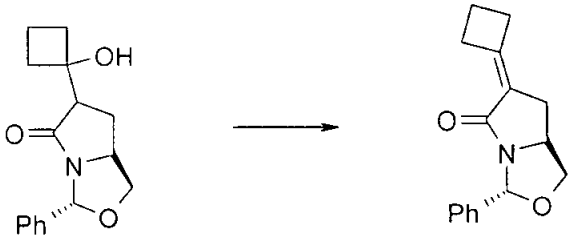
**8a** **10a**

A una solución de DIPA (7.66 mililitros, 54.2 milimoles, 1.1

equivalentes) en tetrahidrofurano (100 mililitros) a 0 °C, se le agrega *n*-BuLi (33.9 mililitros, 1.60 M en hexano 54.2 milimoles, 1.10 equivalentes). La solución se agita a esta temperatura durante 30 minutos. Se agrega a la mezcla una solución del 8a (10.0 gramos, 49.3 milimoles, 1.0 equivalentes) en tetrahidrofurano (10.0 mililitros), y la solución se agita a -78 °C durante 60 minutos.

A esta solución se le agregan ciclobutanona (3.76 gramos, 49.3 milimoles, 1.0 equivalentes) y $Et_2O{\bullet}BF_3$ (6.19 mililitros, 49.3 milimoles). La mezcla de reacción se agita durante otras 2.5 horas, y se apaga mediante la adición de $NH_4Cl$ saturado (100 mililitros). Se agrega EtOAc, y las fases se separan. La capa acuosa se extrae con EtOAc. Las capas orgánicas combinadas se lavan con salmuera, se secan sobre $Na_2SO_4$ y se concentran para proporcionar el 10a, el cual se utiliza en la siguiente reacción sin mayor purificación. m/z encontrada en ES+ = 274.

**Paso 10-B:**

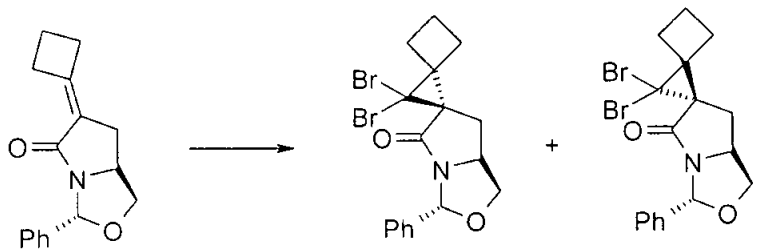



**10a** **10b**

El residuo que contiene al compuesto 10a del paso anterior se disuelve en $CH_2Cl_2$ (150 mililitros). Se agregan trietil-amina (TEA) (52.1 mililitros, 374 milimoles) y MsCl (2.89 mililitros, 37.4

milimoles)a la solución, la cual se agita a reflujo durante 8 horas. A la mezcla de reacción se le agrega entonces agua, y las fases se separan. La capa acuosa se extrae con $CH_2Cl_2$. Las capas orgánicas se combinan, se lavan con salmuera, se secan con $Na_2SO_4$ y se concentran, para proporcionar el compuesto 10b. m/z encontrada en ES+ = 256.

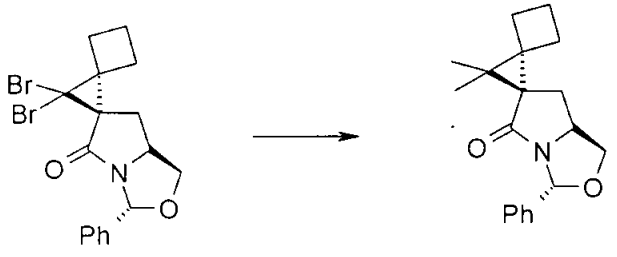
**Paso 10-C:**




**10b** **10c** **10d**

A una solución del 10b (2.54 gramos, 10 milimoles) en $CHBr_3$ (25 mililitros) se le agregan en secuencia, cloruro de bencil-trietil-amonio (0.46 gramos, 2 milimoles) y NaOH al 50 por ciento/agua (20 mililitros) a 0°C. La mezcla se agita a temperatura ambiente durante 2 horas y luego a 50°C durante 1 hora. La mezcla de reacción se diluye con agua y la fase acuosa se extrae cuando menos dos veces con $CH_2Cl_2$. Las fases orgánicas combinadas se lavan con salmuera, se secan sobre $Na_2SO_4$ y se concentran. Los isómeros 10c y 10d se separan mediante cromatografía por evaporación instantánea (Heptano/EtOAc, 4:1). La mancha superior de la cromatografía de capa delgada es el 10c (1.43 gramos). m/z encontrada en ES+ = 428.

**Paso 10-D:**



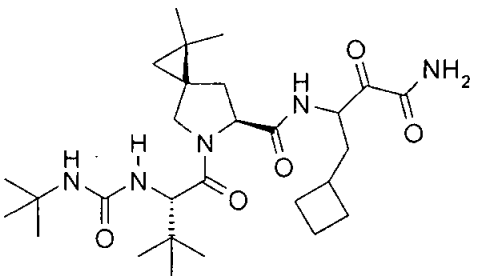

**10c** **10e**

Se agrega por goteo MeLi (16.5 mililitros, solución 1.6 M, 26.4 milimoles) a una suspensión de CuI en tetrahidrofurano a 0°C, para formar una solución transparente, la cual se mantiene a 0°C durante 10 minutos. A la mezcla se le agrega por goteo una solución del 10c (800 miligramos) en tetrahidrofurano (8.0 mililitros), a una temperatura de -50°C o menos. Después de la adición completa, la mezcla de reacción se calienta a 0°C durante 20 minutos. La solución se enfría entonces a -78 °C. A esta solución se le agrega yoduro de metilo (10 mililitros). La mezcla de reacción se calienta a temperatura ambiente durante 1 hora. A la solución se le agrega una solución acuosa saturada de $NH_4Cl$ (50 mililitros), y la solución se agita durante 10 minutos. El precipitado se remueve mediante filtración. El filtrado se divide entre EtOAc y agua. Las dos fases se separan, y la fase acuosa se extrae con EtOAc. Las fases orgánicas combinadas se secan sobre $Na_2SO_4$, y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (heptano/EtOAc, 4/1) para dar el 10e (380 miligramos). m/z encontrada ES+ = 298.

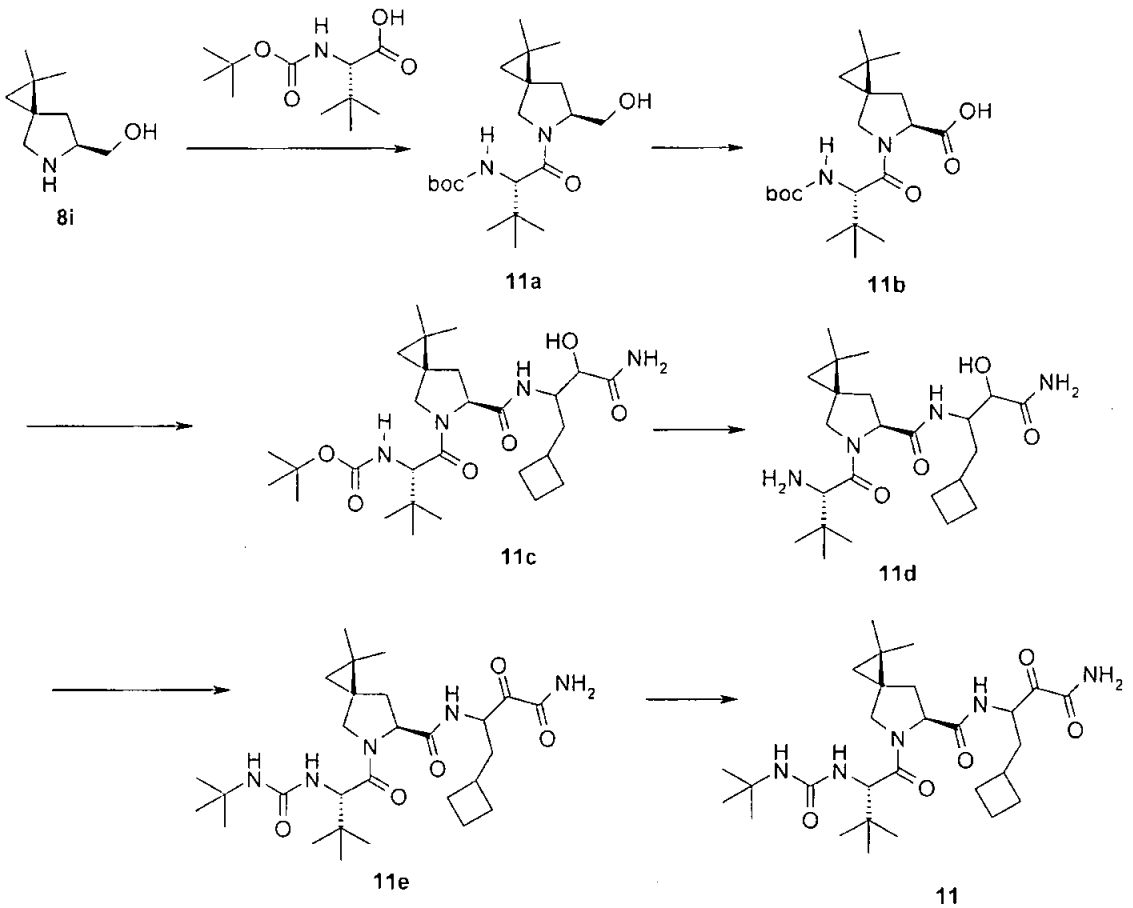
**Paso 10-E:**

El Compuesto 10e se convierte hasta el amino-alcohol 10 de acuerdo con el procedimiento descrito para transformar el compuesto 8f hasta el 8j.

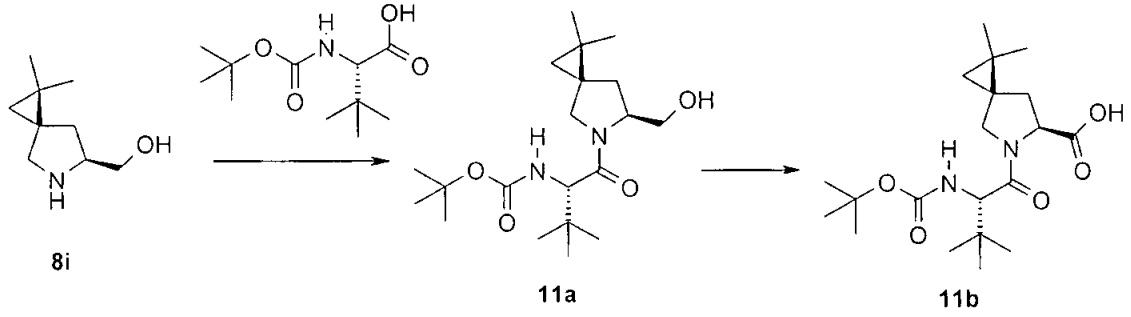
**Ejemplo 11:**



**11**



**Paso 11-A:**

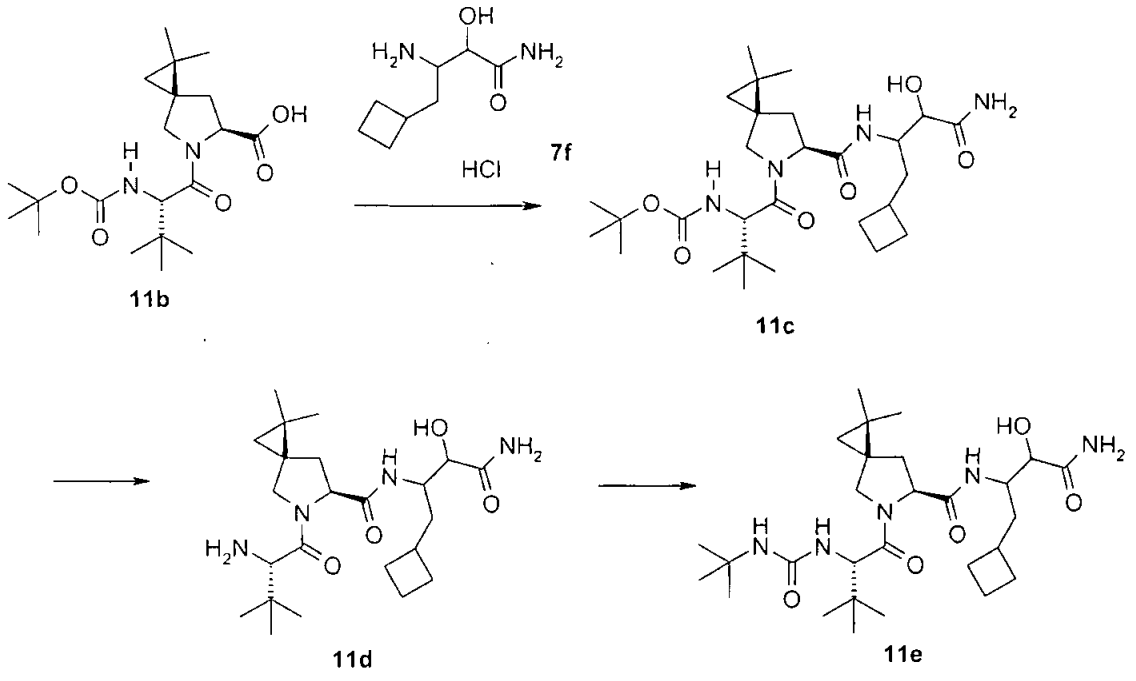



A una solución de Boc-L-terbutil-gly-OH (907 miligramos, 3.92 milimoles, 1.0 equivalentes) y el amino-alcohol 8i (600 miligramos, 3.92 milimoles, 1.0 equivalentes) en $CH_2Cl_2$ (20.0 mililitros) a 0 °C, se le agrega hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.638 gramos, 4.31 milimoles, 1.1 equivalentes), seguido por N-etil-di-isopropil-amina (2.0 mililitros, 11.76 milimoles, 3.0 equivalentes). La solución se agita a -20 °C durante 24 horas, a 0 °C durante 3 horas y a temperatura ambiente durante 1 hora. La mezcla de reacción se diluye con EtOAc y se lava con ácido cítrico al 10 por ciento. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan y se lavan con $HaHCO_3$ acuoso saturado, salmuera, se seca sobre $Na_2SO_4$ y se concentra. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOAc, 1/1) para dar el producto 11a (1.2 gramos).

A una solución del alcohol 11a (1.2 gramos) en acetona (20.0 mililitros) a -5 °C, se le agrega una solución de reactivo de Jones (3.0 M, 5.0 mililitros). La mezcla se calienta a 0 °C y se agita

a esta temperatura durante 2 horas. La reacción se apaga entonces mediante la adición lenta de *i*-PrOH (5.0 mililitros), y entonces la mezcla se diluye con EtOAc. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan ($Na_2SO_4$), y se concentran, para dar el 11b (1.16 gramos).

**Paso 11-B:**



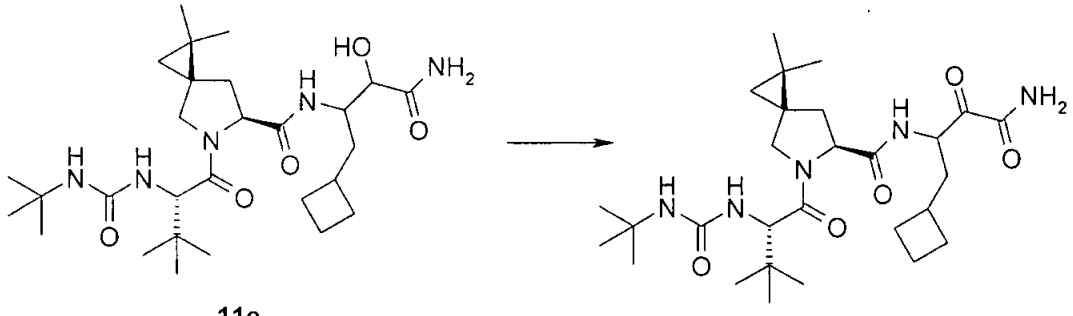

A una solución del 11b (768 miligramos, 2.0 milimoles) en N,N'-dimetil-formamida (2.0 mililitros) y $CH_2Cl_2$ (2.0 mililitros) a 0 °C, se le agrega hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (836 miligramos, 2.2 milimoles, 1.1 equivalentes), el 7f (417 miligramos, 2.0 milimoles, 1.0 equivalentes) y N-metil-morfolina (0.658 mililitros, 6.0 milimoles, 3.0 equivalentes). La solución se agita a temperatura ambiente durante 3 horas. A la mezcla de reacción se le agrega una solución acuosa saturada de

$NaHCO_3$ y EtOAc/dietil-éter 1/1. Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con HCl 1.0 N, salmuera, se secan sobre $Na_2SO_4$ y se concentran. El material crudo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOH, 9/1) para dar el producto 11c.

Se agrega ácido trifluoro-acético (3.0 mililitros) a una solución del 11c en $CH_2Cl_2$ (3.0 mililitros), y la solución se agita a temperatura ambiente durante 1 hora. Entonces se evapora el solvente. Se agregan una solución acuosa saturada de $NaHCO_3$, y $CH_2Cl_2$ al residuo. Las dos fases se separan, y la capa acuosa se extrae con $CH_2Cl_2$. Las capas orgánicas se combinan, se secan sobre $Na_2SO_4$ y se concentran para dar el 11d.

A una solución de N-metil-morfolina (0.028 mililitros) e isocianato de terbutilo (25 miligramos) en $CH_2Cl_2$, se le agrega el 11d (100 miligramos). La solución se agita a temperatura ambiente durante 4 horas. La solución se carga en gel de sílice y se inunda con heptano/acetona (1/1), para dar el producto 11e (91 miligramos).

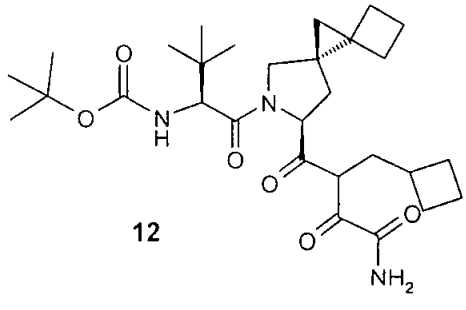
**Paso 11-C:**



11e 11

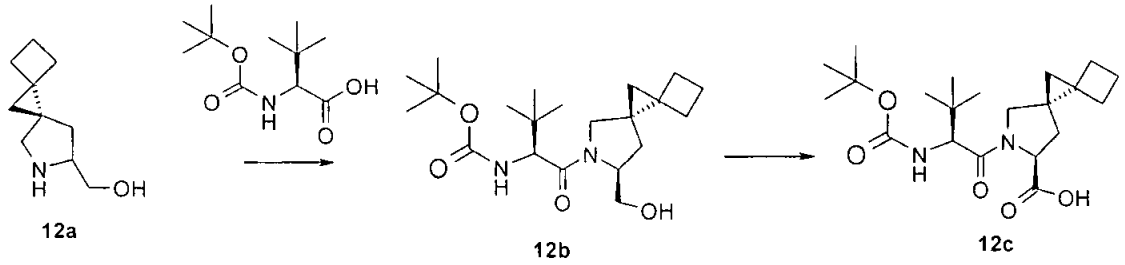
A una solución del alcohol 11e (91 miligramos) en $CH_2Cl_2$ (0.6 mililitros) a 0 °C, se le agrega N-etil-di-isopropil-amina (0.160 mililitros), seguida por una solución de $Py•SO_3$ (89 miligramos) en sulfóxido de dimetilo (0.6 mililitros). La solución se agita a 0 °C durante 10 minutos. La mezcla se carga directamente en una columna de gel de sílice, y se inunda con heptano/acetona (1/1) para dar el producto 11 (65 miligramos). m/z encontrada ES+ = 534.

**Ejemplo 12:**



12

**Paso 12-A:**



12a 12b 12c

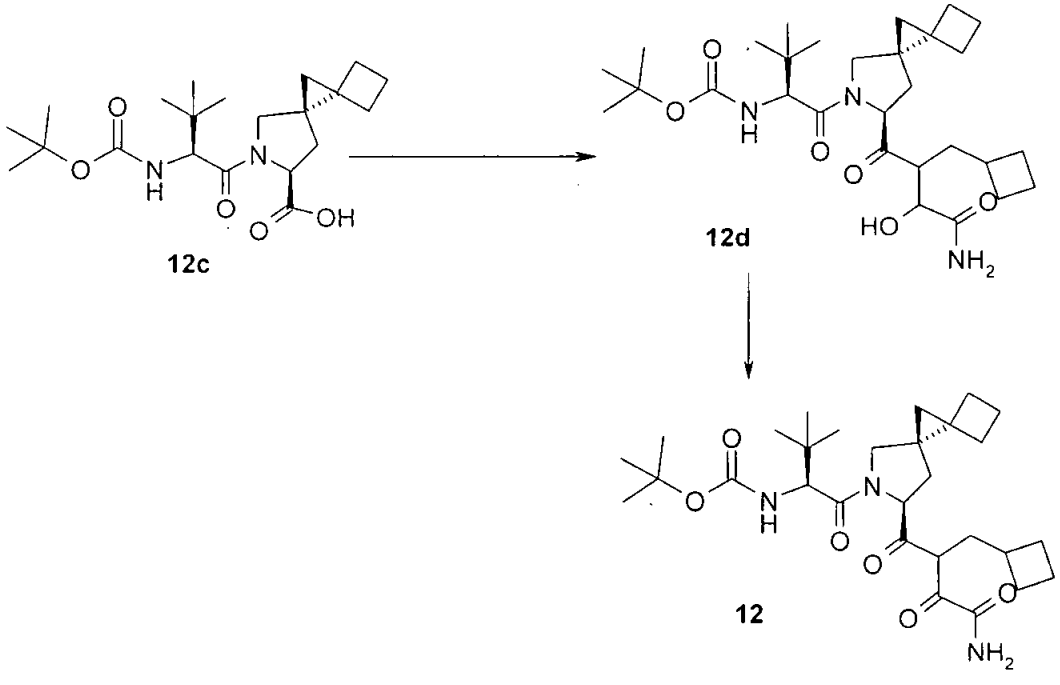
El amino-alcohol 12a se prepara a partir del 8a y ciclobutanona de acuerdo con el procedimiento descrito para la síntesis del 9f a partir del 8a.

A una solución de Boc-L-terbutil-gly-OH (277 miligramos, 1.20 milimoles, 1.0 equivalentes) y el 12a (200 miligramos, 1.20 milimoles, 1.0 equivalentes) en $CH_2Cl_2$ (10.0 mililitros) a -20 °C, se le agrega hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (0.55 gramos, 1.44 milimoles, 1.2 equivalentes), seguido por N-etil-di-isopropil-amina (0.63 mililitros, 3.60 milimoles, 3.0 equivalentes). La solución se agita a -20 °C durante 24 horas, y a 0 °C durante 1 hora. La mezcla de reacción se diluye con EtOAc y se lava con ácido cítrico al 10 por ciento. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan y se lavan con $NaHCO_3$ acuoso saturado, salmuera, se secan ($Na_2SO_4$), y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOAc, 1/1) para dar el producto 12b.

A una solución del 12b (0.40 gramos, 1.05 milimoles) en acetona (10.0 mililitros) a 0 °C, se le agrega una solución de reactivo de Jones (3.0 M, 2.1 mililitros, 5.3 milimoles). La mezcla se

mantiene a 0 °C durante 1 hora. La reacción se apaga entonces mediante la adición lenta de *i*-PrOH (3.0 mililitros), y entonces la mezcla se diluye con EtOAc. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan ($Na_2SO_4$), y se concentran, para proporcionar el 12c.

**Paso 12-B:**

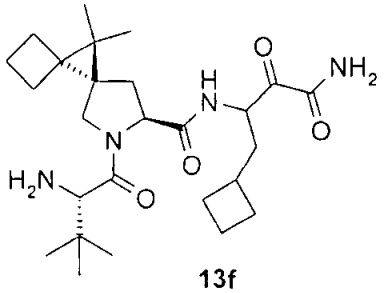



A una solución del ácido 12c (0.39 miligramos, 0.99 milimoles) y el 7f (206 miligramos, 0.99 milimoles, 1.0 equivalentes) en N,N'-dimetil-formamida (8.0 mililitros) y $CH_2Cl_2$ (8.0 mililitros) a 0°C, se le agregan hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (452 miligramos, 1.19 milimoles, 1.2 equivalentes) y N-metil-morfolina (0.33 mililitros, 2.97 milimoles, 3.0

equivalentes). La solución se agita a temperatura ambiente durante 4 horas. A la mezcla de reacción se le agrega una solución acuosa saturada de $NaHCO_3$ y EtOAc/dietil-éter (1/1). Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con solución acuosa de HCl 1.0N, salmuera, se secan ($Na_2SO_4$) y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOH, 9/1) para dar el producto 12d.

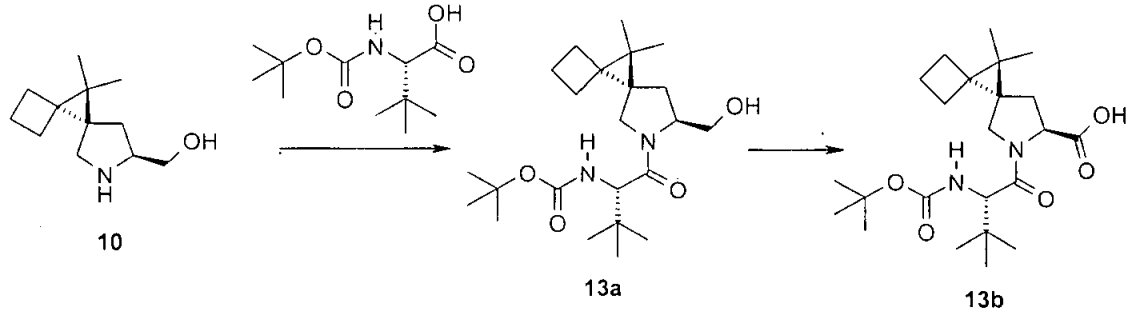
A una solución del 12d (100 miligramos, 0.18 milimoles) en $CH_2Cl_2$ (1.0 mililitros) y sulfóxido de dimetilo (1.0 mililitros) a 0 °C, se le agrega N-etil-di-isopropil-amina (0.19 mililitros, 1.10 milimoles, 6 equivalentes), seguida por $Py{\bullet}SO_3$ (87 miligramos, 0.55 milimoles, 3 equivalentes). La solución se agita a 0 °C durante 10 minutos. La mezcla se carga directamente en una columna de gel de sílice, y se inunda con heptano/acetona (1:1) para dar 55 miligramos del producto 12. m/z encontrada ES+ = 532.

**Ejemplo 13:**



**13f**

**Paso 13-A:**



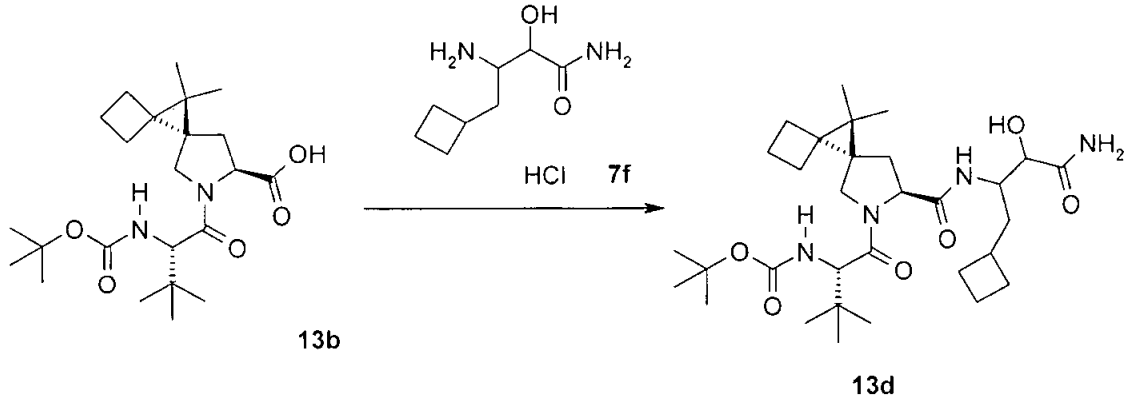
10 13a 13b

A una solución de Boc-L-terbutil-gly-OH (711 miligramos, 3..08 milimoles, 1.0 equivalentes) y el amino-alcohol 10 (600 miligramos, 3.08 milimoles, 1.0 equivalentes) en $CH_2Cl_2$ (15.0 mililitros) a -20 °C, se le agrega hexafluorofosfato de O-(7-aza-benzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.4 gramos, 3.69 milimoles, 1.2 equivalentes), seguido por N-etil-di-isopropil-amina (1.6 mililitros, 9.2 milimoles, 3.0 equivalentes). La solución se agita a -20 °C durante 24 horas, a 0 °C durante 3 horas, y a temperatura ambiente durante 1 hora. La mezcla de reacción se diluye con EtOAc y se lava con una solución acuosa de HCl 1.0N. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan y se lavan con $NaHCO_3$ acuoso saturado, salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOAc, 1/1) para dar el producto 13a. m/z encontrada ES+ = 409.

A una solución del alcohol 13a (890 miligramos) en acetona (10.0 mililitros) a -5 °C, se le agrega una solución del reactivo de Jones (3.0 M, 5.0 mililitros). La mezcla se calienta a 0 °C y se agita

a esta temperatura durante 2 horas. La reacción se apaga entonces mediante la adición lenta de *i*-PrOH (5.0 mililitros) y entonces la mezcla se diluye con EtOAc. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan ($Na_2SO_4$), y se concentran para dar el producto 13b. m/z encontrada ES+ = 423.

**Paso 13-B:**

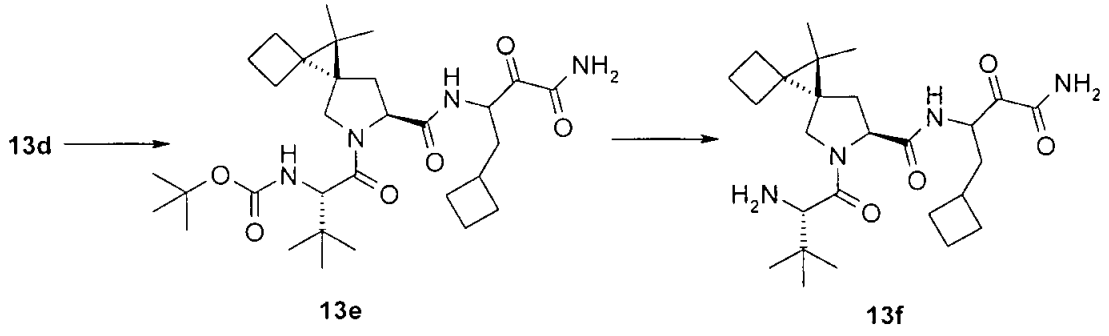



**13b** **13d**

A una solución del ácido (906 miligramos, 2.1 milimoles) en N,N'-dimetil-formamida (8.0 mililitros) y $CH_2Cl_2$ (8.0 mililitros) a 0 °C, se le agregan hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (958 miligramos, 2.5 milimoles, 1.2 equivalentes), amino-alcohol (492 miligramos, 2.4 milimoles, 1.1 equivalentes), y N-metil-morfolina (0.692 mililitros, 6.3 milimoles, 3.0 equivalentes). La solución se agita a temperatura ambiente durante 3 horas. A la mezcla de reacción se le agregan una solución acuosa saturada de $NaHCO_3$, y EtOAc/dietil-éter, 1/1. Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas

orgánicas se combinan, se lavan con HCl 1N, salmuera, se secan sobre $Na_2SO_4$ y se concentran. El material crudo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOH, 9/1) para dar el producto 13d. m/z encontrada ES+ = 577.

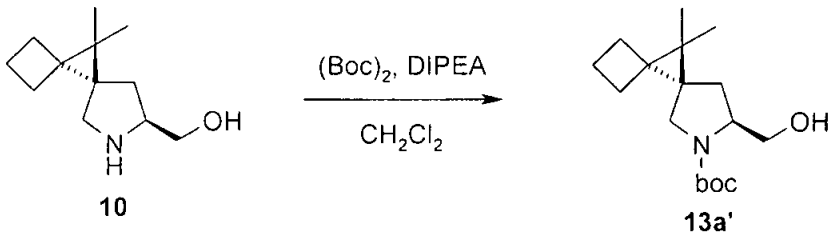
**Paso 13-C:**




A una solución del alcohol 13d (450 miligramos) en $CH_2Cl_2$ (0.6 mililitros) a 0 °C, se le agrega N-etil-di-isopropil-amina (0.504 mililitros), seguida por una solución de complejo $Py{\bullet}SO_3$ (372 miligramos) en sulfóxido de dimetilo (0.6 mililitros). La solución se agita a 0 °C durante 10 minutos. La mezcla se carga directamente en una columna de gel de sílice, y se inunda con heptano/acetona para dar el producto 13e. m/z encontrada ES+ = 575.

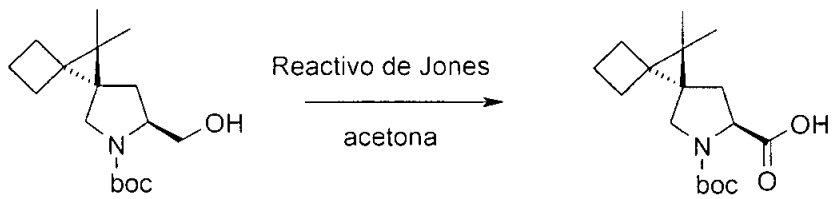
El producto se disuelve en 15 mililitros of HCl 4.0 M en dioxano. La solución se agita a temperatura ambiente durante 2 horas. La solución se diluye con 50 mililitros de heptano y se concentra, para dar el producto crudo 13f, el cual se lleva adelante hasta el siguiente paso sin purificación. m/z encontrada ES+ = 475.

**Ruta sintética alternativa a partir del 10 hasta el 13d.**



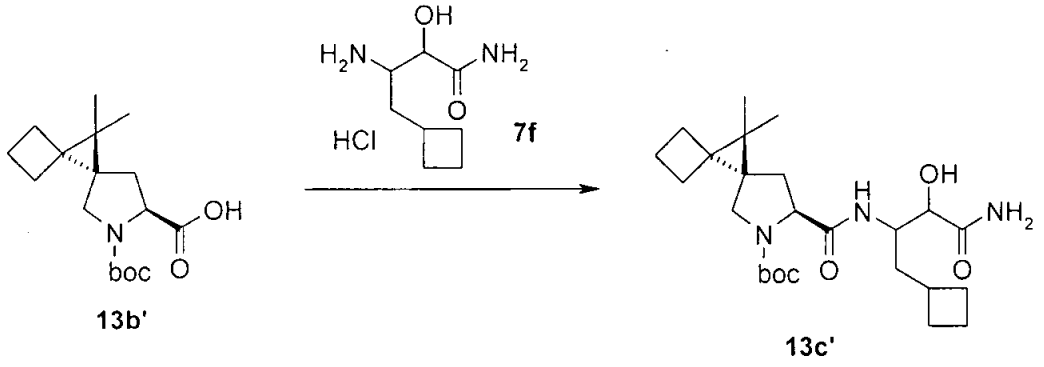

**10** **13a'**

A una solución del 10 (1.95 gramos, 10 milimoles) en $CH_2Cl_2$ (20.0 mililitros) a temperatura ambiente, se le agregan anhídrido de Boc y N-etil-di-isopropil-amina (0.434 mililitros, 10.5 milimoles, 1.05 equivalentes). La solución se agita a temperatura ambiente durante 2 horas. Se evapora el solvente y el residuo se purifica mediante cromatografía en gel de silice (heptano/EtOAc, 2/1) para dar el producto 13a', 2.1 gramos.

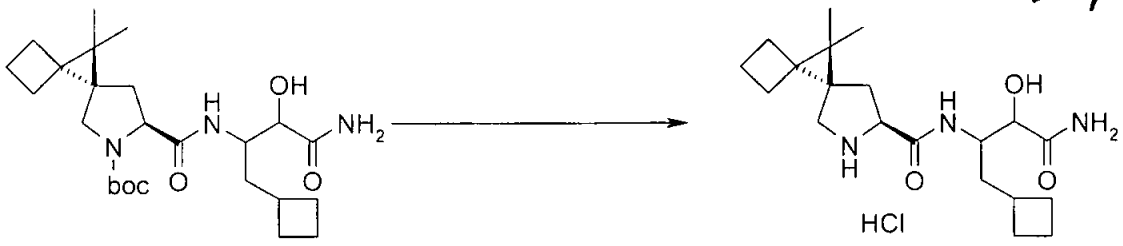



**13a'** **13b'**

A una solución del alcohol 13a' (3.0 gramos, 10.2 milimoles) en acetona (30.0 mililitros) a 0 °C, se le agrega reactivo de Jones (12.2 mililitros, 30.5 milimoles, 3.0 equivalentes). La solución se agita a 0 °C durante 1.0 hora. La reacción se apaga mediante la adición de i-PrOH (5.0 mililitros). La solución se diluye entonces con EtOAc y se filtra. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con salmuera, se secan sobre $Na_2SO_4$ y se concentran. El material crudo se continúa hasta el siguiente paso sin mayor purificación.

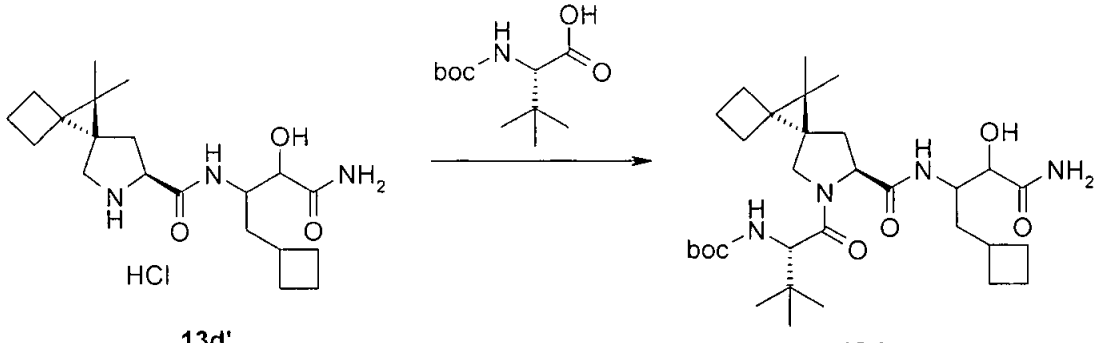



A una solución del ácido carboxílico 13b' (1.0 gramos, 3.2 milimoles) en $CH_2Cl_2$ (8.0 mililitros) y N,N'-dimetil-formamida (8.0 mililitros) a 0 °C, se le agregó el 11c (673 miligramos, 3.2 milimoles, 1.0 equivalentes), seguido por hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.45 gramos, 3.8 milimoles, 1.2 equivalentes) y N-metil morfolina (1.05 mililitros, 9.6 milimoles, 3.0 equivalentes). La solución se agita a temperatura ambiente durante 4 horas. A la solución se le agrega EtOAc y $NaHCO_3$ acuoso saturado. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con una solución acuosa de HCl 1.0N, salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en gel de sílice (heptano/acetona, 1/1) para dar el producto 13c', 975 miligramos. MS encontrada ES+ = 464.



13c' 13d'

A un matraz que contiene el 13c', se le agregan 10 mililitros de HCl 4.0 N en dioxano. La solución se agita a temperatura ambiente durante 1.0 hora. Entonces se evapora el solvente, para dar el producto crudo 13d', el cual se continúa hasta el siguiente paso sin purificación. MS encontrada ES+ = 364, ES- = 362.

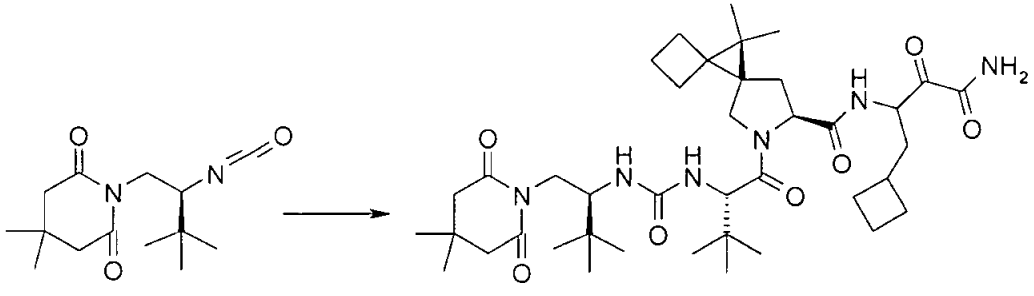


13d' 13d

A las mezclas de Boc-L-terbutil-gly-OH (297 miligramos, 1.29 milimoles, 1.0 equivalentes), el 13d' (515 miligramos, 1.29 milimoles, 1.0 equivalentes) en $CH_2Cl_2$ (7.0 mililitros) a -20 °C, se les agregan hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (585 miligramos, 1.54 milimoles, 1.2 equivalentes) y N-etil-di-isopropil-amina (0.696 mililitros, 4.0 milimoles, 3.0

equivalentes). La solución se agita a -20 °C durante 12 horas, y luego a 0 °C durante 1.0 hora. A la solución se le agrega EtOAc y una solución acuosa saturada de $NaHCO_3$. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con una solución acuosa de HCl 1.0N, salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en gel de sílice (heptano/acetona, 1/1) para dar el producto, 610 miligramos. MS encontrada ES+ = 577, ES- = 575.

**Ejemplo 13h:**

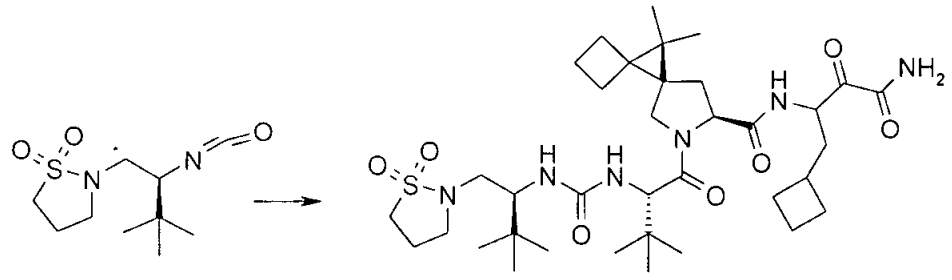


**13g** **13h**

A una solución de la sal de clorhidrato de amina 13f (37.5 miligramos) en $CH_2Cl_2$ (1.0 mililitros), se le agregan N-etil-di-isopropil-amina (0.012 mililitros) y una solución del 13g (23 miligramos) en tolueno (1.5 mililitros). La solución se agita a temperatura ambiente durante 2 horas. La solución se concentra y el material crudo se purifica mediante cromatografía en columna de gel

de sílice, para dar 20 miligramos del producto 13h. m/z encontrada ES+ = 741.

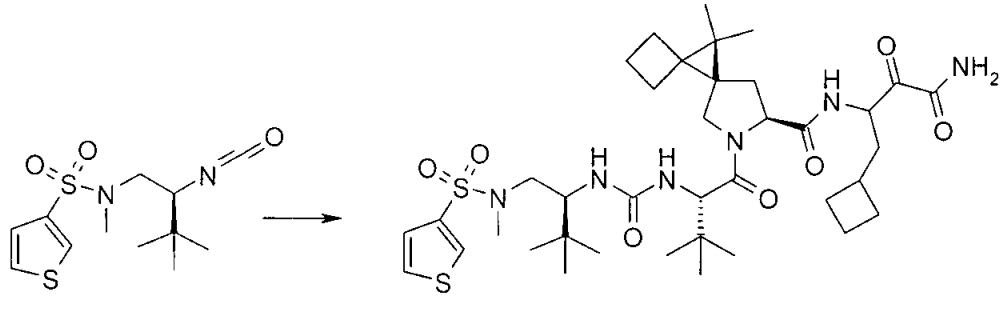
**Ejemplo 13j:**



13i 13j

A una solución de la sal de clorhidrato de amina 13f (37 miligramos) en $CH_2Cl_2$ se le agregan N-etil-di-isopropil-amina (0.012 mililitros) y una solución del 13i (21 miligramos) en tolueno (1.5 mililitros). La solución se agita a temperatura ambiente durante 2 horas. La solución se concentra y el material crudo se purifica mediante cromatografía en columna de gel de sílice, para dar 6 miligramos del producto 13j. m/z encontrada ES+ = 721.

**Ejemplo 13l:**

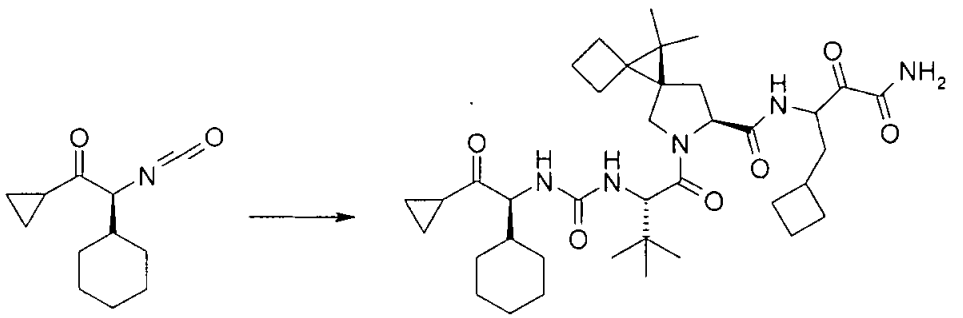


13k 13l

A una solución de la sal de clorhidrato de amina 13f (37 miligramos) en $CH_2Cl_2$ se le agregan N-etil-di-isopropil-amina (0.012 mililitros) y una solución del 13k (26 miligramos) en tolueno (1.5

mililitros). La solución se agita a temperatura ambiente durante 2 horas. La solución se concentra y el material crudo se purifica mediante cromatografía en columna de gel de sílice, para dar 15 miligramos del producto 13l. m/z encontrada ES+ = 777.

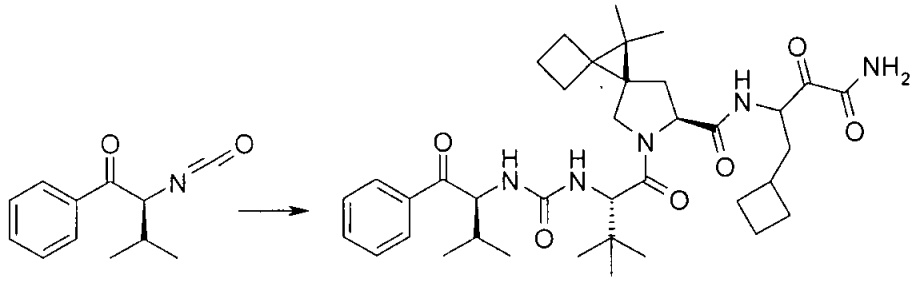
**Ejemplo 13n:**



13m 13n

A una solución de la sal de clorhidrato de amina 13f (37 miligramos) en $CH_2Cl_2$ se le agregan N-etil-di-isopropil-amina (0.012 mililitros) y una solución del 13m (18 miligramos) en tolueno (1.5 mililitros). La solución se agita a temperatura ambiente durante 2 horas. La solución se concentra y el material crudo se purifica mediante cromatografía en columna de gel de sílice, para dar 29 miligramos del producto 13n. m/z encontrada ES+ = 682.

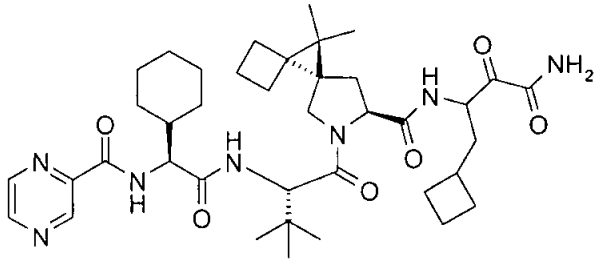
**Ejemplo 13p:**



13o 13p

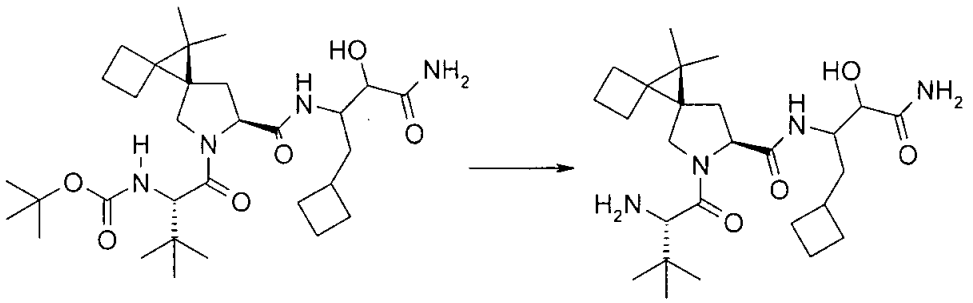
A una solución de la sal de clorhidrato de amina 13f (37 miligramos) en $CH_2Cl_2$ se le agregan N-etil-di-isopropil-amina (0.012 mililitros) y una solución del 13o (18 miligramos) en tolueno (1.5 mililitros). La solución se agita a temperatura ambiente durante 2 horas. La solución se concentra y el material crudo se purifica mediante cromatografía en columna de gel de sílice para dar 37.6 miligramos del producto 13p. m/z encontrada ES+ = 678.

**Ejemplo 14:**



14

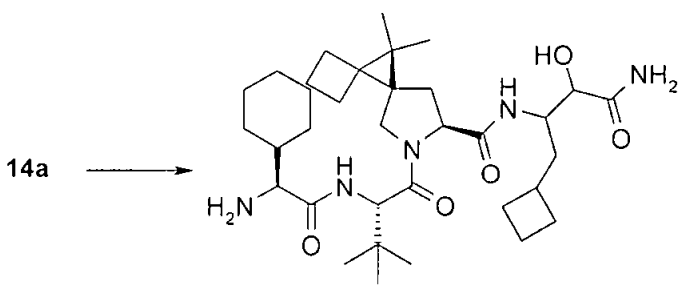
**Paso 14-A:**



13d 14a

A una solución de La N-Boc-amina 13d (690 miligramos) en dicloro-metano (5.0 mililitros) a temperatura ambiente, se le agrega ácido trifluoro-acético (5.0 mililitros). La mezcla se agita durante 3 horas, después de lo cual el solvente se evapora al vacio y se agrega dicloro-metano (100 mililitros) al residuo. The pH se ajusta a un pH de 8 mediante la adición por goteo de bicarbonato de sodio saturado. Las capas se separan, y la capa orgánica se lava con salmuera, se seca sobre $Na_2SO_4$, se filtra y se concentra, para dar el producto de la amina 14a. m/z encontrada ES+ =477.

**Paso 14-B:**

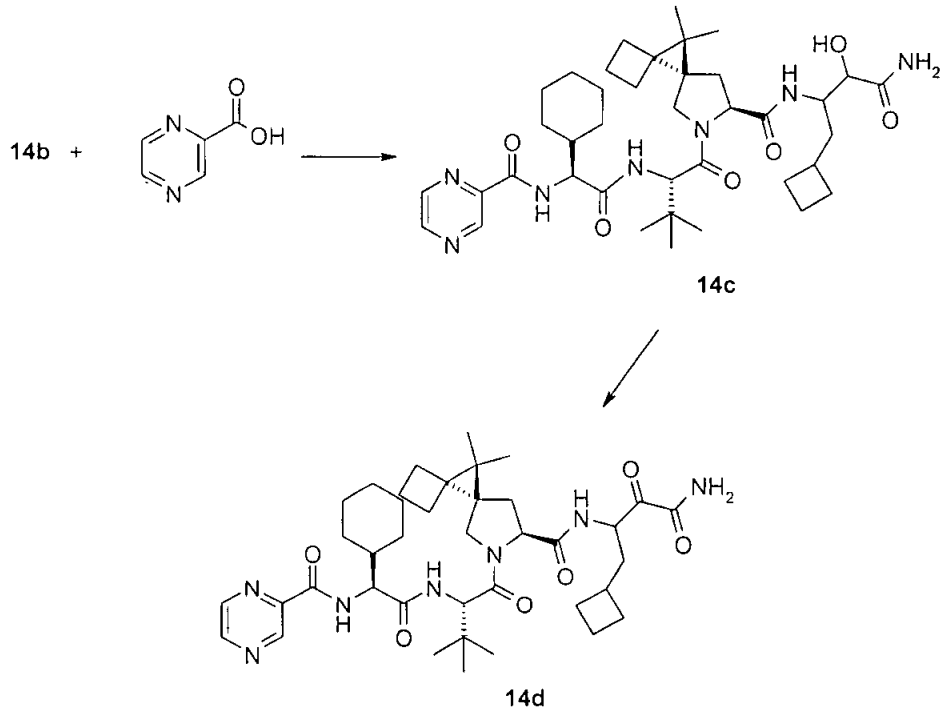


14a 14b

A una solución del ácido (S)-2-(terbutoxi-carbonil-amino)-2-

ciclo-hexil-acético (51.4 miligramos, 0.2 milimoles) en N,N'-dimetil-formamida (1.0 mililitros) y $CH_2Cl_2$ (1.0 mililitros) a 0 °C, se le agregan hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (91 miligramos, 0.24 milimoles, 1.2 equivalentes), la amina 14a (95 miligramos, 0.2 milimoles, 1.0 equivalentes), y N-metil-morfolina (0.066 mililitros, 0.6 milimoles, 3.0 equivalentes). La solución se agita a temperatura ambiente durante 3 horas. A la mezcla de reacción se le agregan una solución acuosa saturada de $NaHCO_3$, y EtOAc/dietil-éter 1/1. Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con HCl 1N, salmuera, se secan sobre $Na_2SO_4$ y se concentran. El material crudo se purifica mediante cromatografía en columna de gel de sílice (hexano/EtOH, 9/1) para dar la amina protegida por Boc (M/z encontrada ES+ =716). El producto se disuelve en dicloro-metano (5 mililitros) a temperatura ambiente, y se agrega ácido trifluoro-acético (5 mililitros). La mezcla se agita durante 3 horas, después de lo cual se evapora el solvente al vacío. El residuo se disuelve en dicloro-metano (100 mililitros). El pH se ajusta a un pH de 8 mediante la adición por goteo de bicarbonato de sodio saturado. Las capas se separan, y la capa orgánica se lava con salmuera, se seca sobre $Na_2SO_4$, se filtra y se concentra, para dar el producto 14b. m/z encontrada ES+ =616.

**Paso 14-C:**

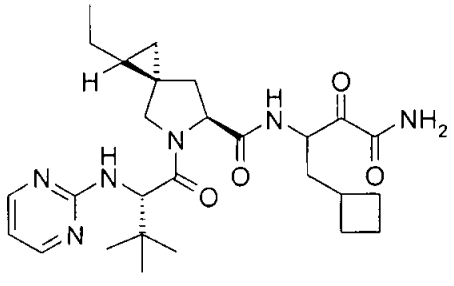



A una solución del ácido pirazin-2-carboxílico (20 miligramos, 0.16 milimoles) en N,N'-dimetil-formamida (1.0 mililitros) y $CH_2Cl_2$ (1.0 mililitros) a 0 °C, se le agregan hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (73 miligramos, 0.19 milimoles, 1.2 equivalentes), la amina 14b (100 miligramos, 0.16 milimoles, 1.0 equivalentes) y N-metil-morfolina (0.053 mililitros, 0.48 milimoles, 3.0 equivalentes). La solución se agita a temperatura ambiente durante 3 horas. A la mezcla de reacción se le agregan una solución acuosa saturada de $NaHCO_3$, y EtOAc/dietil-éter, 1/1. Las dos fases se separan, y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con HCl 1N, salmuera, se secan sobre $Na_2SO_4$ y se concentran. El material crudo se purifica mediante cromatografía en columna de gel de sílice

(hexano/EtOH, 9/1) para dar el producto 14c. m/z encontrada ES+ =722.

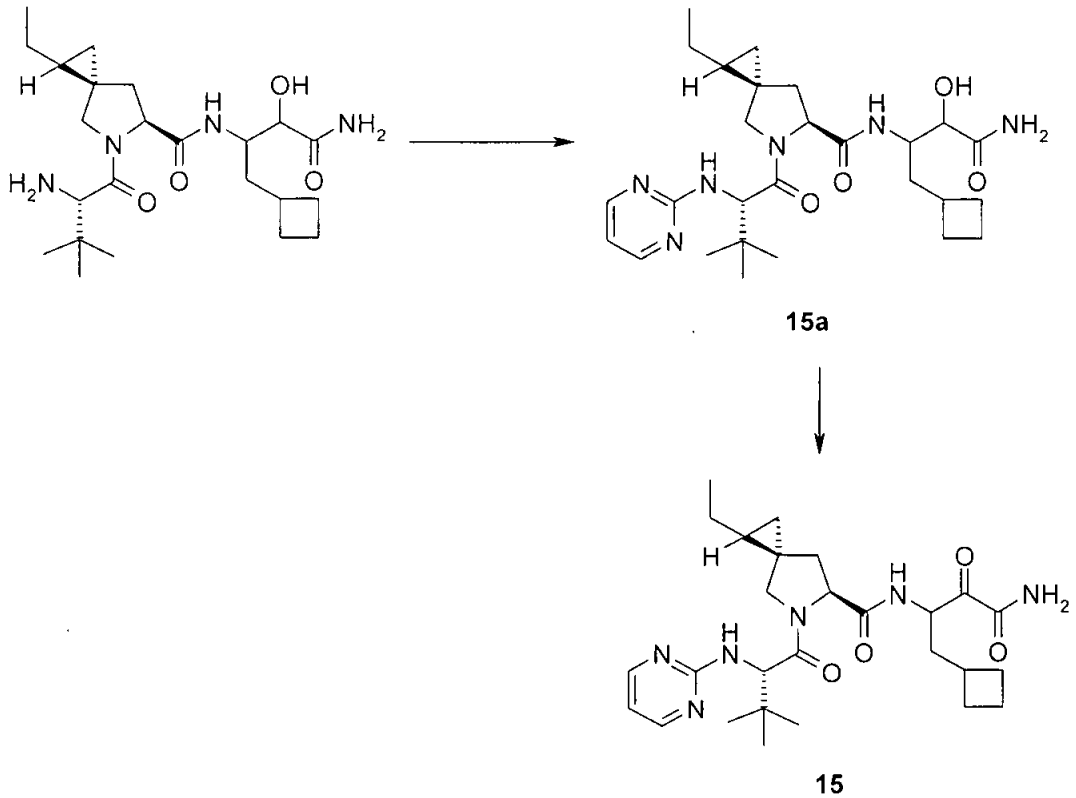
A una solución del alcohol 14c (110 miligramos) en $CH_2Cl_2$ (0.6 mililitros) a 0 °C, se le agrega N-etil-di-isopropil-amina (0.160 mililitros), seguida por una solución del complejo de trióxido de azufre-piridina (89 miligramos) en sulfóxido de dimetilo (0.6 mililitros). La solución se agita a 0 °C durante 10 minutos. La mezcla se carga directamente sobre una columna de gel de sílice, y se inunda con heptano/acetona, para dar el producto 14d (71 miligramos). m/z encontrada ES+ = 720.

**Ejemplo 15:**



**15**

**Esquema:**



15a

15

**Paso 15-A:**

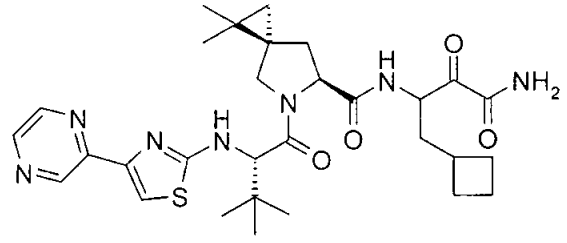
A una solución de amina (87 miligramos, 0.2 milimoles, 1.0 equivalentes) en alcohol isopropílico (0.4 mililitros) a temperatura ambiente, se le agregan 2-bromo-pirimidina (32 miligramos, 0.2 milimoles, 1.0 equivalentes) y N-etil-di-isopropil-amina (0.034 mililitros, 0.2 milimoles, 1.0 equivalentes). La solución se calienta a 80 °C durante 24 horas. El material crudo se purifica mediante cromatografía en gel de sílice (heptano/acetona, 1/1), para dar el producto deseado. m/z encontrada ES+ = 515.

**Paso 15-B:**

A una solución del 15a (90 miligramos) en $CH_2Cl_2$ (0.6 mililitros), se le agregan N-etil-di-isopropil-amina (0.12 mililitros) y

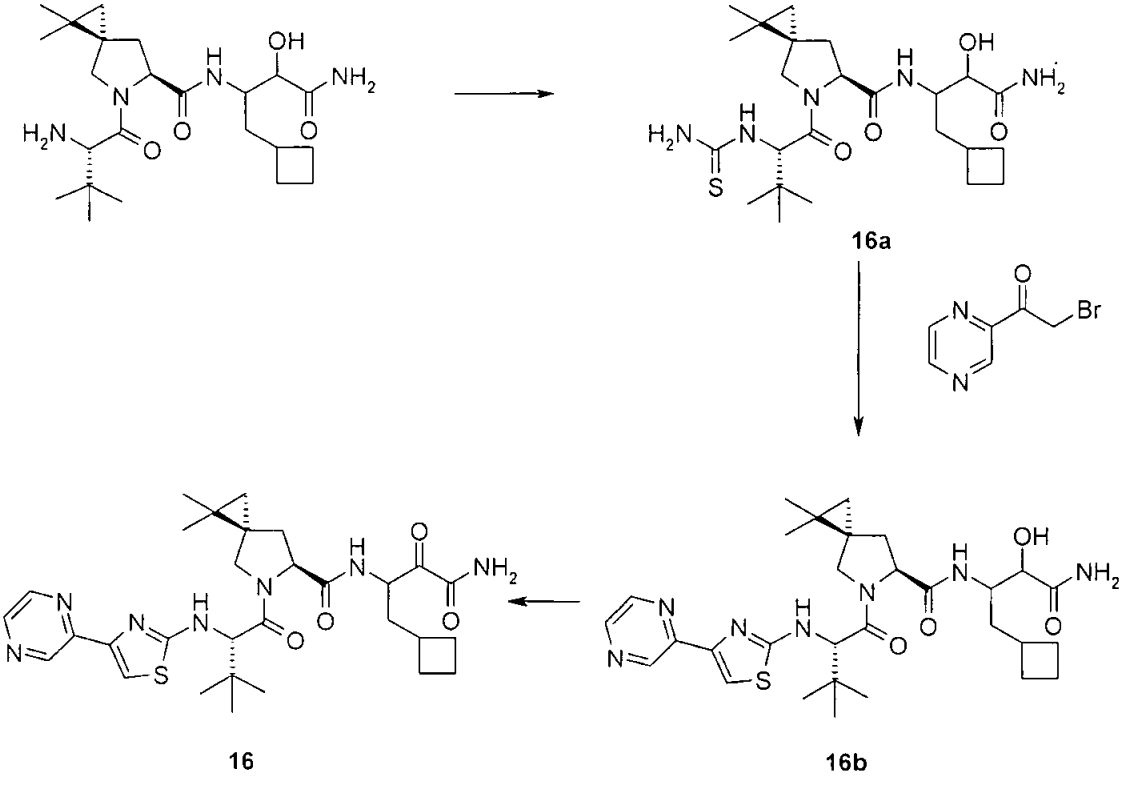
una solución de $Py \cdot SO_3$ (80 miligramos) en sulfóxido de dimetilo (0.6 mililitros). La solución se agita a temperatura ambiente durante 10 minutos. La solución se carga en gel de sílice y se inunda con heptano/acetona (1/1), para dar 28 miligramos del producto 15. m/z encontrada ES+ = 513.

**Ejemplo 16:**



**16**

**Síntesis de tiazol:**




**Paso 16-A:**

Se agrega isotiocianato de benzoílo (162 miligramos) a una solución de amina (400 miligramos) en acetona (4.0 mililitros) . La solución se calienta a 70 °C durante 2 horas. Entonces, a la solución se le agregan carbonato de potasio (40 miligramos), agua (0.4 mililitros), y MeOH (4.0 mililitros). La solución se calienta entonces a 80 °C durante 4 horas. La mezcla se concentra y el residuo crudo se purifica mediante cromatografía en gel de sílice ($CH_2Cl_2$/MeOH, 4/1), para dar el intermediario de tiourea 16a. m/z encontrada ES+ = 497.

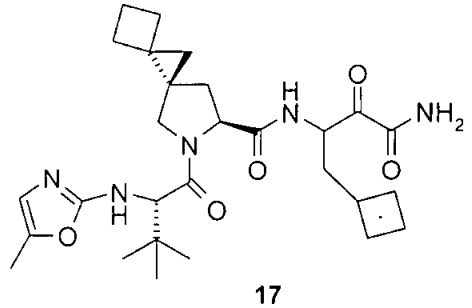
**Paso 16-B:**

La tiourea (70 miligramos) y 2-bromo-1-pirazin-2-il-etanona (30 miligramos) se disuelven en etanol (0.5 mililitros), y la solución se calienta a reflujo durante 1 hora. El material crudo se purifica mediante cromatografía en gel de sílice ($CH_2Cl_2$/EtOH, 9/1), para dar el producto 16b. m/z encontrada ES+ = 598.

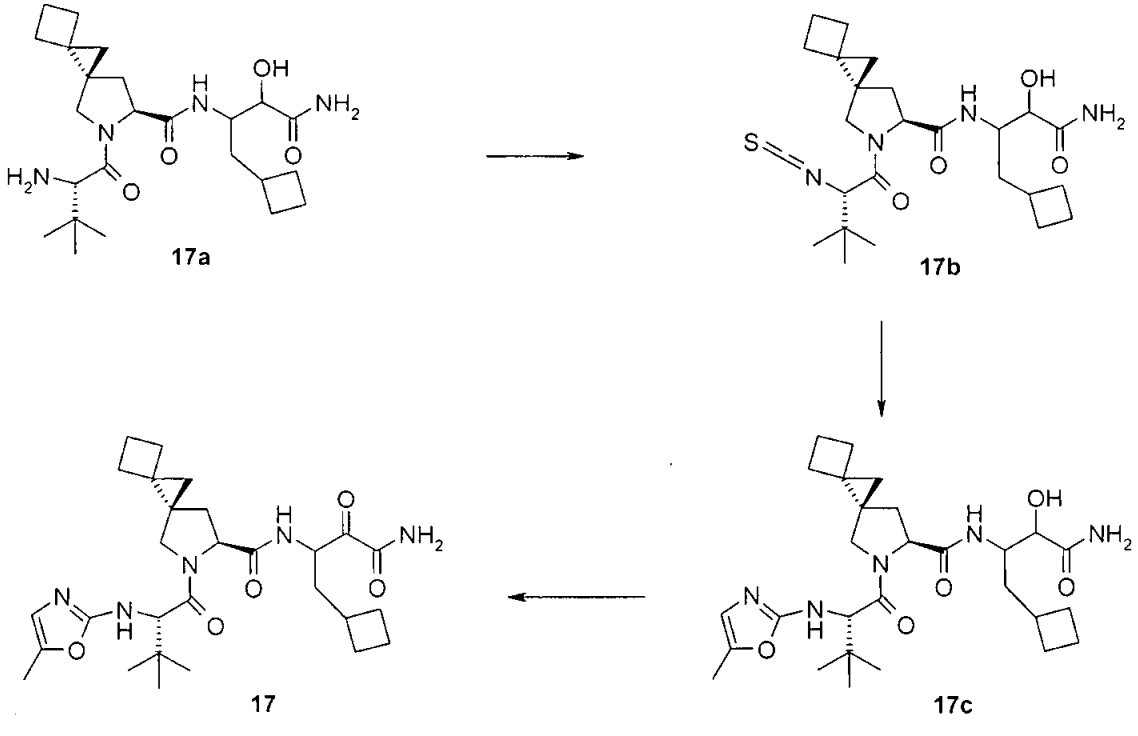
**Paso 16-C:**

A una solución del 16b (70 miligramos) en $CH_2Cl_2$ (1.0 mililitros) se le agregan N-etil-di-isopropil-amina (0.12 mililitros) y una solución de Py•$SO_3$ (80 miligramos) en sulfóxido de dimetilo (0.6 mililitros). La solución se agita a temperatura ambiente durante 10 minutos. La solución se carga en gel de sílice y se inunda con heptano/acetona (1/1), para dar 25 miligramos del producto 16. m/z encontrada ES+ = 513.

**Ejemplo 17:**



17




**Paso 17-A:**

A una solución del 17a (5.31 gramos, 11.86 milimoles) en $CH_2Cl_2$ (40 mililitros) a 0 °C, se le agregan $NaHCO_3$ acuoso saturado (40 mililitros) y $CSCl_2$ (1.1 mililitros, 14.23 milimoles). La mezcla se agita a temperatura ambiente durante 30 minutos. Las fases se separan y la capa orgánica se lava con salmuera, se seca sobre

$Na_2SO_4$, y se concentra. El material crudo se purifica mediante cromatografía en gel de sílice (heptano/EtOAc, 1/1), para dar el producto 17b (1.20 gramos, rendimiento del 21 por ciento) como un sólido amarillo claro. m/z encontrada ES+ = 491.

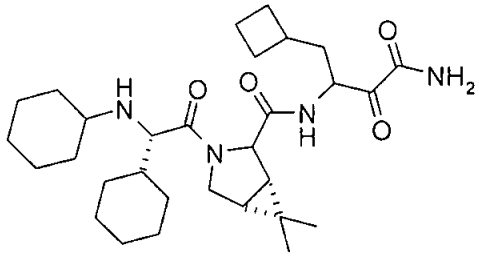
**Paso 17-B:**

A una solución del 17b (60 miligramos, 0.122 milimoles) en dioxano, se le agrega $PPh_3$ (38.6 miligramos, 0.147 milimoles), seguido por 1-azido-propan-2-ona (14.5 miligramos, 0.147 milimoles). La solución se calienta a 90 °C durante 1 hora. Entonces se agrega 2-metil-propan-1,2 diamina (0.20 mililitros), y la solución se calienta a 50 °C durante 30 minutos. La mezcla cruda se separa mediante cromatografía en columna de gel de sílice ($CH_2Cl_2$/EtOH, 4/1) para proporcionar el 17c (22 miligramos). m/z encontrada ES+ = 530.

**Paso 17-C:**

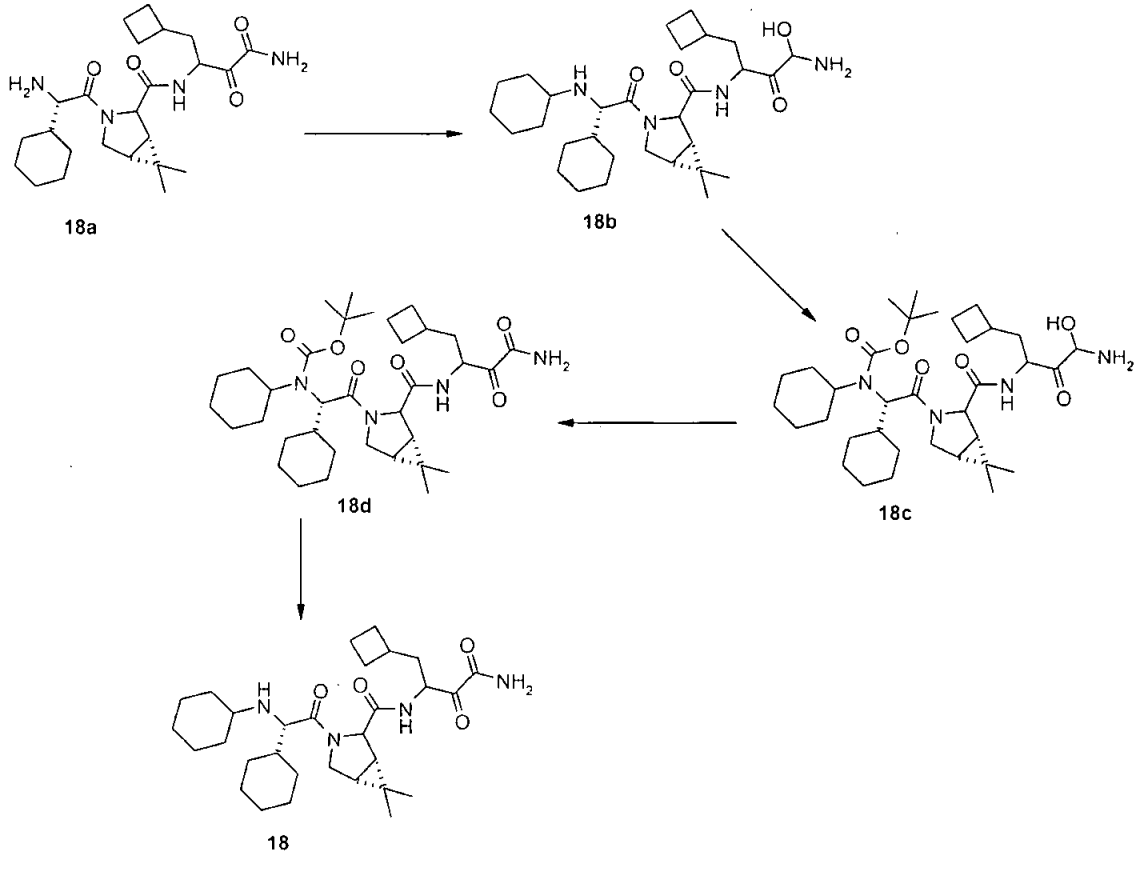
A una solución del 17c (22 miligramos, 0.042 milimoles) en $CH_2Cl_2$, se le agregan N-etil-di-isopropil-amina (0.044 mililitros, 0.252 milimoles) y sulfóxido de dimetilo (0.5 mililitros). Entonces la solución se enfría a 0 °C, y se agrega $Py{\bullet}SO_3$ (20 miligramos, 0.125 milimoles). La solución se agita a 0 °C durante 10 minutos. Las mezclas se separan mediante cromatografía (Heptano/Acetona, 1/1) para proporcionar el 17 (5 miligramos). m/z encontrada ES+ =528.

**Ejemplo18:**



**18**

**Esquema:**




**Paso 18-A:**

A una solución del 18a (89 miligramos, 0.2 milimoles) en $CH_2Cl_2$ (1.0 mililitros), se le agrega ciclohexanona (0.22 milimoles, 0.023 mililitros). La solución se agita durante 20 minutos a

temperatura ambiente, después de lo cual, se agrega triacetoxi-borohidruro de sodio (0.4 milimoles, 84 miligramos, y se agita durante otros 20 minutos. A las mezclas de reacción se les agrega una solución acuosa saturada de $NaHCO_3$. La capa orgánica se separa de la capa acuosa, y la capa acuosa se extrae con dicloro-metano (3 X 10 mililitros). Las capas orgánicas se combinan, se secan ($Na_2SO_4$) y se concentran, para dar 97 miligramos del 18b.

**Paso 18-B:**

A una solución del 18b (97 miligramos, 0.183 milimoles) en dicloro-metano, se le agregan $Et_3N$ (0.366 milimoles, 51 microlitros) y $(Boc)_2O$ (0.274 milimoles, 60 miligramos). La solución se agita a temperatura ambiente durante una hora, después de lo cual se lava con solución acuosa de HCl 1.0N (1 mililitros), solución acuosa saturada de $NaHCO_3$ (1 mililitros), y salmuera. La capa orgánica se seca sobre $Na_2SO_4$, y se concentra. El residuo se purifica mediante cromatografía en columna de gel de sílice (eluyente: acetona/ heptano, 1:1), para dar 95 miligramos del 18c.

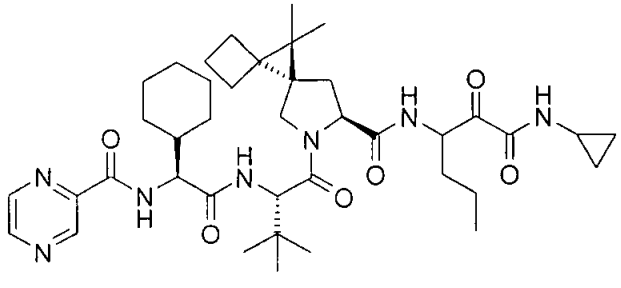
**Paso 18-C:**

A una solución del 18c (73 miligramos, 0.12mmol) en $CH_2Cl_2$ (0.5 mililitros), se le agregan N-etil-di-isopropil-amina (81 microlitros, 0.46 milimoles), y sulfóxido de dimetilo (0.5 mililitros). Entonces la solución se enfría a 0 °C, y se agrega $Py{\bullet}SO_3$ (37 miligramos, 0.23 milimoles). La solución se agita a 0 °C durante 10 minutos. Las mezclas se separan mediante cromatografía en gel de sílice (Heptanos/Acetona, 1/1), para proporcionar 67 miligramos del 18d.

**Paso 18-D:**

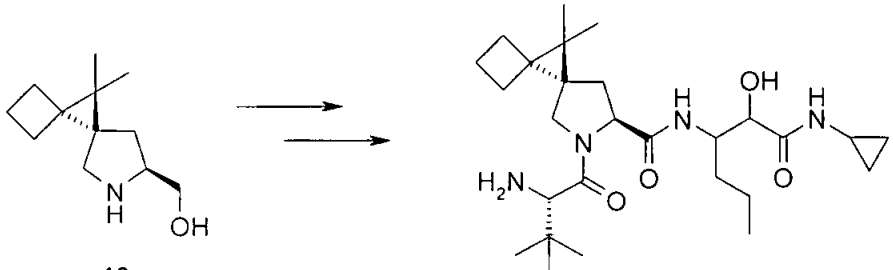
El producto 18d (66 miligramos, 0.104 milimoles) se disuelve en dioxano (0.2 mililitros), y a la solución se le agrega HCl 4.0 N en dioxano (0.105 mililitros) a 0 °C. La mezcla de reacción se agita a temperatura ambiente durante 24 horas, después de lo cual, la mezcla de reacción se concentra. El residuo se disuelve en dicloro-metano y la solución se lava con una solución acuosa saturada de $NaHCO_3$, y salmuera. La capa orgánica se seca sobre $Na_2SO_4$, y se pasa por cromatografía (Eluyente: Acetona/heptano, 1:1), para dar 33.5 miligramos del 18.

**Ejemplo 19:**



**19**

**Paso 19-A:**



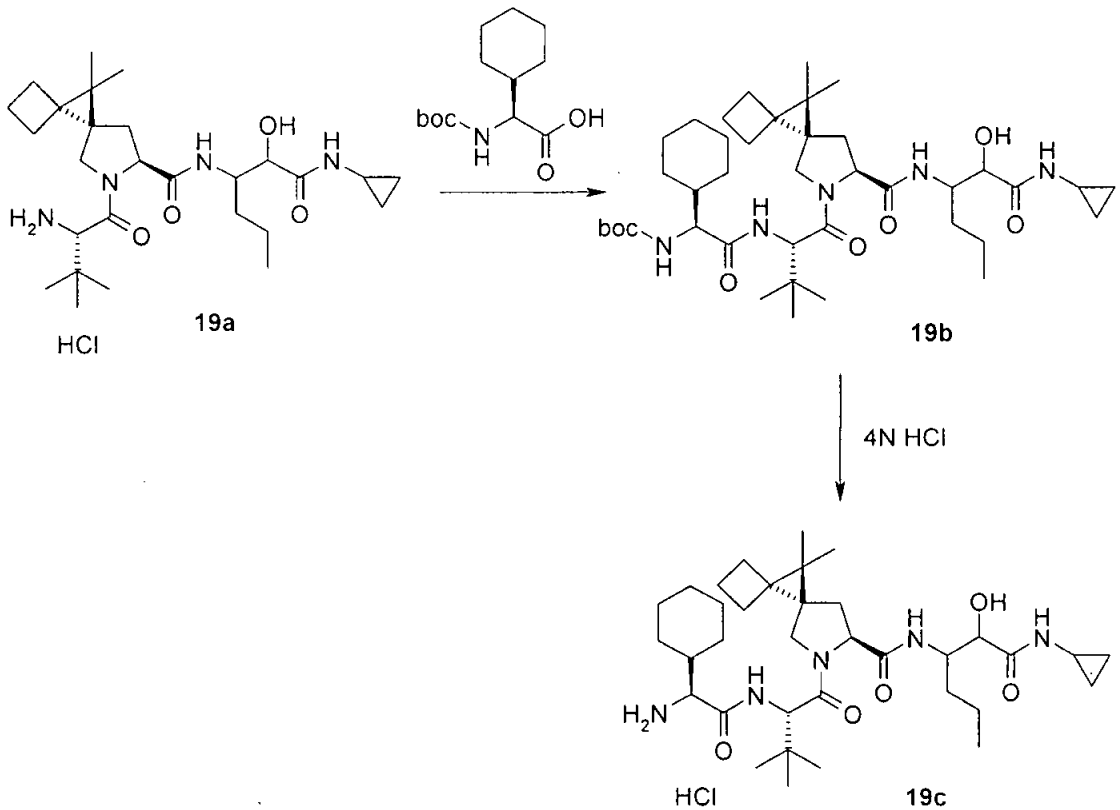
**10** **19a**

HCl

El Intermediario 19a se prepara de acuerdo con el procedimiento descrito para la síntesis del 13d. MS encontrada ES+

= 491.

**Paso 19-B:**

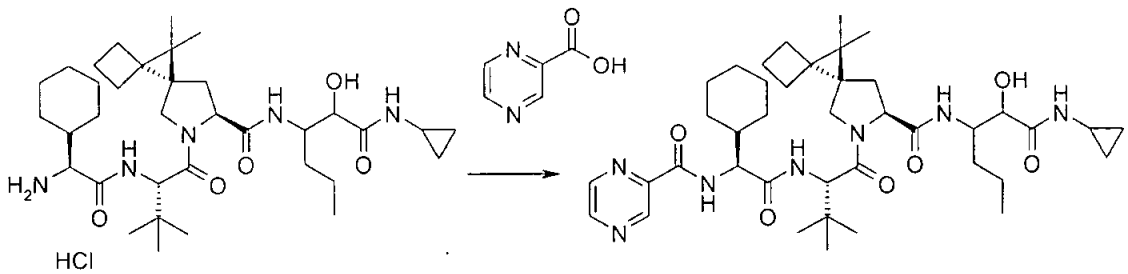



A una solución de Boc-L-ciclohexil-gly-OH (0.391 gramos, 1.53 milimoles) y el 19a (800 miligramos, 1.53 milimoles, 1.0 equivalentes) en $CH_2Cl_2$ (7.0 mililitros) y N,N'-dimetil-formamida (7.0 mililitros) a 0 °C, se le agregan hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (697 miligramos, 1.8 milimoles, 1.2 equivalentes) y N-metil morfolina (0.505 mililitros, 4.6 milimoles, 3.0 equivalentes). La solución se agita a temperatura ambiente durante 4 horas. A la solución se le agrega EtOAc y $NaHCO_3$ acuoso saturado. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con

una solución acuosa de HCl 1.0N, salmuera, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en gel de sílice (heptano/acetona, 1/1) para dar el producto 19b. MS encontrada ES+ = 730, ES- = 728.

A un matraz que contiene el 19b (1.02 gramos), se le agrega HCl 4.0 N en dioxano (10.0 mililitros). Se evapora el solvente para dar el material crudo 19c, el cual se continúa hasta el siguiente paso sin purificación. MS encontrada ES+ = 630, ES- = 628.

**Paso 19-C:**

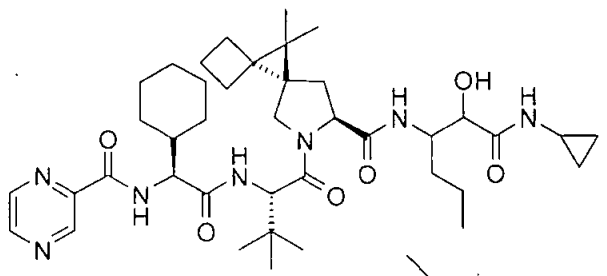



**19c** **19d**

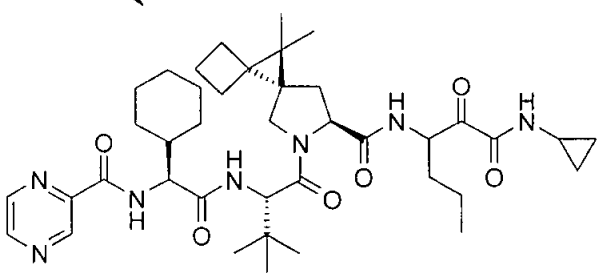
A una solución del ácido pirazin-2-carboxílico (0.175 gramos, 1.40 milimoles) y el 19c (938 miligramos, 1.40 milimoles, 1.0 equivalentes) en $CH_2Cl_2$ (7.0 mililitros) y N,N'-dimetil-formamida (3.0 mililitros) a 0 °C, se le agregan hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (639 miligramos, 1.7 milimoles, 1.2 equivalentes) y N-metil morfolina (0.461 mililitros, 4.2 milimoles, 3.0 equivalentes). La solución se agita a temperatura ambiente durante 4 horas. A la solución se le agrega EtOAc y $NaHCO_3$ acuoso saturado. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se lavan con una solución acuosa de HCl 1.0N, salmuera, se secan sobre $Na_2SO_4$

y se concentran. El residuo se purifica mediante cromatografía en gel de sílice (heptano/acetona, 1/1) para dar el producto 19d. MS encontrada ES+ = 736, ES- = 734.

**Paso 19-D:**



19d

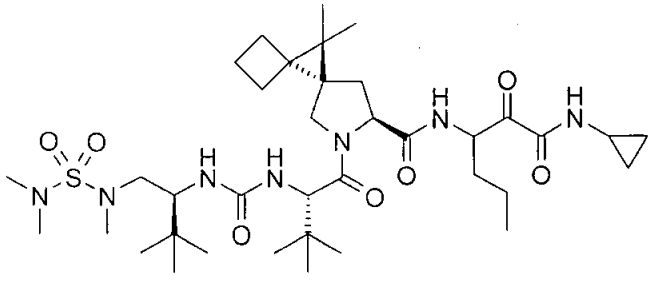


19

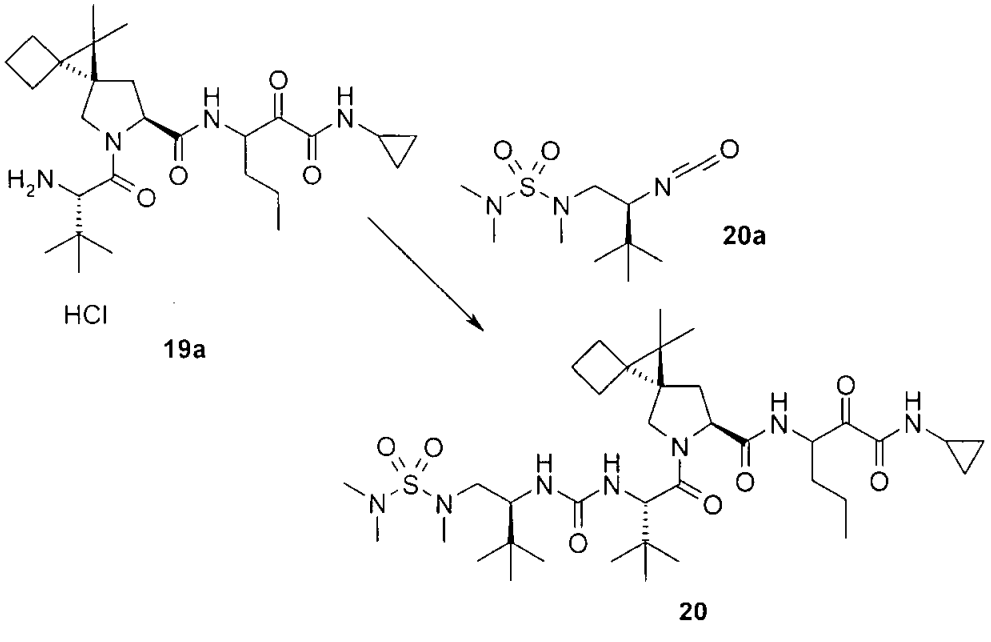
A una solución del 19d (670 miligramos, 0.91 milimoles) en $CH_2Cl_2$ (2.0 mililitros) a 0 °C, se le agrega N-etil-di-isopropil-amina (0.95 mililitros, 5.46 milimoles, 6.0 equivalentes), seguida por una solución de $Py{\cdot}SO_3$ (440 miligramos, 2.73 milimoles, 2.0 equivalentes) en sulfóxido de dimetilo (2.0 mililitros). La solución se agita a 0 °C durante 10 minutos, después de lo cual, se agregan una solución acuosa saturada de. $NH_4Cl$, y EtOAc. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas se combinan, se secan sobre $Na_2SO_4$ y se concentran. El residuo se purifica mediante cromatografía en gel de sílice (heptano/acetona, 1/1) para dar 71 miligramos del 19. MZ encontrada ES+ = 734, ES-

= 732.

**Ejemplo 20:**



**20**

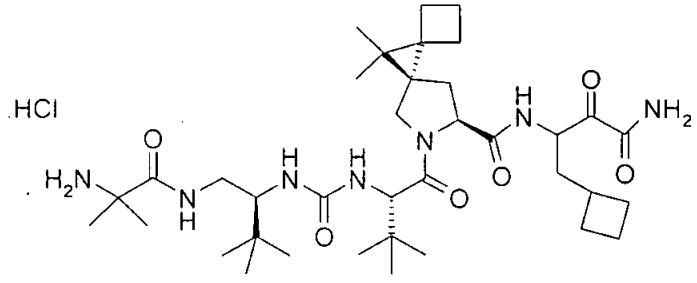


**19a** **20a** **20**

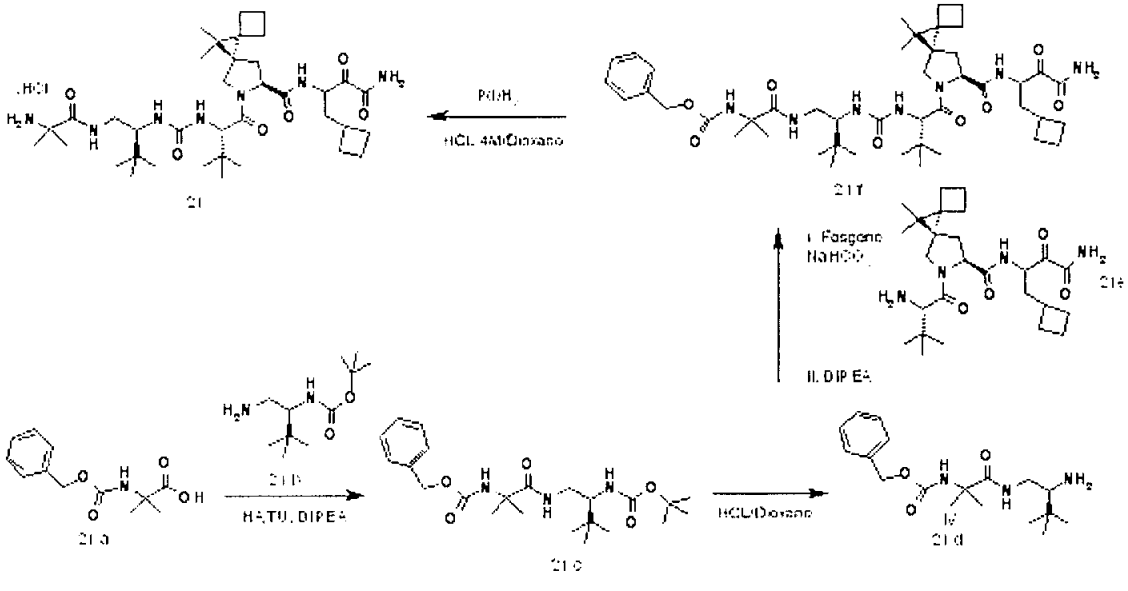
A las mezclas del 19a (75 miligramos, 0.14 milimoles) en $CH_2Cl_2$ (1 mililitros), se les agregan N-etil-di-isopropil-amina (0.05 mililitros, 0.29 milimoles) a 0 °C, y el 20a (0.18 milimoles, en solución de tolueno). La solución se agita a 0°C durante 30 minutos, después de lo cual se apaga mediante la adición de ácido cítrico (solución acuosa al 10 por ciento, 5 mililitros) y EtOAc. Las fases se separan y la capa acuosa se extrae con EtOAc. Las capas orgánicas

combinadas se lavan con salmuera, se secan sobre $Na_2SO_4$, se filtran y se concentran. El residuo se purifica mediante cromatografía en gel de sílice (heptano/acetona, 1/1) para dar 59 miligramos del 20. MZ encontrada, ES+ = 752, ES- = 750.

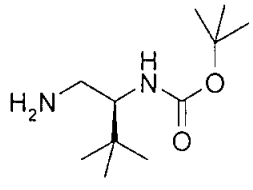
**Ejemplo 21:**



**21**



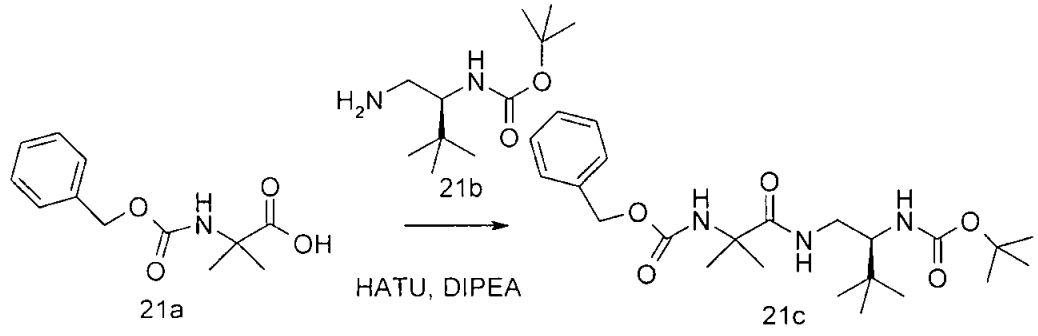

**Paso 21-A:**



21b

La síntesis del compuesto 21b se lleva a cabo en una secuencia de tres pasos, siguiendo un procedimiento de la literatura por Busacca, C. A.; Grossbach, D. Spinelli, E. *Tetrahedron: Asymmetry*, 2000, 11(9), 1907-1910.

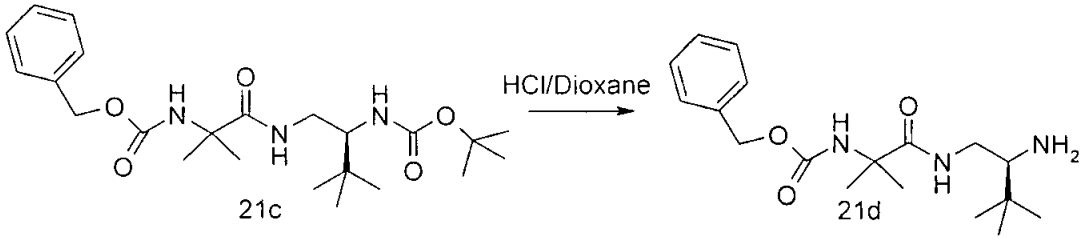
**Paso 21-B:**




A una solución de la N-carbobenciloxi-2-metilalanina 21a (817 miligramos, 3.44 milimoles, 1.2 equivalentes) y la amina 21b (620 miligramos, 2.87 milimoles, 1.0 equivalentes) en $CH_2Cl_2$ (15.0 mililitros) a 0 °C, se le agrega hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (1.31 gramos, 3.44 milimoles, 1.2 equivalentes), seguido por N-etil-di-isopropil-amina (1.25 mililitros, 7.16 milimoles, 2.5 equivalentes). La solución se agita durante la noche a temperatura ambiente. La mezcla de reacción se diluye con EtOAc (75 mililitros) y se lava con HCl 1.0 N (2 X 10 mililitros). Las fases se separan, y la capa acuosa se extrae con EtOAc (2 x 50 mililitros). Las capas orgánicas se combinan y se lavan con $NaHCO_3$ acuoso saturado (50 mililitros), salmuera (50 mililitros), se secan sobre $Na_2SO_4$ y se concentran. El residuo se

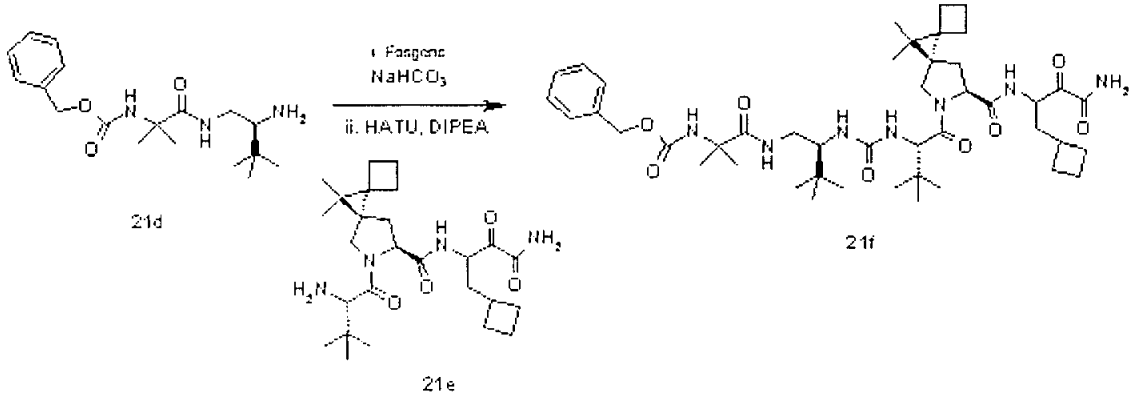
purifica mediante cromatografía en columna de gel de sílice (hexano/EtOAc, 1/1), para dar 1 gramo del producto 21c. ES MS; [M + H ]$^+$ = 436.

**Paso 21-C:**




La amina protegida por N-Boc 21c (388 miligramos, 0.89 milimoles) se disuelve en HCl (2.5 mililitros, HCl 4.0 M en dioxano), y la solución se agita a temperatura ambiente durante 2 horas. La solución se diluye con 50 mililitros de heptano, y se concentra para dar el producto crudo 21d. Este compuesto no requiere de purificación, y se utiliza directamente en el siguiente paso. ES MS; [M + H ]$^+$ = 335.

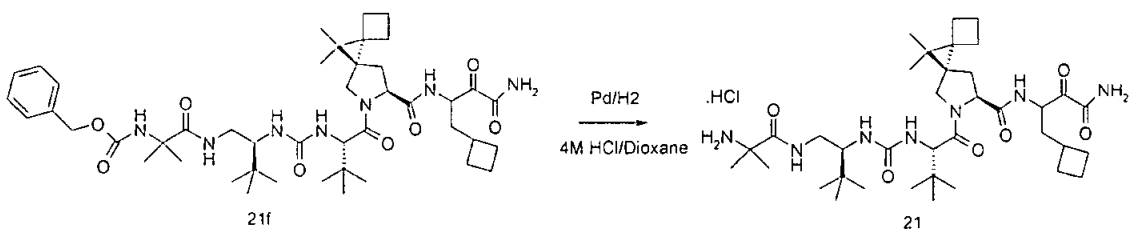
**Paso 21-D:**



La amina 21d (169 miligramos, 0.46 milimoles) se disuelve en dicloro-metano (2.3 mililitros), y la solución se enfría a 0 °C. Se agrega $NaHCO_3$ saturado (2.3 mililitros), y la solución se agita vigorosamente durante 5 minutos. Se detiene la agitación, y se agrega fosgeno (0.46 mililitros, 0.92 milimoles de una solución 2M en Tolueno) a la capa inferior de dicloro-metano, y se continúa la agitación vigorosa durante 1 hora a temperatura ambiente. La solución se diluye con dicloro-metano (10 mililitros), las capas se separan, y la capa orgánica se recolecta y se seca sobre $Na_2SO_4$. La solución entonces se evapora a sequedad, y se utiliza directamente en el siguiente paso.

Una solución del isocianato 21d en $CH_2Cl_2$ (7 mililitros) generado anteriormente, se agrega a una solución enfriada (0 °C) de la sal de clorhidrato de amina 21e (82 miligramos, 0.17 milimoles) en $CH_2Cl_2$ (7 mililitros). Entonces se agrega N-etil-di-isopropil-amina (0.24 mililitros), y la solución se agita a temperatura ambiente durante 2 horas. La solución entonces se concentra, y el material crudo se purifica mediante cromatografía en columna de gel de sílice (Acetona:Heptano, 40 por ciento-75 por ciento acetona) para dar 50 miligramos del producto 21f. ES MS; $[M + H]^+ = 836$.

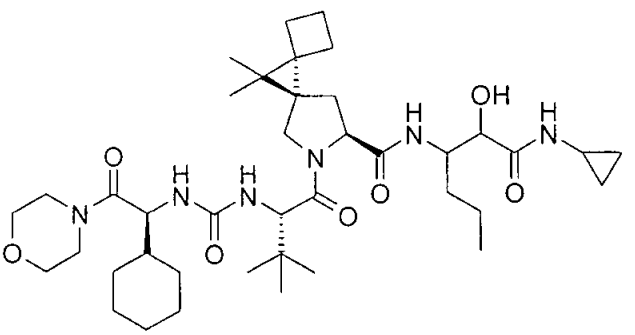
**Paso 21-E:**




21f 21

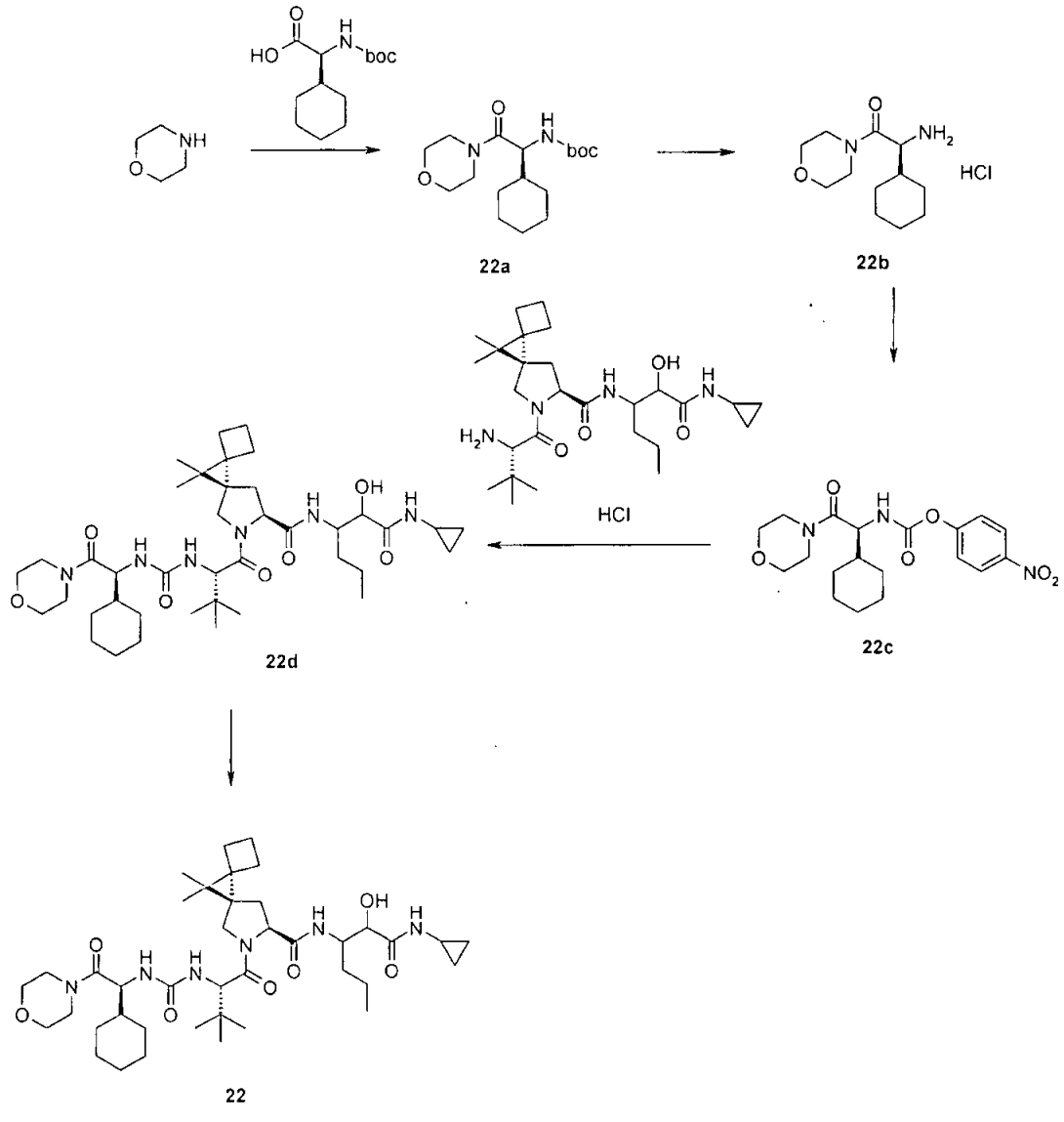
El benciloxicarbamato 21f (11 miligramos, 0.013 milimoles) se disuelve en EtOAc (3 mililitros). Se evacua el aire, y el matraz se purga con $N_2$. Se agrega paladio (al 10 por ciento sobre C, 2 miligramos), y la mezcla se ajusta con un globo de $H_2$. La reacción se deja proceder durante 5 horas, y luego se detiene mediante la filtración de la mezcla a través de un lecho de Celite. Entonces se concentra el filtrado. Se agrega HCl (HCl 4 M en dioxano, 2 mililitros), y la solución se agita durante 2 minutos, y luego se evapora a sequedad. La muestra sólida se lava con heptano (5 mililitros) y EtOAc (2 mililitros), luego se disuelve en $H_2O$ (3 mililitros), y se liofiliza durante la noche, para proporcionar 7 miligramos de un sólido blanco 21. ES MS; $[M + H]^+ = 702$.

**Ejemplo 22:**



**22**

**Esquema:**




**Paso 22-A:**

A una solución del Boc-L-ciclohexil-gly-OH (2.0 gramos, 7.8 milimoles) en $CH_2Cl_2$ (15.0 mililitros) a temperatura ambiente, se le agregan hexafluoro-fosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (3.5 gramos, 9.3 milimoles, 1.2 equivalentes), morfolina (0.679 mililitros, 7.8 milimoles, 1.0 equivalentes), y N-metil-morfolina (2.6 mililitros, 23.4 milimoles, 3.0 equivalentes). La

solución se agita a temperatura ambiente durante 3 horas. A la solución se le agrega entonces EtOAc y $NaHCO_3$ acuoso saturado. Las fases se separan, y la fase orgánica se lava con HCl acuoso 1.0N, y salmuera. La solución se seca sobre $Na_2SO_4$ y se concentra. El residuo se purifica mediante cromatografía en columna de gel de sílice, heptano/EtOAc, 1/1, para dar el producto 22a, 1.2 gramos.

**Paso 22-B:**

El producto 22a se disuelve en HCl 4.0 N en dioxano, y la solución se agita a temperatura ambiente durante 1 hora. La solución se concentra entonces a sequedad, para dar el producto 22b.

A una solución de cloroformato de 4-nitro-fenilo (201 miligramos, 1.1 moles, 1.0 equivalentes) en $CH_2Cl_2$ a temperatura ambiente, se le agregan el 22b (263 miligramos, 1.0 milimoles, 1.0 equivalentes) y piridina (0.242 mililitros, 3.0 milimoles, 3.0 equivalentes). Después de agitar a temperatura ambiente durante 1 hora, la solución se carga directamente en una columna de gel de sílice, y la columna se inunda con heptano/EtOAc (1/1 para el 100 por ciento de EtOAc), para dar el producto 22c, 315 miligramos. Encontrado ES+ = 392.

**Paso 22-C:**

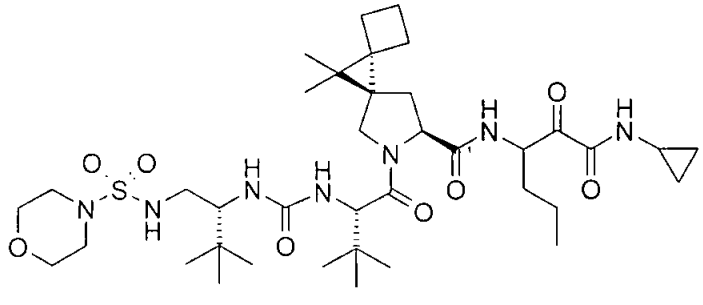
A una solución del 22c (49 miligramos 0.127 milimoles, 1.0 equivalentes) en $CH_2Cl_2$ (0.5 mililitros), se le agregan el 19c (67 miligramos, 0.127 milimoles, 1.0 equivalentes) y trietil-amina (0.042 mililitros, 0.3 milimoles, 3.0 equivalentes). La solución se agita a

temperatura ambiente durante 2 horas. La solución se carga entonces en una columna de gel de sílice, y la columna se inunda con heptano/acetona (1/1), para dar el producto 22d, 80 miligramos. m/z encontrada, ES+ = 743.

**Paso 22-D:**

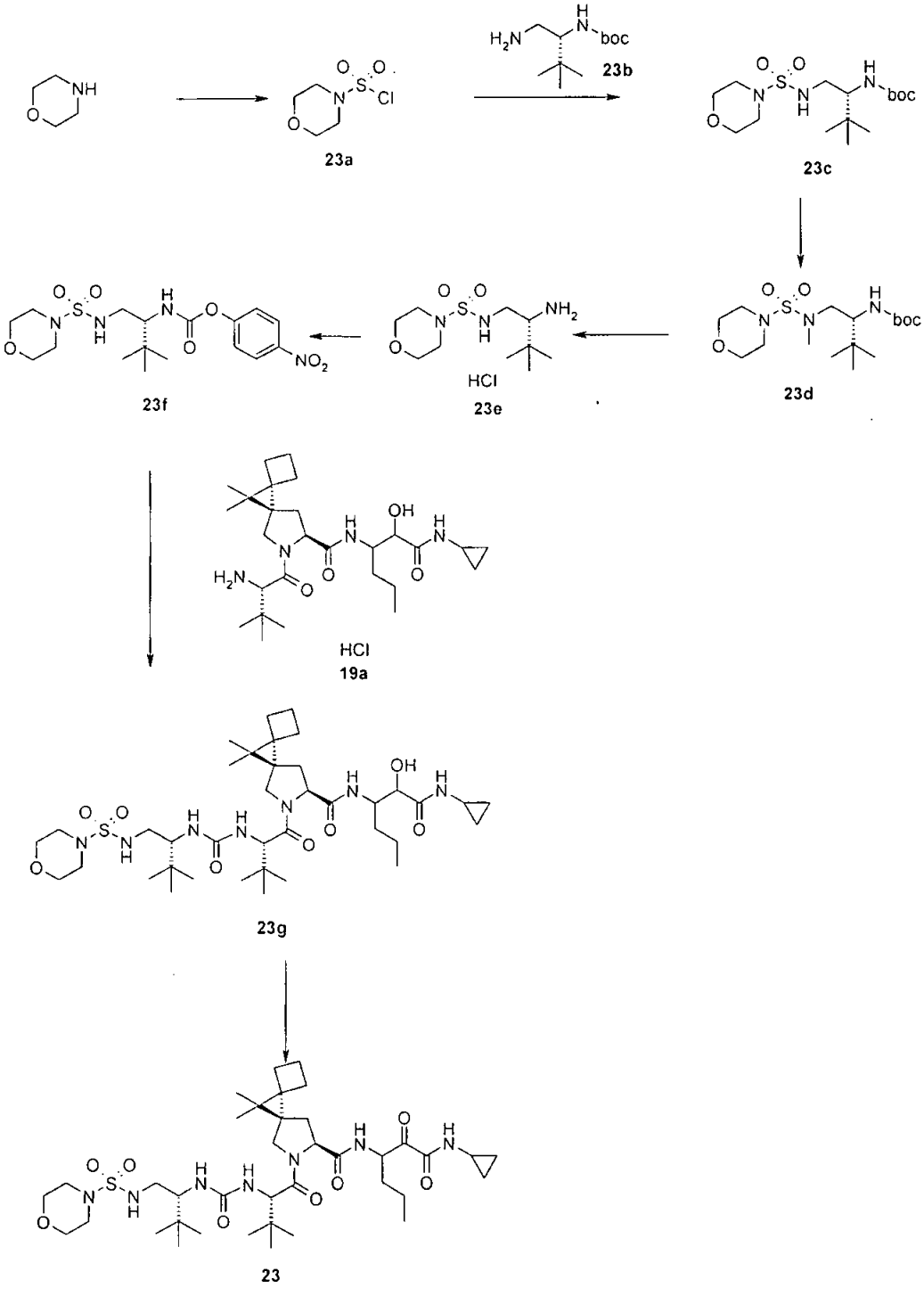
A una solución del 22d (80 miligramos, 0.107 milimoles) en $CH_2Cl_2$ (1.0 mililitros), se le agregan N-etil-di-isopropil-amina (0.093 mililitros, 0.535 milimoles, 5.0 equivalentes) y una solución de $Py{\bullet}SO_3$ (51 miligramos, 0.323 milimoles, 3.0 equivalentes) en sulfóxido de dimetilo (0.5 mililitros). La solución se agita a temperatura ambiente durante 10 minutos. La solución se carga en una columna de gel de sílice, y la columna se inunda con heptano/acetona (1/1), para dar el producto 22, 75 miligramos. m/z encontrada, ES+ = 741.

**Ejemplo 23:**



23

**Esquema:**




**Paso 23-A:**

A una solución de cloruro de sulfurilo (1.62 mililitros, 20.0

milimoles, 1.0 equivalentes) en $CHCl_3$ (20.0 mililitros) a 0 °C, se le agrega lentamente una solución de morfolina (1.7 mililitros, 20.0 milimoles, 1.0 equivalentes) y trietil-amina (2.78 mililitros) en $CHCl_3$ (5.0 mililitros) durante 1 hora. La solución se agita a 0 °C durante 1 hora, y luego a temperatura ambiente durante 1 hora. La solución se concentra y entonces se divide entre éter y una solución acuosa de HCl 1.0 N. Las fases se separan y la capa orgánica se lava con salmuera. La capa orgánica se seca sobre $Na_2SO_4$ y se concentra, para dar el producto 23a (2.5 gramos).

**Paso 23-B:**

A una solución del 23a (559 miligramos, 3.0 milimoles, 1.0 equivalentes) en $CH_2Cl_2$ (10.0 mililitros) a -20 °C, se le agregan el 23b (648 miligramos, 3.0 milimoles, 1.0 equivalentes) y trietil-amina (0.836 mililitros, 6.0 milimoles, 2.0 equivalentes). La solución se agita a temperatura ambiente durante 24 horas, y a 40 °C durante 4 horas. La solución se carga en una columna de gel de sílice, y la columna se inunda con heptano/EtOAc (1/1), para dar el producto 23c (760 miligramos).

**Paso 23-C:**

A una solución del 23c (760 miligramos, 2.07 milimoles, 1.0 equivalentes) en N,N'-dimetil-formamida (6.0 mililitros) a 0 °C, se le agregan $Cs_2CO_3$ (2.0 gramos, 6.2 milimoles, 3.0 equivalentes) y MeI (0.154 mililitros, 2.48 milimoles, 1.2 equivalentes). La solución se agita a temperatura ambiente durante 1.0 horas. La solución se filtra, y se evapora el solvente. El residuo se purifica mediante

cromatografía en columna de gel de sílice, heptano/EtOAc (1/2), para dar el producto 23d (510 miligramos).

**Paso 23-D:**

El producto 23d se disuelve en HCl 4.0 N en dioxano, y se agita a temperatura ambiente durante 1 hora. La solución se concentra entonces a sequedad, para dar el producto 23e.

A una solución del cloroformato de 4-nitro-fenilo (179 miligramos, 0.89 moles, 1.0 equivalentes) en $CH_2Cl_2$ (4.0 mililitros) a temperatura ambiente, se le agregan el 23e (270 miligramos, 0.89 milimoles, 1.0 equivalentes) y piridina (0.144 mililitros, 2.0 milimoles, 2.0 equivalentes). La solución se agita a temperatura ambiente durante 1 hora. La solución se carga en una columna de gel de sílice, y la columna se inunda con heptano/EtOAc (1/1 para el 100 por ciento de EtOAc), para dar el producto 23f (210 miligramos).

**Paso 23-E:**

A una solución del 23f (63 miligramos, 0.14 milimoles, 1.0 equivalentes) en $CH_2Cl_2$ (1.0 mililitros), se le agregan el 19c (75 miligramos, 0.14 milimoles, 1.0 equivalentes) y trietil-amina (0.031 mililitros, 0.42 milimoles, 3.0 equivalentes). La solución se agita a temperatura ambiente durante 2 horas. La solución entonces se carga en una columna de gel de sílice, y la columna se inunda con heptano/acetona (1/1 para el 100 por ciento de acetona), para dar el producto 23g, 101 miligramos. m/z encontrada, ES+ = 796.

**Paso 23-F:**

A una solución del 23g (101 miligramos) en $CH_2Cl_2$ (1.0

mililitros), se le agregan N-etil-di-isopropil-amina (0.120 mililitros) y una solución de $Py \cdot SO_3$ (70 miligramos) en sulfóxido de dimetilo (0.5 mililitros). La solución se agita a temperatura ambiente durante 10 minutos. La solución se carga en una columna de gel de sílice, y la columna se inunda con heptano/acetona (1/1) para dar el producto 22, 71 miligramos. m/z encontrada, ES+ = 794.

## ACTIVIDAD BIOLÓGICA

**Ejemplo 24: Ensayo de proteasa NS3-4A de HCV**

Se determina la actividad inhibidora de ciertos compuestos de la Tabla A contra la proteasa de serina NS3-4A del virus de hepatitis C en un ensayo homogéneo utilizando la proteína NS3-4A de longitud completa (genotipo 1a, cepa HCV-1) y un sustrato de péptido fluorogénico apagado internamente comercialmente disponible, como es descrito por Taliani, M., y colaboradores, 1996 *Anal. Biochem.* 240:60-67, el cual se incorpora como referencia en su totalidad.

**Ejemplo 25: Ensayo de replicón de HCV basado en Luciferasa**

Se determina la actividad antiviral y la citotoxicidad de ciertos compuestos de la Tabla A utilizando una línea celular de replicón de HCV del genotipo subgenómico 1b (Huh-Luc/neo-ET) que contiene un gen reportero de luciferasa, cuya expresión está bajo el control de la réplica y traducción del ARN del virus de hepatitis C. Brevemente, se siembran 5,000 células de replicón en cada pozo de las placas de cultivo de tejido de 96 pozos, y se dejan unirse en un medio de cultivo completo sin G418 durante la noche. Al siguiente día, el

medio de cultivo se remplaza con medio que contenga un compuesto diluido en serie de la Tabla A, en la presencia de suero bovino fetal al 10 por ciento y sulfóxido de dimetilo al 0.5 por ciento. Después de 48 horas de tratamiento con el compuesto de la Tabla A, se determinan las actividades restantes de luciferasa en las células, utilizando el reactivo BriteLite (Perkin Elmer, Wellesley, Massachusetts) con un lector de placas LMaxII (Molecular Probe, Invitrogen). Cada punto de datos representa el promedio de cuatro réplicas en el cultivo celular. La $IC_{50}$ es la concentración en la cual se reduce la actividad de luciferasa en las células de replicón por el 50 por ciento. Se evalúa la citotoxicidad del compuesto de la Tabla A empleando un ensayo de viabilidad celular basado en MTS.

Los compuestos en la Tabla A anterior se han probado en cuando menos uno del ensayo de proteasa del Ejemplo 24, o el ensayo de replicón del Ejemplo 25, y exhiben una $IC_{50}$ de menos de aproximadamente 10 μM o menos en cuando menos uno de los ensayos mencionados en los Ejemplos 24 y 25.

Los expertos en la materia reconocerán, o podrán aseverar empleando no más que una experimentación de rutina, muchos equivalentes de las modalidades específicas y los métodos descritos en la presente. Se pretende que estos equivalentes sean abarcados por el alcance de las siguientes reivindicaciones.

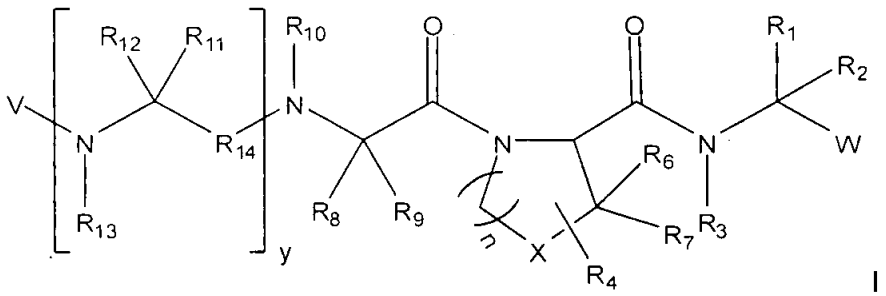
***Incorporación por Referencia***

Los contenidos totales de todas las patentes, solicitudes de patentes publicadas, y otras referencias citadas en la presente, se

incorporan expresamente a la presente en sus totalidades como referencia. Los contenidos totales de las solicitudes de patentes provisionales Números U.S.S.N. 60/791,611, U.S.S.N. 60/791,578, y U.S.S.N. 60/791,320, cada una de las cuales fue presentada el 11 de abril de 2006, y las solicitudes de patentes no provisionales que reivindican el beneficio de las mismas, se incorporan expresamente a la presente, en su totalidad, como se aplica a los compuestos de la presente invención.

## REIVINDICACIONES

1. Un compuesto de la Fórmula I:



I

y las sales farmacéuticamente aceptables y estereoisómeros del mismo;

en donde:

**y** es 0 ó 1;

**n** y **p**, se seleccionan cada uno independientemente a partir de 0, 1, ó 2;

$R_{14}$ es C(O) ó $SO_2$;

$R_1$, $R_2$, W, $R_{13}$, y V se seleccionan cada uno independientemente a partir de hidrógeno o a partir del grupo que consiste en alquilo, alquil-arilo, heteroalquilo, heterociclilo, heteroarilo, aril-heteroarilo, alquil-heteroarilo, cicloalquilo, alquiloxilo, alquil-ariloxilo, ariloxilo, heteroariloxilo, heterocicliloxilo, cicloalquiloxilo, amino, alquil-amino, aril-amino, alquil-aril-amino, aril-amino, heteroaril-amino, cicloalquil-amino, carboxi-alquil-amino, mono- y di-alquil-carboxamida, aril-alquiloxilo, y heterociclil-amino; cada uno de los cuales puede estar además independientemente sustituido una o más veces por $X^1$ y $X^2$; en donde $X^1$ es alquilo,

alquenilo, alquinilo, cicloalquilo, cicloalquil-alquilo, heterociclilo, heterociclil-alquilo, arilo, alquil-arilo, aralquilo, ariloxilo, tioarilo, aril-heteroarilo, heteroarilo, heterociclil-amino, alquil-heteroarilo, o heteroaralquilo; en donde $X^1$ puede estar independientemente sustituido con una o más fracciones $X^2$, las cuales pueden ser iguales o diferentes, y se seleccionan de una manera independiente; en donde $X^2$ es hidroxilo, oxo, alquilo, cicloalquilo, espiro-cicloalquilo, heterociclo-alquilo, arilo, heteroarilo, alcoxilo, ariloxilo, tio, tioalquilo, amino, mono- y di-alquil-amino, aril-amino, alquil-sulfonilo, aril-sulfonilo, alquil-sulfonamido, aril-sulfonamido, carboxilo, carbalcoxilo, carboxamido, alcoxi-carbonil-amino, alcoxi-carbonilo, alcoxi-carboniloxilo, alquil-ureido, aril-ureido, halógeno, ciano, o nitro; en donde cada residuo $X^2$ seleccionado como alquilo, alcoxilo, y arilo puede estar insustituido o de manera opcional independientemente sustituido con una o más fracciones, las cuales pueden ser iguales o diferentes, y se seleccionan independientemente a partir de alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquil-alquilo, heterociclilo, heterociclil-alquilo, arilo, alquil-arilo, aralquilo, aril-heteroarilo, heteroarilo, heterociclil-amino, alquil-heteroarilo, y heteroaralquilo;

W también se selecciona a partir del grupo que consiste en C(O)-C(O)H, C(=N-O-$R_{24}$)-C(O)-amina, C(O)-C(O)-amina, C(O)N$R_{24}$S(O)$_p$$R_{24}$, C(O)N$R_{24}$S(O)$_p$N($R_{24}$)$_2$ y C(O)-[C(O)]$_a$-heterociclo, en donde el heterociclo puede estar independientemente sustituido una o más veces con arilo, alquilo de 1 a 4 átomos de carbono,

alquilo de 1 a 4 átomos de carbono sustituido por uno o más átomos de halógeno, y cicloalquilo de 3 a 6 átomos de carbono, en donde **a** es 0 ó 1, en donde cada $R_{24}$ se selecciona independientemente a partir de hidrógeno o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo sustituido o insustituido, y heterociclo sustituido o insustituido, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono;

V también se selecciona a partir del grupo que consiste en -$Q^1$-$Q^2$, en donde $Q^1$ está ausente, o es C(O), N(H), N(alquilo de 1 a 4 átomos de carbono), C=N(CN), C=N($SO_2CH_3$), C=N-COH-alquilo de 1 a 4 átomos de carbono, o C=N-COH, y $Q^2$ es hidrógeno, o se selecciona a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, O-alquilo de 1 a 4 átomos de carbono, $NH_2$, N(H)-alquilo de 1 a 4 átomos de carbono, N(alquilo de 1 a 4 átomos de carbono)$_2$, $SO_2$-arilo, $SO_2$-alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo, heteroarilo, y heterociclo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno, alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono sustituido por uno o más átomos de halógeno, o cicloalquilo de 3 a 6 átomos de carbono;

o $R_1$ y $R_2$ pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o

más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces;

$R_3$ se selecciona a partir del grupo que consiste en hidrógeno, alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

X es O, S, N, $NR^5$, $CR^5$, ó $CR^5R^{5a}$;

$R_4$ representa de 0 a 4 sustituyentes, cada uno de los cuales se selecciona independientemente a partir de hidrógeno, o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, arilo, heterociclo, y heteroarilo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono;

$R^5$ se selecciona a partir de hidrógeno u oxo, o a partir del grupo que consiste en hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heterociclo-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, cicloalquiloxilo de 3 a 8 átomos de carbono, ariloxilo, y hetero-ariloxilo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno, arilo, trihalo-metilo, o alquilo de 1 a 4 átomos de carbono;

$R^{5a}$ es hidrógeno, o se selecciona a partir del grupo que

consiste en hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, y heteroaril-alquilo de 0 a 4 átomos de carbono;

o $R_4$ y $R^5$ pueden formar juntos un anillo de dimetil-ciclopropilo fusionado, un anillo de ciclopentano fusionado, un anillo de fenilo fusionado, o un anillo de piridilo fusionado, cada uno de los cuales puede estar sustituido con un átomo de halógeno, arilo, trihalometilo, o alquilo de 1 a 4 átomos de carbono;

o $R^5$ y $R_6$ pueden formar juntos un anillo de dimetil-ciclopropilo fusionado, un anillo de ciclopentano fusionado, un anillo de fenilo fusionado, o un anillo de piridilo fusionado, cada uno de los cuales puede estar sustituido con un átomo de halógeno, arilo, trihalometilo, o alquilo de 1 a 4 átomos de carbono;

o $R^5$ y $R^{5a}$ pueden formar juntos un anillo espirocíclico que tiene entre 3 y 7 átomos del anillo, y que tiene 0, 1, ó 2 heteroátomos del anillo, el cual está opcionalmente sustituido por 0 a 4 sustituyentes seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos

de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida, o dos de estos 0 a 4 sustituyentes, tomados juntos, forman un anillo fusionado o espirocíclico de 3 a 7 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono,

heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida;

$R_6$ y $R_7$ se seleccionan cada uno independientemente a partir del grupo que consiste en hidrógeno, hidroxilo, amino, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, y mono- y di-alquilo de 1 a 4 átomos de carbono-amino, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

$R_8$, $R_9$, $R_{10}$, $R_{11}$ y $R_{12}$ se seleccionan cada uno independientemente a partir del grupo que consiste en hidrógeno, alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

o $R_6$ y $R_7$ pueden formar juntos un anillo espirocíclico que tiene entre 3 y 7 átomos del anillo, y que tiene 0, 1, ó 2 heteroátomos del anillo, el cual está opcionalmente sustituido por 0 a 4 sustituyentes seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de

1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida, o dos sustituyentes, tomados juntos, forman un anillo fusionado o espirocíclico de 3 a 7 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alcanoílo de 1 a 4 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-amino, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, alcoxilo de 1 a 4 átomos de carbono-carbonilo, y fenilo;

o $R_3$ y W pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces; y

o cuando y es 0, $R_{10}$ y V pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o más heteroátomos, en donde el anillo puede

estar adicionalmente sustituido una o más veces.

2. El compuesto de la reivindicación 1, en donde:

**y** es 0 ó 1;

**n** es 0 ó 1;

$R_{14}$ es C(O) ó $SO_2$;

$R_1$ se selecciona a partir del grupo que consiste en H y alquilo de 1 a 4 átomos de carbono;

$R_2$ se selecciona a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, C(O)-alquilo de 1 a 4 átomos de carbono, C(O)O-alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

o $R_1$ y $R_2$ forman juntos un anillo de ciclopropano;

W también se selecciona a partir del grupo que consiste en C(O)-C(O)H, C(=N-O-$R_{24}$)-C(O)-amina, C(O)-C(O)-amina, C(O)$NR_{24}S(O)_pR_{24}$, C(O)$NR_{24}S(O)_pN(R_{24})_2$ y C(O)-[C(O)]$_a$-heterociclo, en donde el heterociclo puede estar independientemente sustituido una o más veces con arilo, alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono sustituido por uno o más átomos de halógeno, y cicloalquilo de 3 a 6 átomos de carbono, en donde **a** es 0 ó 1, en donde cada $R_{24}$ se selecciona independientemente a partir de hidrógeno, o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo sustituido o insustituido, y heterociclo sustituido o insustituido, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo

de halógeno o alquilo de 1 a 4 átomos de carbono;

**p** es 0, 1, ó 2;

$R_3$ se selecciona a partir del grupo que consiste en H y alquilo de 1 a 4 átomos de carbono;

X es O, $NR^5$ o $CR^5R^{5a}$;

$R_4$ se selecciona a partir del hidrógeno, o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, arilo, heterociclo, y heteroarilo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono;

$R^5$ se selecciona a partir de hidrógeno u oxo, o del grupo que consiste en hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heterociclo-alquilo de 0 a 4 átomos de carbono, y heteroaril-alquilo de 0 a 4 átomos de carbono, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno, arilo, trihalo-metilo, o alquilo de 1 a 4 átomos de carbono;

$R^{5a}$ se selecciona a partir de hidrógeno, o a partir del grupo que consiste en hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, y

heteroaril-alquilo de 0 a 4 átomos de carbono;

o $R_4$ y $R^5$ pueden formar juntos un anillo de dimetil-ciclopropilo fusionado, un anillo de ciclopentano fusionado, un anillo de fenilo fusionado, o un anillo de piridilo fusionado, cada uno de los cuales puede estar sustituido con un átomo de halógeno, arilo, trihalo-metilo, o alquilo de 1 a 4 átomos de carbono;

o $R^5$ y $R^{5a}$ pueden formar juntos un anillo espirocíclico que tiene entre 3 y 7 átomos del anillo, y que tiene 0, 1, ó 2 heteroátomos del anillo, el cual está opcionalmente sustituido por 0 a 4 sustituyentes seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-

sulfonamida, o dos sustituyentes, tomados juntos, forman un anillo fusionado o espirocíclico de 3 a 7 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alcanoílo de 1 a 4 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-amino, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, alcoxilo de 1 a 4 átomos de carbono-carbonilo, y fenilo;

$R_8$, $R_{10}$, y $R_{11}$ se seleccionan cada uno independientemente a partir del grupo que consiste en H y alquilo de 1 a 4 átomos de carbono;

$R_6$ y $R_7$ se seleccionan cada uno independientemente a partir del grupo que consiste en hidrógeno, hidroxilo, amino, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, y mono- y di-alquilo de 1 a 4 átomos de carbono-amino;

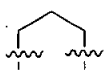
$R_{13}$ es H;

$R_9$ y $R_{12}$ se seleccionan cada uno independientemente a partir del grupo que consiste en hidrógeno, alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono; y

V también se selecciona a partir del grupo que consiste en $-Q^1-Q^2$, en donde $Q^1$ está ausente, o es C(O), N(H), N(alquilo de 1 a 4 átomos de carbono), C=N(CN), $C=N(SO_2CH_3)$, C=N-COH-alquilo de 1 a 4 átomos de carbono, o C=N-COH, y $Q^2$ es hidrógeno, o se

selecciona a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, O-alquilo de 1 a 4 átomos de carbono, $NH_2$, N(H)-alquilo de 1 a 4 átomos de carbono, N(alquilo de 1 a 4 átomos de carbono)$_2$, $SO_2$-arilo, $SO_2$-alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo, heteroarilo, y heterociclo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno, alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono sustituido por uno o más átomos de halógeno, o cicloalquilo de 3 a 6 átomos de carbono;

o $R_3$ y W pueden formar juntos un anillo de 6 miembros de la fórmula II:



II

en donde la fórmula II puede estar adicionalmente sustituida;

o cuando **y** es 0, $R_{10}$ y V pueden formar un anillo de ciclo-propilo que puede estar adicionalmente sustituido o un grupo amida.

3. El compuesto de la reivindicación 1, en donde $R^{14}$ es C(O).

4. El compuesto de la reivindicación 1, en donde **y** es 0, y $R_{10}$ y V forman un anillo de ciclo-propilo que está sustituido con C(O)N(H)-pirazina.

5. El compuesto de la reivindicación 1, en donde $R_4$, $R_6$, y $R_7$ son hidrógeno, y $R^5$ es aril-alquilo de 0 a 3 átomos de carbono,

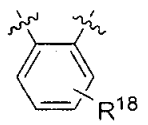
heteroariloxilo, o heteroaril-alquilo de 0 a 3 átomos de carbono, en donde arilo y heteroarilo pueden estar independientemente sustituidos una o más veces con un átomo de halógeno, arilo, trihalometilo, cicloalquilo de 3 a 6 átomos de carbono, o alquilo de 1 a 4 átomos de carbono.

6. El compuesto de la reivindicación 1, en donde $R_1$ y $R_2$ se seleccionan independientemente a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, alquenilo de 2 a 4 átomos de carbono, alquinilo de 2 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, cicloalquenilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono-alquilo de 0 a 4 átomos de carbono, y hetero-cicloalquil-alquilo de 0 a 4 átomos de carbono, cada uno de los cuales está insustituido o sustituido con uno o más grupos seleccionados a partir de flúor, cloro, hidroxilo, alquilo de 1 a 2 átomos de carbono-S, alquilo de 1 a 2 átomos de carbono-S(O), y alquilo de 1 a 2 átomos de carbono-$S(O)_2$, y en donde el hetero-cicloalquilo es un anillo de 3 a 6 miembros que tiene uno o dos átomos de N, O, ó S del anillo.

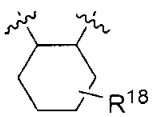
7. El compuesto de la reivindicación 1, en donde $R_1$ es hidrógeno, y $R_2$ se selecciona a partir del grupo que consiste en hidrógeno, metilo, etilo, propilo normal, alilo, propargilo, 3-fluoro-propilo normal, butilo normal, pentilo normal, isopropilo, butilo secundario, isobutilo, 3-metil-butilo normal, 3,3,3-trifluoro-propilo normal, 2,2-difluoro-etilo, trifluoro-metilo, 1,1-difluoro-propilo normal,

2,2,2-trifluoro-etilo, 2,2-difluoro-but-3-enilo normal, 4-pentenilo, 3,3-difluoro-alilo, 2-metil-alilo, 3-butenilo, 2-ciano-etilo, 3,3-difluoro-propilo, 2,2-difluoro-3-butenilo, 2,2-difluoro-propilo normal, 4,4,4-trifluoro-butilo, cicloalquilo de 3 a 6 átomos de carbono, oxetan-2-il-metilo, trietan-2-il-metilo, 3-fluoro-ciclobutil-metilo, 3-hidroxi-ciclobutil-metilo, 3-butinilo, metoxi-metilo, 2-metoxi-etilo, metil-$S(O)_{0-2}$-alquilo de 1 a 2 átomos de carbono, 3,3-difluoro-ciclobutil-metilo, oxetan-3-il-metilo, cicloalquilo de 3 a 6 átomos de carbono-metilo, 1-metil-ciclopropil-metilo, cicloalquilo de 3 a 6 átomos de carbono-difluoro-metilo, cicloalquilo de 3 a 6 átomos de carbono-etilo, trietan-3-il-metilo, 1-fluoro-ciclobutil-metilo, 1-fluoro-ciclopropil-metilo, 2,2-difluoro-ciclopropil-metilo, y ciclopenten-2-il-metilo.

8. El compuesto de la reivindicación 1, en donde **n** es 1, y $R_4$ y $R^5$ forman juntos un sistema de anillos fusionados seleccionado a partir de:




ó

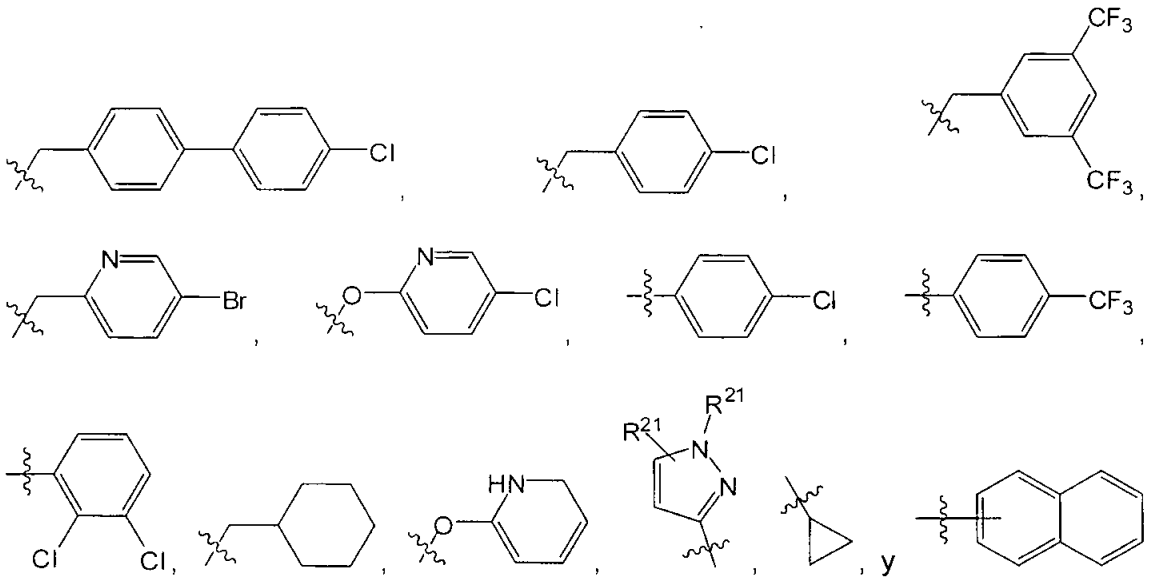



en donde $R^{18}$ se selecciona a partir del grupo que consiste en hidrógeno, un átomo de halógeno, arilo, trihalo-metilo, y alquilo de 1 a 4 átomos de carbono.

9. El compuesto de la reivindicación 1, en donde X es $CR^5R^{5a}$, $R^{5a}$ es hidrógeno, y $R^5$ se selecciona a partir del grupo que consiste en piperidina, fenilo, piridinilo, piridiniloxilo, y piridinil-metilo, en donde los grupos fenilo y piridinilo pueden estar independientemente sustituidos una o más veces con un átomo de

halógeno o alquilo de 1 a 4 átomos de carbono.

10. El compuesto de la reivindicación 9, en donde X es $CR^5R^{5a}$, $R^{5a}$ es hidrógeno, y $R^5$ se selecciona a partir del grupo que consiste en:

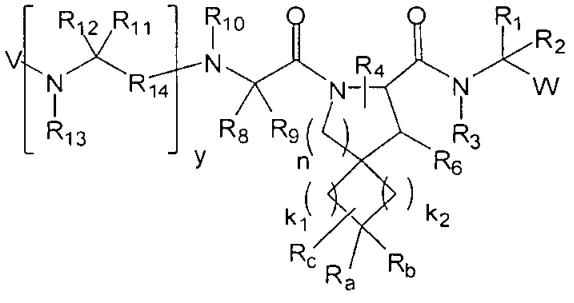


en donde $R^{21}$ se selecciona independientemente a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono y arilo.

11. El compuesto de la reivindicación 1, en donde X es $CR^5R^{5a}$, $R_4$ es hidrógeno, y $R^5$ y $R^{5a}$ tomados en combinación forman un carbociclo espirocíclico de 3 a 6 miembros sustituido con 0 a 2 sustituyentes seleccionados a partir de halógeno, alquilo de 1 a 6 átomos de carbono, alquenilo de 2 a 6 átomos de carbono, alquinilo de 2 a 6 átomos de carbono, alcoxilo de 1 a 6 átomos de carbono, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, fenil-alquilo de 0 a 4 átomos de carbono, naftil-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de

carbono, o dos sustituyentes tomados juntos forman un anillo carbocíclico fusionado o espirocíclico de 3 a 7 miembros, cada uno de los cuales está sustituido con 0 a 3 átomos de halógeno o grupos alquilo de 1 a 4 átomos de carbono independientemente seleccionados.

12. Un compuesto de la reivindicación 1, de acuerdo con la fórmula:



en donde:

$k_1$ y $k_2$ son 0 ó 1, de tal manera que la suma de $k_1$ y $k_2$ es igual a 1 ó 2;

$R_a$ es hidrógeno, alquilo de 1 a 4 átomos de carbono, o fenilo;

$R_b$ es hidrógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono-alquilo de 0 a 4 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, alcanoílo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono-carbonilo, o fenilo;

o $R_a$ y $R_b$, tomados juntos, forman un anillo espirocíclico

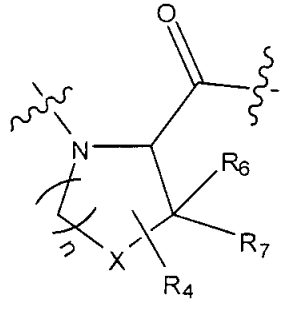
de 3 a 6 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alcanoílo de 1 a 4 átomos de carbono, y fenilo;

$R_c$ representa de 0 a 4 sustituyentes, los cuales se seleccionan independientemente en cada presentación de $R_c$, a partir del grupo que consiste en halógeno, alquilo de 1 a 4 átomos de carbono, y fenilo, o dos sustituyentes $R_c$ *geminales*, tomados en combinación, forman un anillo espirocíclico de 3 a 6 miembros;

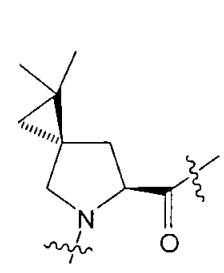
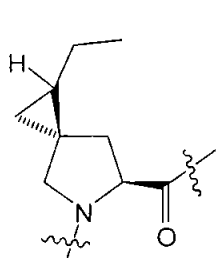
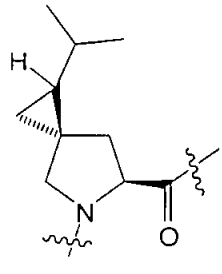
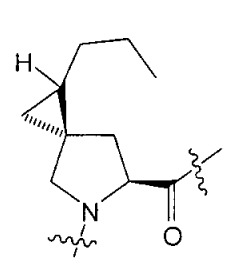
$R_4$ representa 0, 1, ó 2 sustituyentes, cada uno de los cuales se selecciona independientemente a partir de H y alquilo de 1 a 4 átomos de carbono; y

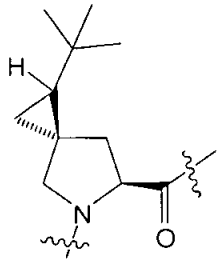
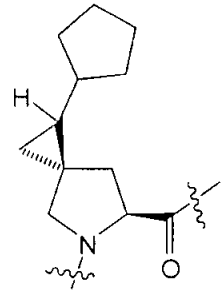
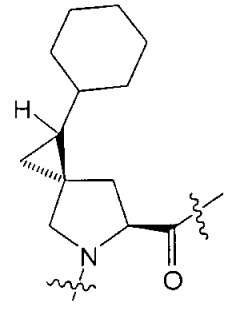
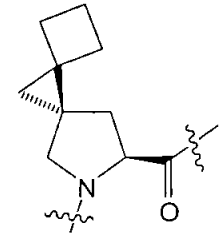
$R_6$ es hidrógeno o alquilo de 1 a 4 átomos de carbono.

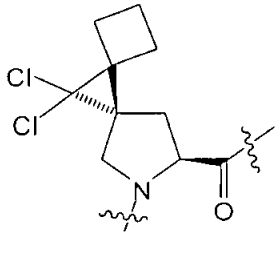
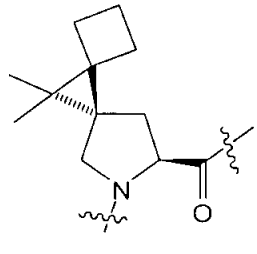
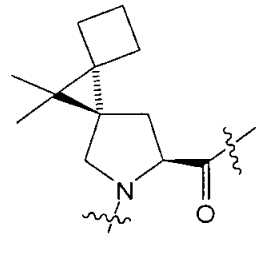
13. El compuesto de la reivindicación 1, en donde el residuo divalente:

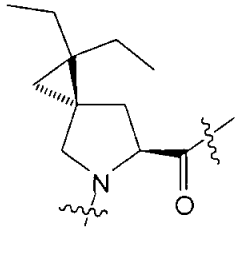
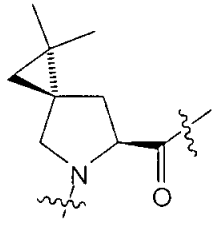
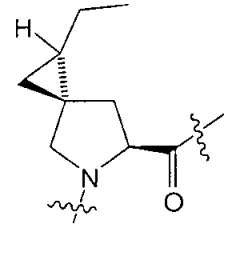
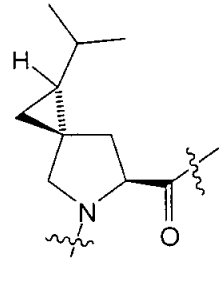


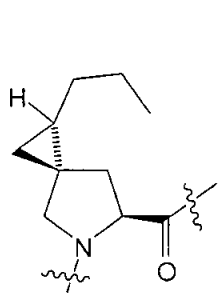
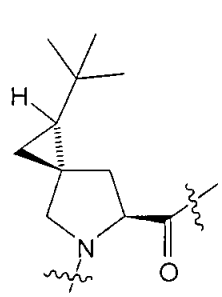
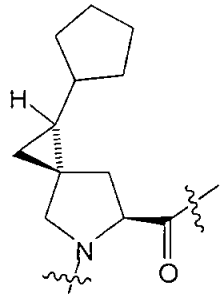
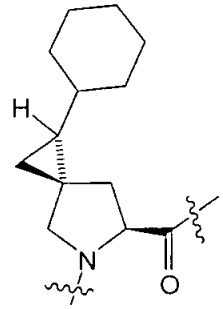

se selecciona a partir del grupo que consiste en:

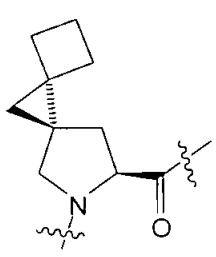
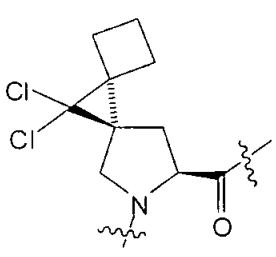
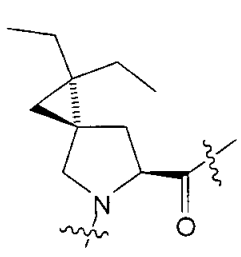
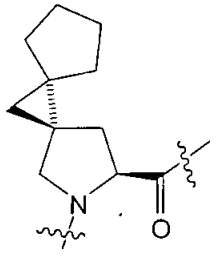

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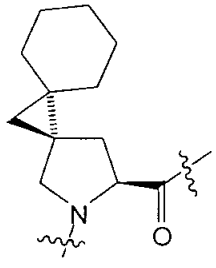
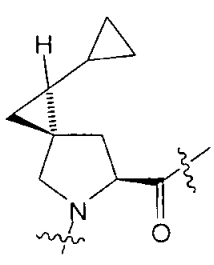
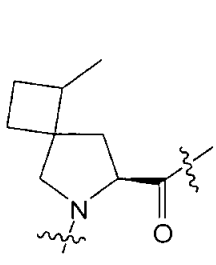
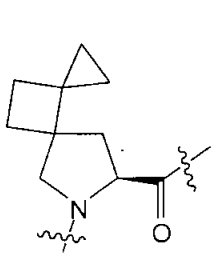

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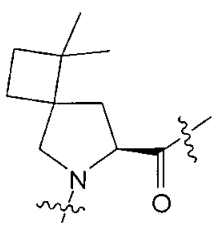
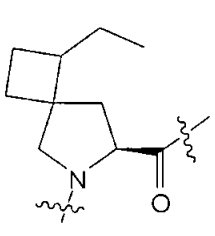
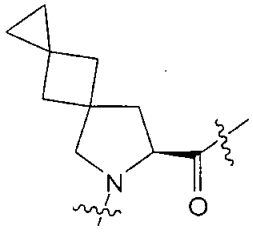
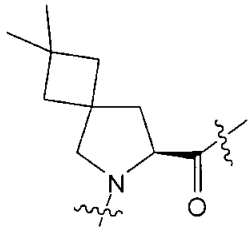

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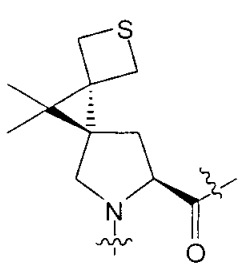
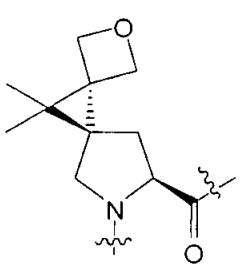
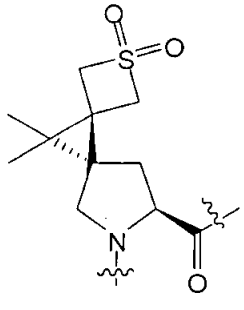
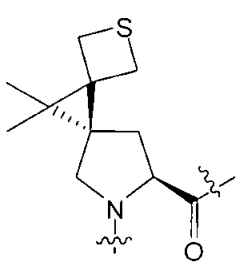

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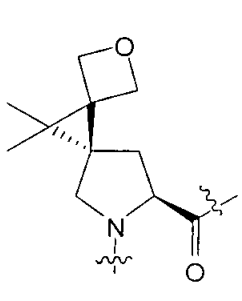
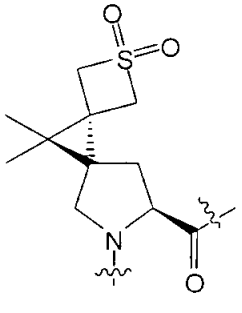
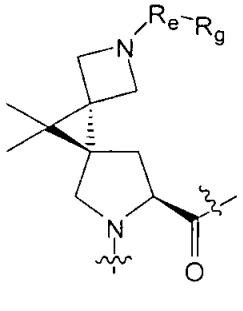
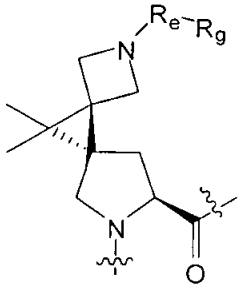

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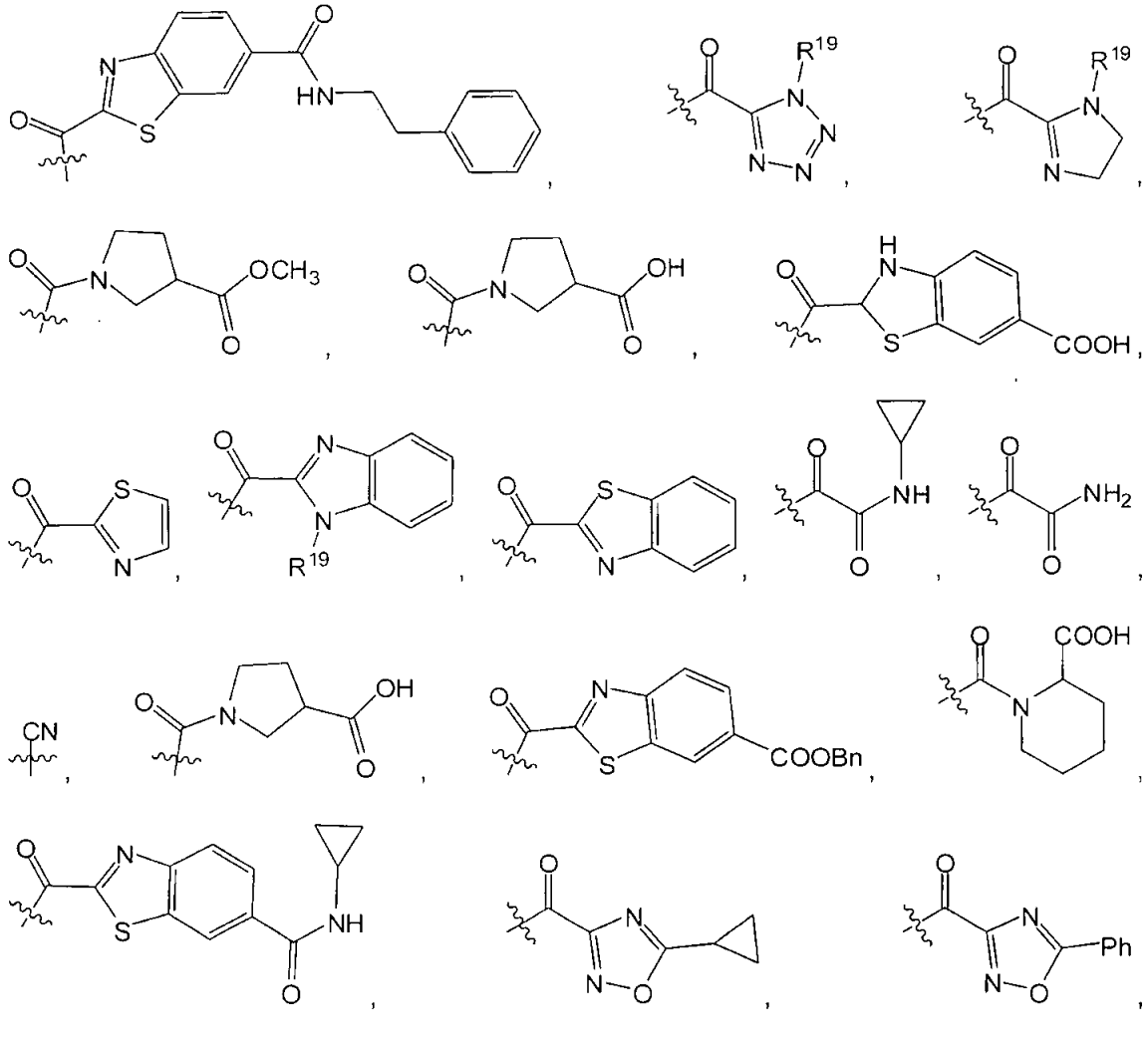
en donde $R_3$ está ausente, o es C(O) o $S(O)_2$; y $R_g$ se

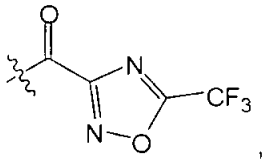
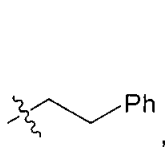
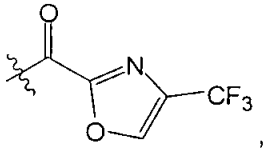
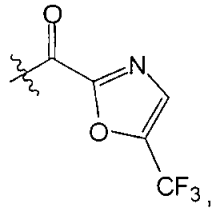
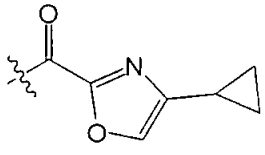
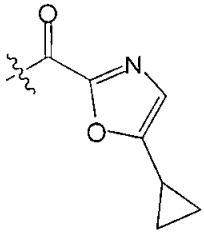
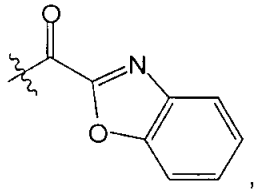
selecciona a partir de hidrógeno, o se selecciona a partir del grupo que consiste en alquilo de 1 a 6 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, heterociclil-alquilo de 0 a 4 átomos de carbono, y cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, cada uno de los cuales está sustituido con 0 a 4 sustituyentes independientemente seleccionados a partir del grupo que consiste en ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida.

14. El compuesto de la reivindicación 1, en donde W se selecciona a partir del grupo que consiste en $C(O)$-$C(O)NH_2$, $C(O)$-

C(O)N(H)-ciclopropilo, C(O)-benzotiazol, C(O)-benzoimidazol, C(O)-oxazol, C(O)-imidazol, y C(O)-oxadiazol, en donde los grupos benzotiazol, benzoimidazol, oxazol, y oxadiazol pueden estar independientemente sustituidos una o más veces con un átomo de halógeno, arilo, trihalo-metilo, cicloalquilo de 3 a 6 átomos de carbono, o alquilo de 1 a 4 átomos de carbono.

15. El compuesto de la reivindicación 14, en donde W se selecciona a partir del grupo que consiste en:

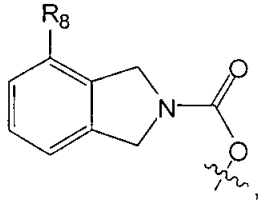
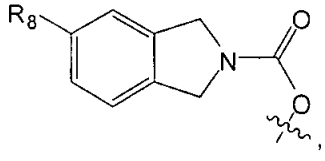
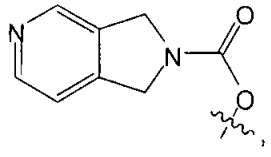
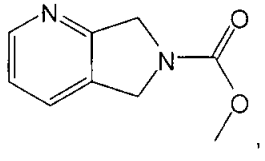
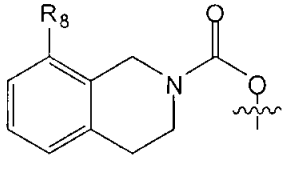
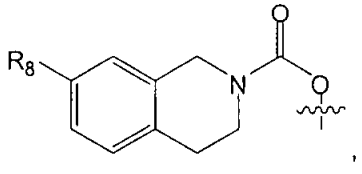


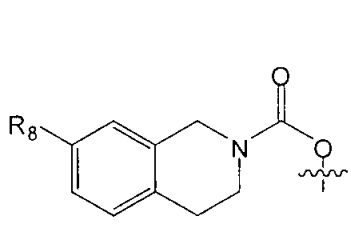
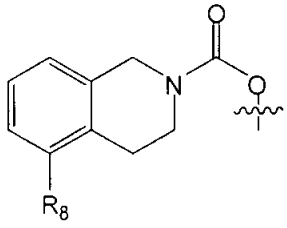
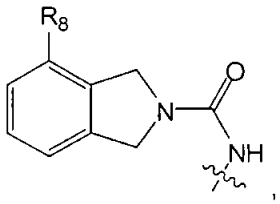
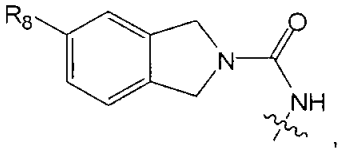
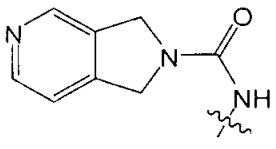
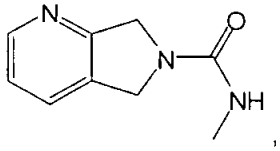
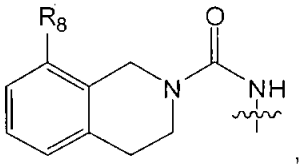
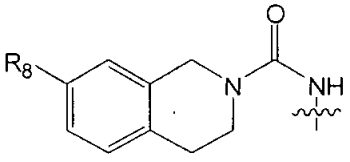
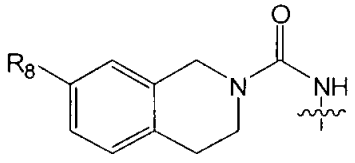
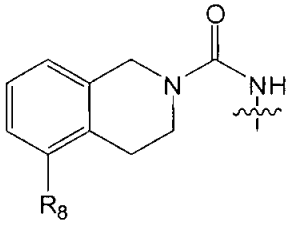






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en donde $R^{19}$ se selecciona a partir del grupo que consiste en hidrógeno, arilo, trihalo-metilo, y alquilo de 1 a 4 átomos de carbono.

16. El compuesto de la reivindicación 1, en donde $R^2$ se selecciona a partir del grupo que consiste en propilo y $(CH_2)_2$-ciclo-butilo.

17. El compuesto de la reivindicación 1, en donde X es $CR_5R_{5a}$, $R_{5a}$ es hidrógeno o metilo, y $R_5$ es un residuo seleccionado a partir del grupo que consiste en:

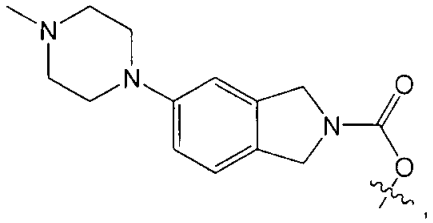
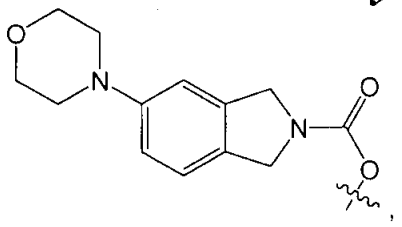
en donde $R_8$ se selecciona a partir de hidrógeno, metilo, etilo, mono-, di-, o tri-fluoro-metilo, mono-, di-, o tri-fluoro-metoxilo, flúor, y cloro.

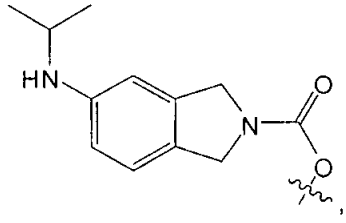
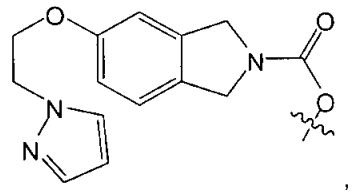
18. El compuesto de la reivindicación 1, en donde X es $CR_5R_{5a}$;

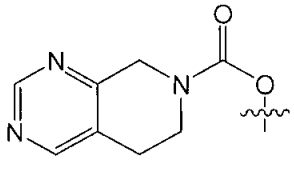
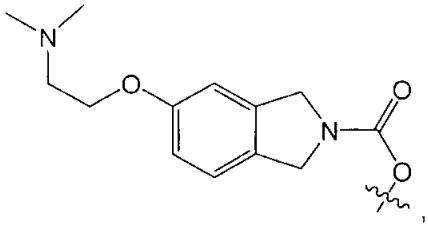
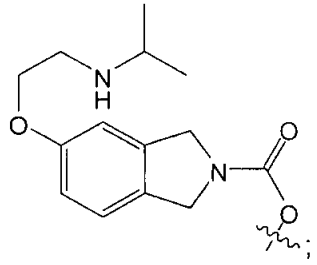
$R_{5a}$ es hidrógeno o metilo;

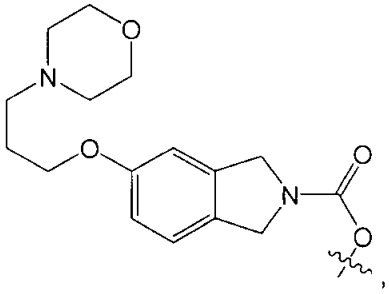
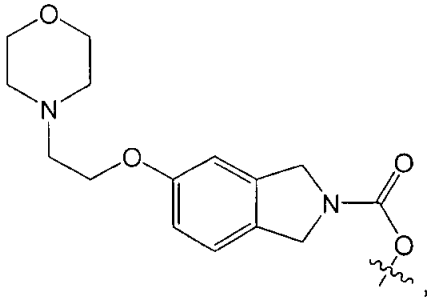
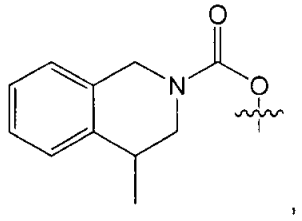
$R_6$ es hidrógeno, metilo, etilo, y mono-, di-, y tri-fluoro-metilo;

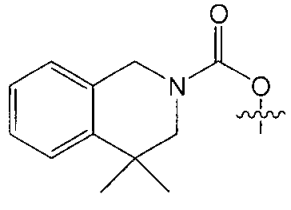
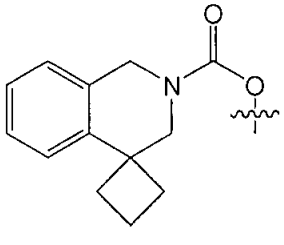
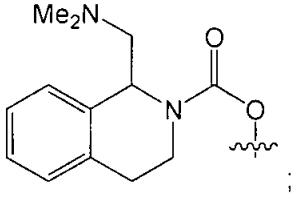
$R_5$ es un residuo seleccionado a partir del grupo que consiste en:

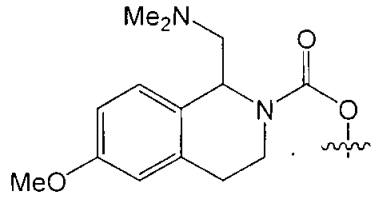
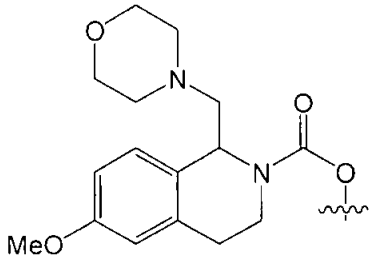
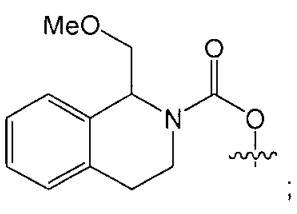

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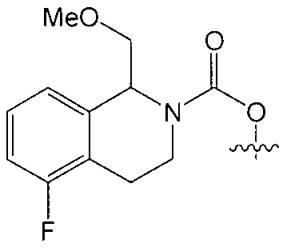

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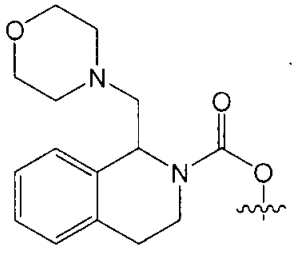

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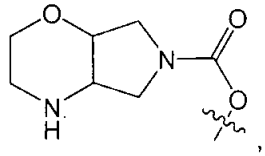

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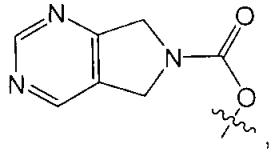
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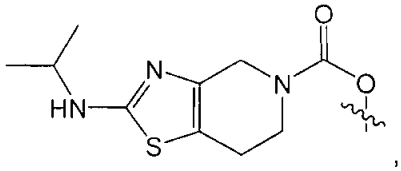
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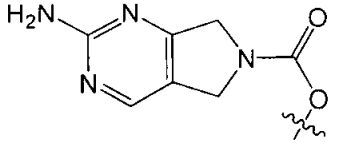
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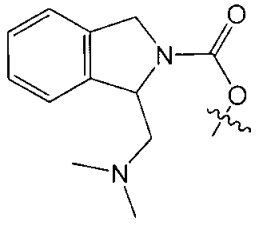
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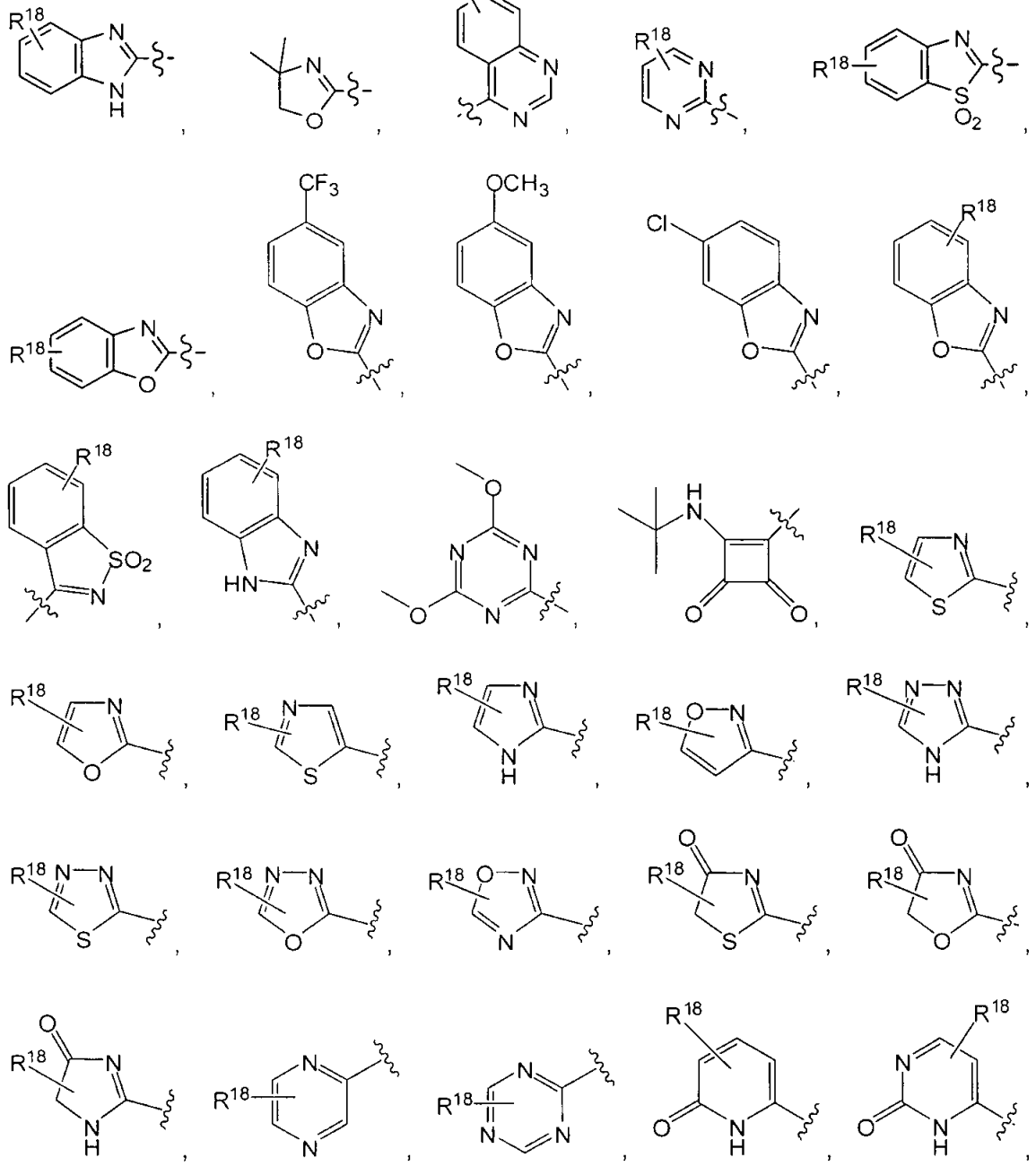
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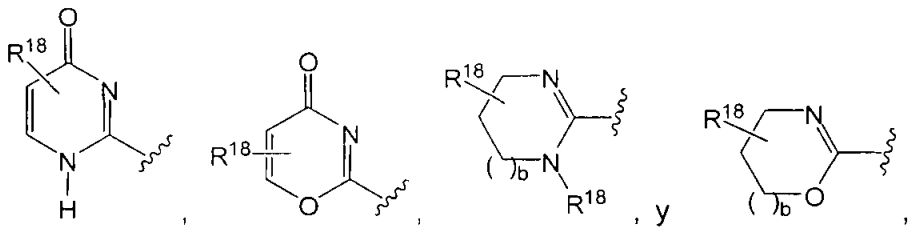
19. El compuesto de la reivindicación 1, en donde $R^{11}$ es H, y $R^{12}$ es cicloalquilo de 3 a 6 átomos de carbono.

20. El compuesto de la reivindicación 1, en donde V es C(O)-$R^{20}$, en donde $R^{20}$ se selecciona a partir del grupo que consiste en cicloalquilo de 3 a 6 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-amino, fenilo, pirazina, benzoxazol, 4,4-dimetil-4,5-dihidro-oxazol, benzoimidazol, pirimidina, 1,1-dióxido de benzotiazol, y quinazolina, cada uno de los cuales puede estar además independientemente sustituido con un átomo de halógeno, $CF_3$, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono.

21. El compuesto de la reivindicación 1, en donde V se selecciona a partir de $R^{20}$ o C(O)-$R^{20}$, en donde $R^{20}$ se selecciona a

partir del grupo que consiste en:



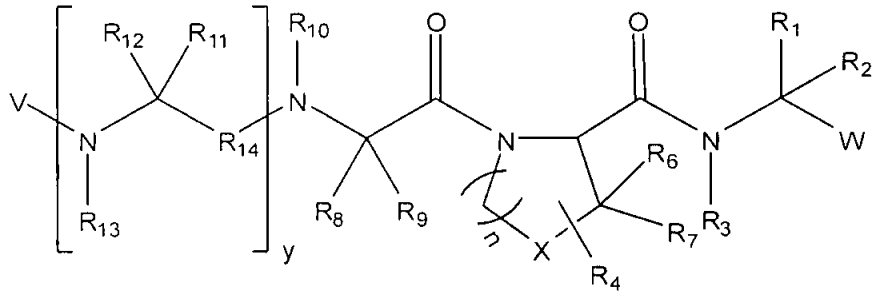


en donde **b** es 0, 1, ó 2; y $R^{18}$ se selecciona a partir del grupo que consiste en hidrógeno, un átomo de halógeno, arilo, trihalo-metilo, y alquilo de 1 a 4 átomos de carbono.

22. El compuesto de la reivindicación 1, en donde X es $CR^5R^{5a}$, $R_4$ y $R^{5a}$ son hidrógeno, y $R^5$ es aril-alquilo de 0 a 3 átomos de carbono, -O-heterociclo, o heterociclo-alquilo de 0 a 3 átomos de carbono, en donde arilo y heterociclo pueden estar independientemente sustituidos una o más veces con un átomo de halógeno, arilo, trihalo-metilo, cicloalquilo de 3 a 6 átomos de carbono, o alquilo de 1 a 4 átomos de carbono.

23. El compuesto de la reivindicación 1, en donde W se selecciona a partir del grupo que consiste en $C(O)\text{-}C(O)N(R^{23})_2$, en donde $R^{23}$ se selecciona independientemente a partir de hidrógeno, o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo, y heterociclo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono.

24. Un compuesto de la fórmula III:



III

y sales farmacéuticamente aceptables y estereoisómeros de los mismos;

en donde:

**y** es 0 ó 1;

**n** es 0, 1, ó 2;

$R_{14}$ es C(O) ó $SO_2$;

$R_1$, $R_2$, W, $R_{13}$, y V se seleccionan cada uno independientemente a partir de hidrógeno o a partir del grupo que consiste en alquilo, alquil-arilo, heteroalquilo, heterociclilo, heteroarilo, aril-heteroarilo, alquil-heteroarilo, cicloalquilo, alquiloxilo, alquil-ariloxilo, ariloxilo, heteroariloxilo, heterocicliloxilo, cicloalquiloxilo, amino, alquil-amino, aril-amino, alquil-aril-amino, aril-amino, heteroaril-amino, cicloalquil-amino, mono- y di-alquil-carboxamida, carboxi-alquil-amino, aril-alquiloxilo, y heterociclil-amino; cada uno de los cuales puede estar además independientemente sustituido una o más veces por $X^1$ y $X^2$; en donde $X^1$ es alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquil-alquilo, heterociclilo, heterociclil-alquilo, arilo, alquil-arilo, aralquilo, ariloxilo, tioarilo, aril-heteroarilo, heteroarilo, heterociclil-amino,

alquil-heteroarilo, o heteroaralquilo; en donde $X^1$ puede estar independientemente sustituido con una o más fracciones $X^2$, las cuales pueden ser iguales o diferentes, y se seleccionan de una manera independiente; en donde $X^2$ es hidroxilo, oxo, alquilo, cicloalquilo, espiro-cicloalquilo, heterociclo-alquilo, arilo, heteroarilo, alcoxilo, ariloxilo, tio, tioalquilo, amino, mono- y di-alquil-amino, aril-amino, alquil-sulfonilo, aril-sulfonilo, alquil-sulfonamido, aril-sulfonamido, carboxilo, carbalcoxilo, carboxamido, alcoxi-carbonil-amino, alcoxi-carbonilo, alcoxi-carboniloxilo, alquil-ureido, aril-ureido, halógeno, ciano, o nitro; en donde cada residuo $X^2$ seleccionado como alquilo, alcoxilo, y arilo puede estar insustituido o de manera opcional independientemente sustituido con una o más fracciones, las cuales pueden ser iguales o diferentes, y se seleccionan independientemente a partir de alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquil-alquilo, heterociclilo, heterociclil-alquilo, arilo, alquil-arilo, aralquilo, aril-heteroarilo, heteroarilo, heterociclil-amino, alquil-heteroarilo, y heteroaralquilo;

W también se selecciona a partir del grupo que consiste en C(O)OH, $C(O)OR_{24}$, C(O)-amina, $P(O)(OR_{24})_2$, C(O)-C(O)OH, $C(=N\text{-}O\text{-}R_{24})$-C(O)-amina, $C(O)NHS(O)_2R_{24}$, $C(O)NHS(O)_pN(R_{24})_2$, $C(O)NR_{24}S(O)_pN(R_{24})_2C(O)$-C(O)-amina, $CON(H)SO_2$-amina, y C(O)-$[C(O)]_a$-heterociclo, en donde el heterociclo puede estar sustituido o insustituido, en donde a es 0 ó 1, en donde cada $R_{24}$ se selecciona independientemente a partir del grupo que consiste en hidrógeno, halógeno, hidroxilo, formilo, carboxilato, amida, amino, alquilo de 1 a

4 átomos de carbono sustituido o insustituido, alcoxilo de 1 a 4 átomos de carbono sustituido o insustituido, alcanoílo de 1 a 4 átomos de carbono sustituido o insustituido, alcoxilo de 1 a 4 átomos de carbono-carbonilo sustituido o insustituido, alcanoiloxilo de 1 a 4 átomos de carbono sustituido o insustituido, mono- y di-alquilo de 1 a 4 átomos de carbono-amino sustituido o insustituido, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono sustituido o insustituido, aril-alquilo de 0 a 4 átomos de carbono sustituido o insustituido, y heterociclo-alquilo de 0 a 4 átomos de carbono sustituido o insustituido;

V también se selecciona a partir del grupo que consiste en $-Q^1-Q^2$, en donde $Q^1$ está ausente, o es C(O), N(H), N(alquilo de 1 a 4 átomos de carbono), C=N(CN), $C=N(SO_2CH_3)$, o C=N-COH, y $Q^2$ es hidrógeno, o se selecciona a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, O-alquilo de 1 a 4 átomos de carbono, $NH_2$, N(H)-alquilo de 1 a 4 átomos de carbono, N(alquilo de 1 a 4 átomos de carbono)$_2$, $SO_2$-arilo, $SO_2$-alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo, heteroarilo, y heterociclo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno, alquilo de 1 a 4 átomos de carbono, alquilo de 1 a 4 átomos de carbono sustituido por uno o más átomos de halógeno, o cicloalquilo de 3 a 6 átomos de carbono;

o $R^1$ y $R^2$ pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o

más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces;

$R^3$ se selecciona a partir del grupo que consiste en hidrógeno, alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

X es $CR^5R^{5a}$;

$R^4$ representa de 0 a 4 sustituyentes, cada uno de los cuales se selecciona independientemente a partir de hidrógeno, o a partir del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono, arilo, heterociclo, y heteroarilo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno o alquilo de 1 a 4 átomos de carbono;

$R^5$ se selecciona a partir de hidrógeno u oxo, o a partir del grupo que consiste en hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heterociclo-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, cicloalquiloxilo de 3 a 8 átomos de carbono, ariloxilo, y hetero-ariloxilo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de halógeno, arilo, trihalo-metilo, o alquilo de 1 a 4 átomos de carbono;

$R^{5a}$ se selecciona a partir del grupo que consiste en

hidrógeno, hidroxilo, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, cicloalquilo de 3 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, y heteroaril-alquilo de 0 a 4 átomos de carbono;

o $R^4$ y $R^5$ pueden formar juntos un anillo de dimetil-ciclopropilo fusionado, un anillo de ciclopentano fusionado, un anillo de fenilo fusionado, o un anillo de piridilo fusionado, cada uno de los cuales puede estar sustituido con un átomo de halógeno, arilo, trihalometilo, o alquilo de 1 a 4 átomos de carbono;

o $R^5$ y $R^{5a}$ pueden formar juntos un anillo espirocíclico que tiene entre 3 y 7 átomos del anillo, o $R^5$ y $R^{5a}$ pueden formar juntos un anillo espirociclico que tiene entre 3 y 7 átomos del anillo y que tiene 0, 1, ó 2 heteroátomos del anillo, el cual está opcionalmente sustituido por 0 a 4 sustituyentes seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo

de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida, o dos de estos 0 a 4 sustituyentes, tomados juntos, forman un anillo fusionado o espirocíclico de 3 a 7 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de

carbono-sulfonamida;

$R^6$ y $R^7$ se seleccionan cada uno independientemente a partir del grupo que consiste en hidroxilo, amino, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, y mono- y di-alquilo de 1 a 4 átomos de carbono-amino, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

$R^8$, $R^9$, $R^{10}$, $R^{11}$ y $R^{12}$ se seleccionan cada uno independientemente a partir del grupo que consiste en hidrógeno, alquilo de 1 a 4 átomos de carbono, y cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono;

o $R^6$ y $R^7$ pueden formar juntos un anillo espirocíclico que tiene entre 3 y 7 átomos del anillo, y que tiene 0, 1, ó 2 heteroátomos del anillo, el cual está opcionalmente sustituido por 0 a 4 sustituyentes seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4

átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida, o dos sustituyentes, tomados juntos, forman un anillo fusionado o espirocíclico de 3 a 7 miembros que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alcanoílo de 1 a 4 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-amino, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, alcoxilo de 1 a 4 átomos de carbono-carbonilo, y fenilo;

en donde cuando menos uno de $R^5$ y $R^{5a}$, o $R_6$ y $R_7$, tomados en combinación, forman un anillo espirocíclico que tiene cuando menos un sustituyente del anillo espirocíclico;

o $R^3$ y W pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces; y

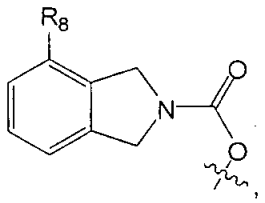
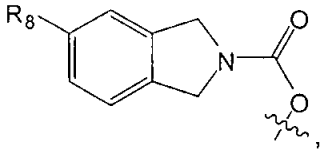
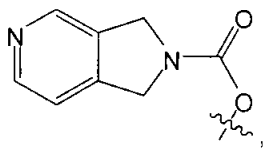
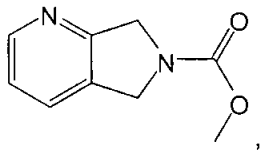
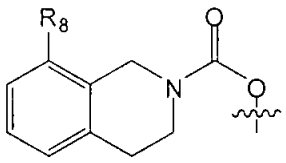
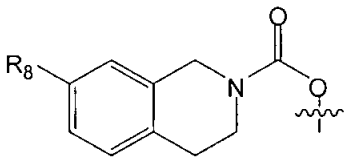
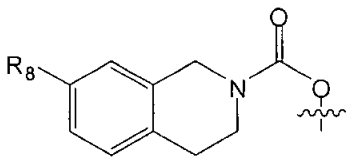
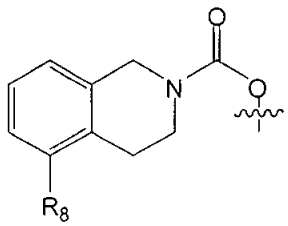
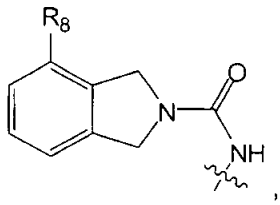
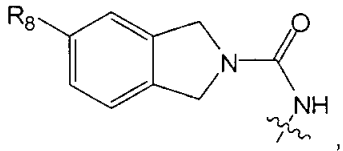
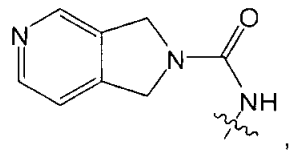
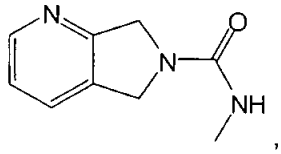
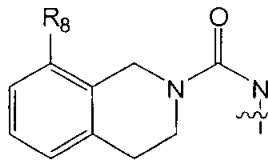
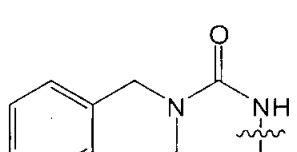
o cuando y es 0, $R_{10}$ y V pueden formar juntos un anillo de 3, 4, 5, 6, ó 7 miembros, que es aromático o no aromático, y puede contener uno o más heteroátomos, en donde el anillo puede estar adicionalmente sustituido una o más veces.

25. El compuesto de la reivindicación 24, en donde $R^5$ y $R^{5a}$, tomados en combinación, forman un anillo espirocíclico que tiene entre 3 y 7 átomos del anillo y que tiene 0, 1, ó 2 heteroátomos del anillo, cuyo anillo espirocíclico está sustituido con un anillo espirocíclico de 3 a 7 miembros y que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, y en donde cada uno de los anillos espirocíclicos tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de ciano, halógeno, hidroxilo, amino, tiol, alquilo de 1 a 8 átomos de carbono, alquenilo de 2 a 8 átomos de carbono, alquinilo de 2 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-alquilo de 0 a 4 átomos de carbono, haloalquilo de 1 a 8 átomos de carbono, haloalquenilo de 2 a 8 átomos de carbono, haloalquinilo de 2 a 8 átomos de carbono, haloalcoxilo de 1 a 8 átomos de carbono, tioalquilo de 1 a 8 átomos de carbono, alquilo de 1 a 8 átomos de carbono-sulfonilo, alquilo de 1 a 8 átomos de carbono-sulfoxilo, alcanoílo de 1 a 8 átomos de carbono, alcoxilo de 1 a 8 átomos de carbono-carbonilo, cicloalquilo de 3 a 7 átomos de carbono-alquilo de 0 a 4 átomos de carbono, aril-alquilo de 0 a 4 átomos de carbono, heteroaril-alquilo de 0 a 4 átomos de carbono, COOH, $C(O)NH_2$, mono- y di-alquilo de 1 a 4 átomos de carbono-carboxamida, mono- y di-alquilo de 1 a 4 átomos de carbono-amino-alquilo de 0 a 4 átomos de carbono, $SO_3H$, $SO_2NH_2$, y mono- y di-alquilo de 1 a 4 átomos de carbono-sulfonamida.

26. El compuesto de la reivindicación 24, en donde $R^{14}$ es

C(O).

27. El compuesto de la reivindicación 24, en donde X es $CR_5R_{5a}$, $R_{5a}$ es hidrógeno o metilo, y $R_5$ es un residuo seleccionado a partir del grupo que consiste en:


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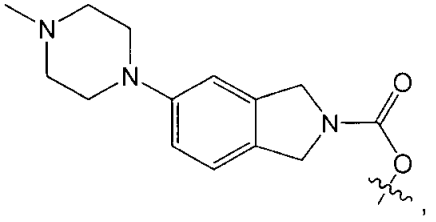
en donde $R_8$ se selecciona a partir de hidrógeno, metilo, etilo, mono-, di-, o tri-fluoro-metilo, mono-, di-, o tri-fluoro-metoxilo, flúor, y cloro.

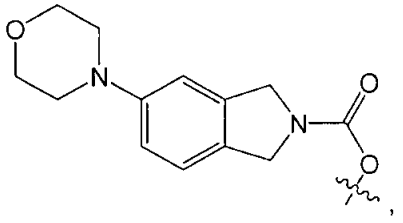
28. El compuesto de la reivindicación 24, en donde X es $CR_5R_{5a}$;

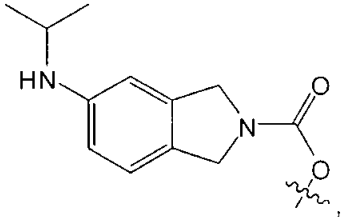
$R_{5a}$ es hidrógeno o metilo;

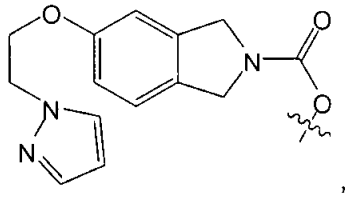
$R_6$ es hidrógeno, metilo, etilo, y mono-, di-, y tri-fluoro-metilo;

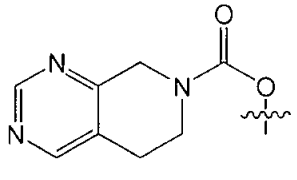
$R_5$ es un residuo seleccionado a partir del grupo que consiste en:

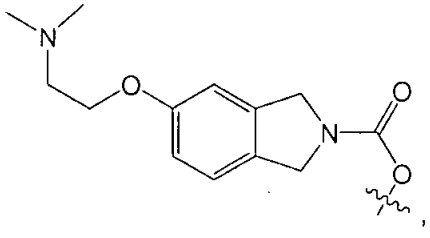

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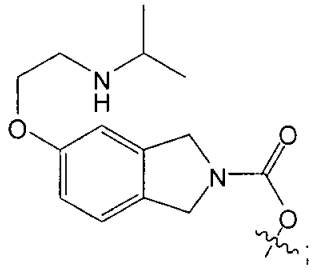

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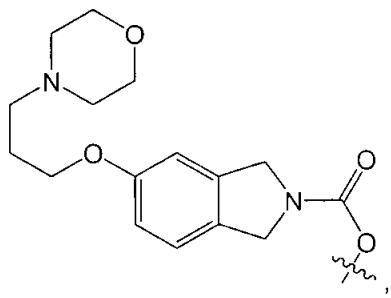
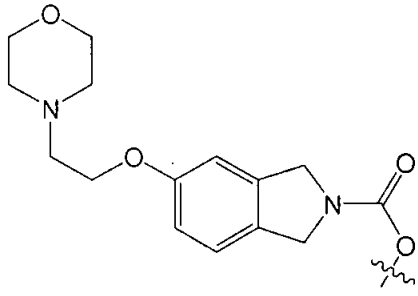
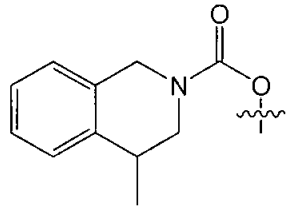
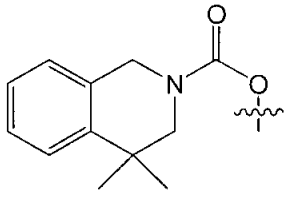
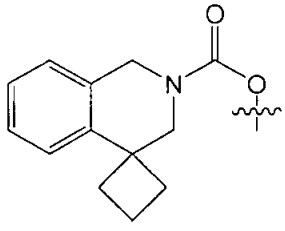
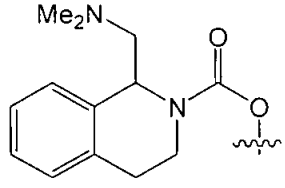
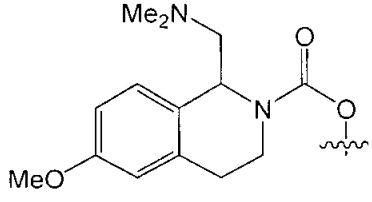
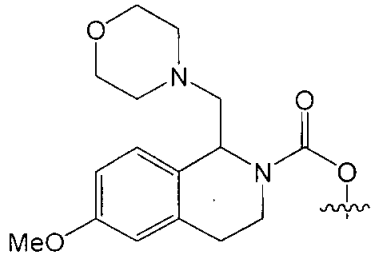
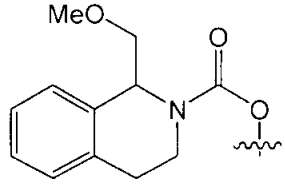
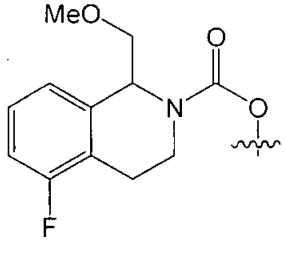
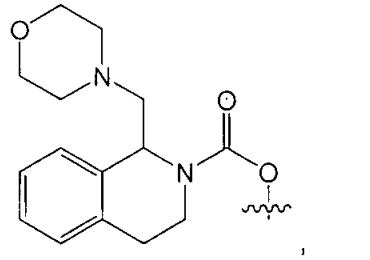
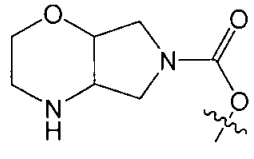
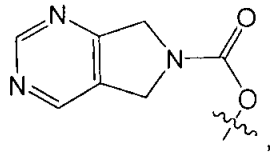
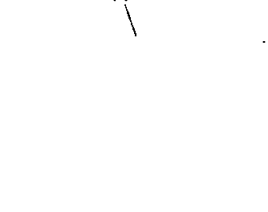

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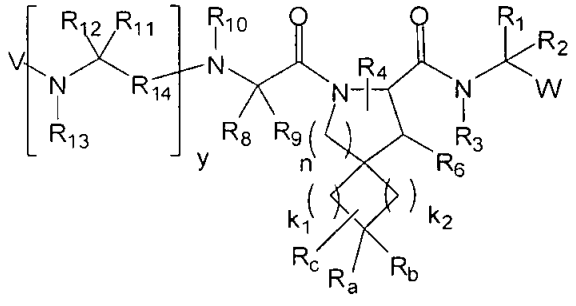

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29. Un compuesto de la reivindicación 24, de acuerdo con la fórmula:



en donde:

$k_1$ y $k_2$ son 0 ó 1, de tal manera que la suma de $k_1$ y $k_2$ es igual a 1 ó 2;

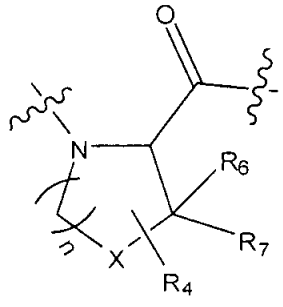
$R_a$ y $R_b$, tomados juntos, forman un anillo espirocíclico de 3 a 6 miembros, que tiene 0, 1, ó 2 heteroátomos del anillo seleccionados a partir de N, O, y S, cuyo anillo fusionado o espirocíclico tiene de 0 a 2 sustituyentes independientemente seleccionados a partir de halógeno, alquilo de 1 a 4 átomos de carbono, alcoxilo de 1 a 4 átomos de carbono, alcanoílo de 1 a 4 átomos de carbono, y fenilo;

$R_c$ representa de 0 a 2 sustituyentes, los cuales se seleccionan independientemente en cada presentación de $R_c$ a partir del grupo que consiste en halógeno, alquilo de 1 a 4 átomos de carbono, y fenilo, o dos sustituyentes $R_c$ *geminales*, tomados en combinación, forman un anillo espirocíclico de 3 a 6 miembros;

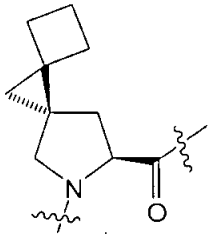
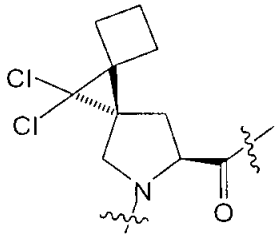
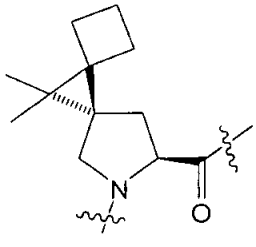
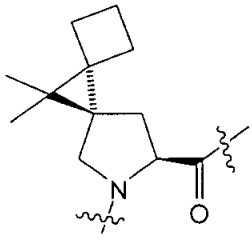
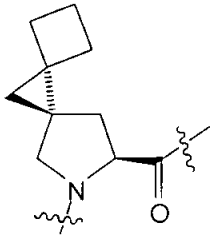
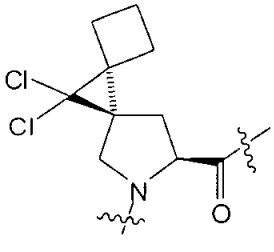
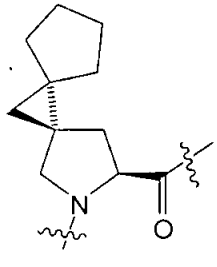
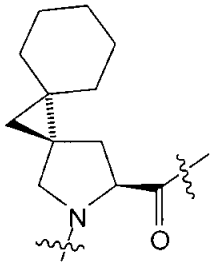
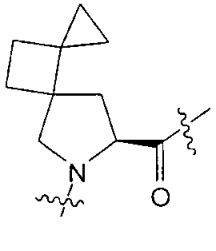
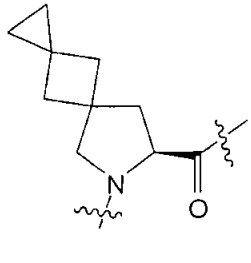
$R_4$ representa 0, 1, ó 2 sustituyentes, cada uno de los cuales se selecciona independientemente a partir de H y alquilo de 1 a 4 átomos de carbono; y

$R_6$ es hidrógeno o alquilo de 1 a 4 átomos de carbono.

30. El compuesto de la reivindicación 24, en donde el residuo divalente:



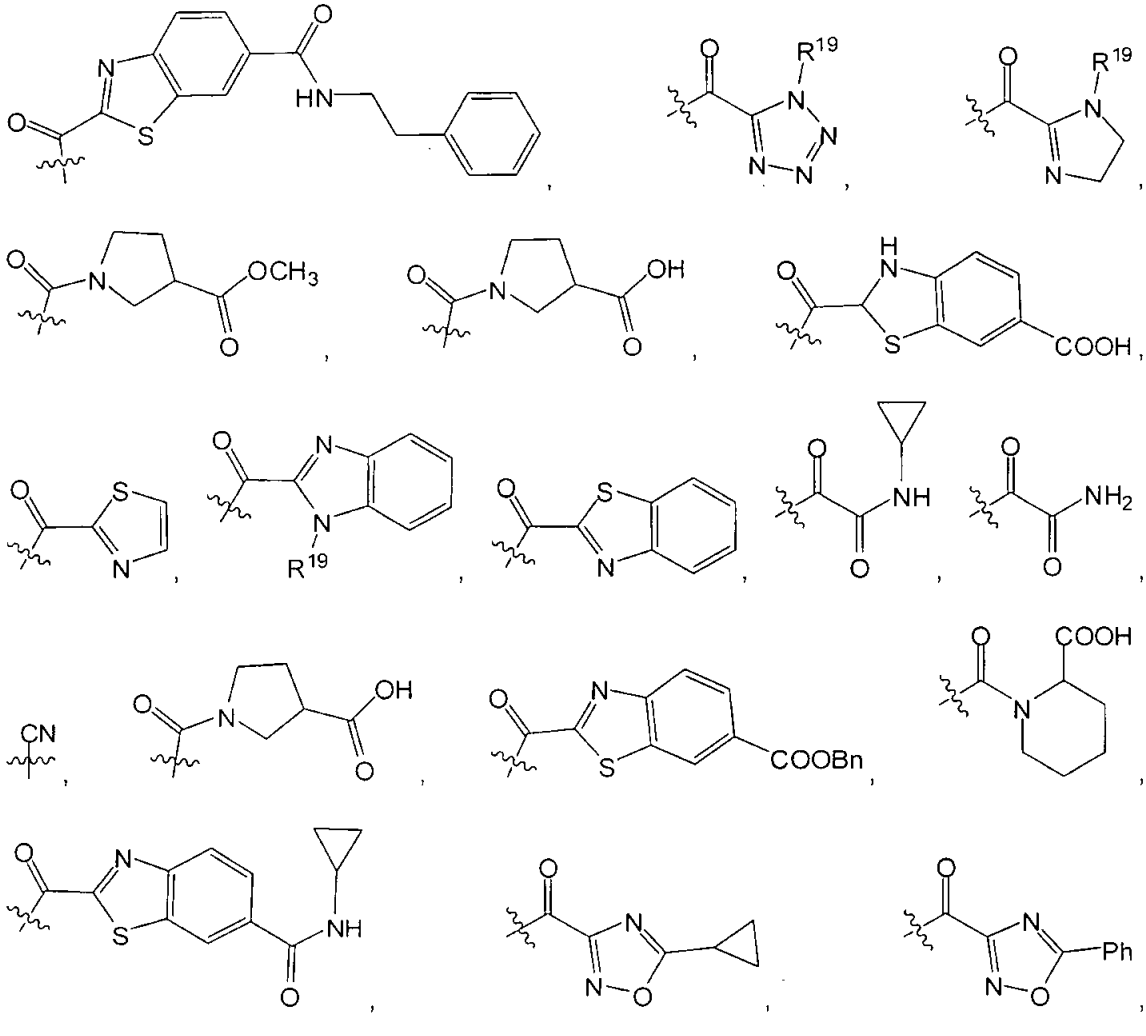
se selecciona a partir del grupo que consiste en:

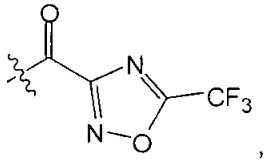
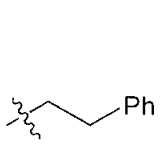
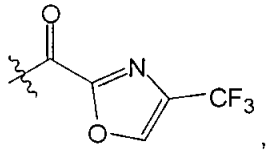
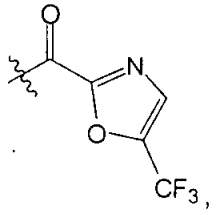
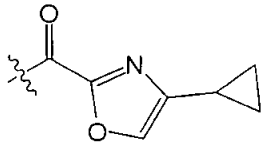
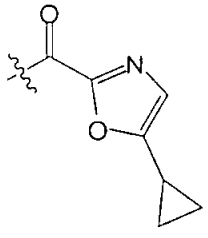
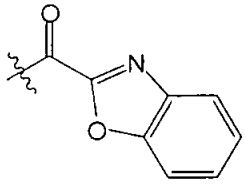










y

31. El compuesto de la reivindicación 24, en donde W se selecciona a partir del grupo que consiste en C(O)-$C(O)NH_2$, C(O)-

C(O)N(H)-ciclopropilo, C(O)-benzotiazol, C(O)-benzoimidazol, C(O)-oxazol, C(O)-imidazol, y C(O)-oxadiazol, en donde los grupos benzotiazol, benzoimidazol, oxazol, y oxadiazol pueden estar independientemente sustituidos una o más veces con un átomo de halógeno, arilo, trihalo-metilo, cicloalquilo de 3 a 6 átomos de carbono, o alquilo de 1 a 4 átomos de carbono.

32. El compuesto de la reivindicación 24, en donde W se selecciona a partir del grupo que consiste en:









y


en donde $R^{19}$ se selecciona a partir del grupo que consiste en hidrógeno, arilo, trihalo-metilo, y alquilo de 1 a 4 átomos de carbono.

33. El compuesto de la reivindicación 24, en donde $R_2$ se selecciona a partir del grupo que consiste en propilo y $(CH_2)_2$-ciclo-butilo.

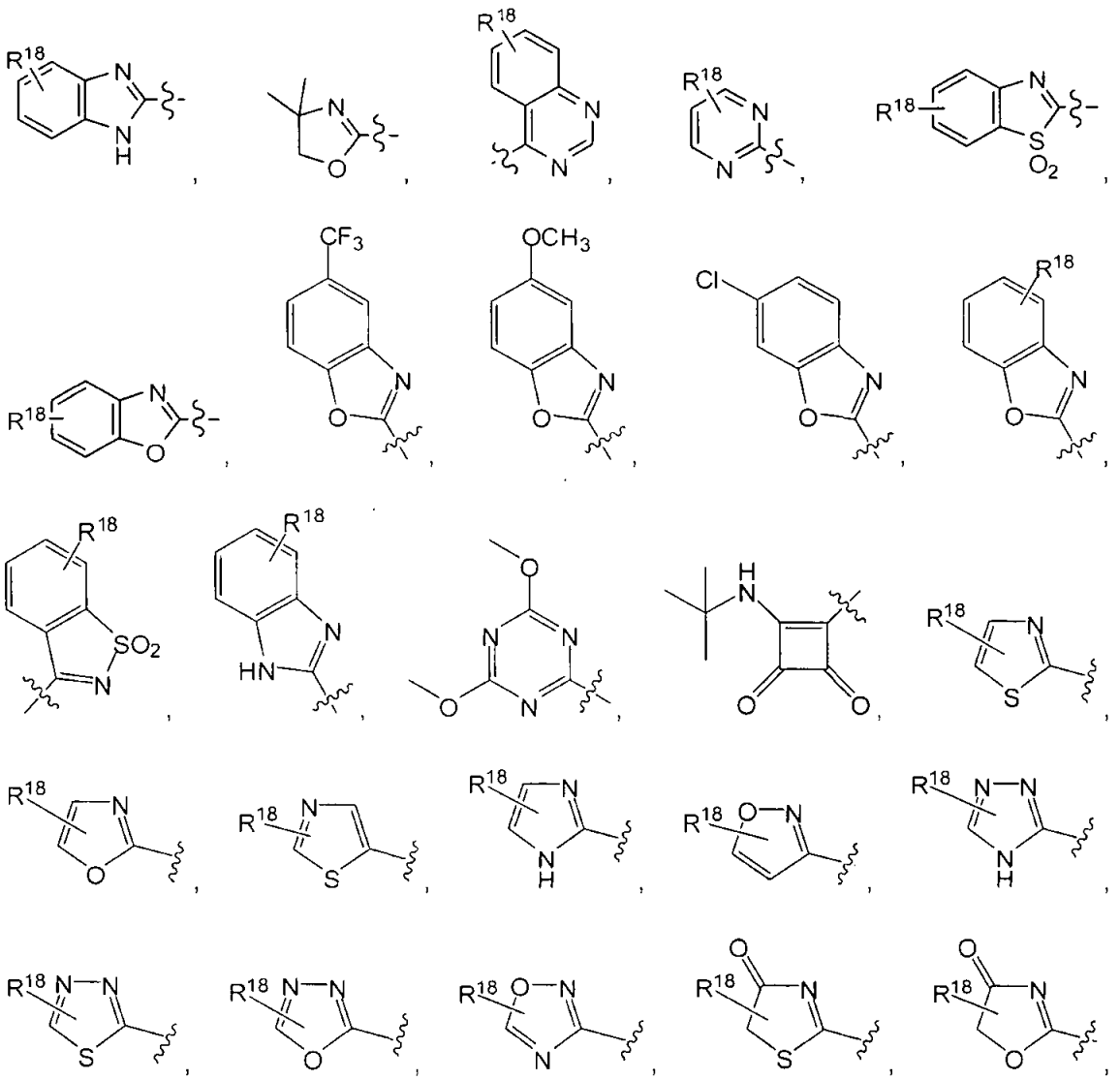
34. El compuesto de la reivindicación 24, en donde $R_{11}$ es H, y $R_{12}$ es cicloalquilo de 3 a 6 átomos de carbono.

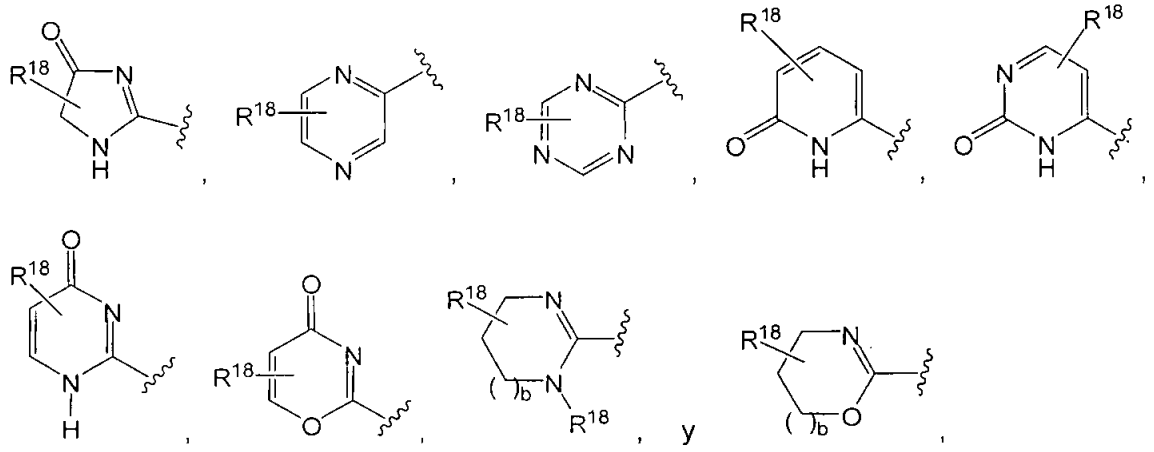
35. El compuesto de la reivindicación 24, en donde $R_{12}$ es ciclo-hexilo.

36. El compuesto de la reivindicación 24, en donde V es $R^{20}$ o $C(O)$-$R^{20}$, en donde $R^{20}$ se selecciona a partir del grupo que consiste en cicloalquilo de 3 a 6 átomos de carbono, mono- y di-alquilo de 1 a 4 átomos de carbono-amino, fenilo, pirazina, benzoxazol, 4,4-dimetil-4,5-dihidro-oxazol, benzo-imidazol, pirimidina, 1,1-dióxido de benzotiazol, y quinazolina, cada uno de los cuales puede estar

además independientemente sustituido con un átomo de halógeno, $CF_3$, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono.

37. El compuesto de la reivindicación 24, en donde V es $R^{20}$ o $C(O)-R^{20}$, en donde $R^{20}$ se selecciona a partir del grupo que consiste en:





en donde **b** es 0, 1, ó 2; y $R^{18}$ se selecciona a partir del grupo que consiste en hidrógeno, un átomo de halógeno, arilo, trihalo-metilo, y alquilo de 1 a 4 átomos de carbono.

38. El compuesto de la reivindicación 24, en donde X es $CR^5R^{5a}$, $R_4$ and $R^{5a}$ son hidrógeno, y $R^5$ es aril-alquilo de 0 a 3 átomos de carbono, -O-heterociclo, o heterociclo-alquilo de 0 a 3 átomos de carbono, en donde arilo y heterociclo pueden estar independientemente sustituidos una o más veces con un átomo de halógeno, arilo, trihalo-metilo, cicloalquilo de 3 a 6 átomos de carbono, o alquilo de 1 a 4 átomos de carbono.

39. El compuesto de la reivindicación 24, en donde W se selecciona a partir del grupo que consiste en $C(O)\text{-}C(O)N(R^{23})_2$, en donde $R^{23}$ se selecciona independientemente a partir de hidrógeno, o del grupo que consiste en alquilo de 1 a 4 átomos de carbono, cicloalquilo de 3 a 6 átomos de carbono-alquilo de 0 a 4 átomos de carbono, arilo, y heterociclo, cada uno de los cuales puede estar independientemente sustituido una o más veces con un átomo de

halógeno o alquilo de 1 a 4 átomos de carbono.

40. Un método para el tratamiento de un trastorno asociado con el virus de hepatitis C, el cual comprende administrar a un sujeto que lo necesite, una cantidad farmacéuticamente aceptable de un compuesto de la reivindicación 1 o de la reivindicación 24, de tal manera que se trate el trastorno asociado con el virus de hepatitis C.

41. El método de la reivindicación 40, en donde el trastorno asociado con el virus de hepatitis C se selecciona a partir del grupo que consiste en infección por el virus de hepatitis C, cirrosis hepática, enfermedad crónica del hígado, carcinoma hepatocelular, crioglobulinemia, linfoma que no es de Hodgkin, y una respuesta inmune intracelular innata suprimida.

42. Un método para el tratamiento de una infección por el virus de hepatitis C, el cual comprende administrar a un sujeto que lo necesite, una cantidad farmacéuticamente aceptable de un compuesto de la reivindicación 1 o de la reivindicación 24.

43. Un método para el tratamiento, la inhibición, o la prevención de la actividad del virus de hepatitis C en un sujeto que lo necesite, el cual comprende administrar al sujeto una cantidad farmacéuticamente aceptable de un compuesto de la reivindicación 1 o de la reivindicación 24.

44. Un método para inhibir la actividad de una proteasa de serina, el cual comprende el paso de poner en contacto esta proteasa de serina con un compuesto de acuerdo con la reivindicación 1 o con la reivindicación 24.

45. El método de la reivindicación 44, en donde se inhibe la actividad de la proteasa NS2.

46. El método de la reivindicación 44, en donde se inhibe la actividad de la proteasa NS3.

47. El método de la reivindicación 44, en donde se inhibe la actividad de la helicasa NS3.

48. El método de la reivindicación 44, en donde se inhibe la actividad de la proteína NS5a.

49. El método de la reivindicación 44, en donde se inhibe la actividad de la polimerasa NS5b.

50. El método de la reivindicación 44, en donde se interrumpe la interacción entre la proteasa NS3 y el co-factor NS4A.

51. El método de la reivindicación 44, en donde se previene o se altera la ruptura de una o más de las uniones NS4A-NS4B, NS4B-NS5A, y NS5A-NS5B del virus de hepatitis C.

52. El método de cualquiera de las reivindicaciones 44 a 51, en donde se trata un trastorno asociado con el virus de hepatitis C en un sujeto que lo necesite.

53. El método de la reivindicación 52, en donde el trastorno asociado con el virus de hepatitis C se selecciona a partir del grupo que consiste en infección por el virus de hepatitis C, cirrosis hepática, enfermedad crónica del hígado, carcinoma hepatocelular, crioglobulinemia, linfoma que no es de Hodgkin, y una respuesta inmune intracelular innata suprimida.

54. Un método para el tratamiento, la inhibición, o la

prevención de la actividad del virus de hepatitis C en un sujeto que lo necesite, el cual comprende administrar al sujeto una cantidad farmacéuticamente aceptable de un compuesto de la reivindicación 1 o de la reivindicación 24, en donde el compuesto interactúa con cualquier objetivo en el ciclo de vida del virus de hepatitis C.

55. El método de la reivindicación 54, en donde el objetivo se selecciona a partir del grupo que consiste en proteasa NS2, proteasa NS3, helicasa NS3, proteína NS5a, y polimerasa NS5b.

56. Un método para reducir la carga de ARN del virus de hepatitis C en un sujeto que lo necesite, el cual comprende administrar al sujeto una cantidad farmacéuticamente aceptable de un compuesto de la reivindicación 1 o de la reivindicación 24, de tal manera que se reduzca la carga de ARN del virus de hepatitis C en el sujeto.

57. Un compuesto que exhibe actividad de proteasa del virus de hepatitis C, en donde el compuesto es un compuesto de la reivindicación 1 o de la reivindicación 24.

58. El compuesto de la reivindicación 57, en donde el compuesto es un inhibidor de la proteasa NS3-4A del virus de hepatitis C.

59. Un método para el tratamiento de un trastorno asociado con el virus de hepatitis C en un sujeto, el cual comprende administrar a un sujeto que lo necesite, una cantidad farmacéuticamente aceptable de un compuesto de la reivindicación 1 o de la reivindicación 24, y un vehículo farmacéuticamente

aceptable, de tal manera que se trate el trastorno asociado con el virus de hepatitis C.

60. Un método para el tratamiento de un trastorno asociado con el virus de hepatitis C, el cual comprende administrar a un sujeto que lo necesite, una cantidad farmacéuticamente efectiva de un compuesto de la reivindicación 1 o de la reivindicación 24, en combinación con una cantidad farmacéuticamente efectiva de un compuesto modulador del virus de hepatitis C adicional, de tal manera que se trate el trastorno asociado con el virus de hepatitis C.

61. El método de la reivindicación 60, en donde el compuesto modulador del virus de hepatitis C adicional se selecciona a partir del grupo que consiste en Sch 503034 y VX-950.

62. El método de la reivindicación 60, en donde el compuesto modulador del virus de hepatitis C adicional es interferón, o interferón derivado.

63. El método de la reivindicación 62, en donde el interferón se selecciona a partir del grupo que consiste en interferón alfa 2B, interferón alfa pegilado, interferón en consenso, interferón alfa 2A, interferón linfoblastoide, e interferón tau; y el compuesto que tiene actividad contra el virus de hepatitis C se selecciona a partir del grupo que consiste en interleucina 2, interleucina 6, interleucina 12, un compuesto que mejore el desarrollo de una respuesta de células-T auxiliares tipo 1, ARN de doble cadena, ARN de doble cadena formando complejo con tobramicina, Imiquimod, ribavirina, un inhibidor de deshidrogenasa de 5'-mono-fosfato de inosina,

amantadina, y rimantadina.

64. El método de la reivindicación 60, en donde el compuesto modulador del virus de hepatitis C adicional es un inhibidor de mono-oxigenasa del citocromo P450.

65. El método de la reivindicación 64, en donde el inhibidor del citocromo P450 se selecciona a partir del grupo que consiste en ritonavir, quetoconazol, troleandomicina, 4-metil-pirazol, ciclosporina, y clometiazol.

66. El método de la reivindicación 59 o de la reivindicación 60, en donde el trastorno asociado con el virus de hepatitis C se selecciona a partir del grupo que consiste en infección por el virus de hepatitis C, cirrosis hepática, enfermedad crónica del hígado, carcinoma hepatocelular, crioglobulinemia, linfoma que no es de Hodgkin, y una respuesta inmune intracelular innata suprimida.

67. Un método para inhibir la réplica del virus de hepatitis C en una célula, el cual comprende poner en contacto esta célula con un compuesto de la reivindicación 1 o de la reivindicación 24.

68. Un tratamiento para un trastorno asociado con el virus de hepatitis C empacado, el cual comprende un compuesto modulador del virus de hepatitis C de la reivindicación 1 o de la reivindicación 24, empacado con instrucciones para utilizar una cantidad efectiva del compuesto modulador del virus de hepatitis C para tratar un trastorno asociado con el virus de hepatitis C.

69. El tratamiento de la reivindicación 68, en donde el trastorno asociado con el virus de hepatitis C se selecciona a partir

del grupo que consiste en infección por el virus de hepatitis C, cirrosis hepática, enfermedad crónica del hígado, carcinoma hepatocelular, crioglobulinemia, linfoma que no es de Hodgkin, y una respuesta inmune intracelular innata suprimida.

70. Un método para el tratamiento de infección por el virus de hepatitis C, cirrosis hepática, enfermedad crónica del hígado, carcinoma hepatocelular, crioglobulinemia, linfoma que no es de Hodgkin, y/o una respuesta inmune intracelular innata suprimida en un sujeto que lo necesite, el cual comprende administrar al sujeto una cantidad farmacéuticamente aceptable de un compuesto de la reivindicación 1 o de la reivindicación 24.

71. El método de la reivindicación 40, en donde el virus de hepatitis C se selecciona a partir de cualquier genotipo del virus de hepatitis C.

72. El método de la reivindicación 71, en donde el virus de hepatitis C se selecciona a partir de los genotipos 1, 2, y/o 3 del virus de hepatitis C.

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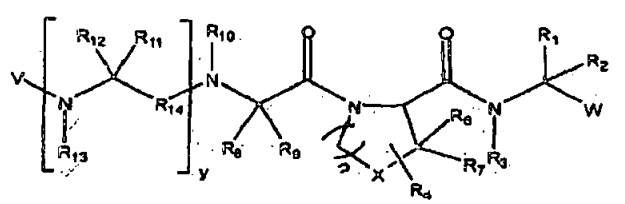
**Published:**

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(54) Title: HCV/HIV INHIBITORS AN THEIR USES



(I)

(57) Abstract: The present application describes organic compounds of formula (I): that are useful for the treatment, prevention and/or amelioration of human diseases such as HCV and HIV.

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# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/066204

A. CLASSIFICATION OF SUBJECT MATTER
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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)
C07K A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 03/062265 A (SCHERING CORP [US]; CORVAS INT INC [US] SCHERING CORP [US]; DENDREON C) 31 July 2003 (2003-07-31) claims 51-53 | 1 |
| X | WO 2006/017295 A (IDUN PHARMACEUTICALS INC [US]; CHAO BIN [US]; DECKWERTH THOMAS L [US];) 16 February 2006 (2006-02-16) claims 195, 196; example 20; page 51, 52; example 43; claims 58, 83, 84, 189 | 1,3, 40-43, 52-54, 57-59, 68-72 |

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
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| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 22 April 2008 | 21/05/2008 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Schleifenbaum, A |

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

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/066204

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | US 2003/216325 A1 (SAKSENA ANIL K [US] ET AL SAKSENA ANIL K [US] ET AL) 20 November 2003 (2003-11-20)<br><br>Page 625, claim 39<br>claim 39<br>Formula Ib, paragraphs [0082,0083, 0088, 0106]<br>compounds 74-78, 87-88, 90, 98-102, 108-154, 167-200, 208-217, 221-223, 230, 231, 238, 240, 242-248, 251, 254, 271, 278-280, 290, 292, 328, p 393,claims 23,24,28,39 | 1-4,6,7, 14-16, 19-21, 23,40-72 |
| Y | MALCOLM B A ET AL: "SCH 503034, a Mechanism-Based Inhibitor of Hepatitis C Virus NS3 Protease, Suppresses Polyprotein Maturation and Enhances the Antiviral Activity of Alpha Interferon in Replicon Cells"<br>ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, DC, US,<br>vol. 50, no. 3, March 2006 (2006-03), pages 1013-1020, XP002451894<br>ISSN: 0066-4804<br>cited in the application<br>figure 1 | 1-4,6,7, 14-16, 19-21, 23,40-72 |
| X | US 2005/107304 A1 (BRITT SHAWN D [US] ET AL) 19 May 2005 (2005-05-19)<br><br>paragraphs [0060] - [0432], [0476] - [0483], [0489] - [0501], [0508] - [0535], [0555] - [0567], [0603] - [0605], [0609]-[0611]; claims 2-5; example 2 | 1-4,6,7, 11,12, 14-16, 19-21, 23-26, 31-37, 39-72 |
| X | US 2005/137140 A1 (COTTRELL KEVIN M [US] ET AL) 23 June 2005 (2005-06-23)<br><br>paragraphs [0432], [0652], [0715]; claims 12,49<br><br>-/-- | 1-4,6,7, 11,12, 14-16, 19-21, 23-26, 31-37, 39-72 |

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/066204

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2005/267043 A1 (BOGEN STEPHANE L [US] ET AL BOGEN STEPHANE L [US] ET AL) 1 December 2005 (2005-12-01)<br><br>claims 9,10; compounds 4536,4555,4570,4597 | 1-4,6,7, 11,12, 14-16, 19-21, 23-26, 31-37, 39-72 |
| X | US 2003/036501 A1 (SAKSENA ANIL K [US] ET AL SAKSENA ANIL K [US] ET AL) 20 February 2003 (2003-02-20)<br><br>claims 29,39; examples 43-45,86,87 | 1-4,6,7, 11,12, 14-16, 19-21, 23-26, 31-37, 39-72 |
| X | BOGEN STÉPHANE L ET AL: "Discovery of SCH446211 (SCH6): a new ketoamide inhibitor of the HCV NS3 serine protease and HCV subgenomic RNA replication." JOURNAL OF MEDICINAL CHEMISTRY 4 MAY 2006, vol. 49, no. 9, 5 April 2006 (2006-04-05), pages 2750-2757, XP002477384 ISSN: 0022-2623<br>compounds 12-14 | 1-4,6,7, 11,12, 14-16, 19-21, 23-26, 31-37, 39-72 |
| X | EP 0 326 974 A (HOECHST AG [DE]) 9 August 1989 (1989-08-09)<br><br>Compounds page 15, lines 22-31 | 1-4,6,7, 11,12, 14-16, 19-21, 23-26, 31-37, 39-72 |
| P,X | WO 2007/025307 A (VERTEX PHARMA [US]; COTTRELL KEVIN M [US]; MAXWELL JOHN [US]; TANG QIN) 1 March 2007 (2007-03-01)<br>the whole document | 1 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2007/066204

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

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

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

Although claims 40-56, 59-67 and 70-72 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

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

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

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

see additional sheet

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

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

3. [X] As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

11-13, 25, 29, 30 (all completely) and 1-4, 6, 7, 14-16, 19-21, 23, 24, 26 31-37, 39-72 (all in part) (subject matter of inventions 1 and 9)

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.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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

1. claims: 1-4, 6, 7, 14-16, 19-21, 23, 40-72 (partially)

Compounds of formula I wherein X is O and methods using such compounds.

---

2. claims: 1, 3, 4, 6, 7, 14-16, 19-21, 23, 40-72 (partially)

Compounds of formula I wherein X is S and methods using such compounds.

---

3. claims: 1, 3, 4, 6, 7, 14-16, 19-21, 23, 40-72 (partially)

Compounds of formula I wherein X is N and methods using such compounds.

---

4. claims: 1-7, 14-16, 19-21, 23, 40-72 (partially)

Compounds of formula I wherein X is NR5 and R5 is selected from hydrogen, oxo, hydroxyl, C1-8-alkyl, C2-8-alkenyl, C2-8-alkynyl, C3-8-cycloalkyl-C0-4-alkyl, aryl-C0-4-alkyl, heterocycle-C0-4-alkyl, heteroaryl-C0-4-alkyl, C3-8-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C1-4-alkyl; and uses of such compounds.

---

5. claims: 1-4, 6, 7, 14-16, 19-21, 23, 40-72 (partially)

Compounds of formula I wherein X is NR5 and R5 together with R4 or with R6 forms a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring, or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or C1-4-alkyl; and uses of such compounds.

---

6. claims: 1, 3-7, 14-16, 19-21, 23, 40-72 (partially)

Compounds of formula I wherein X is CR5 and R5 is selected from hydrogen, oxo, hydroxyl, C1-8-alkyl, C2-8-alkenyl, C2-8-alkynyl, C3-8-cycloalkyl-C0-4-alkyl, aryl-C0-4-alkyl, heterocycle-C0-4-alkyl, heteroaryl-C0-4-alkyl, C3-8-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C1-4-alkyl; and uses of such compounds.

---

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. claims: 1, 3, 4, 6-8, 14-16, 19-21, 23, 40-72 (partially)

Compounds of formula I wherein X is CR5 and R5 together with R4 or with R6 forms a fused dimethyl cyclopropyl ring, a fused cyclopentane ring, a fused phenyl ring, or a fused pyridyl ring, each of which may be substituted with a halogen atom, aryl, trihalomethyl, or C1-4-alkyl; and uses of such compounds.

---

8. claims: 9, 10, 17, 18, 22, 27, 28, 38 (completely); 1-8, 15-16, 19-21, 23, 24, 26, 31-37, 39-72 (partially)

Compounds of formula I or of formula III wherein X is CR5R5a and R5 is selected from hydrogen, oxo, hydroxyl, C1-8-alkyl, C2-8-alkenyl, C2-8-alkynyl, C3-8-cycloalkyl-C0-4-alkyl, aryl-C0-4-alkyl, heterocycle-C0-4-alkyl, heteroaryl-C0-4-alkyl, C3-8-cycloalkyloxy, aryloxy, and heteroaryloxy each of which may be independently substituted one or more times with a halogen atom, aryl, trihalomethyl, or C1-4-alkyl; and R5a is selected from hydroxyl, C1-8-alkyl, C2-8-alkenyl, C2-8-alkynyl, C3-8-cycloalkyl-C0-4-alkyl, aryl-C0-4-alkyl, heteroaryl-C0-4-alkyl; and uses of such compounds.

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9. claims: 11-13, 25, 29, 30 (completely); 1-4, 6, 7, 14-16, 19-21, 23, 24, 26, 31-37, 39-72 (partially)

Compounds of formula I or of formula III wherein X is CR5R5a and wherein R5 and R5a form a spirocyclic ring having between 3 and 7 ring atoms and having 0, 1 or 2 ring heteroatoms.

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# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/066204

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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Act: 411 PRESENTACION Folios: 829

**Industria y Comercio**
SUPERINTENDENCIA

## REQUISITOS MINIMOS PARA ADMISION A TRAMITE
## PCT

PATENTE DE INVENCION [1] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [1]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [1]
- Descripción de la invención [1]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [1]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha 9 oct/08

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