04-68146

Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 04-68146

54. **TÍTULO** NUEVOS PEPTIDOS COMO INHIBIDORES DE LA PROTEASA SERINA NS3 DEL VIRUS DE LA HEPATITIS C (HCV).

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** SCHERING CORPORATION Y ENDREON CORPORATION.

DOMICILIO _____

74. **APODERADO** CARLOS OLARTE

22. **BOGOTÁ, D. C.,** _____

(FORMA P-10)

04189

OLARTE RAISBECK

1

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04068146 00000000 Folios: 1281
Fecha (AMD): 2004-07-16 17:41:52
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) SOLICITANTE (71)

Nombre: SCHERING CORPORATION y DENDREON CORPORATION.
Dirección: 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530, y 3005 first Avenue Seattle WA 98121 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Kenilworth y Delaware E.U.A.

Teléfono: _____ Fax: _____
E-mail: _____

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

(3) 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 79.782.747 Btá
TP 74.295

(4) INVENT R (ES) (72)

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

(5) PCT (86)

Solicitud Internacional No. PCT/US03/01430 Fecha 16 de enero de 2003
Publicación Internacional No. WO 03/062265 Fecha 31 de julio de 2003

(6) Título (54) **NUEVOS PÉPTIDOS COMO INHIBIDORES DE LA PROTEASA SERINA NS3 DEL VIRUS DE LA HEPATITIS C.**

(7) Clasificación Internacional (51) **C07K.**

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Enero 18, 2002	10/052,386

(9) Comprobante de pago No. 55,085 **Fecha** 12 de julio de 2004

(10) 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.
- [ ] Documento de cesión del interventor 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

INVENTORES

SAKSENA, Anil K. 53 Beverley Road Upper Montclair, New Jersey 07043, USA	GANGULY, Ashit K. 96 Cooper Avenue Upper Montclair, New Jersey 07043, USA
GIRIJAVALLABHN, Viyyoor M. 10 Maplewood Drive Parsippany, New Jersey 07054, USA	CHEN, Kevin X. 9 Gloria Avenue Edison, New Jersey 08820, USA
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JAO, Edwin 20 Crosswood Way Warren, New Jersey 07059, USA	VACCARO, Henry A. 123 Somerset Avenue South Plainfield, New Jersey 07080, USA
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MC CORMICK, Jinping L. 5 Pace Drive Edison, New Jersey 08820, USA	SANTHANAM, Bama 10 Somerset Avenue Bridgewater, New Jersey 08807, USA
WANG, Haiyan 5 Cubberly Court Cranbury, New Jersey 08512, USA	KEMP, Scott Jeffrey 7873 Avenida Navidad #263 San Diego, California 92122, USA
PIKE, Russell E. RD #1, 31 Florence Street Stanhope, New Jersey 07874, USA	LEVY, Odile Esther 5304 Ruette de Mer San Diego, California 92130, USA
BOGEN, Stephane L. 13 Dahlia Road Somerset, New Jersey 08873, USA	LIM-WILBY, Marguerita 6333 Castenjon Drive La Jolla, California 92037, USA
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ZHU, Zhaoning 6 Cypress Court Plainsboro, New Jersey 08536, USA	HENDRATA, Siska P.O. Box 116 Kenilworth, New Jersey 07033, USA
NJOROGE, F. George 11 Softwood Way Warren, New Jersey 07059, USA	HUANG, Yuhua 132 Roger Avenue Westfield, New Jersey 07090, USA
ARASAPPAN, Ashok 18 Larsen Court Bridgewater, New Jersey 08807, USA	WONG, Jesse K. 2 Hampshire Place Monroe Township, New Jersey 08831, USA
PAREKH, Tejal 1885 Ednamary Way, Unit C Mountain View, California 94040, USA	NAIR, Latha G. 560 Darwin Boulevard Edison, New Jersey 08820, USA

A

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04068146 00000000 Folios: 1281
Fecha (AMD): 2004-07-16 17:41:52
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 55,085
FECHA : JULIO 12 DE 2004

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
FREDERICK TORRES	CONSIGNACION	BANCO POPULAR	050-00110-6	23286882	12/07/2004	9,344,000.00

***** 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	422,000.00
		TOTAL : $	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Estados Unidos de América
   - Este documento Público
2. ha sido firmado por Marguerite La Corte
3. Quien ejerce funciones de Notario público de Nueva Jersey
4. Lleva el sello de Marguertie La Corte Notario

CERTIFICADO

5. En Trenton, Nueva Jersey
6. El 29 de agosto 2003
7. Por John E. McCormac Contador Publico- Tesorero de Nueva Jersey 8. No. A 180345
9. Gran Sello del Estado de Nueva Jersey
10. Firma legible de John M.

PODER DE REPRESENTACIÓN

Bilingüe inglés- español otorgado en Kenilworth, Nueva Jersey, Estados Unidos, el 7 de agosto de 2003 y firmado por Edward H. Mazer - Director Juridico senior.

CERTIFICADO NOTARIAL

Bilingüe inglés- español, fechado el 7 de agosto, 2003 certificando las funciones de Edward H. Mazer - Director Juridico senior, de Schering Corporation.

Las certificaciones anteriores se basan en el poder de representación fechado el 4 noviembre de 2002.

Sello: Marguerite La Corte- Notario público,
Estado de Nueva Jersey
Su comisión vence el 7 de octubre de 2003.
Sello en alto relieve del Notario Público

Es traducción fiel del inglés, con copia a la vista para confrontación. Bogotá 5 septiembre, 2003.

COMO NOTARIO ONCE DE ESTE CÍRCULO ... AGO CONSTAR QUE ÉSTA FOTOCOPIA ... CON EL ORIGINAL ... A LA VISTA.
05 MAY 2003
BOGOTÁ, D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE

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

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MARGUERITE LA CORTE

3. ACTING IN THE CAPACITY OF:
NOTARY PUBLIC OF NEW JERSEY

4. BEARS THE SEAL/STAMP OF:
MARGUERITE LA CORTE, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

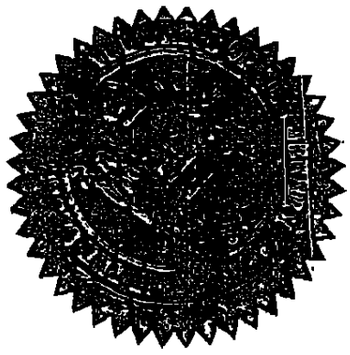
6. THE 29TH DAY OF AUGUST 2003

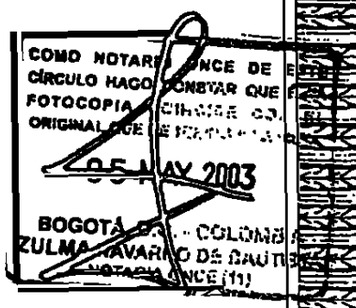
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:

10. SIGNATURE





OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

The undersigned,
SCHERING CORPORATION

domiciled in
2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0532, U.S.A.

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

Poder

El suscrito,

domiciliado en
2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0532, U.S.A.

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

Signature/Firma: _____
Edward H. Mazer, Senior Legal Director

Date/Fecha: August 7, 2003

City,Country/Ciudad,País: Kenilworth, New Jersey, U.S.A.

COMO NOTARIO DICE DE ESTE CIRCULO ... GO CONTAR QUE ESTA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
05 MAY 2003
BOGOTA D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

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

WORLD TRADE CENTER – TORRE C
CALLE 100 No. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-8200
Fax: +57-1 638-8201

www.olarteraisbeck.com

Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

of legal age and domiciled in 119 GreenwoodDrive, Millburn, New Jersey 07041, U.S.A.
signed the foregoing document.

2. That the grantor has executed the foregoing document as Senior Legal Director of SCHERING CORPORATION

3. That SCHERING CORPORATION having its principal place of business located in 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, U.SA.. is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):
Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

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

de

4. Que

con sede principal ubicada en

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

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

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

COMO NOTARIO DEL CIRCULO DE ESTE CÍRCULO HAGO CONSTAR QUE ÉSTA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A VISTA
05 MAY 2003
BOGOTÁ D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

PUBLIC (Signature):

Marguerite La Corte
Notary Public of New Jersey
My Commission Expires October 7, 2003

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

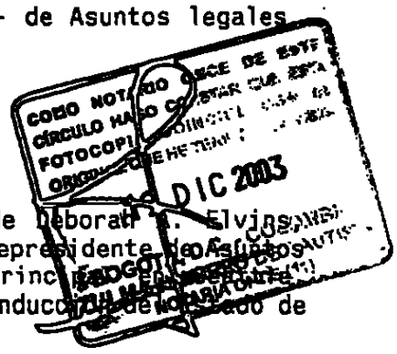
APOSTILLA EN PODER DE DENDREON CORPORATION

APOSTILLA
(Convención de la Haya del 5 de octubre de 1961)

1. País :Estados Unidos de América-
   Este documento Público
2. ha sido firmado por Gloria M. Teves
3. ejerce funciones de Notario público- Estado de Washington
4. Lleva el sello de Gloria M. Teves
   CERTIFICADO
5. En Olympia, Washington
6. El 9 de diciembre de 2003
7. Por Sam Reed Secretario de Estado
8. No. 200312456
9. Sello del Estado de Washington
10. Firma de Sam Reed Secretario de Estado - Expedido con mi firma y el sello del Estado de Washington en Olympia, La Capital Estado

PODER DE REPRESENTACIÓN

Bilingüe inglés- español, firmado por Deborah A. Elvins- de Asuntos legales Vicepresidente .
Fechado el 2, diciembre 2003.
Ciudad, país: Seattle, Washington - Estados Unidos



CERTIFICACION NOTARIAL

Bilingüe inglés- español certificando las funciones de Deborah A. Elvins, domiciliada en el Estado de Washington, en su cargo de Vicepresidente de Asuntos legales de Dendreon Corporation, compañía con sede principal en [illegible] Washington. Basa sus certificaciones en la Licencia de Conducción [illegible] Estado de Washington.

Firma de Notario Público: Gloria M. Teves - sello de notario público-
Fecha: 12/ 2/ 03. Estado de Washington.

DELAWARE
El primer Estado

Yo, Harriet Smith Windsor, Secretario de Estado del Estado de Delaware, por el presente certifico que anexo al presente se encuentra una copia verdadera y correcta del Certificado de fusión que fusiona a:
"Corvas International, Inc. ", compañía de Delaware, con y dentro de "Dendreon San Diego LLC", compañía de responsabilidad limitada, establecida y en operaciones conforme a las leyes de Delaware, tal como se recibió y archivó en esta oficina el 29 de julio de 2003 a las 3:36 pm.

Certifico además por el presente que la fecha de vigencia del Certificado de fusión mencionado es el 30 de julio de 2003, a las 12:02 A.M.

Harriet Smith Windsor, Secretario de Estado
2335856 8100 M Autenticación : 2612550
030567717 Fecha: 09- 03- 03

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

10

2/2 D

Estado de Delaware- Secretario de Estado
División de Compañías- Entregado el 03- 24 PM 07- 29- 2003
Archivado el 03:36 PM . 07- 29 -2003- SRV 030494696 - 3628268 Archivo

CERTIFICADO DE FUSIÓN

"CORVAS INTERNATIONAL, INC." CON Y DENTRO DE "DENDREON SAN DIEGO LLC"

Conforme a la sección 264 (c) de la Ley general de Compañías de Delaware y la sección 18- 209 de la Ley de Compañías de responsabilidad limitada, Dendreon San Diego LLC, compañía de responsabilidad limitada de Delaware y la compañía de responsabilidad limitada que sobrevive en esta fusión (en adelante La Fusión), presenta este Certificado de Fusión y por el presente certifica lo siguiente:

1. Las entidades comerciales constituyentes (las Entidades Constituyentes, cada una individualmente, una Entidad Constituyente) y sus estados de domicilio son Corvas International, Inc, compañía de Delaware, y Dendreon San Diego LLC, compañía de responsabilidad limitada de Delaware.

2. Las entidades Constituyentes son parte de un acuerdo y plan de fusión fechado el 24 de febrero de 2003, tal como se modificó mediante Renuncia y Enmienda fechada el 12 de junio de 2003 (El Acuerdo de Fusión). Cada una de la Entidades Constituyentes ha aprobado, adoptado, certificado, suscrito y reconocido el Acuerdo de Fusión conforme a la Ley general de Compañías de Delaware y a la Ley de Compañías de responsabilidad limitada, Dendreon, en lo aplicable.

3. La fusión será vigente desde las 12:02 a.m. del 30 de julio de 2003.

4. Dendreon San Diego LLC, compañía de responsabilidad limitada de Delaware es la compañía de responsabilidad limitada que sobrevive en la Fusión.

5. El Certificado de Constitución de Dendreon San Diego LLC, compañía de responsabilidad limitada de Delaware será el Certificado de constitución de la Compañía de responsabilidad limitada que sobrevive.

6. El Acuerdo de Fusión suscrito se encuentra en archivo en la oficina principal de negocios de la compañía de responsabilidad limitada que sobrevive en el número 3005 First Avenue, Seattle, Washington 98121.

7. Compañía de responsabilidad limitada que sobrevive entregará copia del Acuerdo de fusión por solicitud y sin costo, a cualquier miembro o accionista de una Entidad Constituyente.

En testimonio de lo anterior, Dendreon San Diego LLC, compañía de responsabilidad limitada de Delaware suscribe el Acuerdo de fusión el 29 de julio de 2003.

Dendreon San Diego LLC-
Una Compañía de responsabilidad limitada de Delaware.
Por: Dendreon Corporation
Su único Miembro.

Por: /s/ Dr. Mitchell H. Gold-
Director Ejecutivo- Firma y nombre

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
19 DIC 2003
BOGOTA, D.C. - COLOMBIA
ZULMA NAVARRO DE BARRETO
NOTARIA ONCE (11)

--

Es traducción conforme con copia para confrontar- Bogotá, Dic. 16- 2003

MARLEN NEIRA CASTRO
Traductor e Intérprete Ofic
Inglés - Español - Inglés

UNITED STATES OF AMERICA

The State of Washington

Secretary of State

APOSTILLE

(Convention de la Haye du 5 Octobre 1961)

1. Country: **United States of America**

2. This public document has been signed by: GLORIA M. TEVES

3. acting in the capacity of: Notary Public, state of Washington

4. bears the seal/stamp of: GKLORIA M. TEVES

CERTIFIED

5. at: Olympia, Washington

6. the: 9 day of December, 2003

7. by: Sam Reed, Secretary of State

8. No: 200312456

9. Seal/Stamp:

10. Signature:

COMO NOTARIO DE ESTE CÍRCULO HAGO CONSTAR QUE ÉSTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE TENGO A LA VISTA.
19 DIC 2003
BOGOTA, D.C. COLOMBIA
ZULMA [illegible]
NOTARIA [illegible]

Given under my hand and the Seal of the State of Washington at Olympia, the State Capital

Sam Reed, Secretary of State

12
16036CC
16037CC
12

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

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

Poder

El suscrito,

domiciliado en

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

Signature/Firma: Deborah A. Dunn, US Legal Affairs

Date/Fecha: December 2, 2003

City,Country/Ciudad,Pais: Seattle, Washington, USA

COMO NOTARIO ENCE DE ESTE CÍRCULO HAGO CONSTAR QUE ÉSTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

10 DIC 2003

BOGOTA D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

16036 CO
16038 CO
Page 2
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OLARTERAISBECK

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Notarial Certification

On this date,

The undersigned Notary Public certifies:

1. That Deborah Elvins is

of legal age and domiciled in Washington State

signed the foregoing document.

2. That the grantor has executed the foregoing document as Vice President, Legal Affairs of Dendreon Corporation

3. That Dendreon Corporation, having its principal place of business located in Seattle, Washington is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

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

4. Que
con sede principal ubicada en

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

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

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

COMO NOTARIO ONCE DE ESTE CÍRCULO HAGO CONSTAR QUE ÉSTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
19 DIC 2003
BOGOTÁ, D.C. - COLOMBIA
ZULMA [illegible] DE BAUTISTA
NOTARIA ONCE (11)

NOTARY PUBLIC (Signature): Gloria M. Teves
Gloria M. Teves

SEAL (optional)

Delaware

The First State

I, HARRIET SMITH WINDSOR, SECRETARY OF STATE OF THE STATE OF DELAWARE, DO HEREBY CERTIFY THE ATTACHED IS A TRUE AND CORRECT COPY OF THE CERTIFICATE OF MERGER, WHICH MERGES:

"CORVAS INTERNATIONAL, INC.", A DELAWARE CORPORATION,

WITH AND INTO "DENDREON SAN DIEGO LLC" UNDER THE NAME OF "DENDREON SAN DIEGO LLC", A LIMITED LIABILITY COMPANY ORGANIZED AND EXISTING UNDER THE LAWS OF THE STATE OF DELAWARE, AS RECEIVED AND FILED IN THIS OFFICE THE TWENTY-NINTH DAY OF JULY, A.D. 2003, AT 3:36 O'CLOCK P.M.

AND I DO HEREBY FURTHER CERTIFY THAT THE EFFECTIVE DATE OF THE AFORESAID CERTIFICATE OF MERGER IS THE THIRTIETH DAY OF JULY, A.D. 2003, AT 12:02 O'CLOCK A.M.

COMO NOTARIO ONCE DE ESTE CÍRCULO BOGOTÁ D.C. CONSTA QUE ESTA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA

19 DIC 2003

BOGOTÁ D.C. - COLOMBIA
ZULMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

Harriet Smith Windsor

Harriet Smith Windsor, Secretary of State

2335856 8100M

030567717

AUTHENTICATION: 2612550

DATE: 09-03-03

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State of Delaware
Secretary of State
Division of Corporations
Delivered 03:24 PM 07/29/2003
FILED 03:36 PM 07/29/2003
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CERTIFICATE OF MERGER

CORVAS INTERNATIONAL, INC. INTO DENDREON SAN DIEGO LLC

Pursuant to Section 264(c) of the Delaware General Corporation Law and Section 18-209 of the Delaware Limited Liability Company Act, Dendreon San Diego LLC, a Delaware limited liability company and the surviving limited liability company in this merger (the "Merger"), files this Certificate of Merger and does hereby certify the following:

1. The constituent business entities (the "Constituent Entities" and, each individually, a "Constituent Entity") and their states of domicile are Corvas International, Inc., a Delaware corporation, and Dendreon San Diego LLC, a Delaware limited liability company.

2. The Constituent Entities are parties to an Agreement and Plan of Merger dated February 24, 2003, as amended by a Waiver and Amendment dated June 12, 2003 (the "Merger Agreement"). Each of the Constituent Entities has approved, adopted, certified, executed and acknowledged the Merger Agreement in accordance with the Delaware General Corporation Law and the Delaware Limited Liability Company Act, as applicable.

3. The Merger shall be effective as of 12:02 a.m. on July 30, 2003.

4. Dendreon San Diego LLC, a Delaware limited liability company, is the surviving limited liability company in the Merger.

5. The Certificate of Formation of Dendreon San Diego LLC, a Delaware limited liability company, as amended to date, shall be the Certificate of Formation of the surviving limited liability company.

6. The executed Merger Agreement is on file at the principal place of business of the surviving limited liability company at 3005 First Avenue, Seattle, Washington 98121.

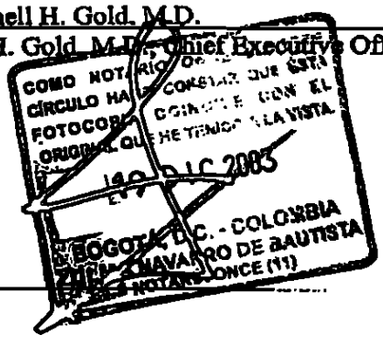
7. A copy of the Merger Agreement will be furnished by the surviving corporation on request and without cost, to any member or stockholder of a Constituent Entity.

IN WITNESS WHEREOF, Dendreon San Diego LLC, a Delaware limited liability company, has executed this Certificate of Merger on this 29th day of July, 2003.

DENDREON SAN DIEGO LLC,
a Delaware limited liability company

By: DENDREON CORPORATION,
Its sole member

By: /s/ Mitchell H. Gold, M.D.
Mitchell H. Gold, M.D., Chief Executive Officer



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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM.

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Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL PEPTIDES AS NS3-SERINE PROTEASE INHIBITORS OF HEPATITIS C VIRUS

(57) Abstract: The present invention discloses novel compounds which have HCV protease inhibitory activity as well as methods for preparing such compounds. In another embodiment, the invention discloses pharmaceutical compositions comprising such compounds as well as methods of using them to treat disorders associated with the HCV protease.

WO 03/062265 A2

Novel Peptides as NS3-Serine Protease Inhibitors of Hepatitis C Virus

Field of Invention

The present invention relates to novel hepatitis C virus ("HCV") protease inhibitors, pharmaceutical compositions containing one or more such inhibitors, methods of preparing such inhibitors and methods of using such inhibitors to treat hepatitis C and related disorders. This invention specifically discloses novel peptide compounds as inhibitors of the HCV NS3/NS4a serine protease. Priority for the invention is based on U.S. patent applications Serial Number 60/220,108 filed July 21, 2000, and Serial Number 09/908,955 filed July 19, 2001.

Background of the Invention

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)(see, International Patent Application Publication No. WO 89/04669 and European Patent Application Publication No. EP 381 216). 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. Patent 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. Other chymotrypsin-like enzymes are elastase, factor Xa, thrombin, trypsin, plasmin, urokinase, tPA and PSA. 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*).

Analysis of the natural cleavage sites for HCV protease revealed the presence of cysteine at P1 and serine at P1' and that these residues are strictly conserved in the NS4a/NS4b, NS4b/NS5a and NS5a/NS5b junctions. The NS3/NS4a junction contains a threonine at P1 and a serine at P1'. The Cys→Thr substitution at NS3/NS4a is postulated to account for the requirement of *cis* rather than *trans* processing at this junction. See, e.g., Pizzi et al. (1994) Proc. Natl. Acad. Sci (USA) 91:888-892; Failla et al. (1996) Folding & Design 1:35-42. The NS3/NS4a cleavage site is also more tolerant of mutagenesis than the other sites. See, e.g., Kollykhalov et al. (1994) J. Virol. 68:7525-7533. It has also been found that acidic residues in the region upstream of the cleavage site are required for efficient cleavage. See, e.g., Komoda et al. (1994) J. Virol. 68:7351-7357.

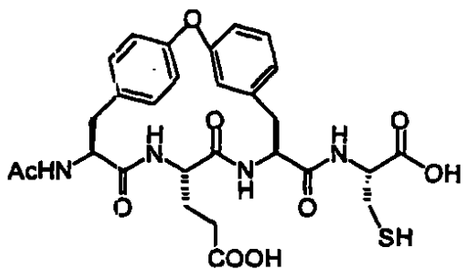
Inhibitors of HCV protease that have been reported include antioxidants (see, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (see, International Patent Application Publication No. WO 98/17679, Landro et al. (1997) Biochem. 36:9340-9348, Ingallinella et al.

(1998) Biochem. 37:8906-8914, Llinàs-Brunet et al. (1998) Bioorg. Med. Chem. Lett. 8:1713-1718), inhibitors based on the 70-amino acid polypeptide eglin c (Martin et al. (1998) Biochem. 37:11459-11468, inhibitors affinity selected from human pancreatic secretory trypsin inhibitor (hPSTI-C3) and minibody repertoires (MBip) (Dimasi et al. (1997) J. Virol. 71:7461-7469), cV_HE2 (a "camelized" variable domain antibody fragment) (Martin et al.(1997) Protein Eng. 10:607-614), and α1-antichymotrypsin (ACT) (Elzouki et al.) (1997) J. Hepat. 27:42-28). A ribozyme designed to selectively destroy hepatitis C virus RNA has recently been disclosed (see, *BioWorld Today* 9(217): 4 (November 10, 1998)).

Reference is also made to the PCT Publications, No. WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (F. Hoffmann-La Roche AG); and WO 99/07734, published February 18, 1999 (Boehringer Ingelheim Canada Ltd.).

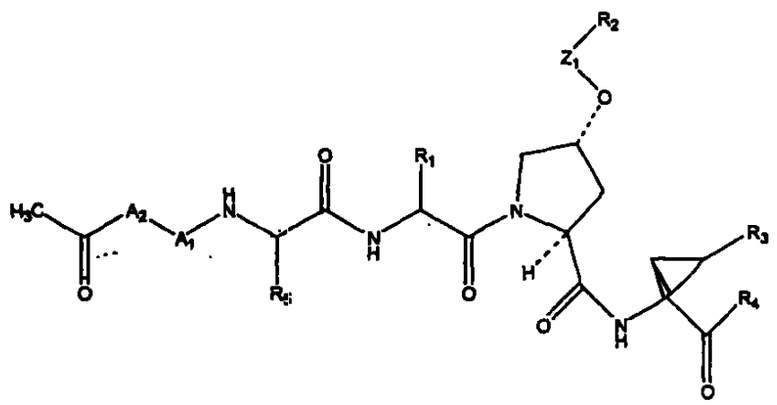
HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV 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%.

Reference is made to A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicylic analogs of an inhibitor of HCV NS3 protease. A compound disclosed therein has the formula:

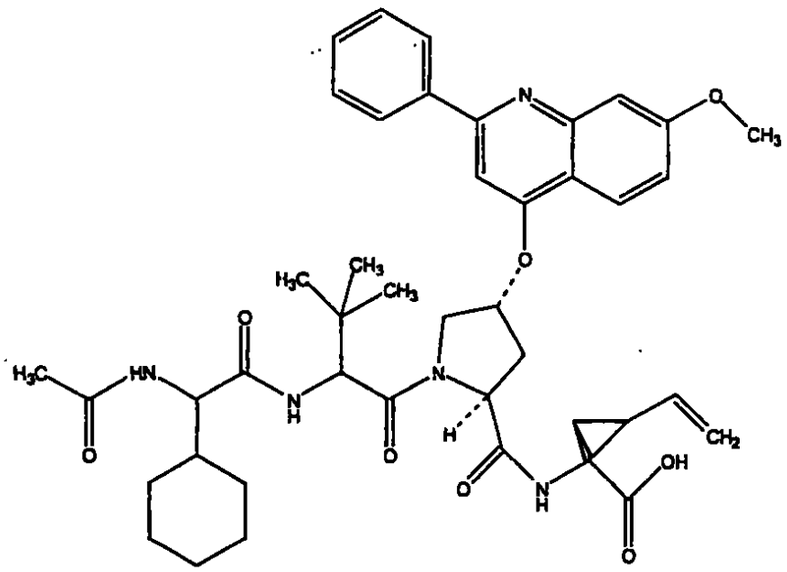


Reference is also made to W. Han *et al; Bioorganic & Medicinal Chem. Lett,* (2000) 10, 711-713, which describes the preparation of certain α-ketoamides, α-ketoesters and α-diketones containing allyl and ethyl functionalities.

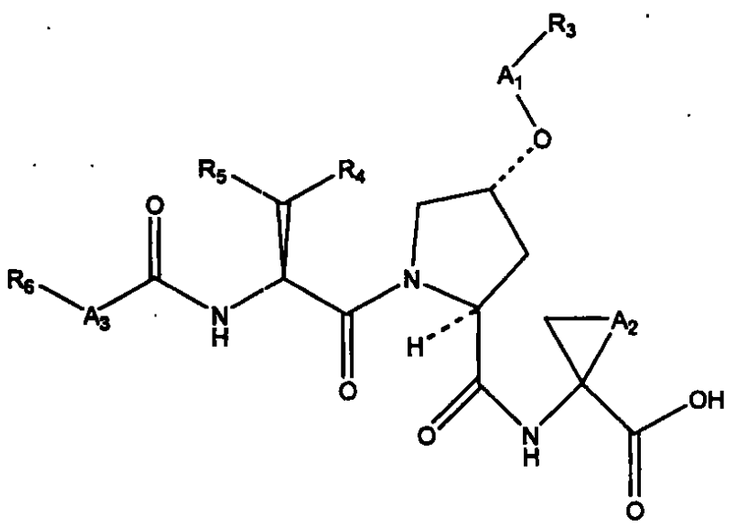
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



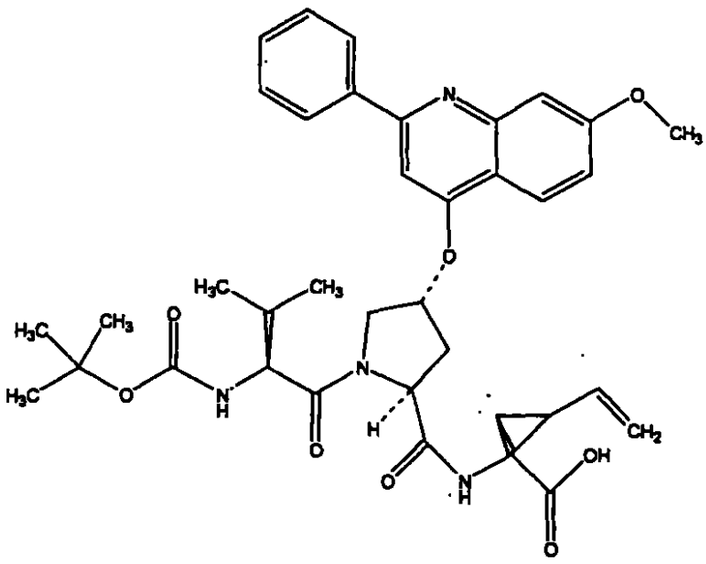
where the various elements are defined therein. An illustrative compound of that series is:



Reference is also made to WO 00/09543 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



where the various elements are defined therein. An illustrative compound of that series is:



Current therapies for hepatitis C include interferon-α (INF_α) 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.

Pending and copending U. S. patent applications, Serial No. 60/194,607, filed April 5, 2000, and Serial No. 60/198,204, filed April 19, 2000, Serial No. 60/220,110, filed July 21, 2000, Serial No. 60/220,109, filed July 21, 2000, Serial No. 60/220,107, filed July 21, 2000, Serial No. 60/254,869, filed December 12, 2000, and Serial No. 60/220,101, filed July 21, 2000, disclose various types of peptides and/or other compounds as NS-3 serine protease inhibitors of hepatitis C virus.

There is a need for new treatments and therapies for HCV infection. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of one or more symptoms of hepatitis C.

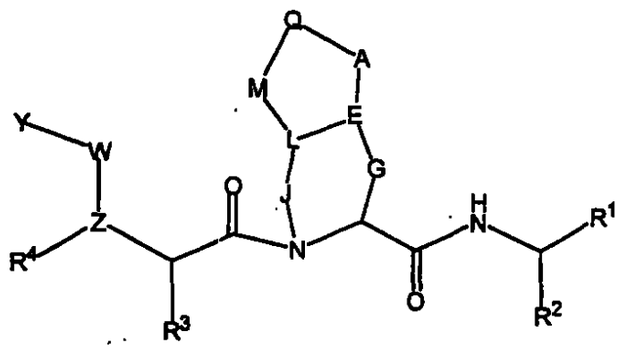
It is a further object herein to provide methods of treatment or prevention or amelioration of one or more symptoms of hepatitis C.

A still further object of the present invention is to provide methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

Another object herein is to provide methods of modulating the processing of the HCV polypeptide using the compounds provided herein.

Summary of the invention

In its many embodiments, the present invention provides a novel class of inhibitors of the HCV protease, pharmaceutical compositions containing one or more of the compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention or amelioration or one or more of the symptoms of hepatitis C. Also provided are methods of modulating the interaction of an HCV polypeptide with HCV protease. Among the compounds provided herein, compounds that inhibit HCV NS3/NS4a serine protease activity are preferred. The present application discloses a compound, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound having the general structure shown in Formula I:



Formula I

wherein:

Y is selected from the group consisting of alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe optionally substituted with X^{11} or X^{12};

X^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X^{11} may be additionally optionally substituted with X^{12};

X^{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and aryl may be additionally optionally substituted with moieties independently selected from X^{12};

R^1 is $-C(O)R^5$ or $-B(OR)_2$, wherein R^5 is H, -OH, $-OR^6$, $-NR^9R^{10}$, $-CF_3$, $-C_2F_5$, $-C_3F_7$, $-CF_2R^6$, $-R^6$, or $-C(O)R^7$ wherein R^7 is H, -OH, $-OR^8$, $-CHR^9R^{10}$, or $-NR^9R^{10}$, wherein R^6, R^8, R^9 and R^{10} are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, cycloalkyl, arylalkyl, heteroarylalkyl, $-[CH(R^{1'})]_pC(O)OR^{11}$, $-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$, $-[CH(R^{1'})]_pS(O_2)R^{11}$, $-[CH(R^{1'})]_pC(O)R^{11}$, $-[CH(R^{1'})]_pCH(OH)R^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})R'$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)NR^{12}R^{13}$,

$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)N(H)CH(R^{5'})C(O)OR^{11}$ and

$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)N(H)CH(R^{5'})C(O)NR^{12}R^{13}$,

wherein $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, and R' are independently selected from the group consisting of H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl and heteroaralkyl;

Z is selected from O, N, C(H) or C(R);

W maybe present or absent, and if W is present, W is selected from C(=O), C(=S), C(=N-CN), or $S(O_2)$;

Q maybe present or absent, and when Q is present, Q is C(H), N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, NR, S, or SO_2; and when Q is absent, M may be present or absent; when Q and M are absent, A is directly linked to L;

A is O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, N(R), S, $S(O_2)$ or a bond;

E is CH, N, CR, or a double bond towards A, L or G;

G may be present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$; and when G is absent, J is present and E is directly connected to the carbon atom in Formula I as G is linked to;

J maybe present or absent, and when J is present, J is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$, $S(O_2)$, N(H), N(R) or O; and when J is absent, G is present and E is directly linked to N shown in Formula I as linked to J;

L may be present or absent, and when L is present, L is C(H), C(R), O, S or N(R); and when L is absent, then M may be present or absent; and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, NR, S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$;

p is a number from 0 to 6; and

R, R', R^2, R^3 and R^4 can be the same or different and are independently from the group consisting of H; C_1-C_{10} alkyl; C_2-C_{10} alkenyl; C_3-C_8 cycloalkyl; C_3-C_8

heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

wherein said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally and chemically-suitably substituted, with said term "substituted" referring to optional and chemically-suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamido, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate;

further wherein said unit N-C-G-E-L-J-N in Formula I represents either a five-membered cyclic ring structure or a six-membered cyclic ring structure with the proviso that when said unit N-C-G-E-L-J-N represents a five-membered cyclic ring structure, or when the bicyclic ring structure in Formula I comprising N, C, G, E, L, J, N, A, Q, and M represents a five-membered cyclic ring structure, then said five-membered cyclic ring structure lacks a carbonyl group as part of the cyclic ring.

Among the above-stated definitions for the various moieties of Formula I, the preferred groups for the various moieties are as follows:

Preferred definition for R^1 is $-C(O)R^5$ with R^5 being H, -OH, $-C(O)OR^8$ or $-C(O)NR^9R^{10}$, where R^8, R^9 and R^{10} are defined above. Still preferred moiety for R^1 is $-C(O)C(O)NR^9R^{10}$, where R^9 is H; and R^{10} is H, $-R^{14}$, $-[CH(R^{1'})]_pC(O)OR^{11}$, $-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$, $-[CH(R^{1'})]_pS(O_2)R^{11}$, $-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$, $-[CH(R^{1'})]_pC(O)R^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$,

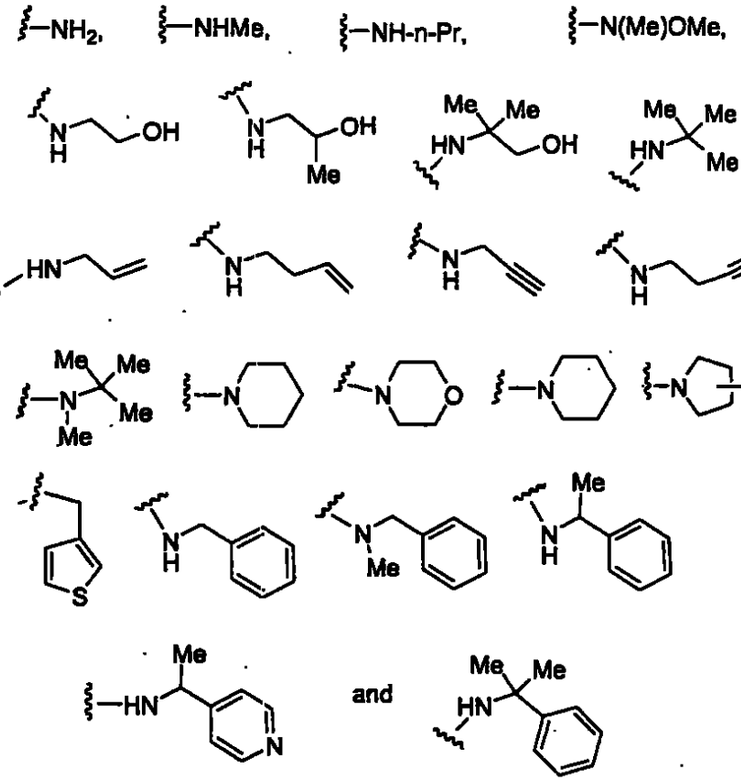
$-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$, or $-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$, wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaralkyl.

Among the above for R^{10}, preferred moieties for R^{10} are: H, $-R^{14}$, $-CH(R^{1'})C(O)OR^{11}$, $-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$, $-CH(R^{1'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$, $-CH(R^{1'})CH(R^{1'})S(O_2)N\ R^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})C(O)R^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$, or $-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$, wherein $R^{1'}$ is H or alkyl, and $R^{2'}$ is phenyl, substituted phenyl, hetero atom-substituted phenyl, thiophenyl, cycloalkyl, piperidyl or pyridyl.

More preferred moieties are: for $R^{1'}$ is H, for R^{11} is H, methyl, ethyl, allyl, *tert*-butyl, benzyl, α-methylbenzyl, α,α-dimethylbenzyl, 1-methylcyclopropyl or 1-methylcyclopentyl; for

R' is hydroxymethyl or $-CH_2C(O)NR^{12}R^{13}$ where

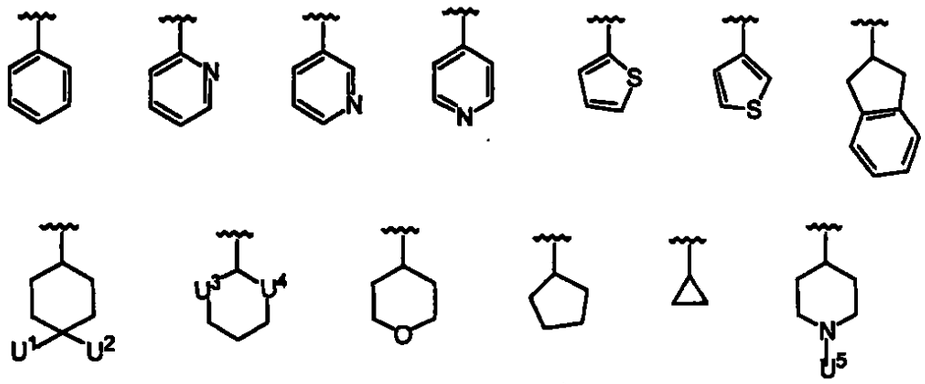
$NR^{12}R^{13}$ is selected from the group consisting of:



wherein U^6 is H, OH, or CH_2OH;

R^{14} is preferably selected from the group consisting of: H, Me, Et, *n*-propyl, methoxy, cyclopropyl, *n*-butyl, 1-but-3-ynyl, benzyl, α-methylbenzyl, phenethyl, allyl, 1-but-3-enyl, OMe and cyclopropylmethyl;

and $R^{2'}$ is preferably independently selected from the group consisting of:



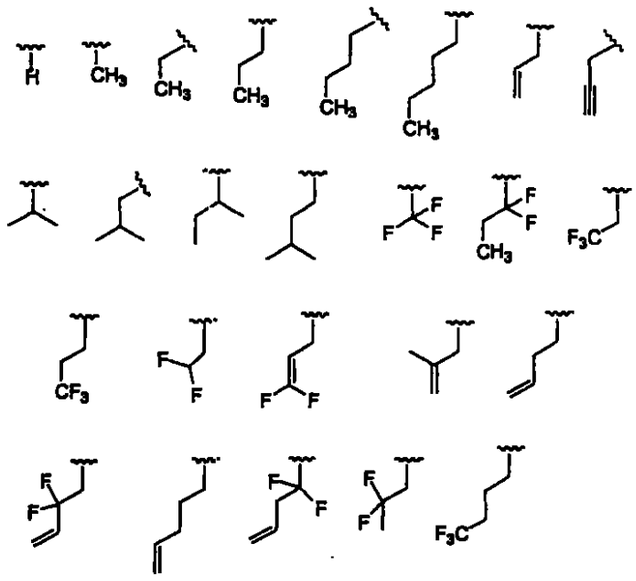
wherein:

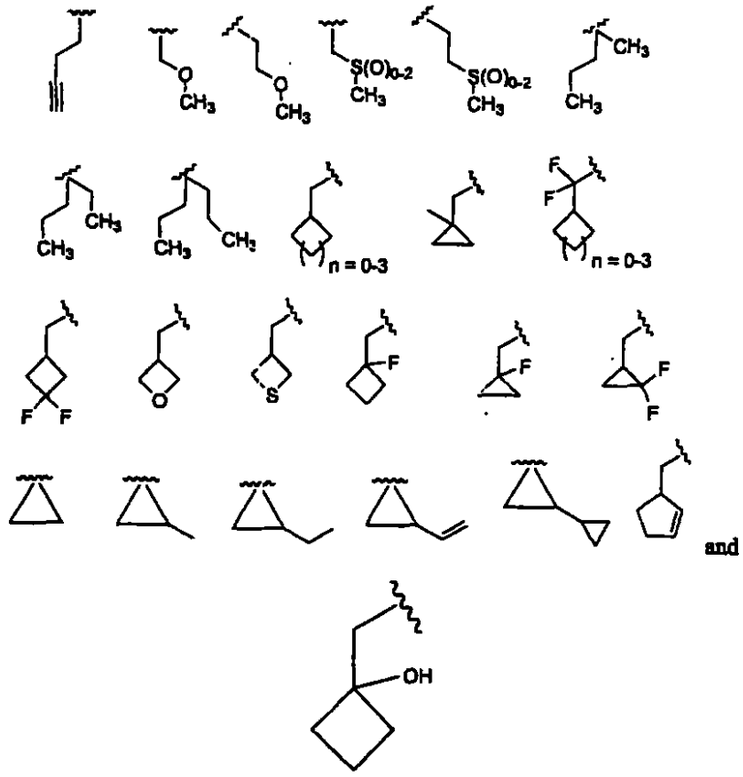
U^1 and U^2 maybe same or different and are selected from the group consisting of H, F, CH_2COOH, CH_2COOMe, CH_2CONH_2, $CH_2CONHMe$, CH_2CONMe_2, azido, amino, hydroxyl, substituted amino and substituted hydroxyl;

U^3 and U^4 maybe same or different and are selected from O and S;

U^5 is selected from the moieties consisting of alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl or a combination thereof.

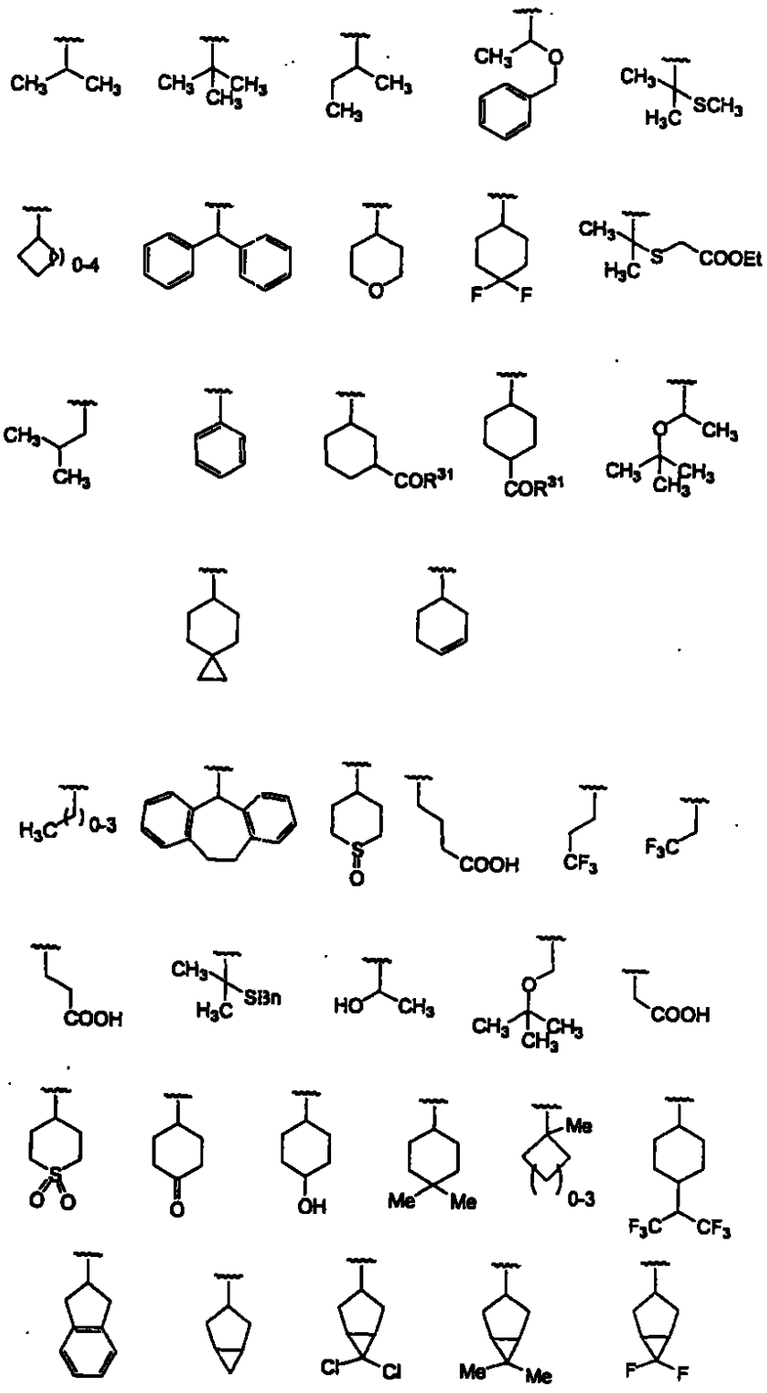
Preferred moieties for R^2 are:

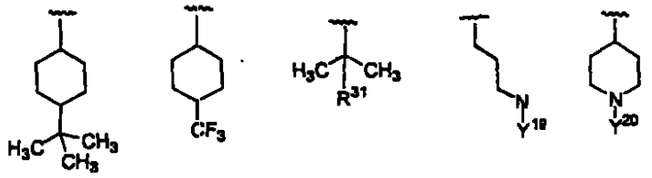




and

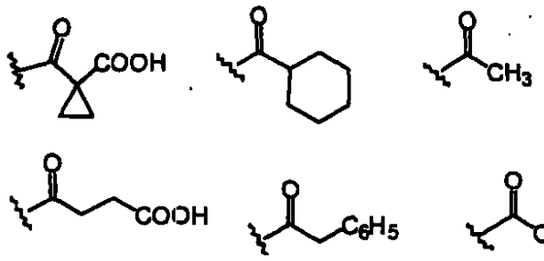
Preferred moieties for R^3 are:


CH3
CH3
CH3
CH3
CH3
CH3
CH3
O
CH3
H3C
SCH3
0-4
O
F
F
CH3
H3C
S
COOEt
CH3
CH3
COR31
COR31
O
CH3
CH3
CH3
CH3
H3C
0-3
S
O
COOH
CF3
F3C
COOH
CH3
H3C
SI3n
HO
CH3
O
CH3
CH3
CH3
COOH
S
O
O
O
OH
Me
Me
Me
0-3
F3C
CF3
Cl
Cl
Me
Me
F
F

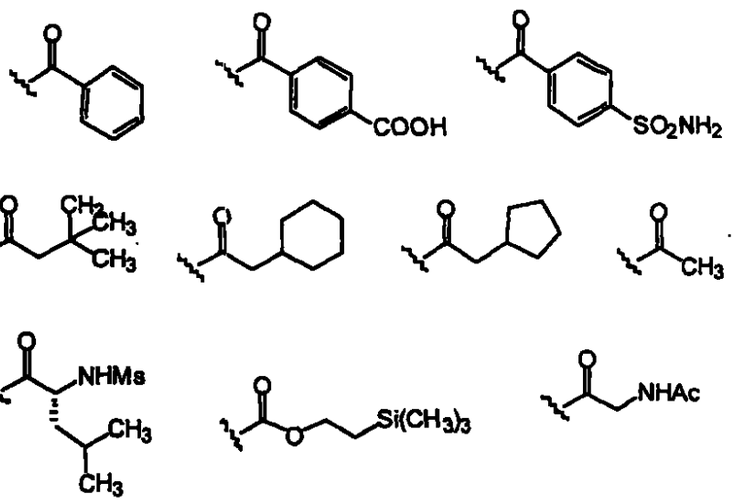


wherein R^{31} = OH or O-alkyl;

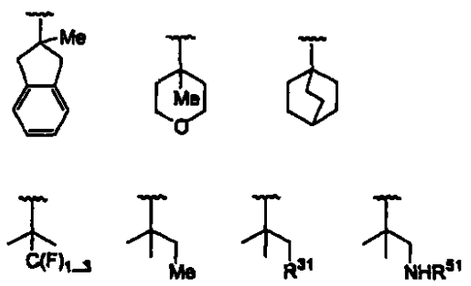
Y^{19} is selected from the following moieties:



and Y^{20} is selected from the following moieties:

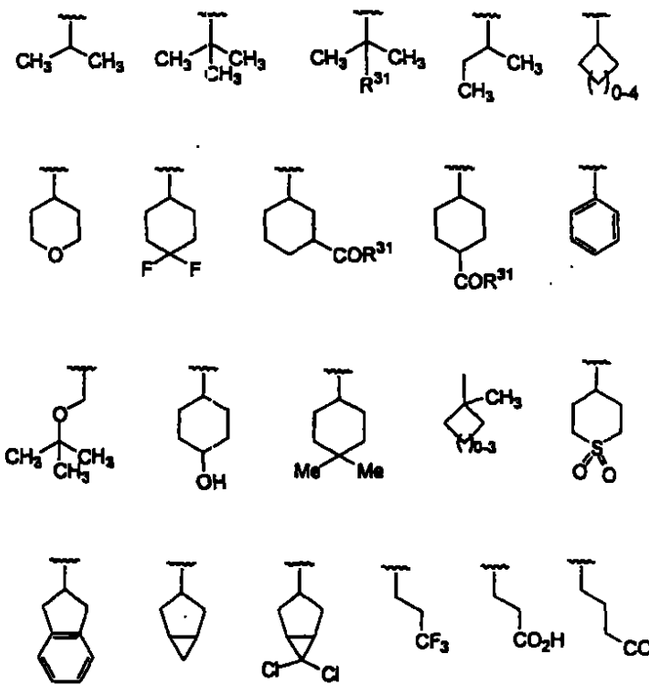


Additional R^3 moieties include the following:

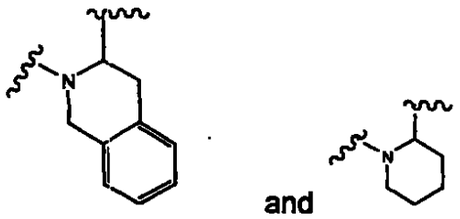


where R^{51}= H, -$COCH_3$, -COOtBu or -CONHtBu.

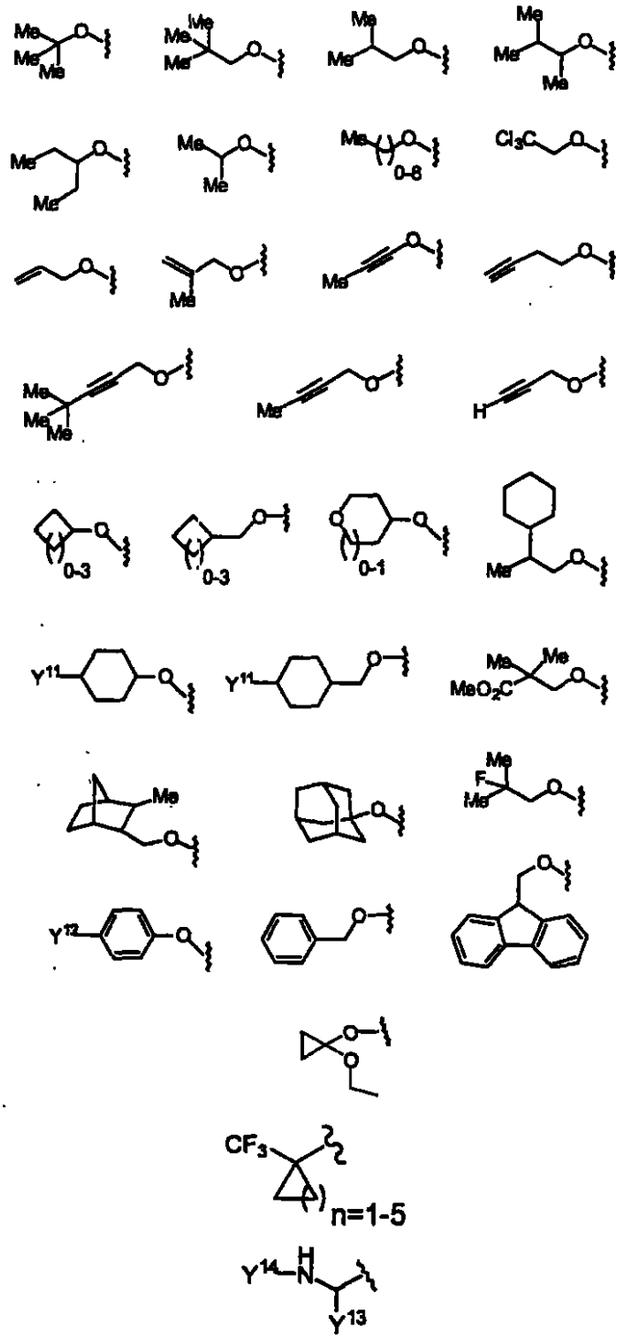
Most preferred moieties for R^3 are:

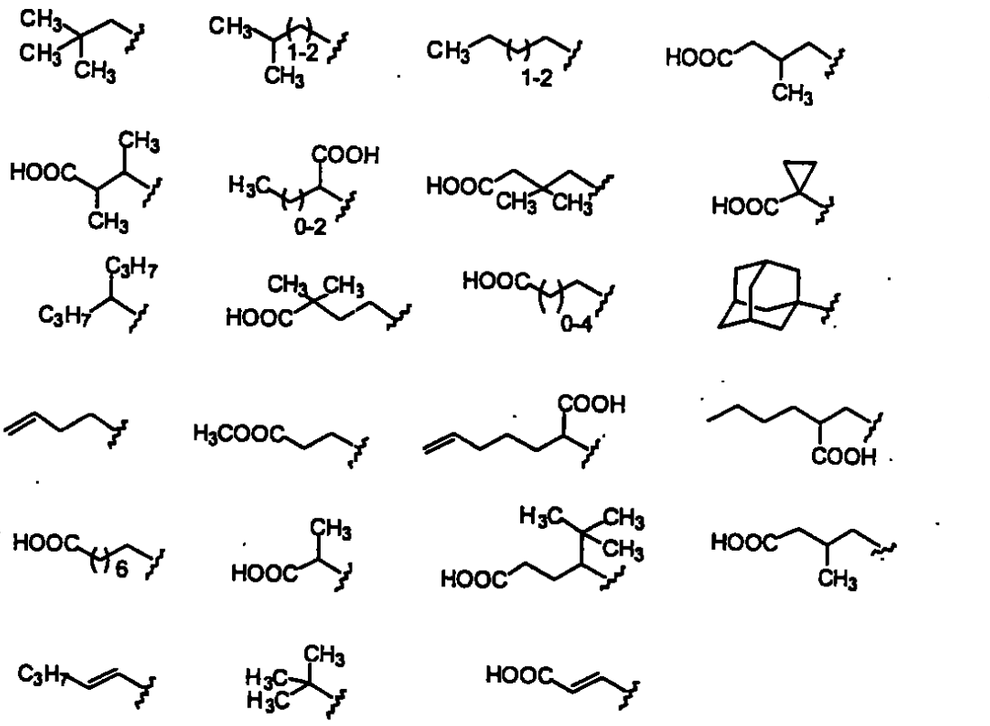


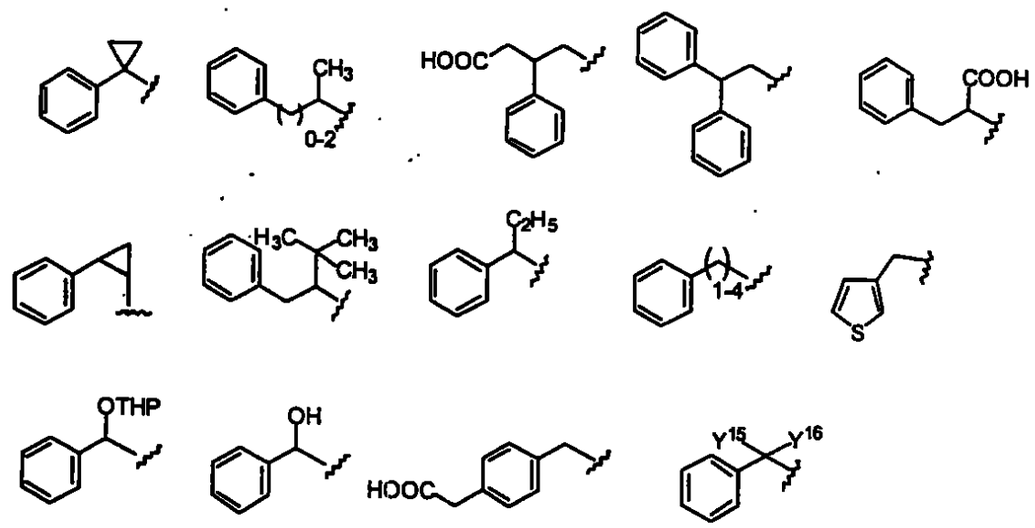
Some other preferred moieties are: for Z it is N, for R^4 it is H, and for W it is C=O. Additionally, the moiety Z-C-R^3 in Formula I, with R^4 being absent, may be represented by the following structures:

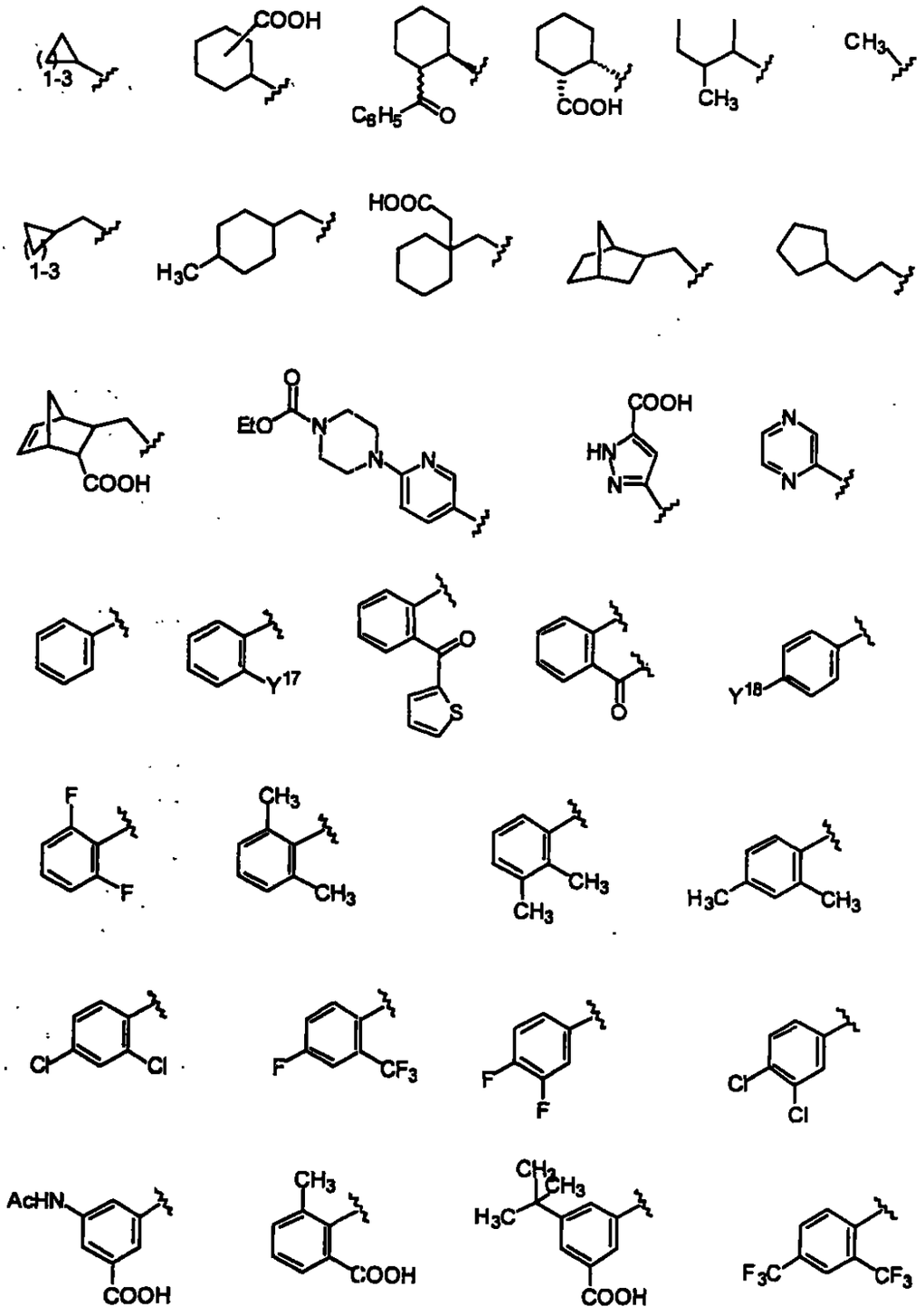


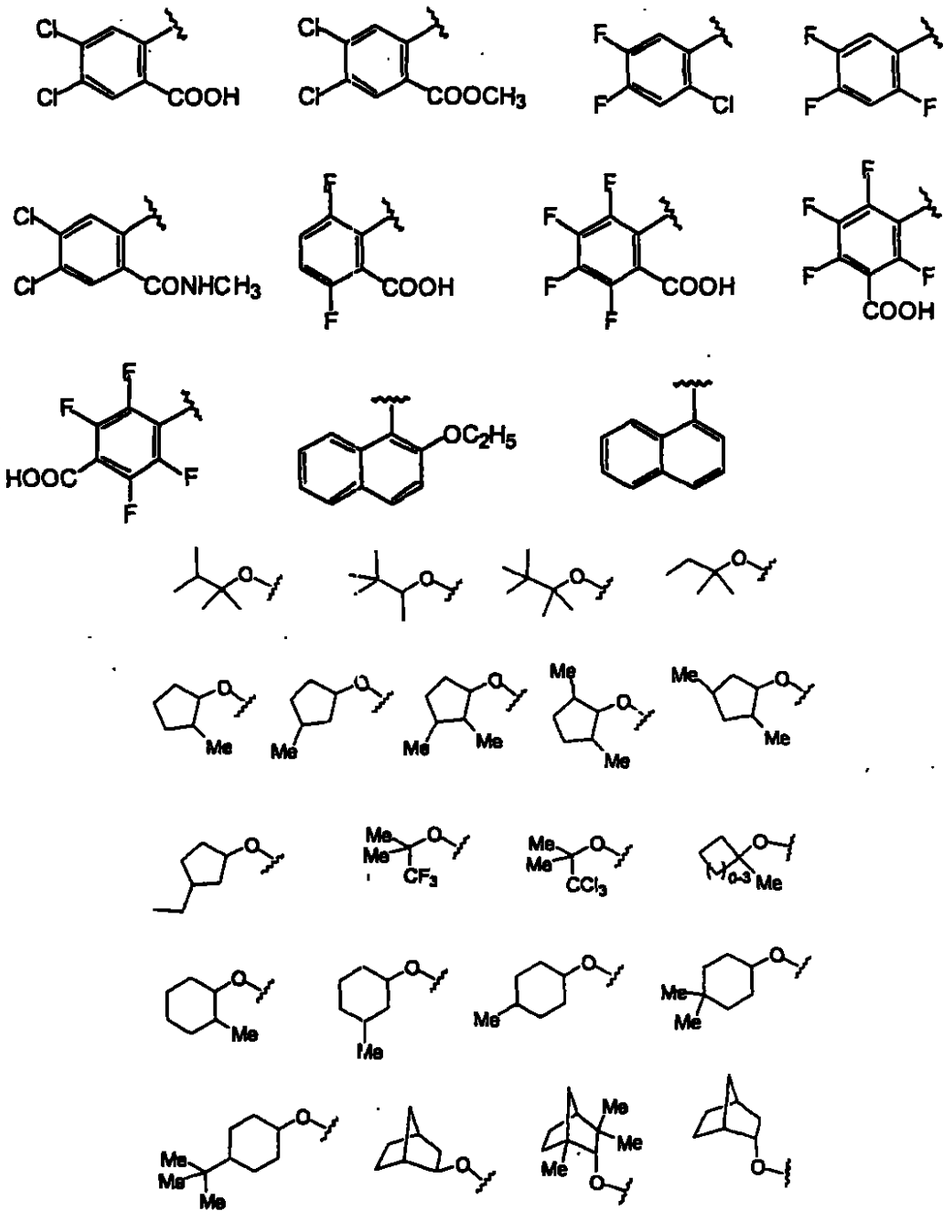
Preferred moieties for Y are:

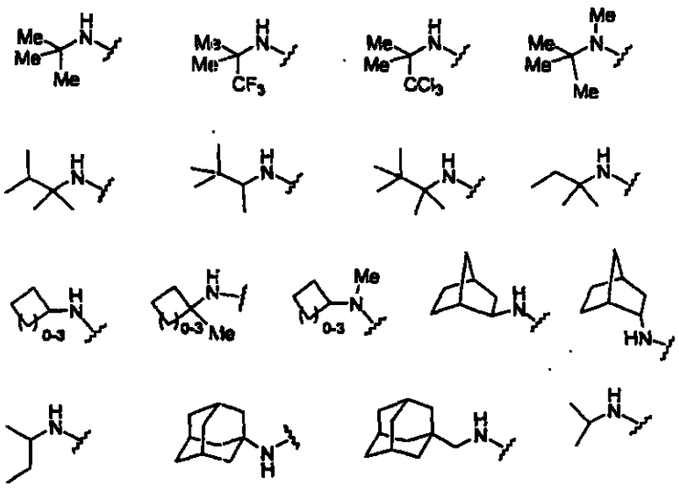



CH3
CH3
CH3
1-2
CH3
CH3
1-2
HOOC
CH3
HOOC
CH3
CH3
COOH
H3C
0-2
HOOC
CH3
CH3
HOOC
C3H7
C3H7
CH3
CH3
HOOC
HOOC
0-4
H3COOC
COOH
COOH
HOOC
6
CH3
HOOC
H3C
CH3
CH3
HOOC
HOOC
CH3
C3H7
CH3
H3C
H3C
HOOC


CH3
0-2
HOOC
COOH
H3C
CH3
CH3
C2H5
1-4
S
OTHP
OH
HOOC
Y15
Y16


1-3
COOH
C8H5
O
COOH
CH3
CH3
1-3
H3C
HOOC
COOH
EtO
N
N
N
COOH
HN
N
N
N
Y17
O
S
O
Y18
F
F
CH3
CH3
CH3
CH3
H3C
CH3
Cl
Cl
F
CF3
F
F
Cl
Cl
AcHN
COOH
CH3
COOH
CH2
CH3
H3C
COOH
F3C
CF3


Cl
Cl
COOH
Cl
Cl
COOCH3
F
F
Cl
F
F
F
Cl
Cl
CONHCH3
F
F
COOH
F
F
F
COOH
F
F
F
F
COOH
F
F
F
HOOC
F
OC2H5
O
Me
CF3
CCl3
0-3
Me

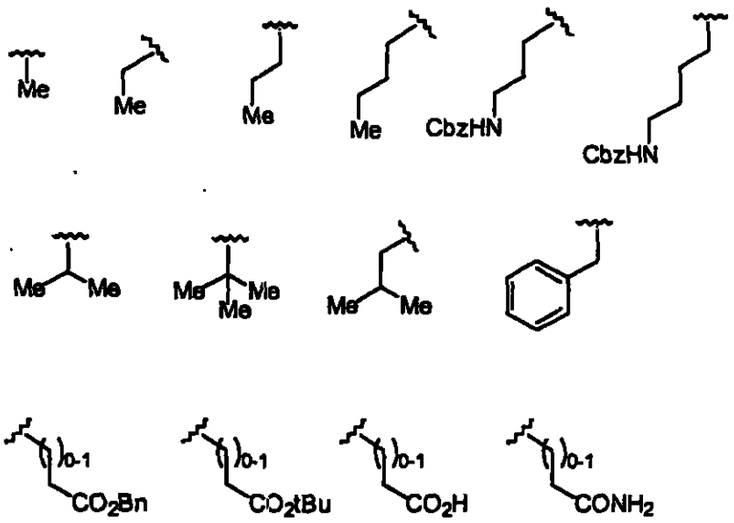


wherein:

Y^{11} is selected from H, COOH, COOEt, OMe, Ph, OPh, NHMe, NHAc, NHPh, $CH(Me)_2$, 1-triazolyl, 1-imidazolyl, and $NHCH_2COOH$;

Y^{12} is selected from H, COOH, COOMe, OMe, F, Cl, or Br;

Y^{13} is selected from the following moieties:



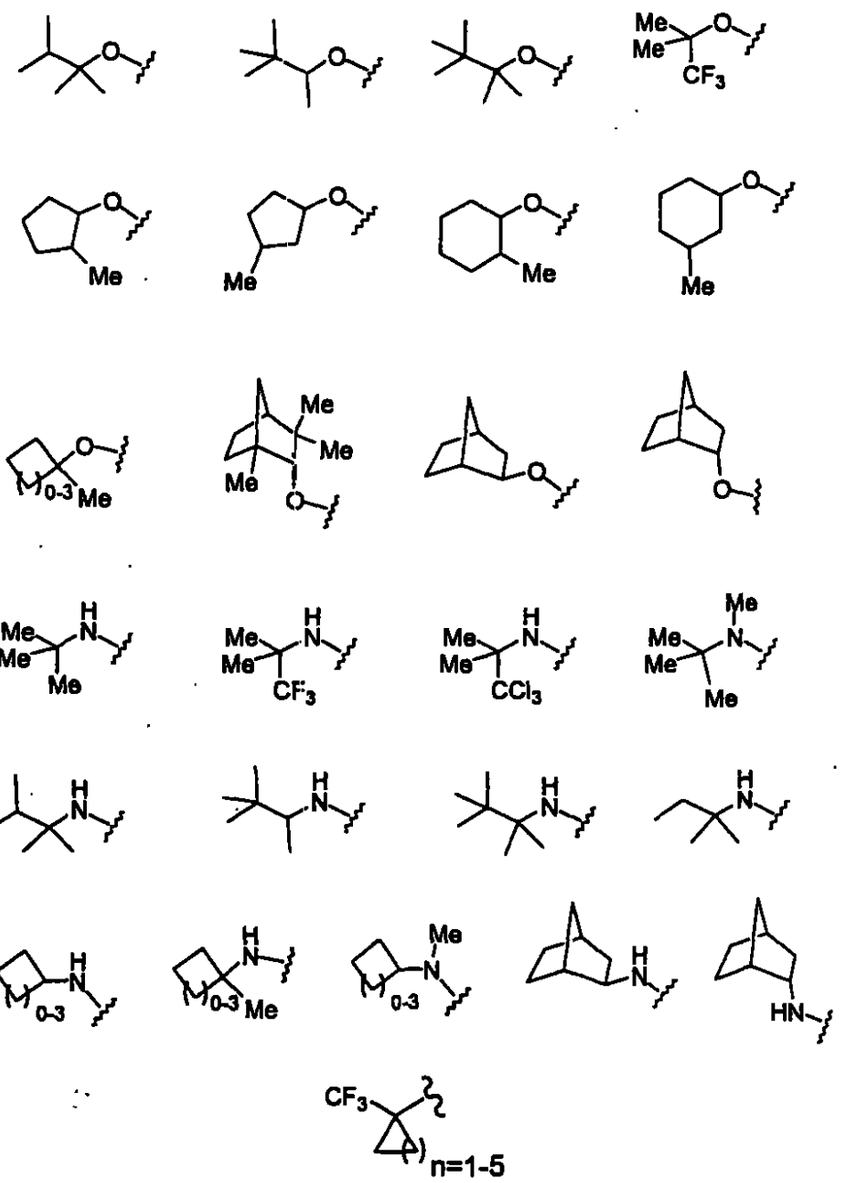
Y^{14} is selected from $MeS(O_2)$, Ac, Boc, iBoc, Cbz, or Alloc;

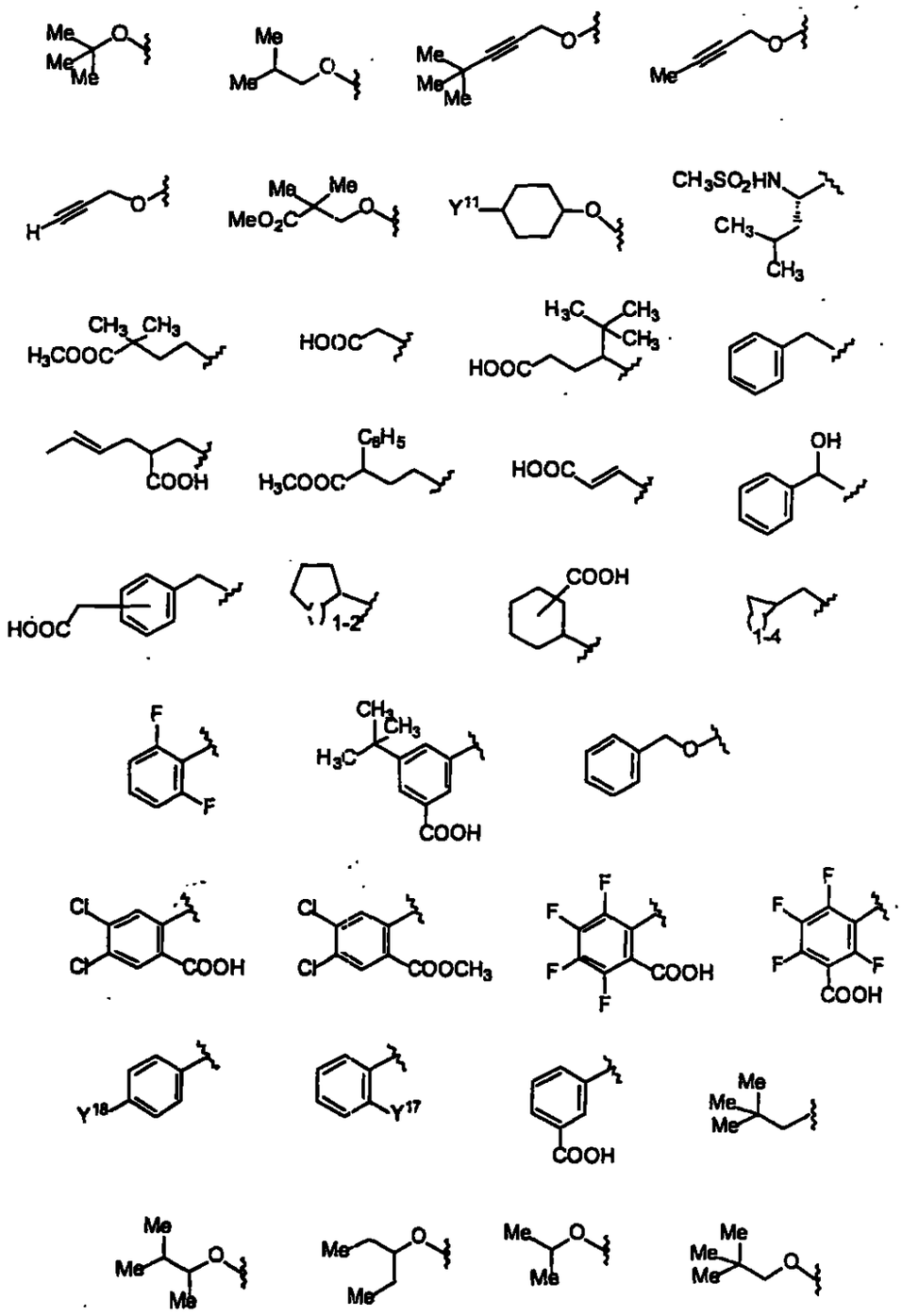
Y^{15} and Y^{16} are independently selected from alkyl, aryl, heteroalkyl, and heteroaryl;

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, $-OCH_3$, $-CH_2C(O)OH$, $-C(O)OH$, $-S(O_2)NH_2$, or $-NHCOCH_3$.

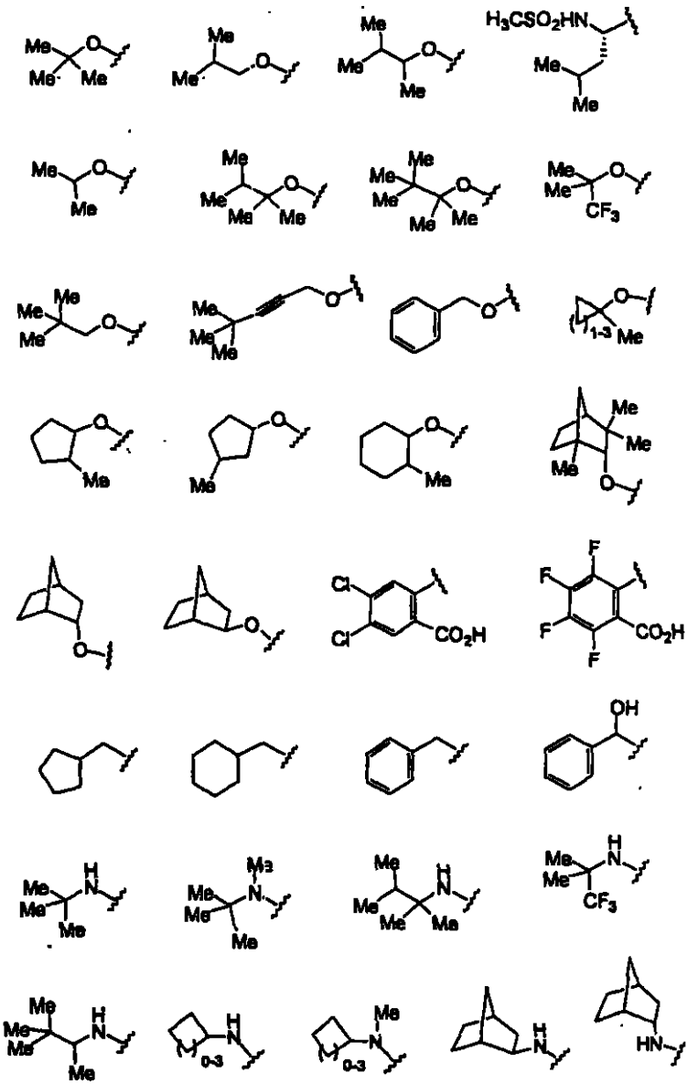
Y may be more preferably represented by:



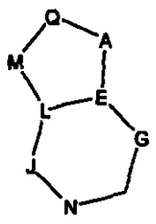


wherein:
Y^{17} = CF_3, NO_2, $CONH_2$, OH, NH_2, or COOH;
Y^{18}= F, COOH,

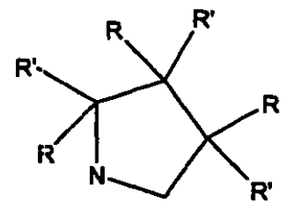
Still more preferred moieties for Y are:



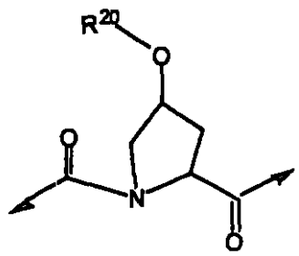
As shown in Formula I, the unit:



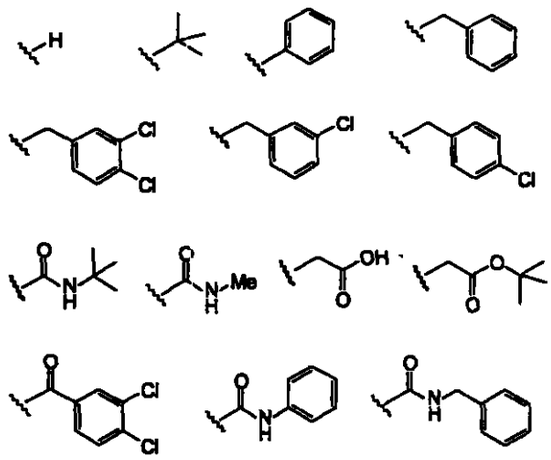
represents a cyclic ring structure, which may be a five-membered or six-membered ring structure. When that cyclic ring represents a five-membered ring, it is a requirement of this invention that that five-membered cyclic ring does not contain a carbonyl group as part of the cyclic ring structure. Preferably, that five-membered ring is of the structure:



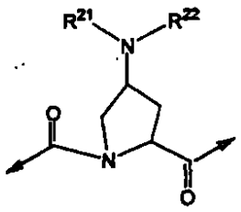
wherein R and R' are defined above. Preferred representations for that five-membered cyclic ring structure is:



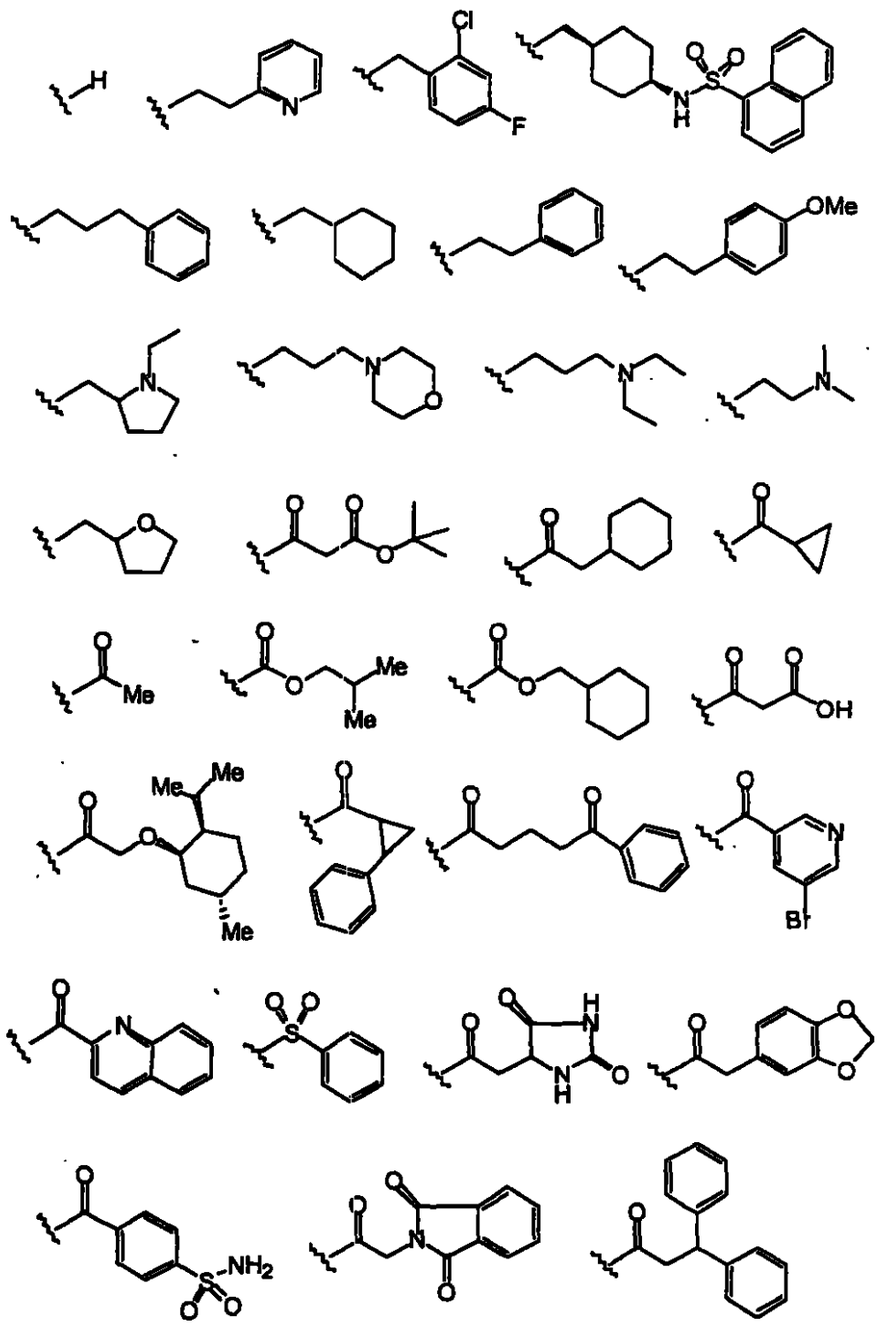
where R^{20} is selected from the following moieties:



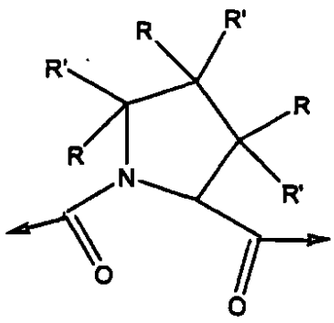
Furthermore, that five-membered ring, along with its adjacent two exocyclic carbonyls, may be represented as follows:



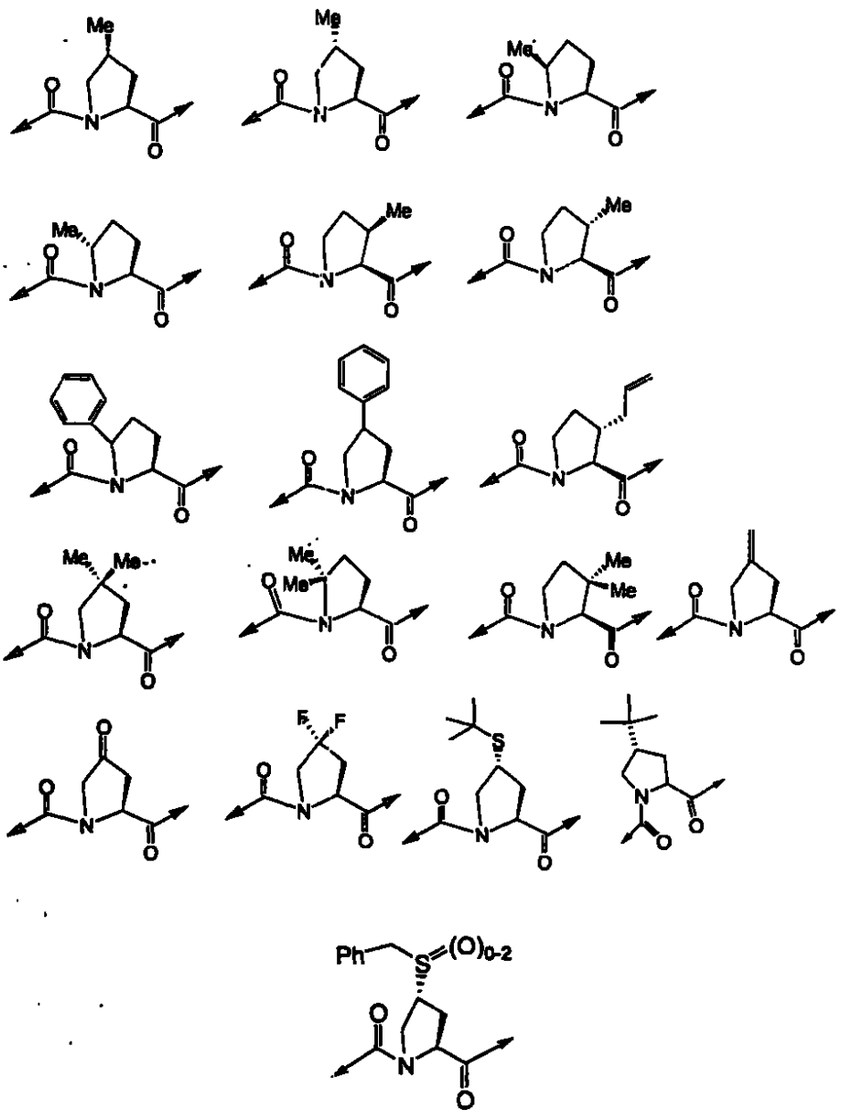
in which case, R^{21} and R^{22} may be the same or different and are independently selected from the following moieties:



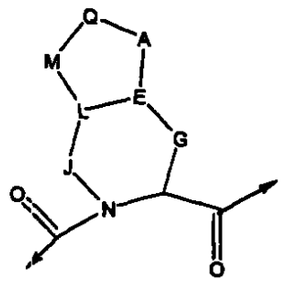
Some preferred illustrations for the five-membered ring structure:



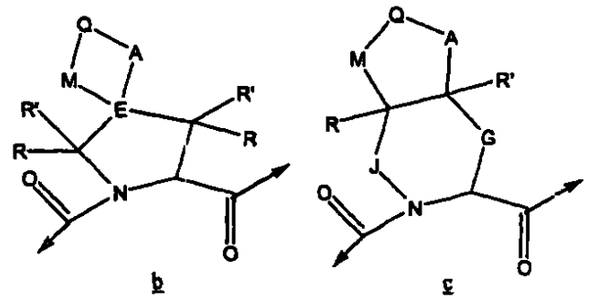
are as follows:



Additionally, the unit:

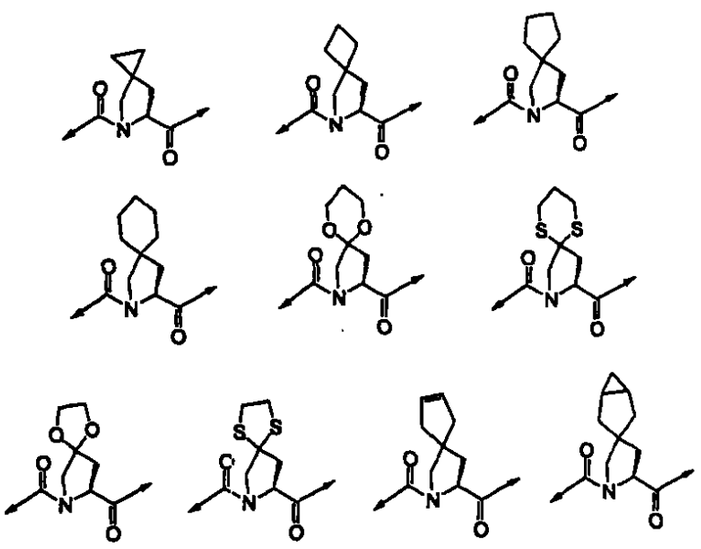


in Formula I may be represented by the following structures b and c:



b c

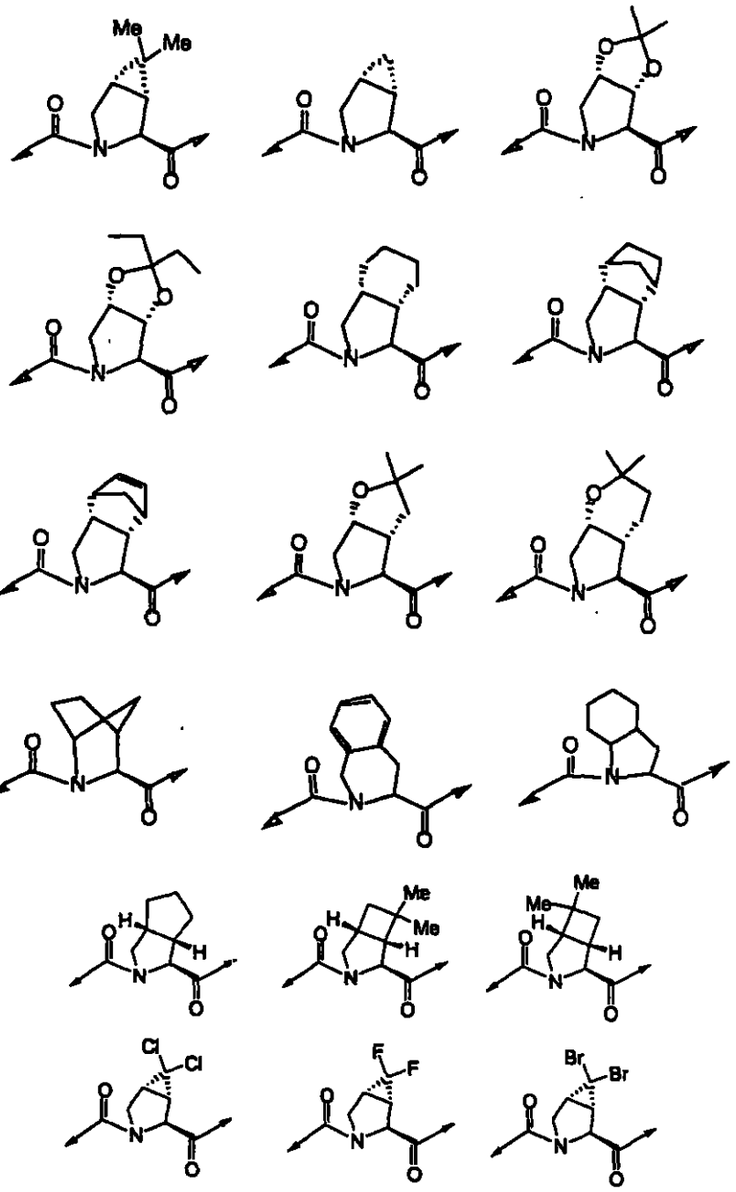
Preferred definitions for b are:

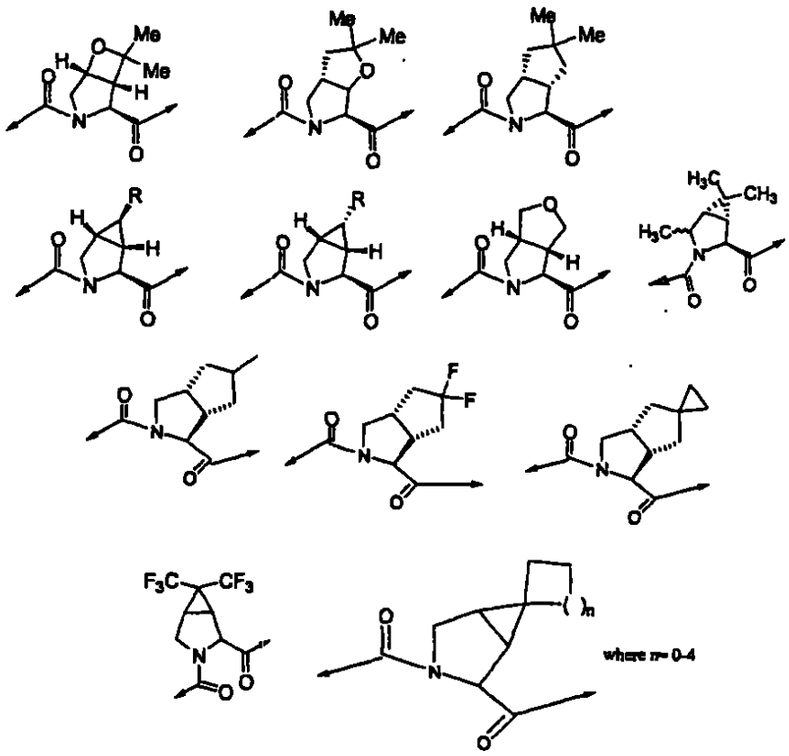


In c, G and J are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; A and M are independently selected from the

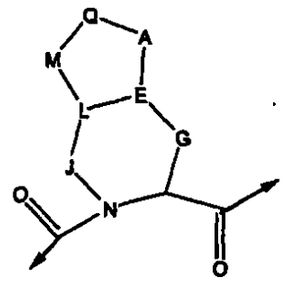
group consisting of O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; and Q is CH_2, CHR, CRR', NH, NR, O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, and $(CRR')_p$.

Preferred definitions for c are:

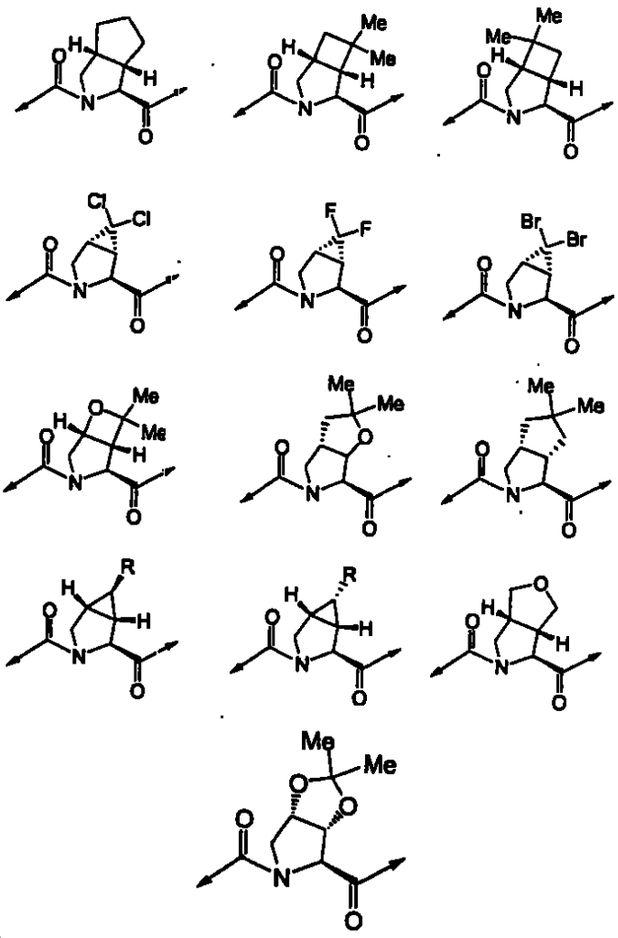


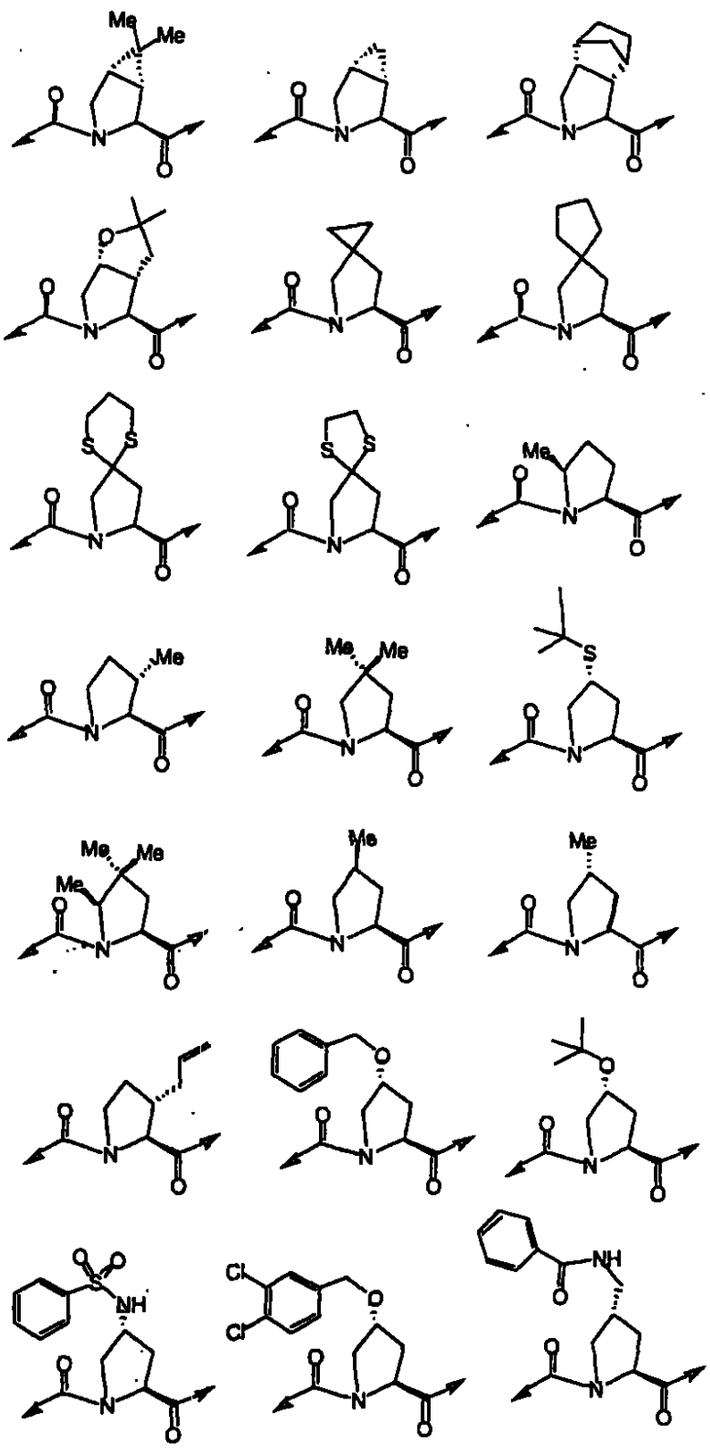


When the cyclic ring structure is depicted as:

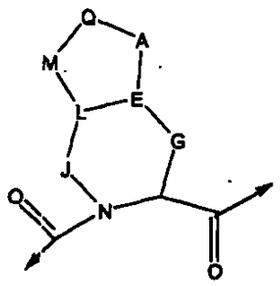


its most preferred illustrations are as follows:

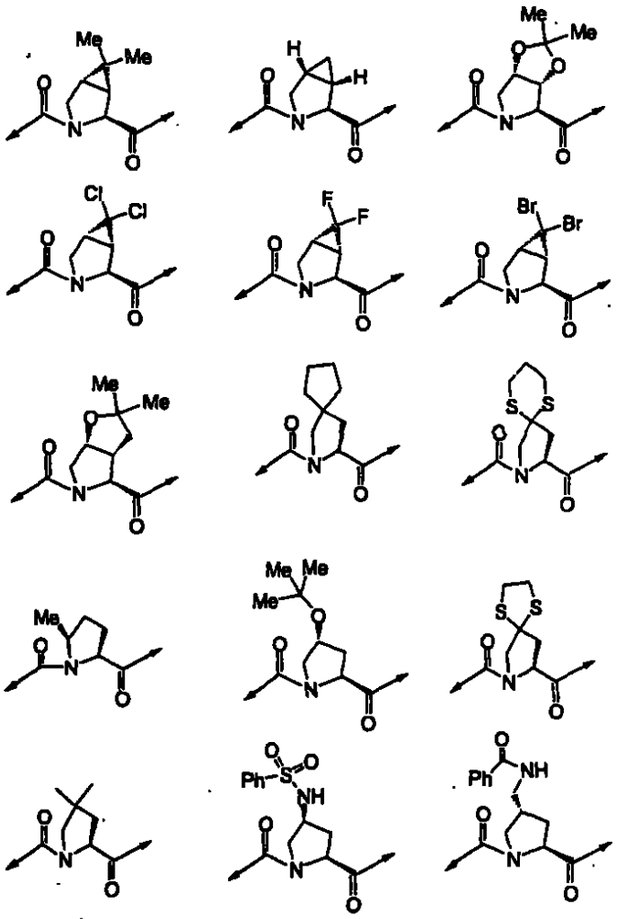

H
O
N
O
Me
Me
Cl
Cl
F
F
Br
Br
R



Some of the still preferred moieties for the unit:



shown above, are:



Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. Thus, for example, the term alkyl (including the alkyl portions of alkoxy) refers to a monovalent group derived from a straight or

branched chain saturated hydrocarbon by the removal of a single atom having from 1 to 8 carbon atoms, preferably from 1 to 6;

aryl – represents a carbocyclic group having from 6 to 14 carbon atoms and having at least one benzenoid ring, with all available substitutable aromatic carbon atoms of the carbocyclic group being intended as possible points of attachment. Preferred aryl groups include phenyl, 1-naphthyl, 2-naphthyl and indanyl, and especially phenyl and substituted phenyl;

aralkyl – represents a moiety containing an aryl group linked vial a lower alkyl;

alkylaryl – represents a moiety containing a lower alkyl linked via an aryl group;

cycloalkyl – represents a saturated carbocyclic ring having from 3 to 8 carbon atoms, preferably 5 or 6, optionally substituted.

heterocyclic – represents, in addition to the heteroaryl groups defined below, saturated and unsaturated cyclic organic groups having at least one O, S and/or N atom interrupting a carbocyclic ring structure that consists of one ring or two fused rings, wherein each ring is 5-, 6- or 7-membered and may or may not have double bonds that lack delocalized pi electrons, which ring structure has from 2 to 8, preferably from 3 to 6 carbon atoms, e.g., 2- or 3-piperidinyl, 2- or 3-piperazinyl, 2- or 3-morpholinyl, or 2- or 3-thiomorpholinyl;

halogen – represents fluorine, chlorine, bromine and iodine;

heteroaryl – represents a cyclic organic group having at least one O, S and/or N atom interrupting a carbocyclic ring structure and having a sufficient number of delocalized pi electrons to provide aromatic character, with the aromatic heterocyclyl group having from 2 to 14, preferably 4 or 5 carbon atoms, e.g., 2-, 3- or 4-pyridyl, 2- or 3-furyl, 2- or 3-thienyl, 2-, 4- or 5-thiazolyl, 2- or 4-imidazolyl, 2-, 4- or 5-pyrimidinyl, 2-pyrazinyl, or 3- or 4-pyridazinyl, etc. Preferred heteroaryl groups are 2-, 3- and 4-pyridyl; such heteroaryl groups may also be optionally substituted. Additionally, unless otherwise specifically defined, as stated above, the term "substituted or unsubstituted" or "optionally substituted"

refers to the subject moiety being optionally and chemically-suitably substituted with a moiety belonging to R^{12} or R^{13}. As used herein, "prodrug" means compounds that are drug precursors which, following administration to a patient, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH or through enzyme action is converted to the desired drug form).

Also included in the invention are tautomers, rotamers, enantiomers and other optical isomers, as well as prodrugs, of compounds of Formula I, as well as pharmaceutically acceptable salts, solvates and derivatives thereof.

A further feature of the invention is pharmaceutical compositions containing as active ingredient a compound of Formula I (or its salt, solvate or isomers) together with a pharmaceutically acceptable carrier or excipient.

The invention also provides methods for preparing compounds of Formula I, as well as methods for treating diseases such as, for example, HCV, AIDS (Acquired Immune Deficiency Syndrome), and related disorders. The methods for treating comprise administering to a patient suffering from said disease or diseases a therapeutically effective amount of a compound of Formula I, or pharmaceutical compositions comprising a compound of Formula I.

Also disclosed is the use of a compound of Formula I for the manufacture of a medicament for treating HCV, AIDS, and related disorders.

Also disclosed is a method of treatment of a hepatitis C virus associated disorder, comprising administering an effective amount of one or more of the inventive compounds.

Also disclosed is a method of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more inventive compounds.

Also disclosed is a method of treating, preventing, or ameliorating one or more symptoms of hepatitis C, comprising administering an effective amount of one or more of the inventive compounds. The HCV protease is the NS3 or NS4a

protease. The inventive compounds inhibit such protease. They also modulate the processing of hepatitis C virus (HCV) polypeptide.

Detailed description of preferred embodiments

In one embodiment, the present invention discloses compounds of Formula I as inhibitors of HCV protease, especially the HCV NS3/NS4a serine protease, or a pharmaceutically acceptable derivative thereof, where the various definitions are given above.

Representative compounds of the invention which exhibit excellent HCV protease inhibitory activity are listed below in **Tables 1 to 5** along with their activity (ranges of Ki* values in nanomolar, nM). Several compounds as well as additonal compounds are additionally disclosed in the Claims.

Table 1: Compounds and HCV protease continuous assay results

Compound from Example No.	Ki* Range
1	C
2	C
3	C
4	C
5	C
6	C
7	C
8	C
9	C
10	C
11	C
12	C
13	C
14	C
15	C
16	C
17	C
18	C
19	C
20	C
21	C
22	C
23	C
24	C
25	C
26	C
27	C
28	C
29	C
30	C
31	C
32	C
33	C
34	C
35	C
36	C
37	C

38	C
39	C
40	C
41	C
42	C
43	C
44	C
45	C
46	C
47	C
48	C
49	C
50	C
51	C
52	C
53	C
54	C
55	C
56	C
57	C
58	C
59	C
60	C
61	C
62	C
63	C
64	C
65	C
66	C
67	C
68	B
69	C
70	C
71	B
72	C
73	B
74	C
75	C
76	A
77	B
78	A
79	C
80	A
81	C

82	A
83	B
84	C
85	C
86	B
87	B
88	A
89	B
90	C
91	C
92	C
93	C
94	C
95	C
96	C
97	C
98	B
99	B
100	A
101	A
102	C
103	C
104	C
105	C
106	C
107	B
108	A
109	A
110	A
111	A
112	A
113	B
114	A
115	B
116	A
117	A
118	A
119	A
120	A
121	B
122	B
123	A
124	B
125	B

126	B
127	A
128	A
129	A
130	B
131	A
132	A
133	A
134	B
135	A
136	A
137	A
138	A
139	A
140	B
141	A
142	A
143	B
144	B
145	C
146	A
147	A
148	B
149	A
150	A
151	A
152	A
153	A
154	A
155	B
156	B
157	B
158	C
159	B
160	A
161	A
162	A
163	C
164	A
165	C
166	B
167	A
168	C
169	B

170	B
171	A
172	A
173	A
174	A
175	A
176	B
177	B
178	A
179	A
180	B
181	A
182	B
183	A
184	A
185	A
186	A
187	A
188	A
189	B
190	B
191	B
192	A
193	A
194	B
195	A
196	B
197	A
198	A
199	A
200	A
201	B
202	A
203	B
204	B
205	B
206	B
207	B
208	A
209	A
210	A
211	A
212	A
213	B

214	B
215	B
216	B
217	C
218	A
219	A
220	A
221	A
222	A
223	B
224	C
225	C
226	A
227	A
228	C
229	A
230	A
231	A
232	C
233	C
234	C
235	C
236	B
237	C
238	A
239	C
240	A
241	C
242	B
243	C
244	B
245	C
246	B
247	A
248	A
249	C
250	C
251	B
252	C
253	C
254	B
255	B
256	A
257	C

258	A
259	A
260	C
261	C
262	A
263	B
264	B
265	C
266	B
267	A
268	C
269	A
270	C
271	A
272	C
273	C
274	C
275	C
276	A
277	B
278	A
279	B
280	A
281	C
282	C
283	C
284	C
285	C
286	C
287	C
288	B
289	B
290	C
291	C
292	C
293	C
294	C
295	C
296	B
297	C
298	C
299	B
300	B
301	C

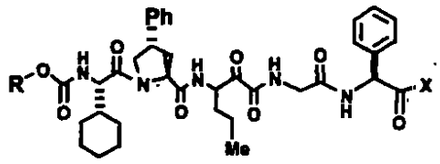
302	C
303	B
304	C
305	C
306	C
307	B
308	B
309	C
310	C
311	C
312	C
313	B
314	A
315	B
316	B
317	A
318	A
319	A
320	A
321	C
322	C
323	C
324	C
325	A
326	A
327	C
328	B
329	B
330	A
331	A
332	A
333	B
334	B
335	B
336	A
337	A
338	C
339	A
340	C
341	C
342	C
343	A
344	C
345	C

346	C
347	B
348	B
349	C
350	C
351	C
352	C
353	C
354	C
355	C
356	A
357	A
358	C
359	A
360	B
361	B
362	C

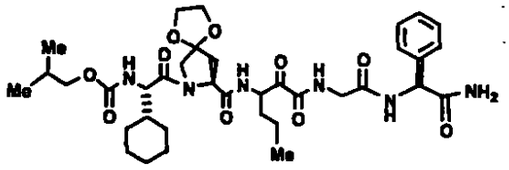
HCV continuous assay Ki* range:

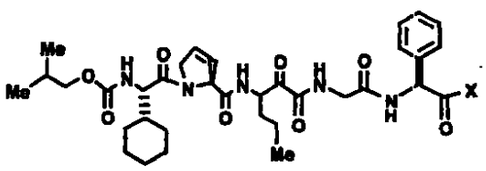
Category A = 1-100 nM; Category B = 101-1,000 nM; Category C >1000 nM.

Some of the types of the inventive compounds and methods of synthesizing the various types of the inventive compounds of Formula I are listed below, then schematically described, followed by the illustrative Examples.

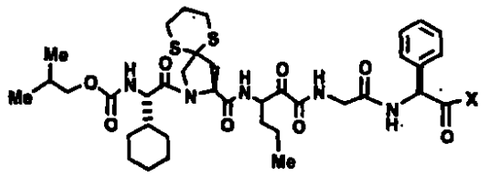


(R = t-butyl, X = NH_2)
(R = Isobutyl, X = NH_2)
(R = t-butyl, X = OH)
(R = Trichloroethyl, X = OH)

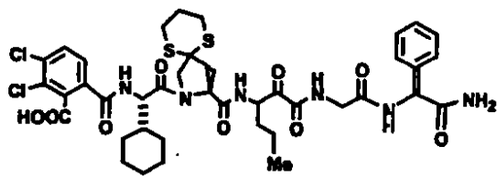


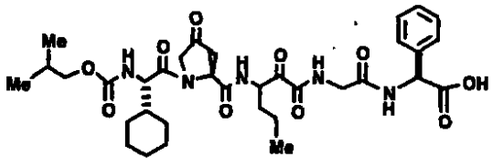


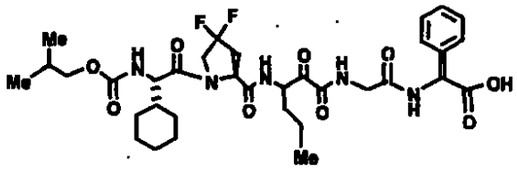
(X = O^{t}Bu)
(X = OH)

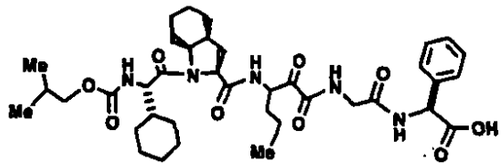


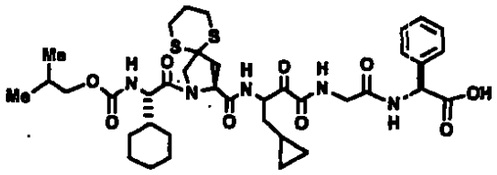
(X = OH)
(X = O^{t}Bu)
(X = NH_2)
(X = NHMe)
(X = NMe_2)

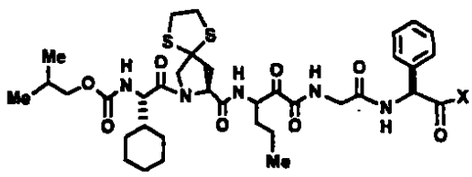




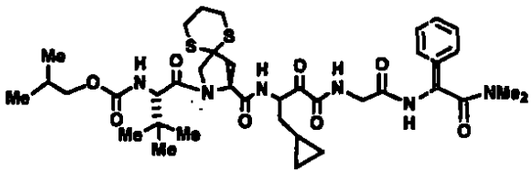


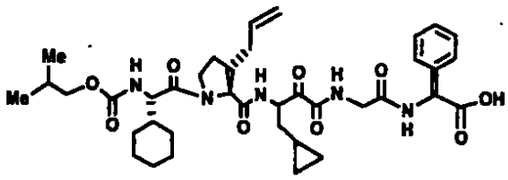


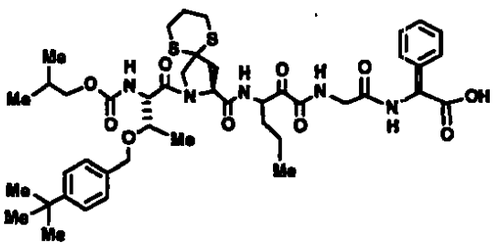


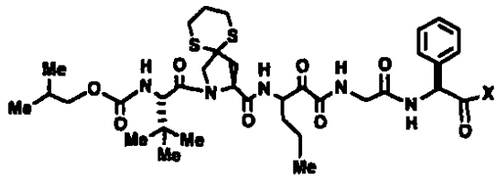


(X = NH_2)
(X = NMe_2)
(X = NHMe)
(X = OH)

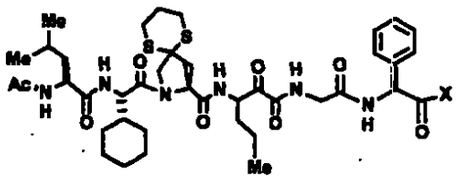




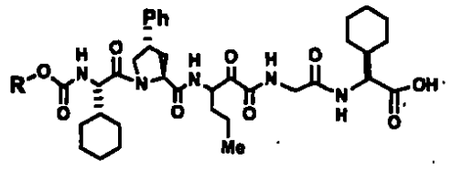




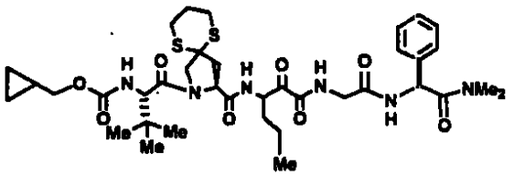
(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)

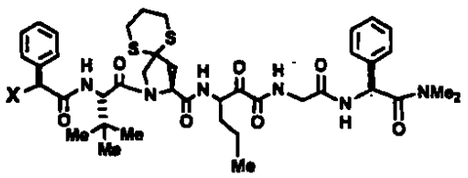


(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)
(X = NMeOMe)

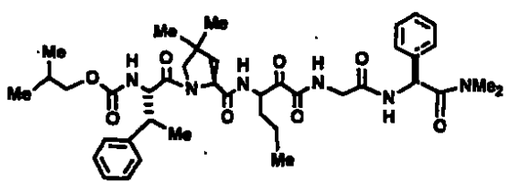


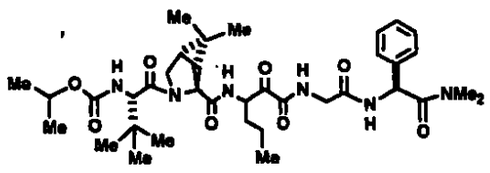
(R = t-butyl)
(R = Isobutyl)

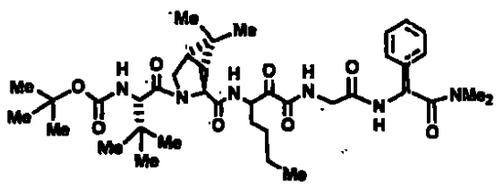


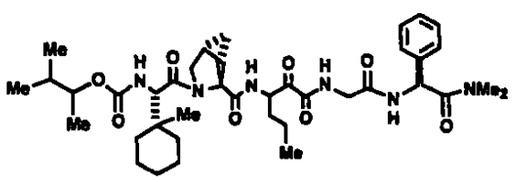


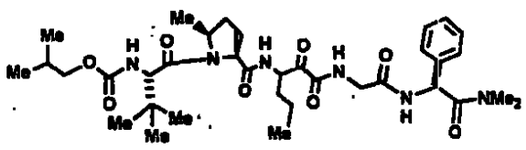
(X = Me, Y = CH_2Me)
(X = OAc, Y = Me)

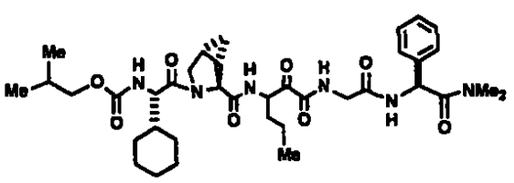


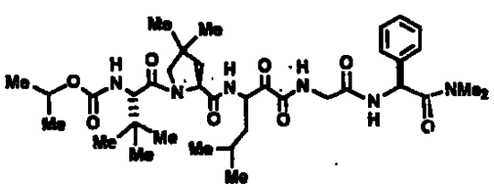


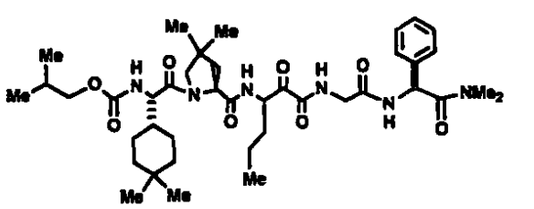


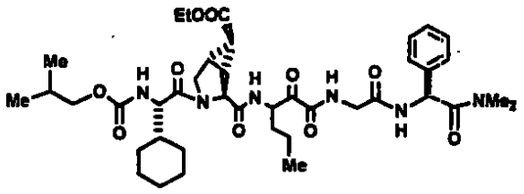


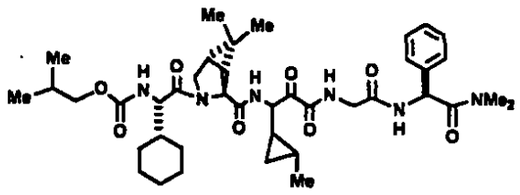


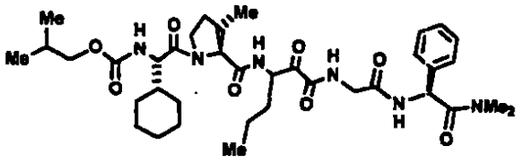


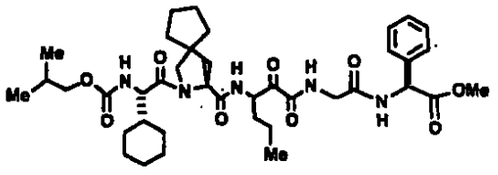


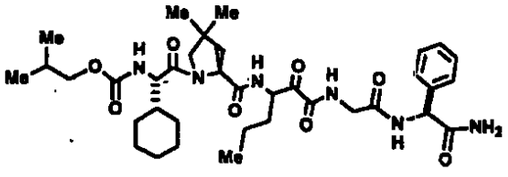


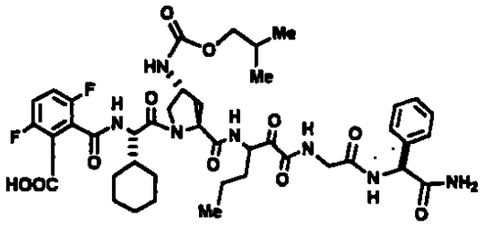


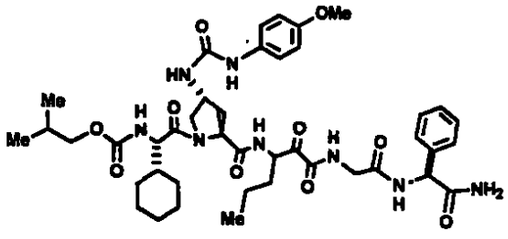


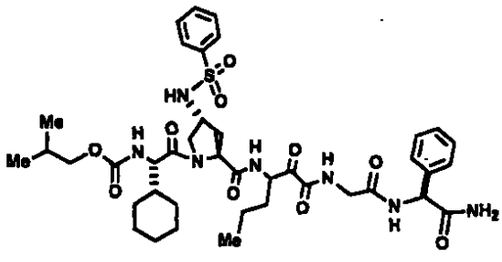


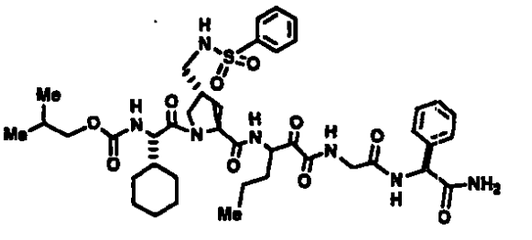


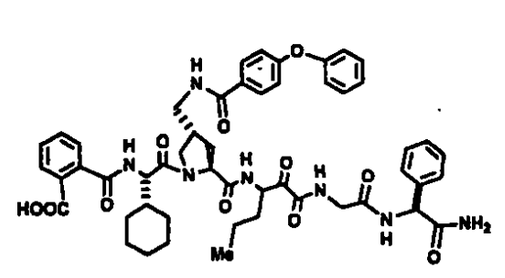


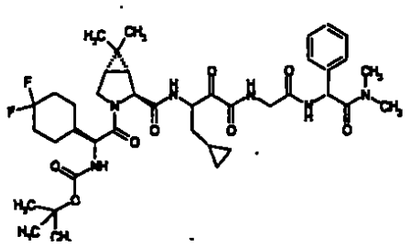


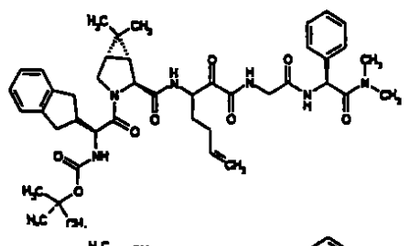


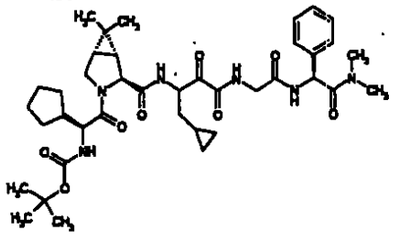


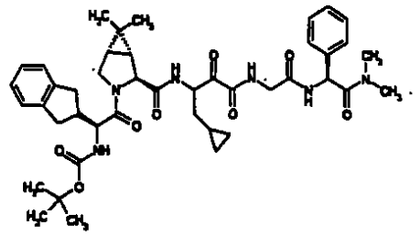


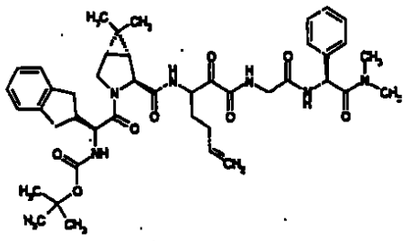


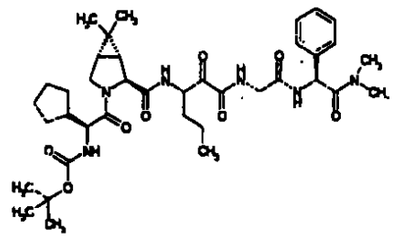


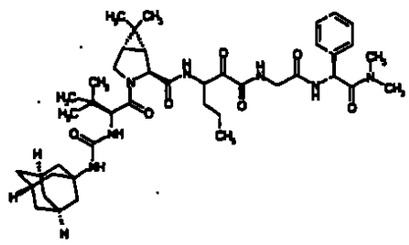


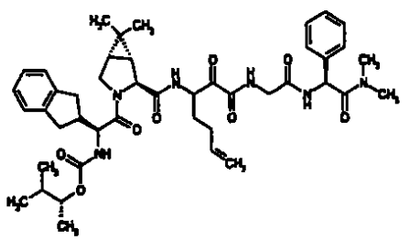


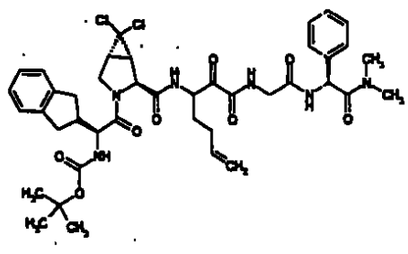


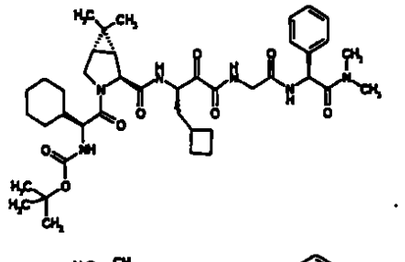


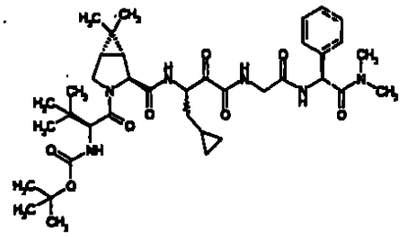


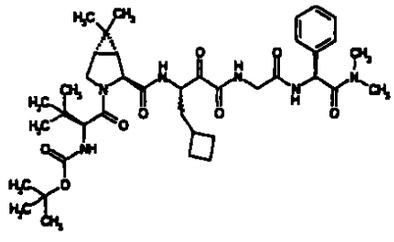


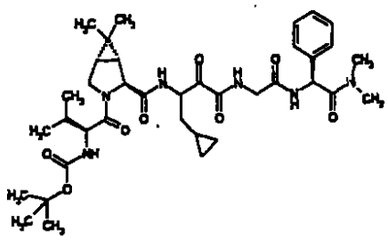


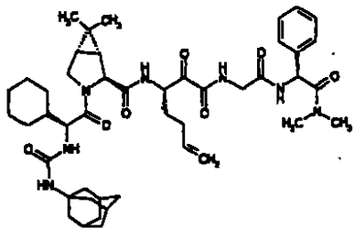


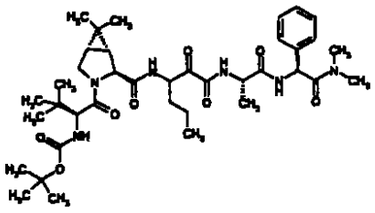


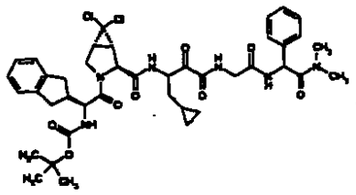


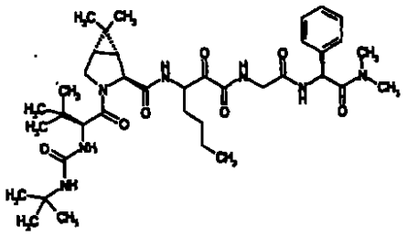


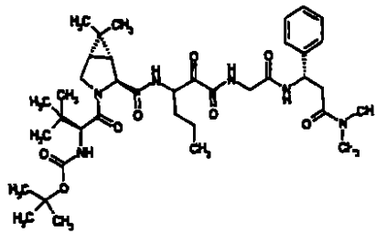


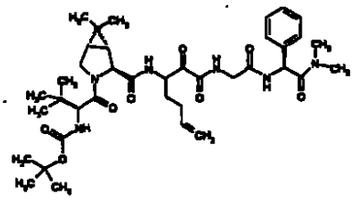


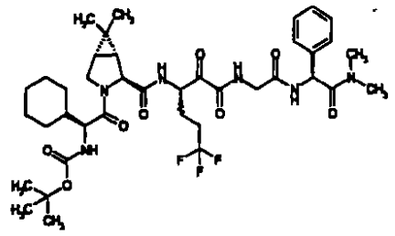


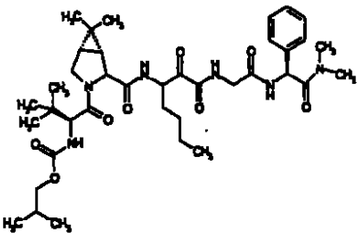


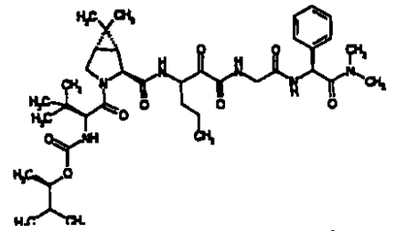


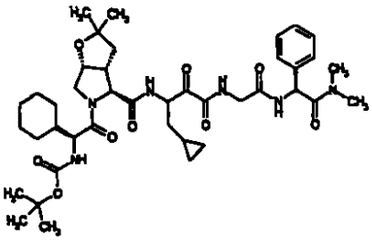


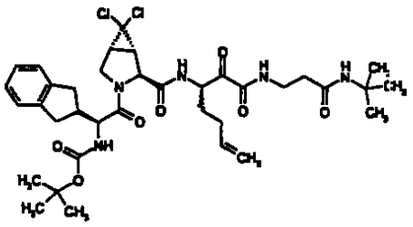


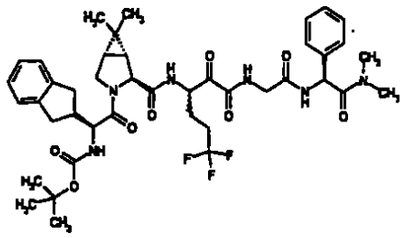


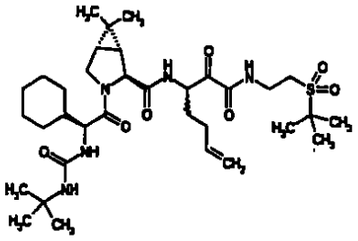


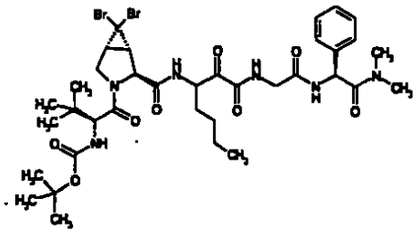


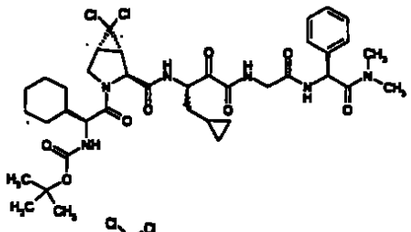


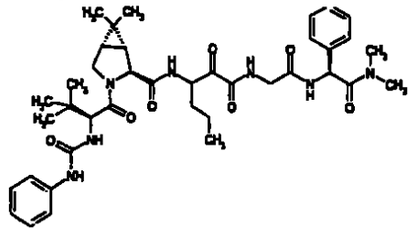


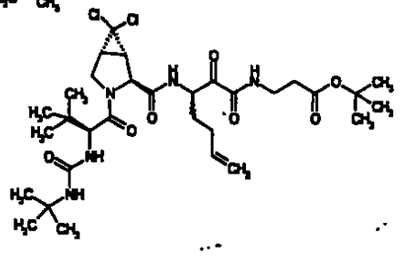


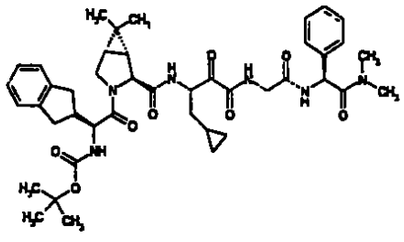


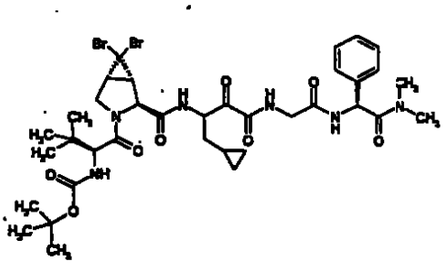


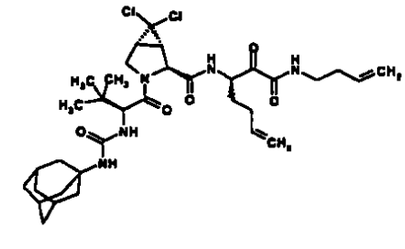


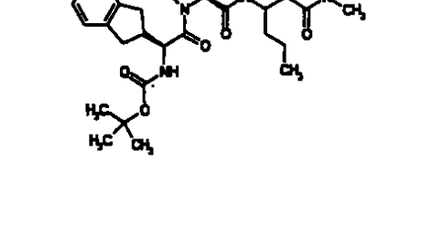


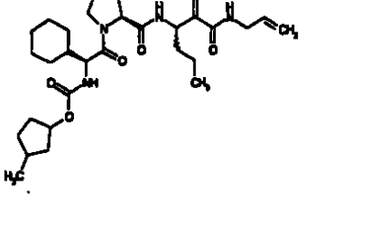


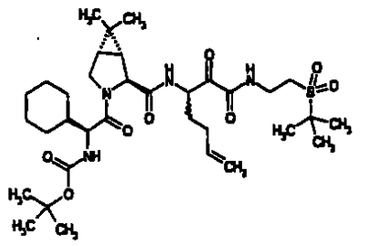


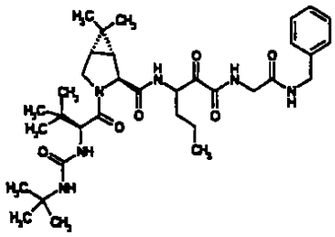


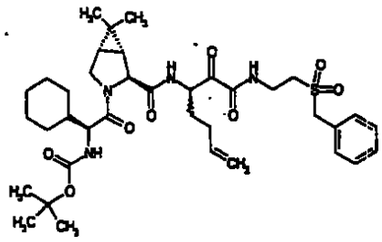


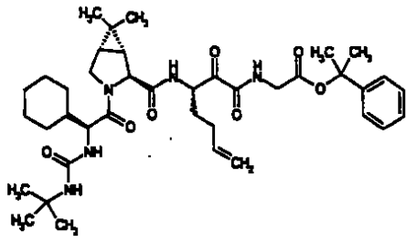


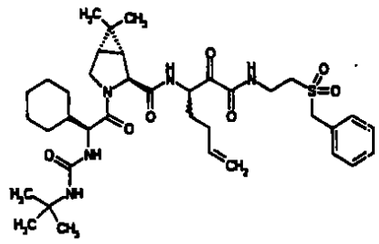


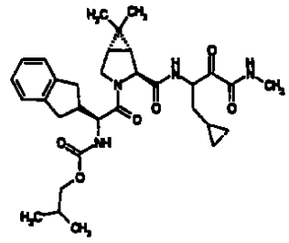


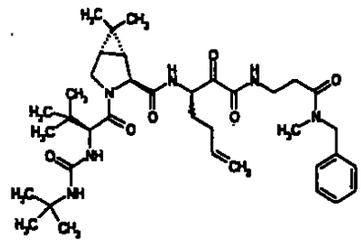


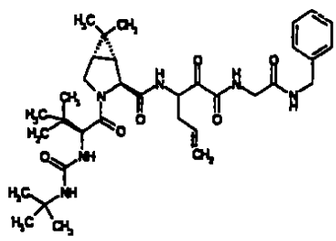


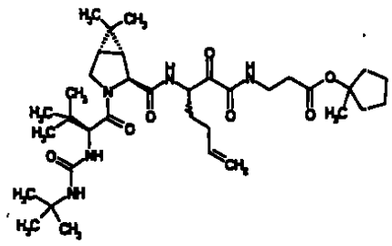


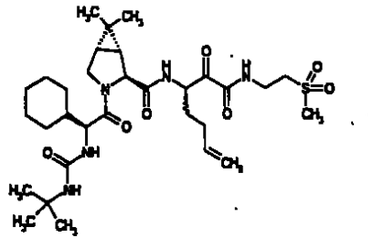


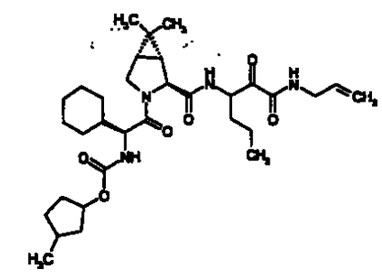


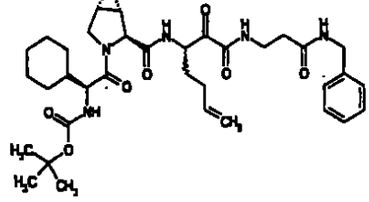


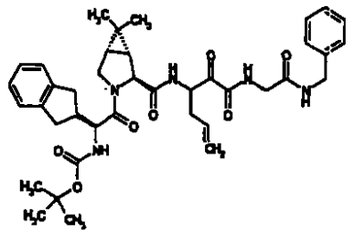


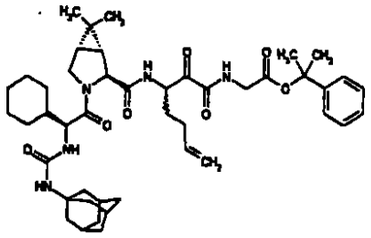


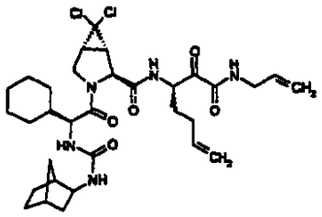


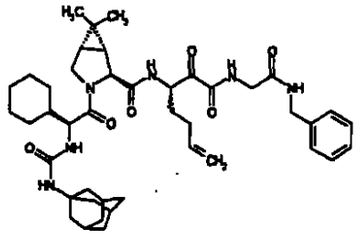


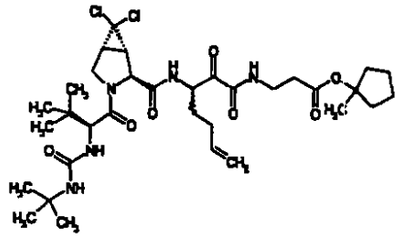


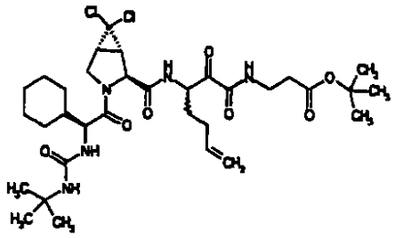


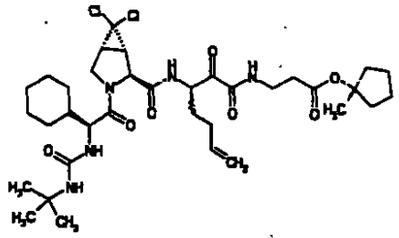


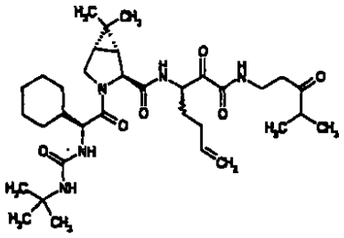


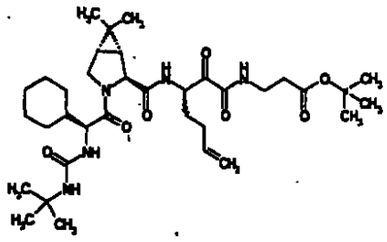


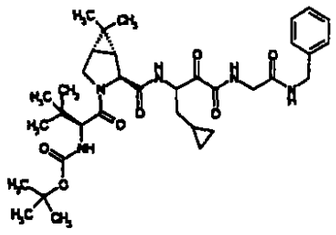


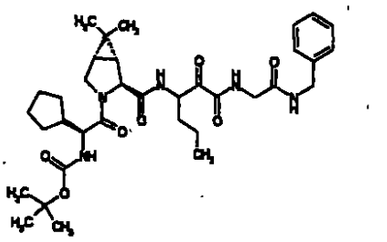


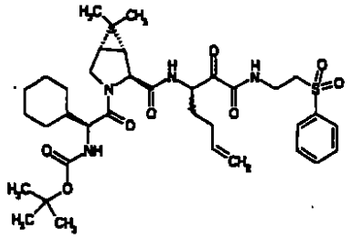


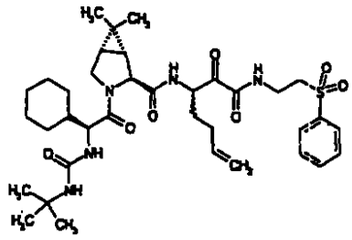


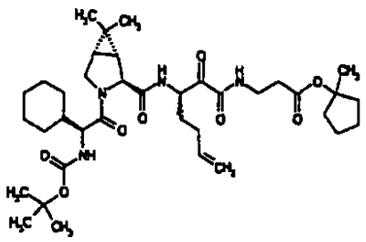


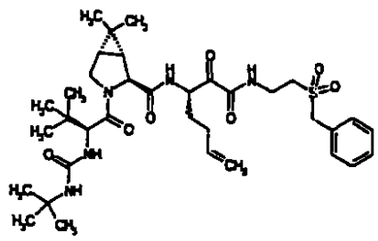


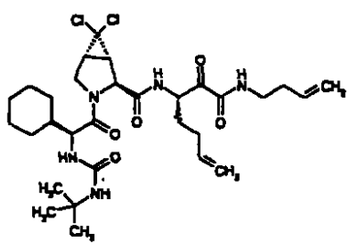


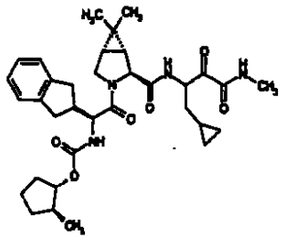


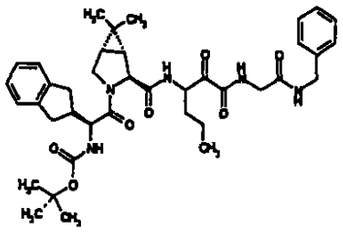


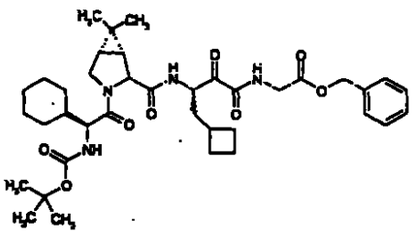


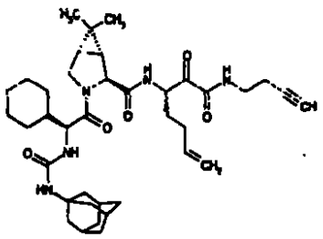


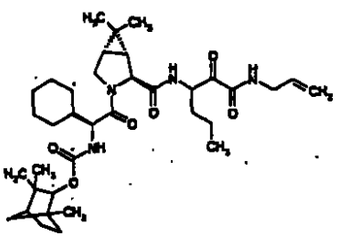


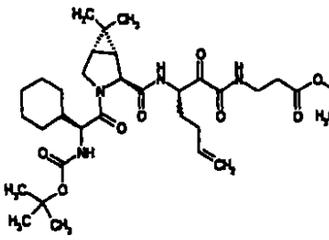


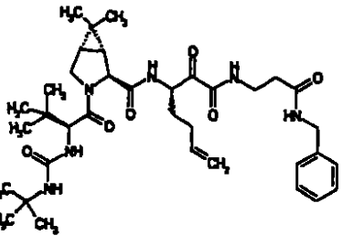


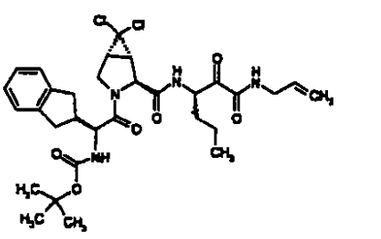


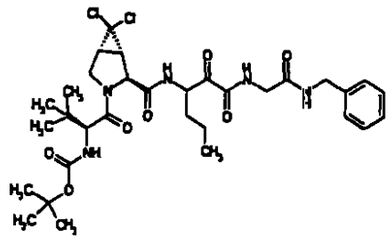


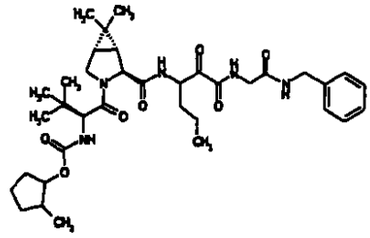


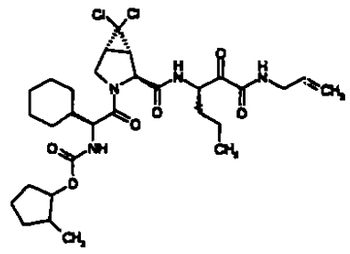


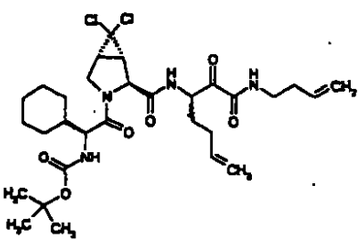


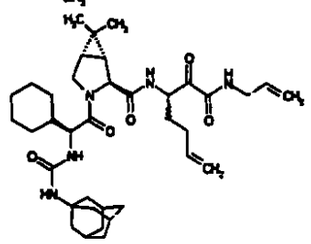


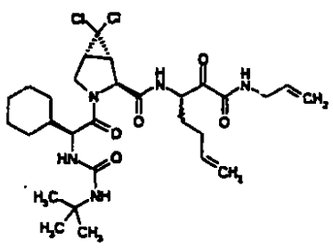


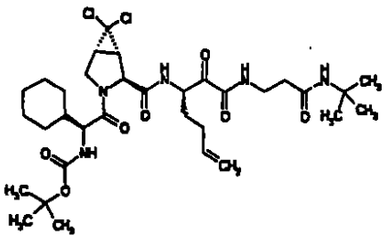


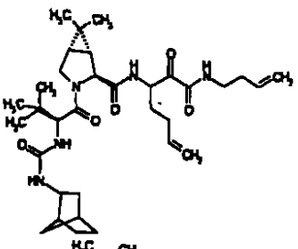


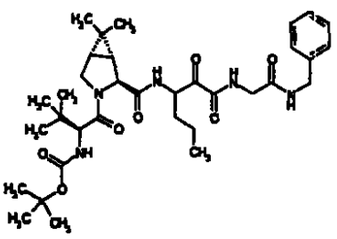


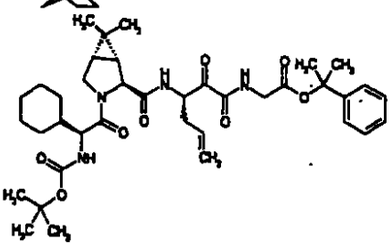


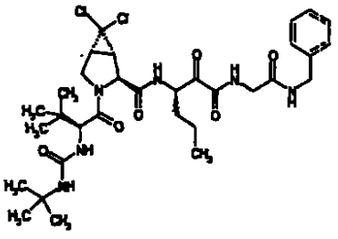


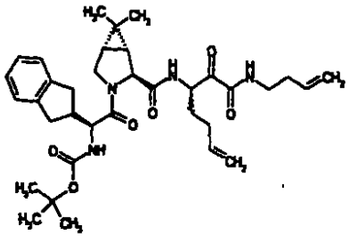


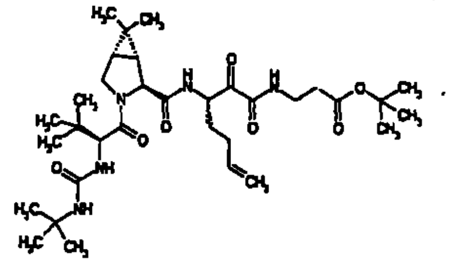


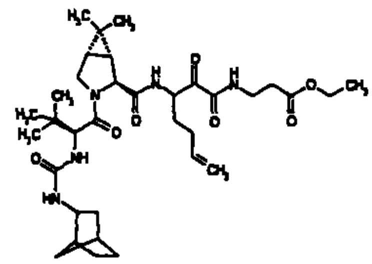


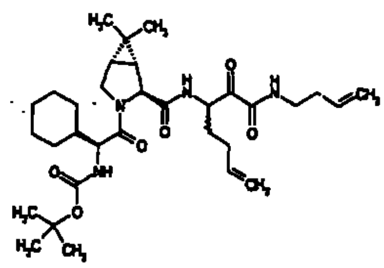


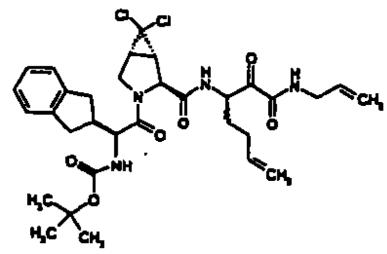


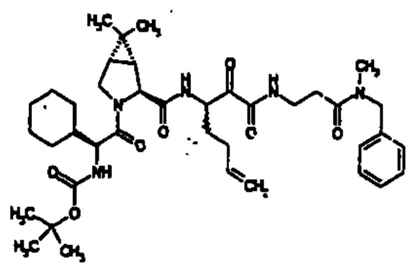


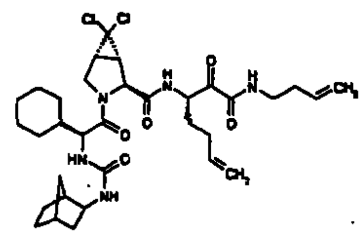


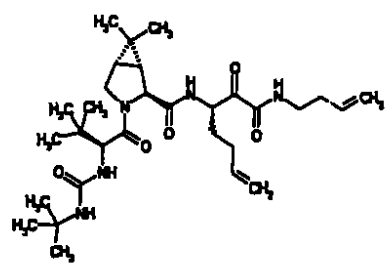


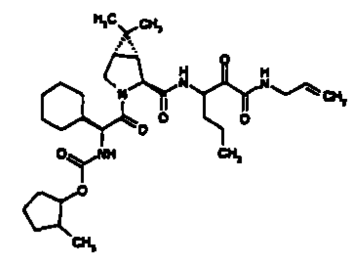


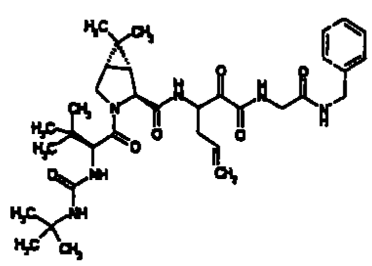


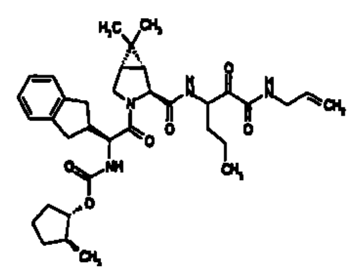


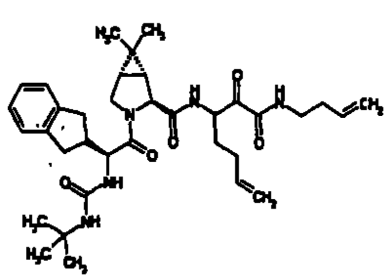


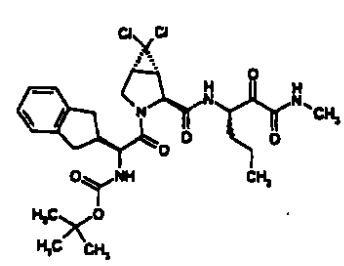


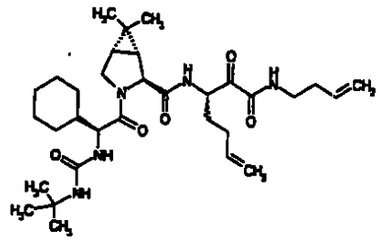


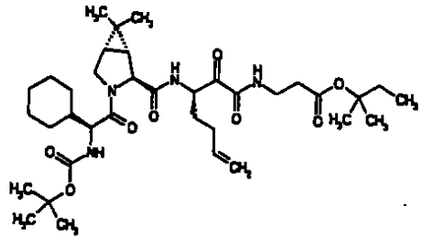


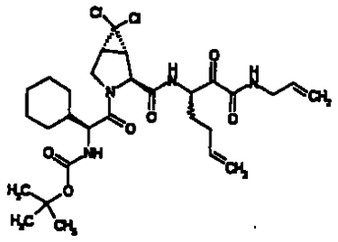


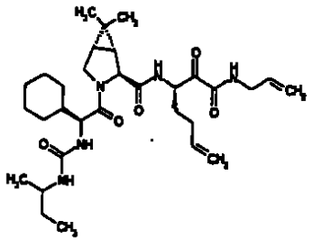


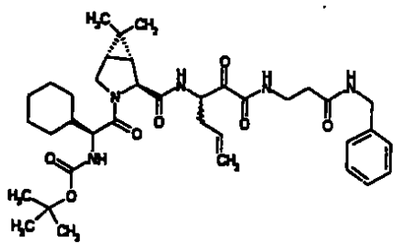


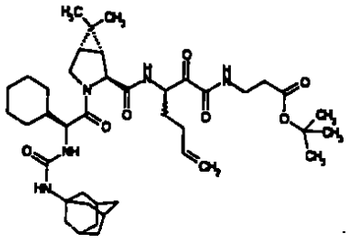


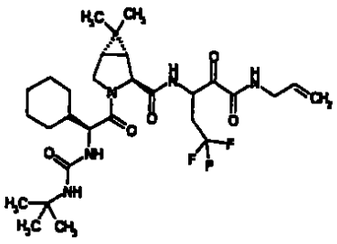


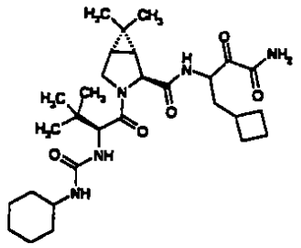


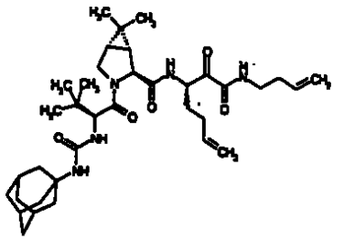


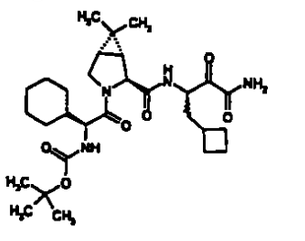


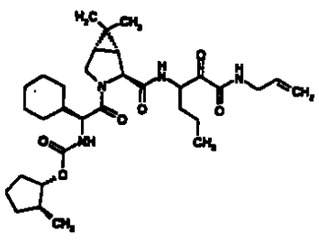


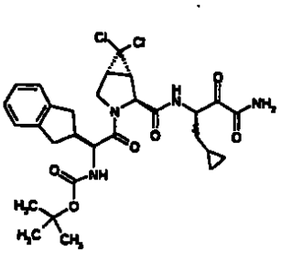


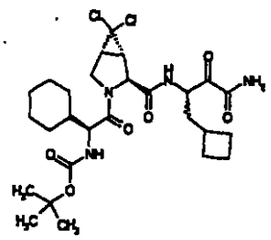


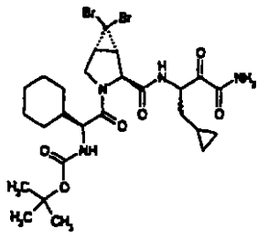


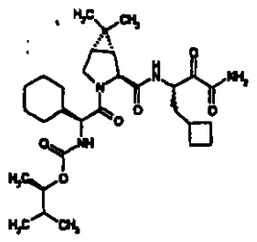


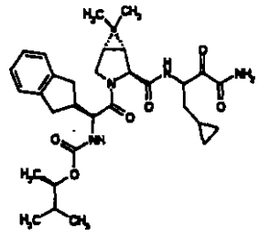


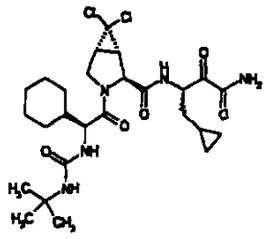


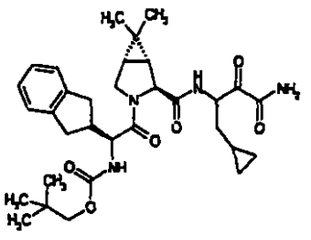


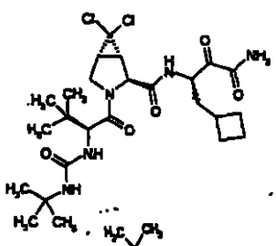


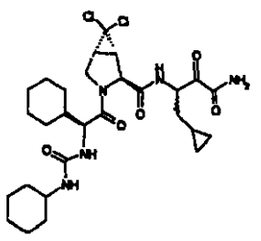


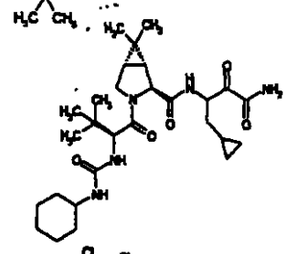


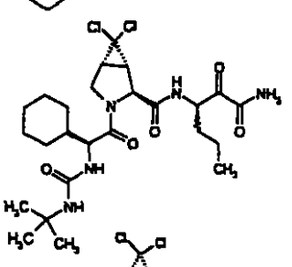


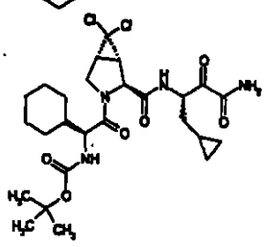


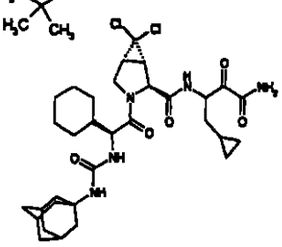


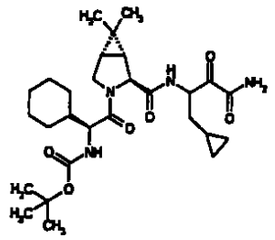


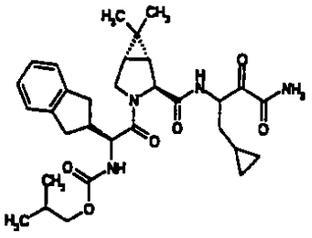


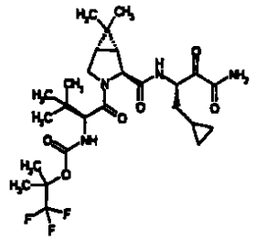


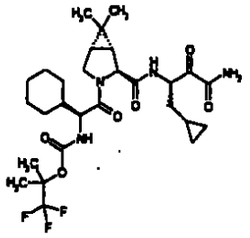


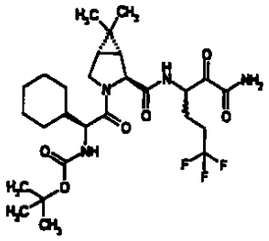


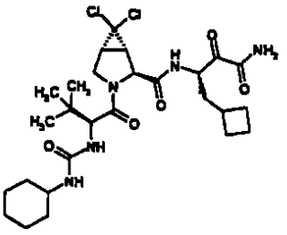


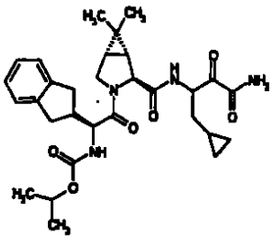


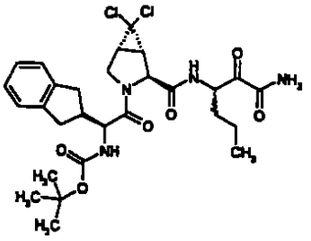


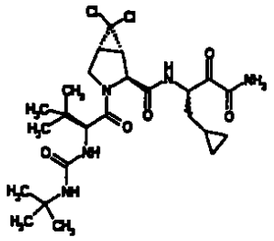


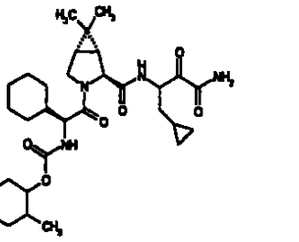


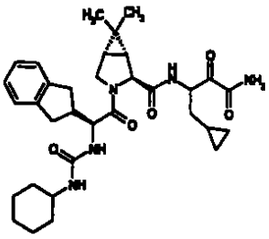


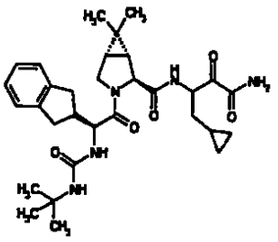


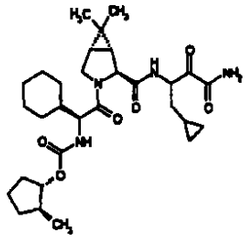
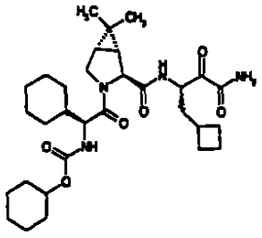
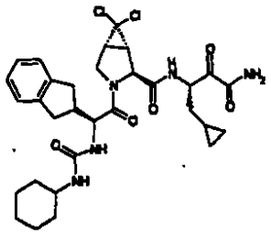
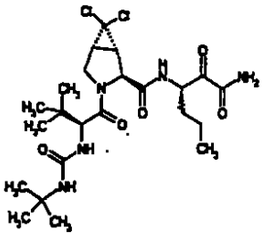
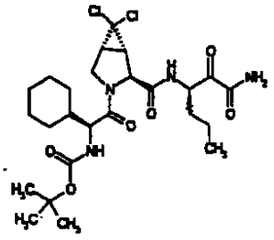
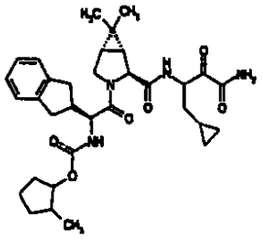
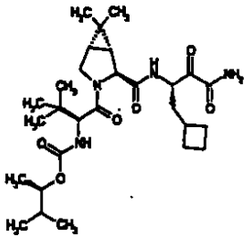
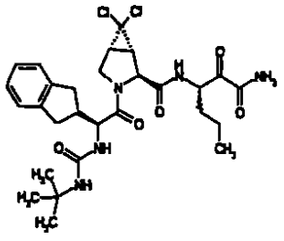
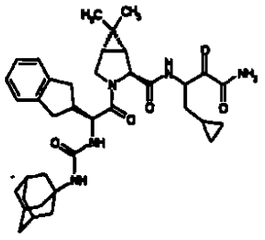
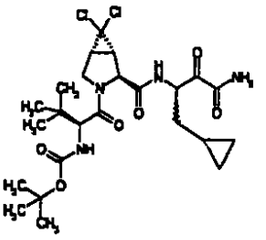
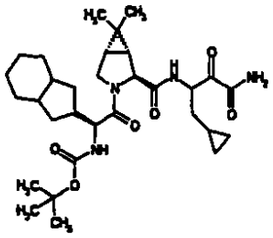
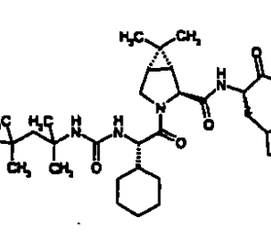


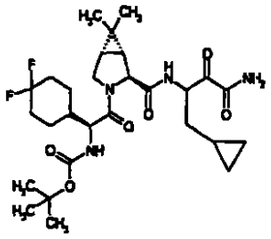


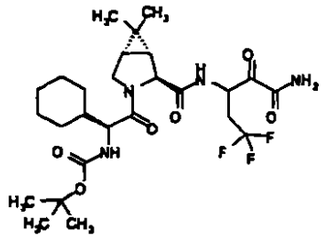


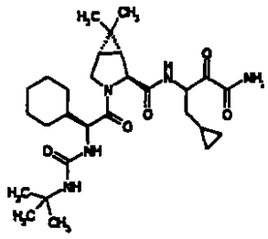


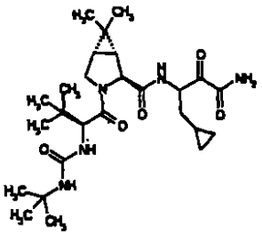


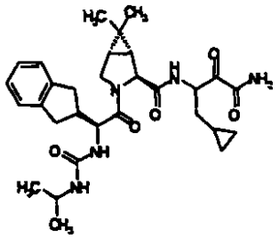













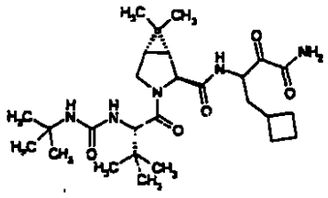


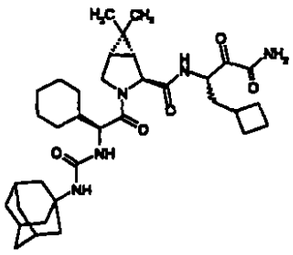


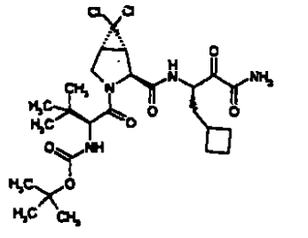


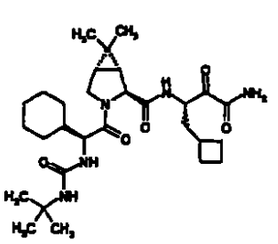


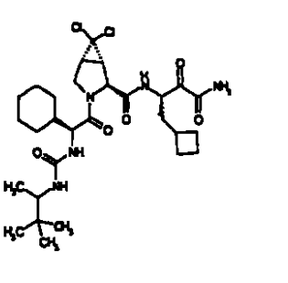


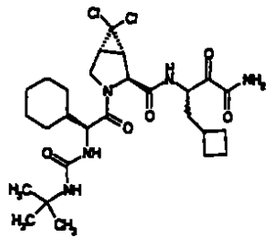


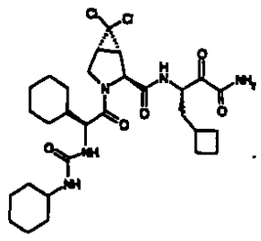


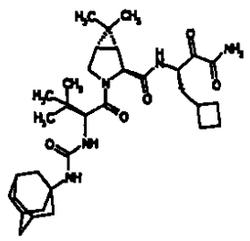


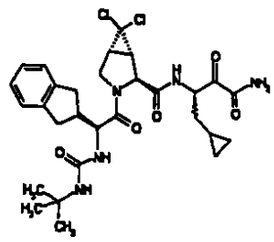


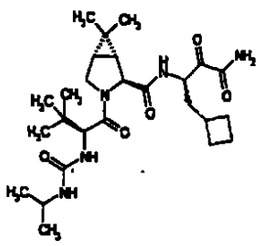


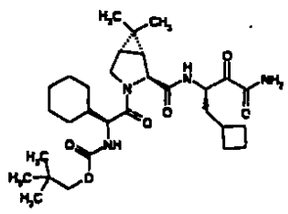


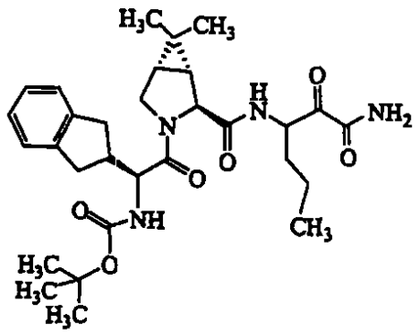


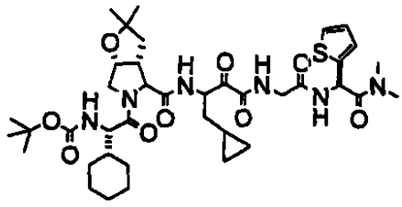


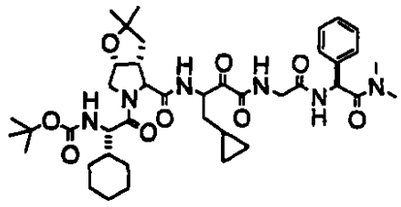


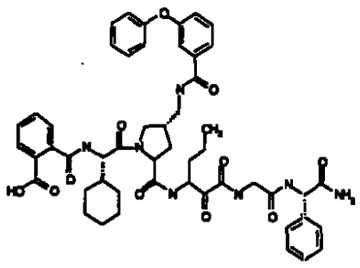


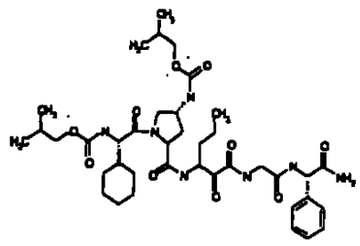


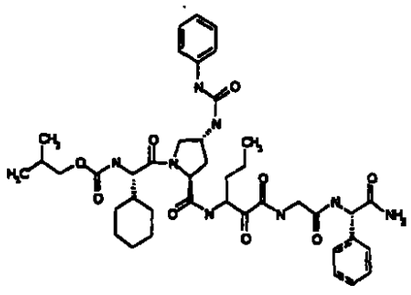


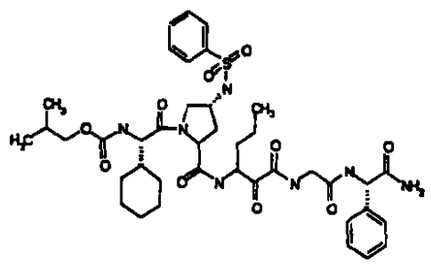


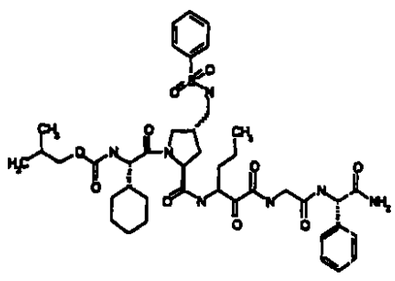


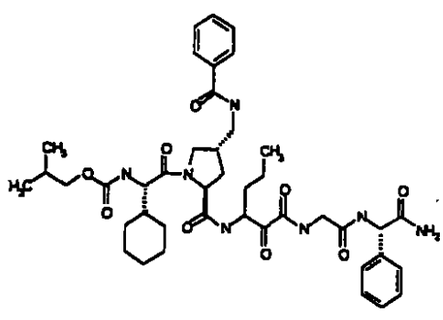


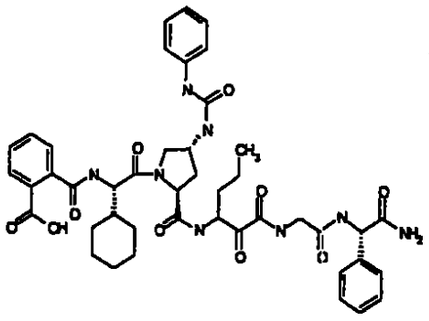


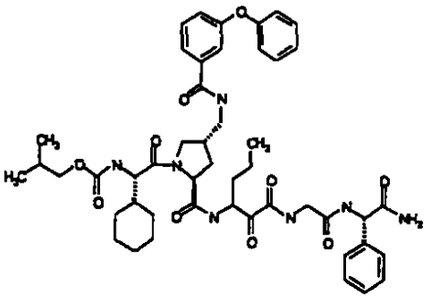


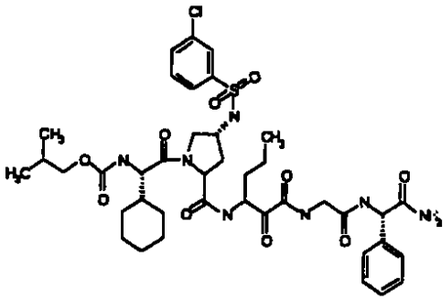


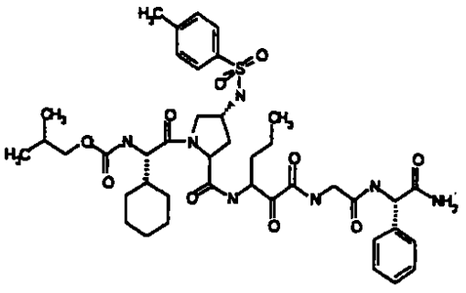


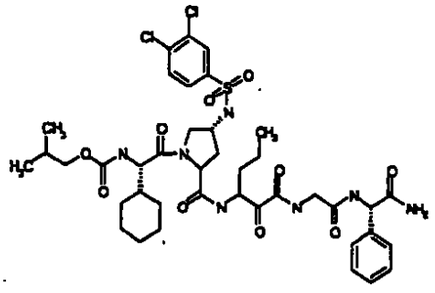


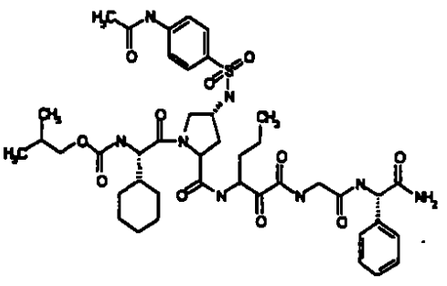


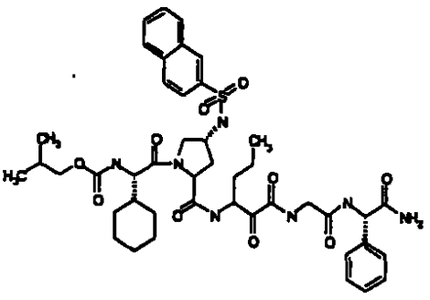


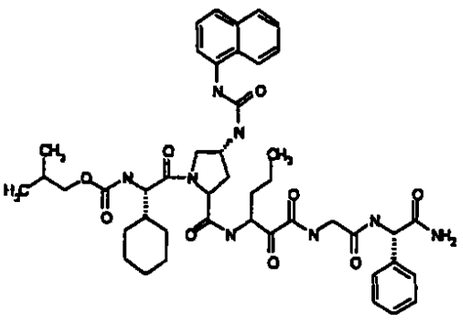




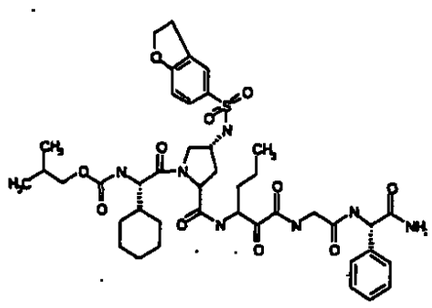


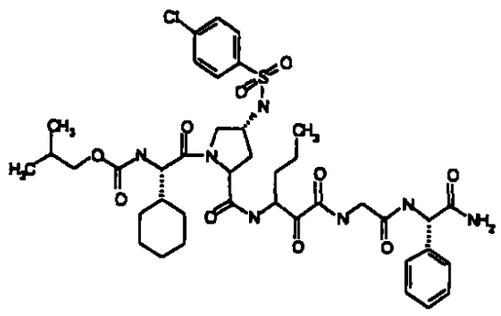


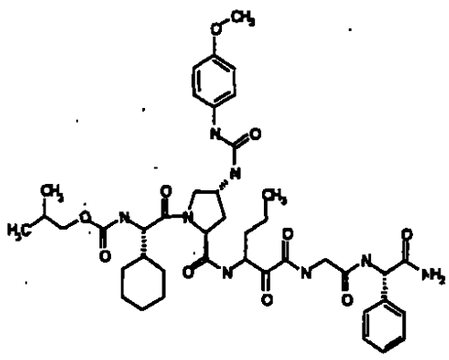


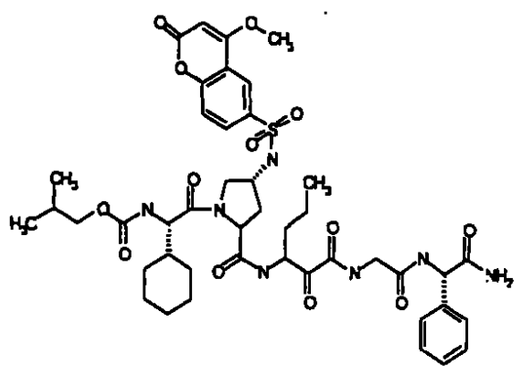


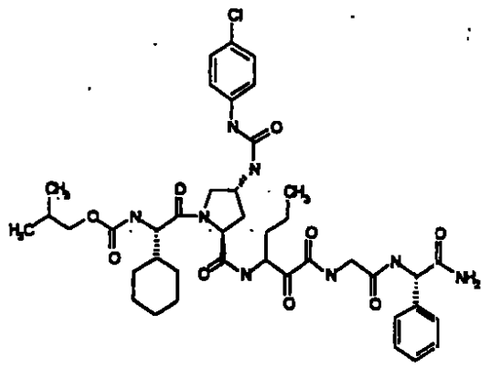
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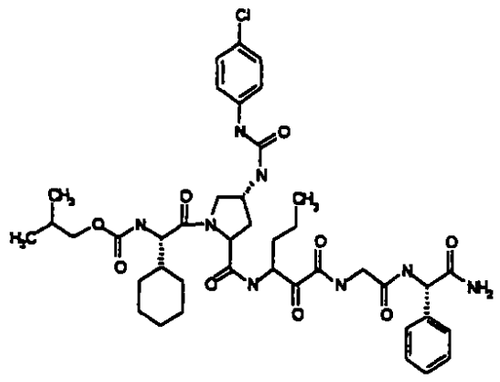


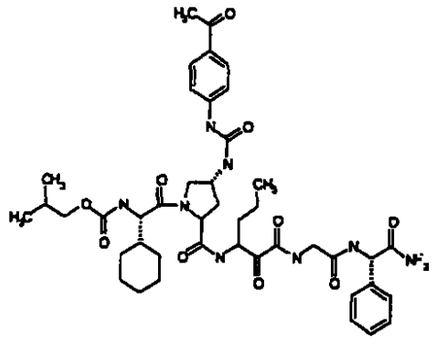


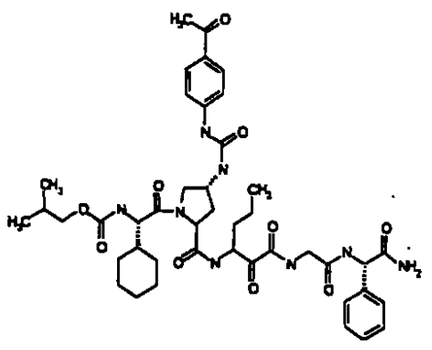


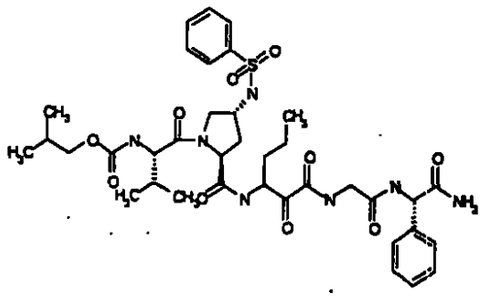


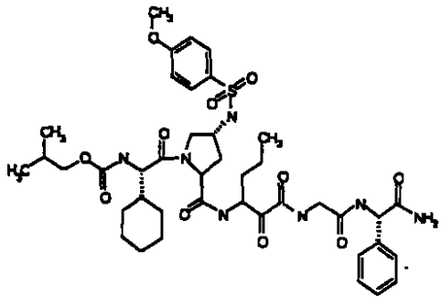


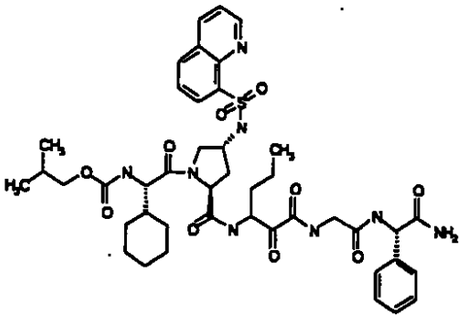


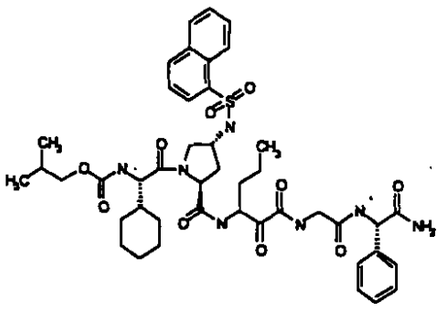


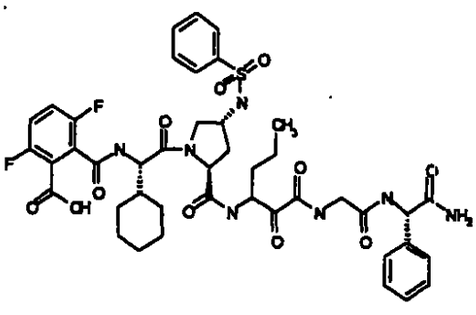


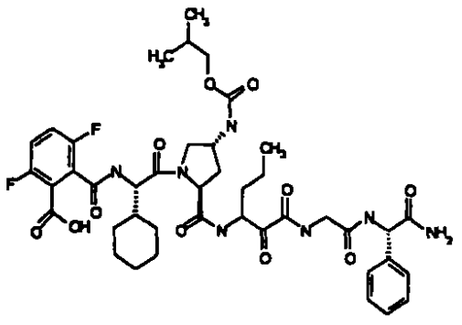


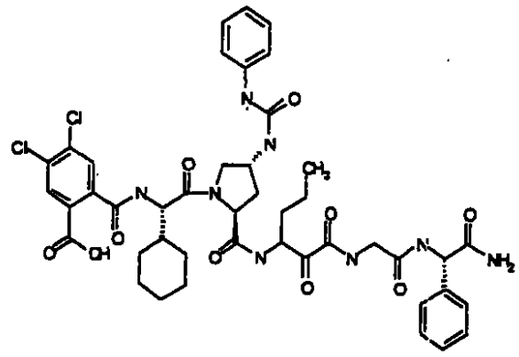


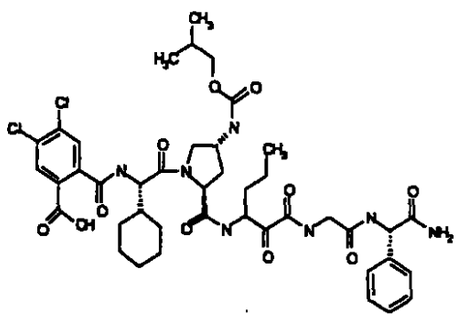


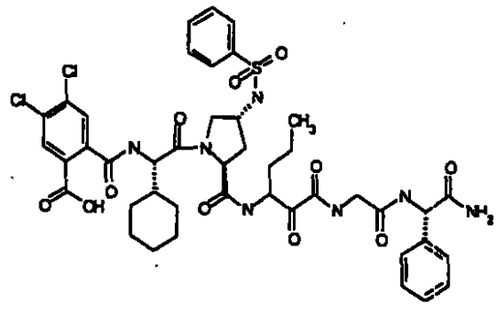


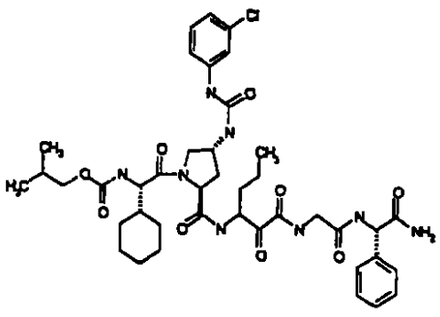


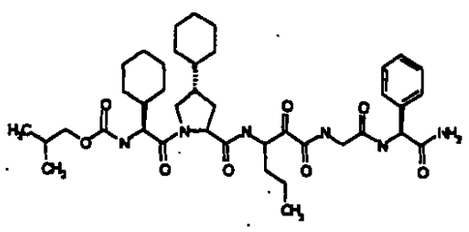


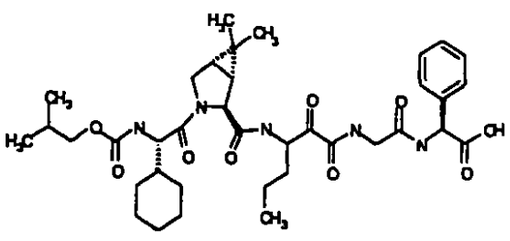


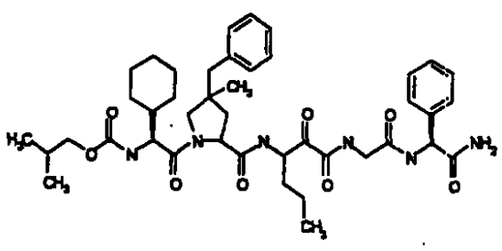


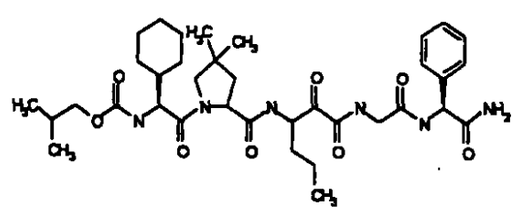




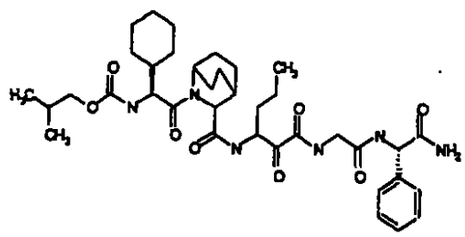


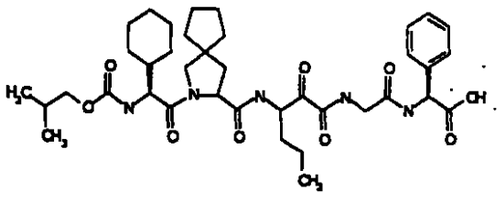


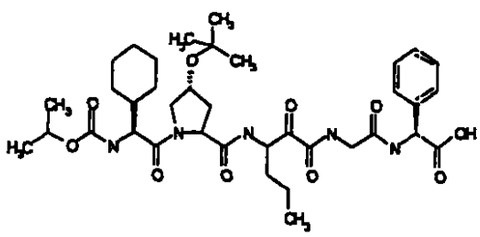


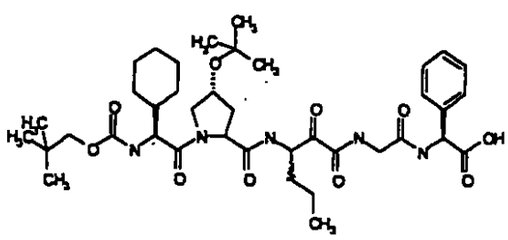


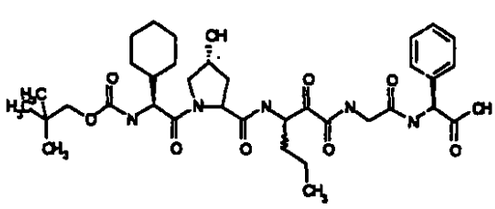
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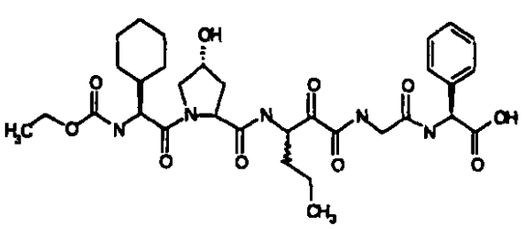


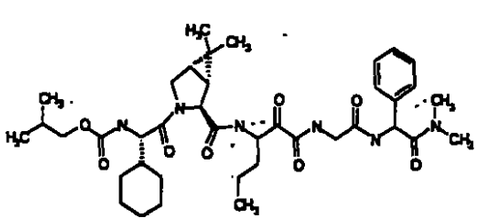


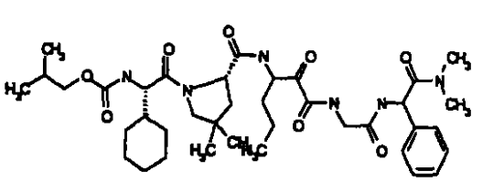


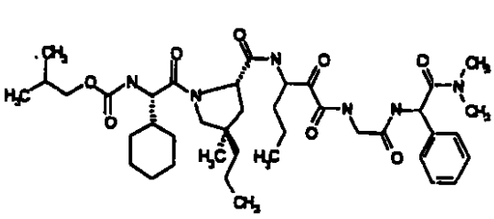


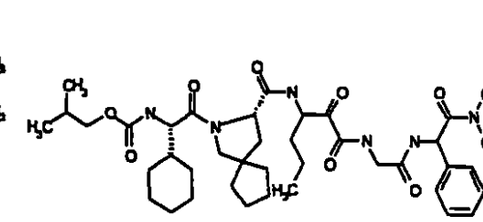


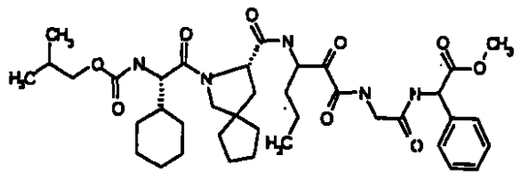
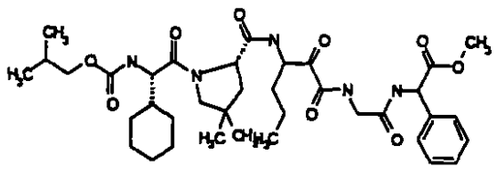
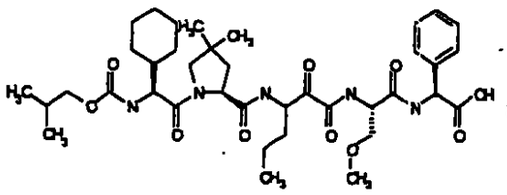
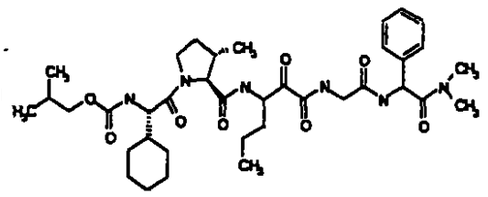
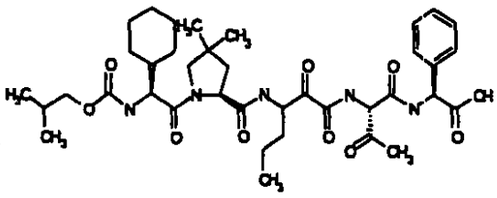
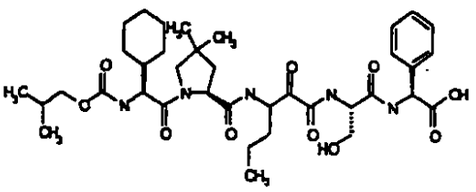
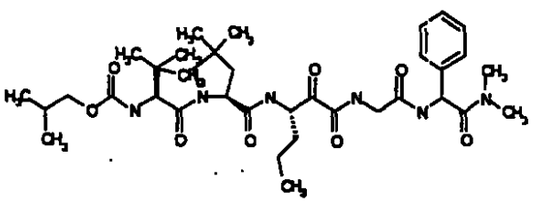
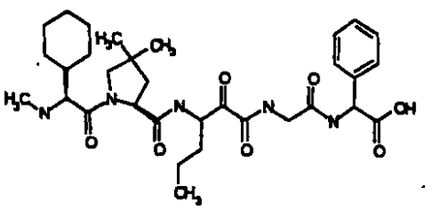
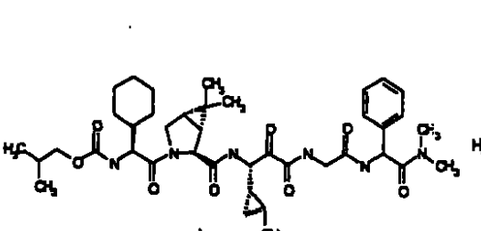
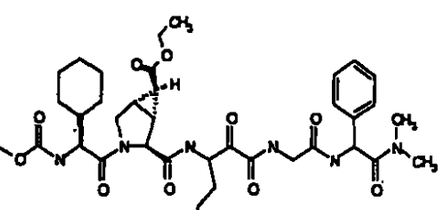
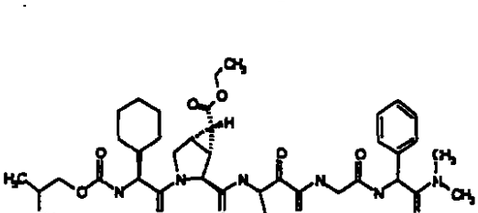
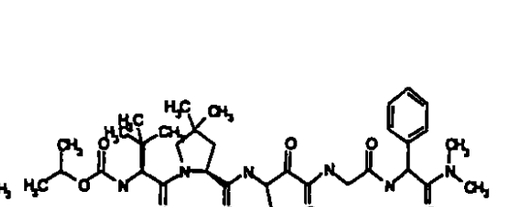
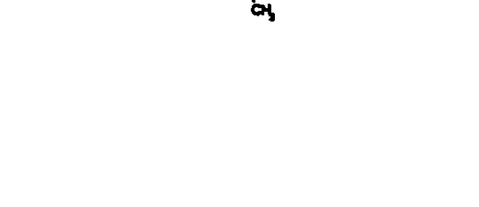
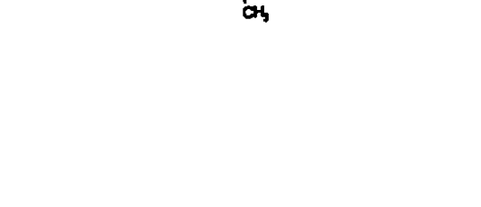


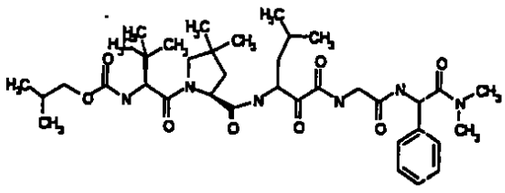


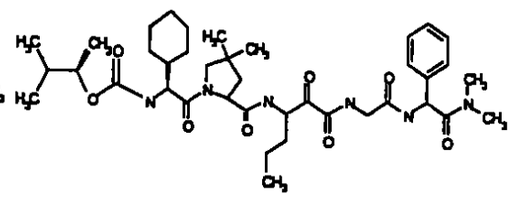


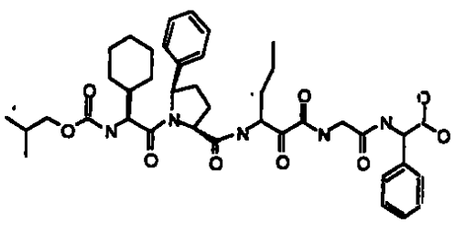


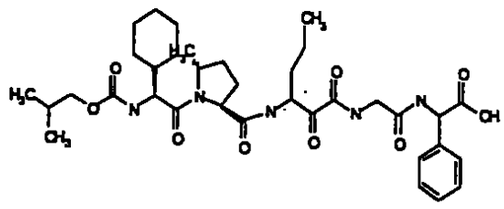


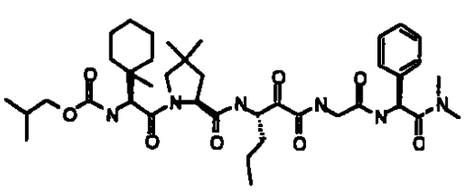















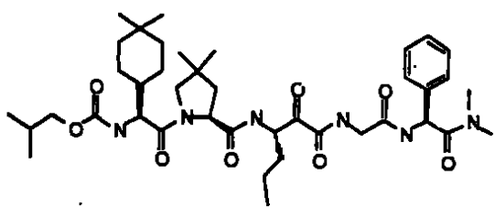


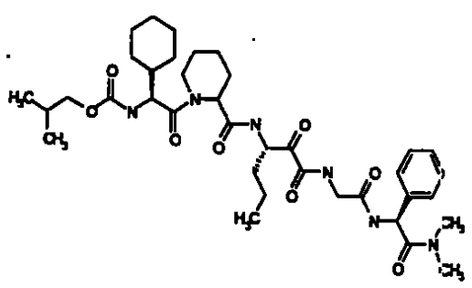


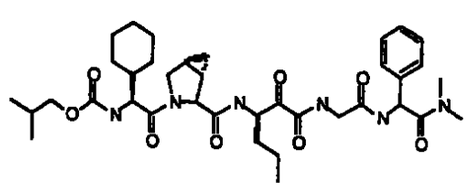


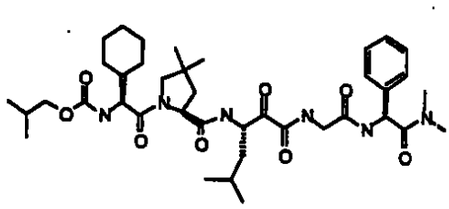


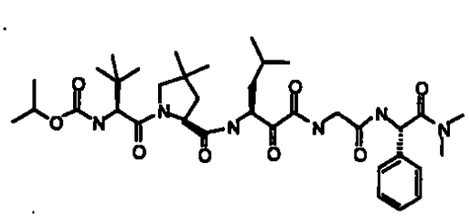


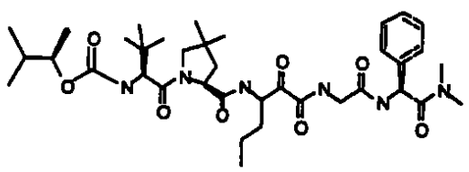


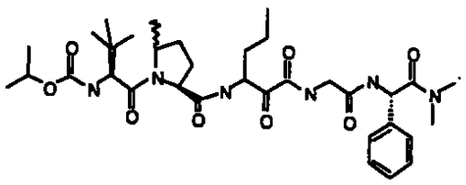


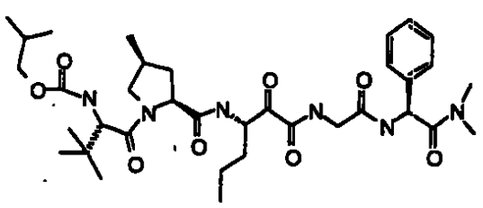


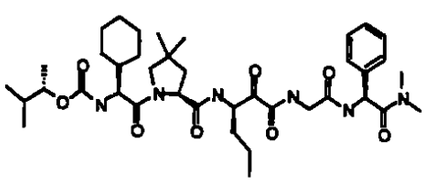


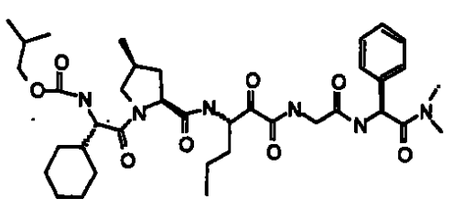


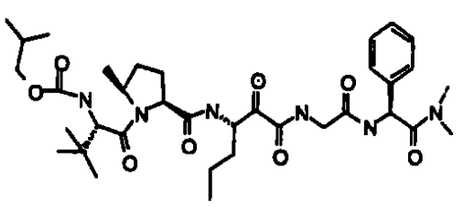


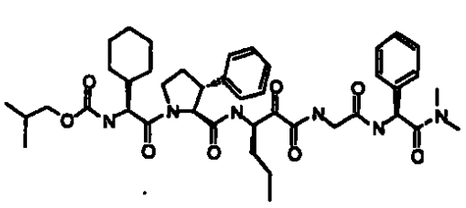


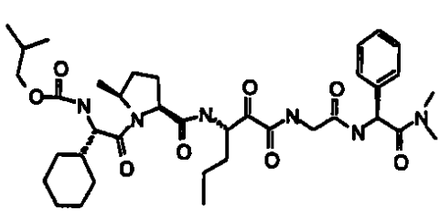


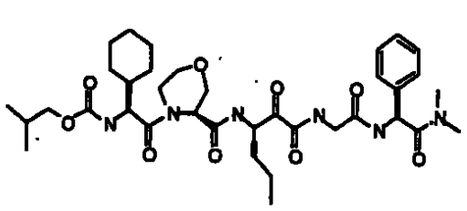


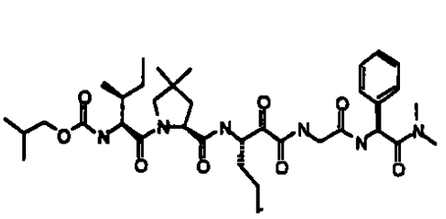


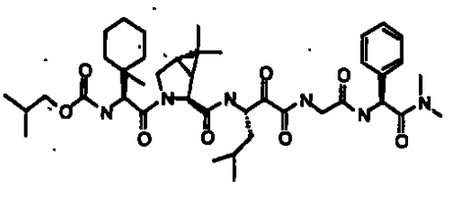


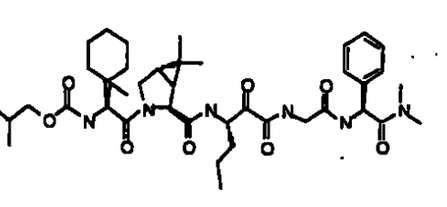


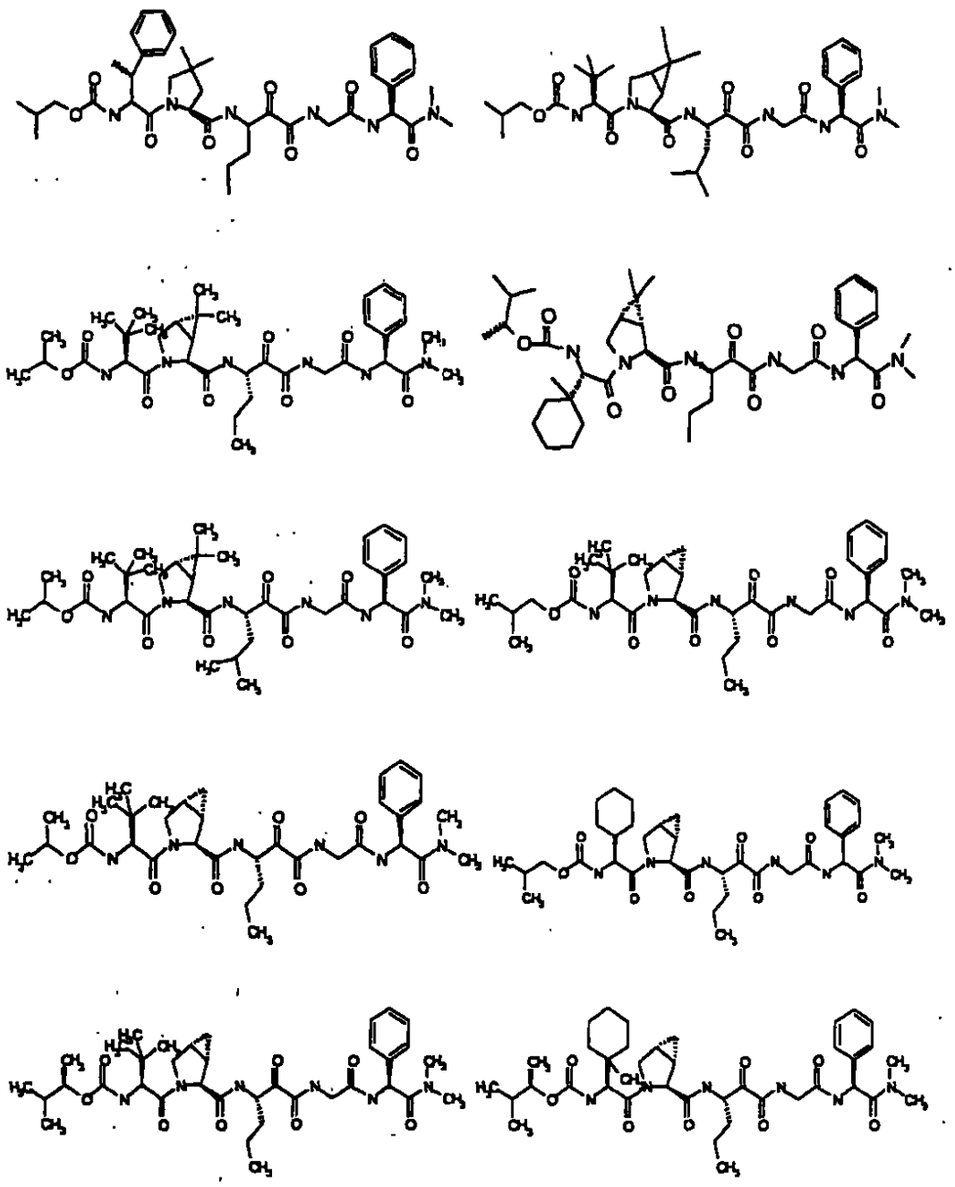












Depending upon their structure, the compounds of the invention may form pharmaceutically acceptable salts with organic or inorganic acids, or organic or inorganic bases. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those skilled in the art. For formation of salts with bases,

suitable bases are, for example, NaOH, KOH, NH_4OH, tetraalkylammonium hydroxide, and the like.

In another embodiment, this invention provides pharmaceutical compositions comprising the inventive peptides as an active ingredient. The pharmaceutical compositions generally additionally comprise a pharmaceutically acceptable carrier diluent, excipient or carrier (collectively referred to herein as carrier materials). Because of their HCV inhibitory activity, such pharmaceutical compositions possess utility in treating hepatitis C and related disorders.

In yet another embodiment, the present invention discloses methods for preparing pharmaceutical compositions comprising the inventive compounds as an active ingredient. In the pharmaceutical compositions and methods of the present invention, the active ingredients will typically be administered in admixture with suitable carrier materials suitably selected with respect to the intended form of administration, i.e. oral tablets, capsules (either solid-filled, semi-solid filled or liquid filled), powders for constitution, oral gels, elixirs, dispersible granules, syrups, suspensions, and the like, and consistent with conventional pharmaceutical practices. For example, for oral administration in the form of tablets or capsules, the active drug component may be combined with any oral non-toxic pharmaceutically acceptable inert carrier, such as lactose, starch, sucrose, cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, talc, mannitol, ethyl alcohol (liquid forms) and the like. Moreover, when desired or needed, suitable binders, lubricants, disintegrating agents and coloring agents may also be incorporated in the mixture. Powders and tablets may be comprised of from about 5 to about 95 percent inventive composition. Suitable binders include starch, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium alginate, carboxymethylcellulose, polyethylene glycol and waxes. Among the lubricants there may be mentioned for use in these dosage forms, boric acid, sodium benzoate, sodium acetate, sodium chloride, and the like. Disintegrants include starch, methylcellulose, guar gum and the like.

Sweetening and flavoring agents and preservatives may also be included

where appropriate. Some of the terms noted above, namely disintegrants, diluents, lubricants, binders and the like, are discussed in more detail below.

Additionally, the compositions of the present invention may be formulated in sustained release form to provide the rate controlled release of any one or more of the components or active ingredients to optimize the therapeutic effects, i.e. HCV inhibitory activity and the like. Suitable dosage forms for sustained release include layered tablets containing layers of varying disintegration rates or controlled release polymeric matrices impregnated with the active components and shaped in tablet form or capsules containing such impregnated or encapsulated porous polymeric matrices.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injections or addition of sweeteners and pacifiers for oral solutions, suspensions and emulsions. Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier such as inert compressed gas, e.g. nitrogen.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides such as cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein by stirring or similar mixing. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions may take the form of creams, lotions, aerosols

and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally, intravenously or subcutaneously.

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active components, e.g., an effective amount to achieve the desired purpose.

The quantity of the inventive active composition in a unit dose of preparation may be generally varied or adjusted from about 1.0 milligram to about 1,000 milligrams, preferably from about 1.0 to about 950 milligrams, more preferably from about 1.0 to about 500 milligrams, and typically from about 1 to about 250 milligrams, according to the particular application. The actual dosage employed may be varied depending upon the patient's age, sex, weight and severity of the condition being treated. Such techniques are well known to those skilled in the art.

Generally, the human oral dosage form containing the active ingredients can be administered 1 or 2 times per day. The amount and frequency of the administration will be regulated according to the judgment of the attending clinician. A generally recommended daily dosage regimen for oral administration may range from about 1.0 milligram to about 1,000 milligrams per day, in single or divided doses.

Some useful terms are described below:

Capsule - refers to a special container or enclosure made of methyl cellulose, polyvinyl alcohols, or denatured gelatins or starch for holding or containing compositions comprising the active ingredients. Hard shell capsules are typically made of blends of relatively high gel strength bone and pork skin gelatins. The capsule itself may contain small amounts of dyes, opaquing agents, plasticizers and preservatives.

Tablet- refers to a compressed or molded solid dosage form containing the active ingredients with suitable diluents. The tablet can be prepared by compression of mixtures or granulations obtained by wet granulation, dry granulation or by compaction.

Oral gel- refers to the active ingredients dispersed or solubilized in a hydrophillic semi-solid matrix.

Powder for constitution refers to powder blends containing the active ingredients and suitable diluents which can be suspended in water or juices.

Diluent - refers to substances that usually make up the major portion of the composition or dosage form. Suitable diluents include sugars such as lactose, sucrose, mannitol and sorbitol; starches derived from wheat, corn, rice and potato; and celluloses such as microcrystalline cellulose. The amount of diluent in the composition can range from about 10 to about 90% by weight of the total composition, preferably from about 25 to about 75%, more preferably from about 30 to about 60% by weight, even more preferably from about 12 to about 60%.

Disintegrant - refers to materials added to the composition to help it break apart (disintegrate) and release the medicaments. Suitable disintegrants include starches; "cold water soluble" modified starches such as sodium carboxymethyl starch; natural and synthetic gums such as locust bean, karaya, guar, tragacanth and agar; cellulose derivatives such as methylcellulose and sodium carboxymethylcellulose; microcrystalline celluloses and cross-linked microcrystalline celluloses such as sodium croscarmellose; alginates such as alginic acid and sodium alginate; clays such as bentonites; and effervescent mixtures. The amount of disintegrant in the composition can range from about 2 to about 15% by weight of the composition, more preferably from about 4 to about 10% by weight.

Binder - refers to substances that bind or "glue" powders together and make them cohesive by forming granules, thus serving as the "adhesive" in the formulation. Binders add cohesive strength already available in the diluent or bulking agent. Suitable binders include sugars such as sucrose; starches derived

from wheat, corn rice and potato; natural gums such as acacia, gelatin and tragacanth; derivatives of seaweed such as alginic acid, sodium alginate and ammonium calcium alginate; cellulosic materials such as methylcellulose and sodium carboxymethylcellulose and hydroxypropylmethylcellulose; polyvinylpyrrolidone; and inorganics such as magnesium aluminum silicate. The amount of binder in the composition can range from about 2 to about 20% by weight of the composition, more preferably from about 3 to about 10% by weight, even more preferably from about 3 to about 6% by weight.

Lubricant - refers to a substance added to the dosage form to enable the tablet, granules, etc. after it has been compressed, to release from the mold or die by reducing friction or wear. Suitable lubricants include metallic stearates such as magnesium stearate, calcium stearate or potassium stearate; stearic acid; high melting point waxes; and water soluble lubricants such as sodium chloride, sodium benzoate, sodium acetate, sodium oleate, polyethylene glycols and d'l-leucine. Lubricants are usually added at the very last step before compression, since they must be present on the surfaces of the granules and in between them and the parts of the tablet press. The amount of lubricant in the composition can range from about 0.2 to about 5% by weight of the composition, preferably from about 0.5 to about 2%, more preferably from about 0.3 to about 1.5% by weight.

Glident - material that prevents caking and improve the flow characteristics of granulations, so that flow is smooth and uniform. Suitable glidents include silicon dioxide and talc. The amount of glident in the composition can range from about 0.1% to about 5% by weight of the total composition, preferably from about 0.5 to about 2% by weight.

Coloring agents - excipients that provide coloration to the composition or the dosage form. Such excipients can include food grade dyes and food grade dyes adsorbed onto a suitable adsorbent such as clay or aluminum oxide. The amount of the coloring agent can vary from about 0.1 to about 5% by weight of the composition, preferably from about 0.1 to about 1%.

Bioavailability - refers to the rate and extent to which the active drug ingredient or therapeutic moiety is absorbed into the systemic circulation from an administered dosage form as compared to a standard or control.

Conventional methods for preparing tablets are known. Such methods include dry methods such as direct compression and compression of granulation produced by compaction, or wet methods or other special procedures. Conventional methods for making other forms for administration such as, for example, capsules, suppositories and the like are also well known.

Another embodiment of the invention discloses the use of the pharmaceutical compositions disclosed above for treatment of diseases such as, for example, hepatitis C and the like. The method comprises administering a therapeutically effective amount of the inventive pharmaceutical composition to a patient having such a disease or diseases and in need of such a treatment.

In yet another embodiment, the compounds of the invention may be used for the treatment of HCV in humans in monotherapy mode or in a combination therapy (e.g., dual combination, triple combination etc.) mode such as, for example, in combination with antiviral and/or immunomodulatory agents. Examples of such antiviral and/or immunomodulatory agents include Ribavirin (from Schering-Plough Corporation, Madison, New Jersey) and Levovirin™ (from ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (from Viropharma, Incorporated, Exton, Pennsylvania), ISIS 14803™ (from ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (from Ribozyme Pharmaceuticals, Boulder, Colorado), VX 497™ (from Vertex Pharmaceuticals, Cambridge, Massachusetts), Thymosin™ (from SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), mycophenolate mofetil (from Hoffman-LaRoche, Nutley, New Jersey), interferon (such as, for example, interferon-alpha, PEG-interferon alpha conjugates) and the like. "PEG-interferon alpha conjugates" are interferon alpha molecules covalently attached to a PEG molecule. Illustrative PEG-interferon alpha conjugates include interferon alpha-2a (Roferon™, from Hoffman La-Roche, Nutley, New Jersey) in the form of

pegylated interferon alpha-2a (e.g., as sold under the trade name Pegasys™), interferon alpha-2b (Intron™, from Schering-Plough Corporation) in the form of pegylated interferon alpha-2b (e.g., as sold under the trade name PEG-Intron™), interferon alpha-2c (Berofor Alpha™, from Boehringer Ingelheim, Ingelheim, Germany) or consensus interferon as defined by determination of a consensus sequence of naturally occurring interferon alphas (Infergen™, from Amgen, Thousand Oaks, California).

As stated earlier, the invention includes tautomers, rotamers, enantiomers and other stereoisomers of the inventive compounds also. Thus, as one skilled in the art appreciates, some of the inventive compounds may exist in suitable isomeric forms. Such variations are contemplated to be within the scope of the invention.

Another embodiment of the invention discloses a method of making the compounds disclosed herein. The compounds may be prepared by several techniques known in the art. Representative illustrative procedures are outlined in the following reaction schemes. It is to be understood that while the following illustrative schemes describe the preparation of a few representative inventive compounds, suitable substitution of any of both the natural and unnatural amino acids will result in the formation of the desired compounds based on such substitution. Such variations are contemplated to be within the scope of the invention.

Abbreviations which are used in the descriptions of the schemes, preparations and the examples that follow are:

THF: Tetrahydrofuran

DMF: *N*,*N*-Dimethylformamide

EtOAc: Ethyl acetate

AcOH: Acetic acid

HOOBt: 3-Hydroxy-1,2,3-benzotriazin-4(3*H*)-one

EDCI: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

NMM: *N*-Methylmorpholine

ADDP: 1,1'-(Azodicarbobyl)dipiperidine

DEAD: Diethylazodicarboxylate

MeOH: Methanol

EtOH: Ethanol

Et_2O: Diethyl ether

DMSO: Dimethylsulfoxide

HOBt: N-Hydroxybenzotriazole

PyBrOP: Bromo-*tris*-pyrrolidinophosphonium hexafluorophosphate

DCM: Dichloromethane

DCC: 1,3-Dicyclohexylcarbodiimide

TEMPO: 2,2,6,6-Tetramethyl-1-piperidinyloxy

Phg: Phenylglycine

Chg: Cyclohexylglycine

Bn: Benzyl

Bzl: Benzyl

Et: Ethyl

Ph: Phenyl

iBoc: isobutoxycarbonyl

iPr: isopropyl

^{t}Bu or Bu^t: *tert*-Butyl

Boc: tert-Butyloxycarbonyl

Cbz: Benzyloxycarbonyl

Cp: Cylcopentyldienyl

Ts: p-toluenesulfonyl

Me: Methyl

HATU: O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

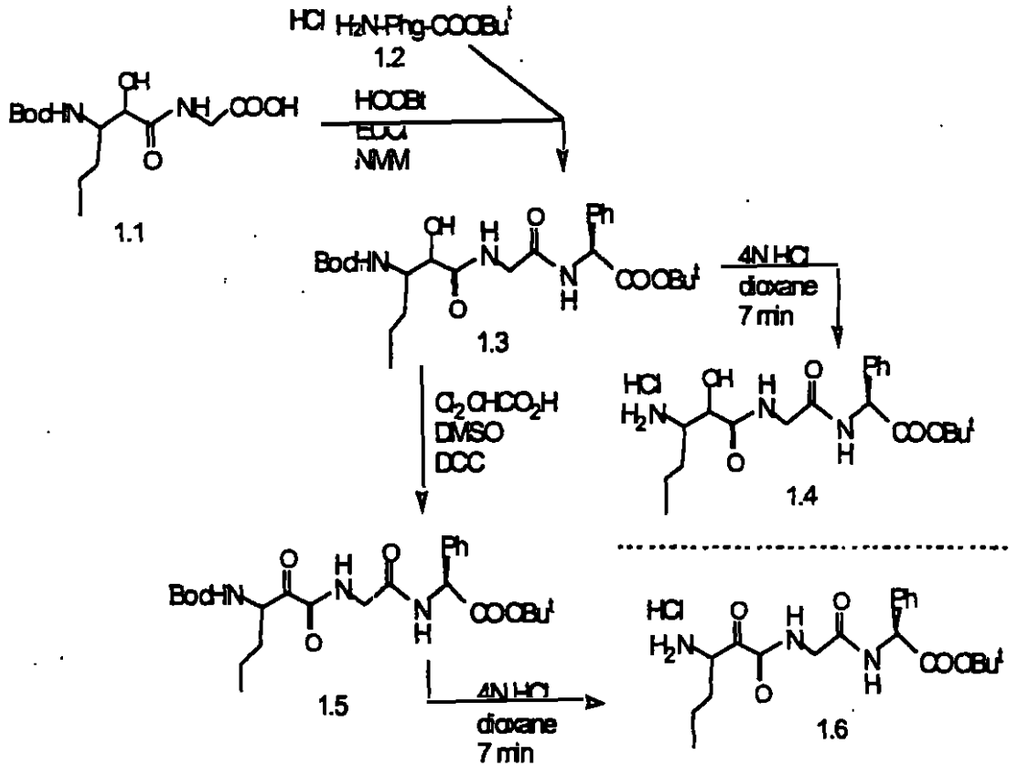
DMAP: 4-N,N-Dimethylaminopyridine

Bop: Benzotriazol-1-yl-oxy-tris(dimethylamino)hexafluorophosphate

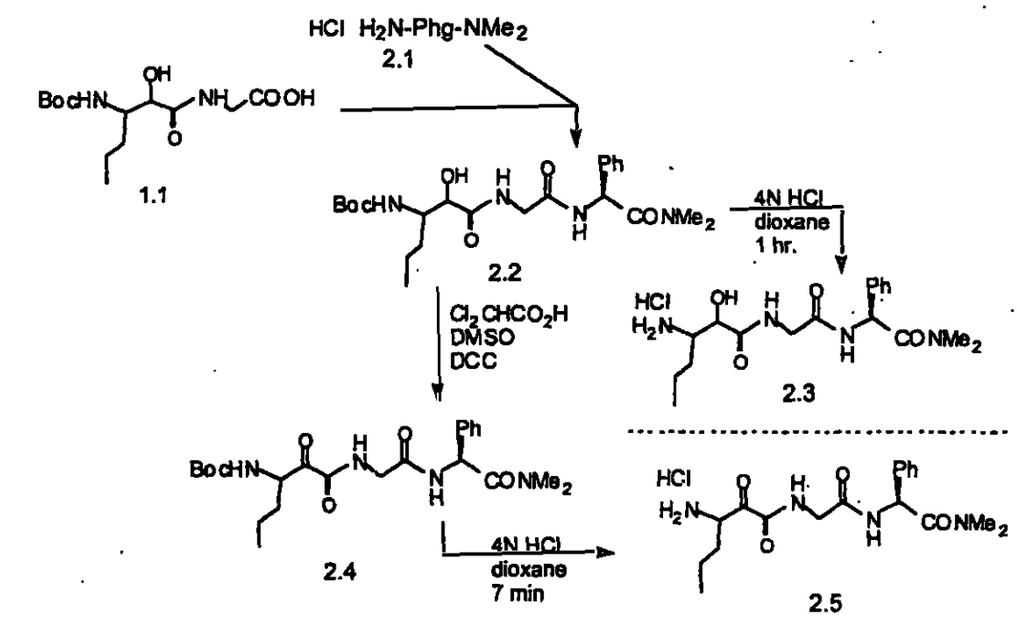
General Preparative Schemes:

The following schemes describe the methods of synthesis of intermediate building blocks:

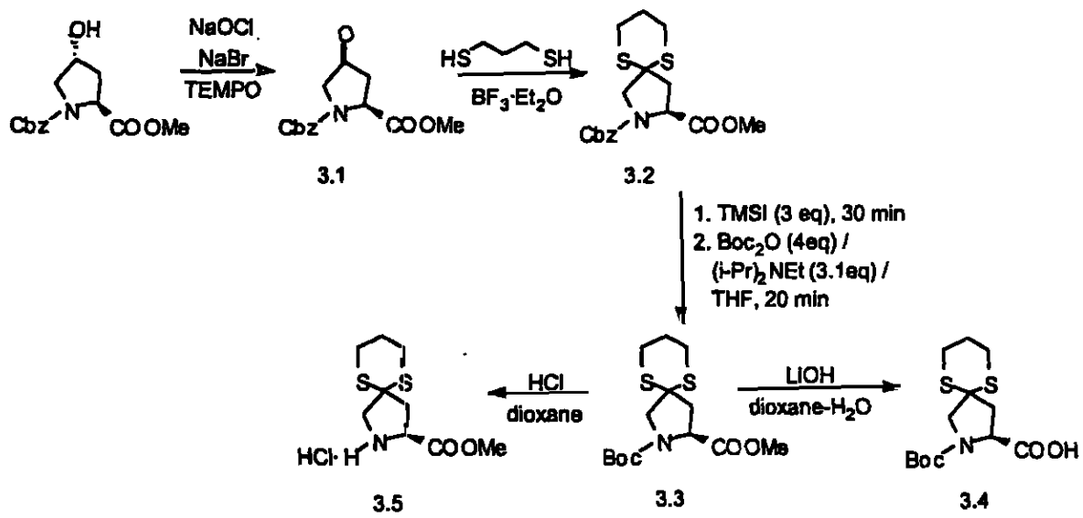
SCHEME 1



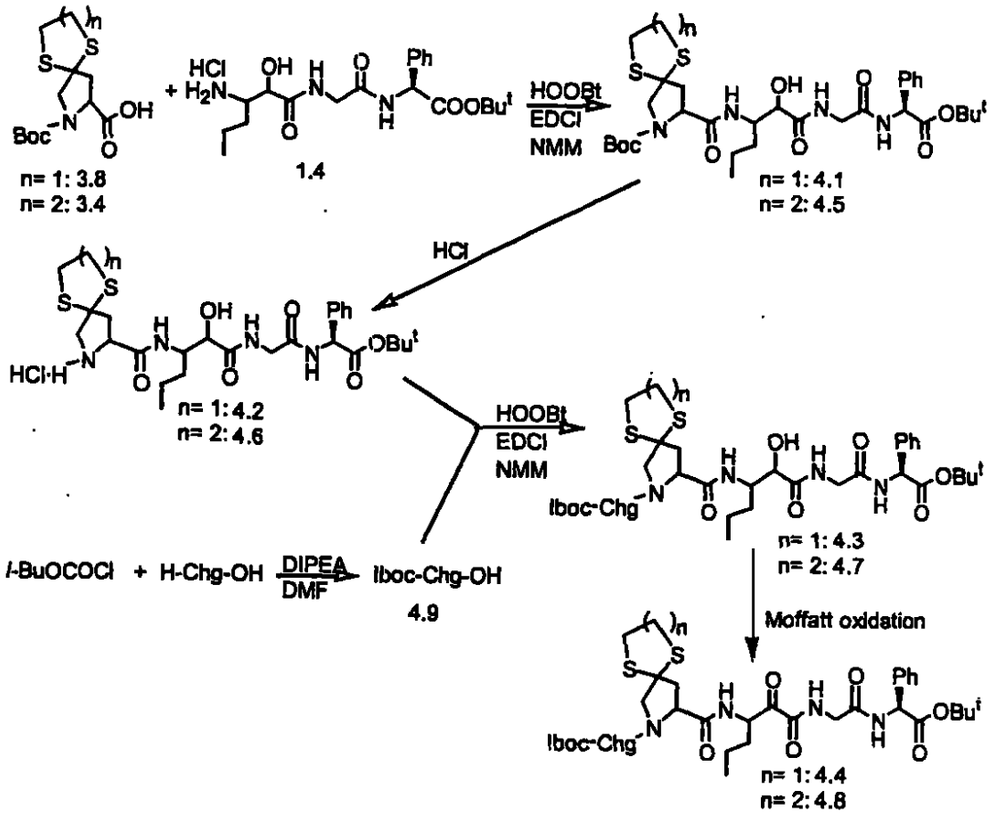
SCHEME 2



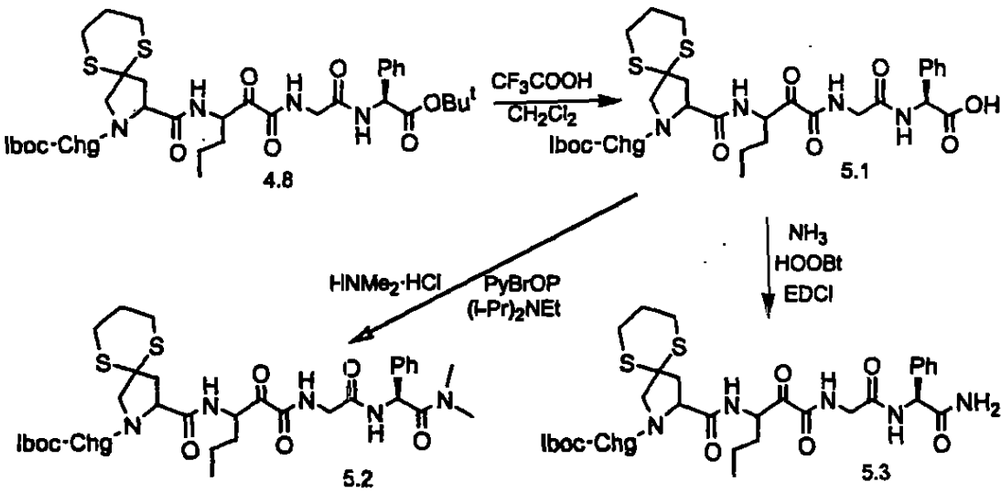
SCHEME 3



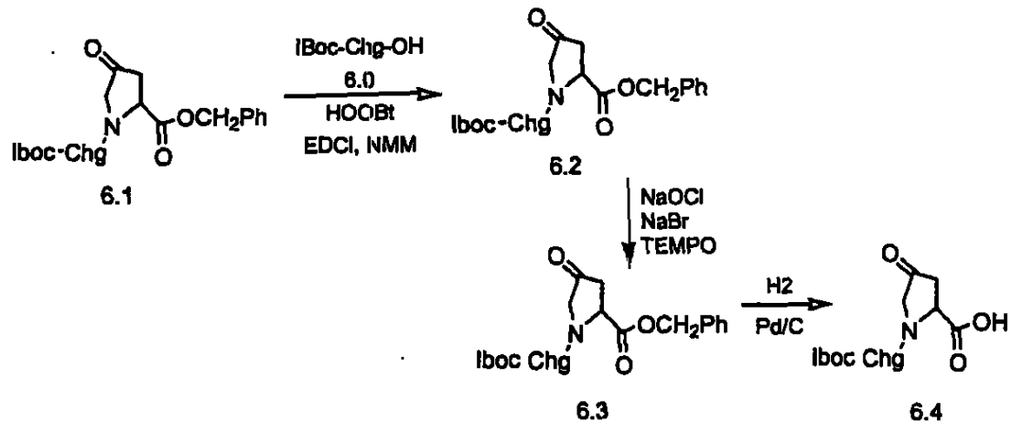
SCHEME 4


n= 1: 3.8
n= 2: 3.4
1.4
HOOBt
EDCI
NMM
n= 1: 4.1
n= 2: 4.5
HCl
n= 1: 4.2
n= 2: 4.6
HOOBt
EDCI
NMM
n= 1: 4.3
n= 2: 4.7
t-BuOCOCl + H-Chg-OH
DIPEA
DMF
Iboc-Chg-OH
4.9
Moffatt oxidation
n= 1: 4.4
n= 2: 4.8

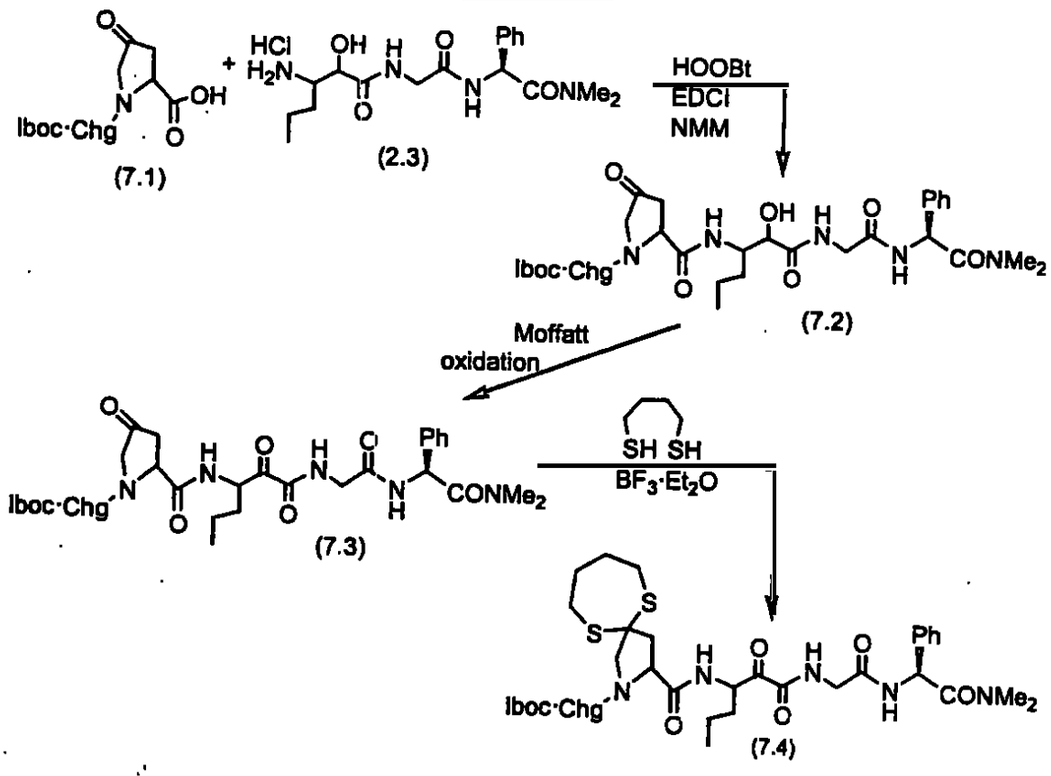
SCHEME 5



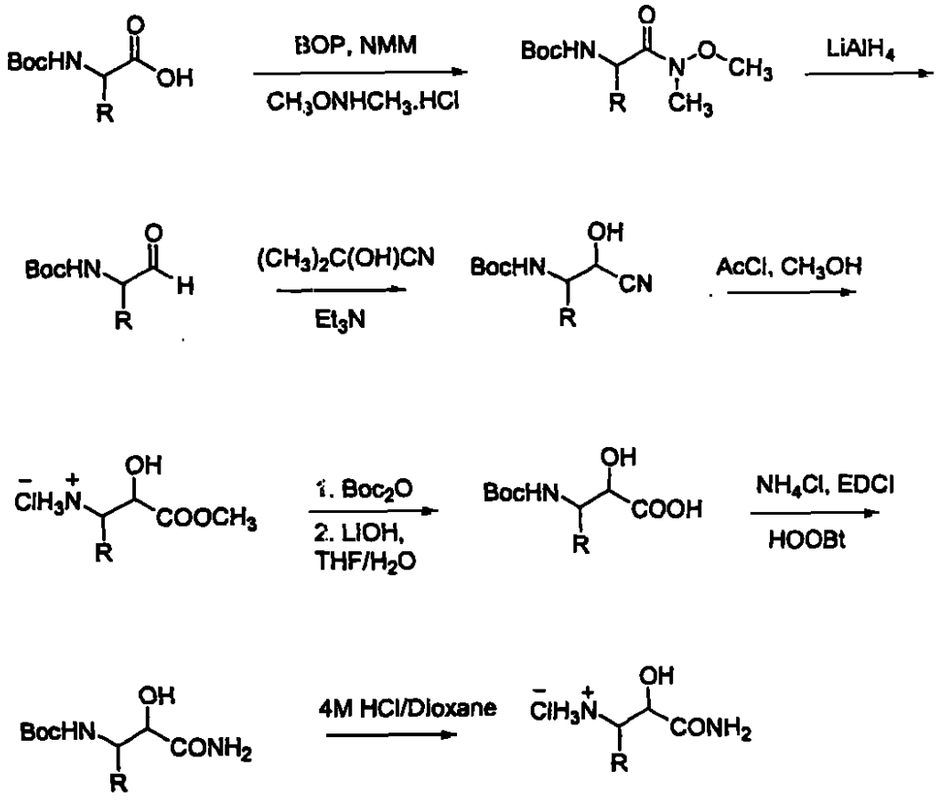
SCHEME 6



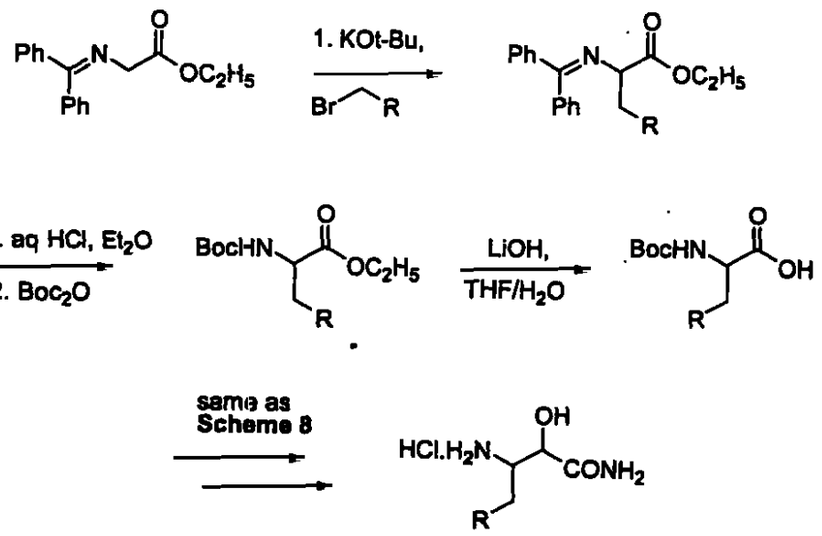
SCHEME 7


Iboc·Chg
(7.1)
(2.3)
HOOBt
EDCI
NMM
(7.2)
Moffatt
oxidation
(7.3)
SH SH
$BF_3 \cdot Et_2O$
(7.4)

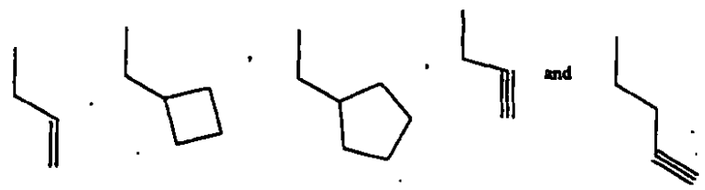
SCHEME 8


BocHN
OH
R
BOP, NMM
CH3ONHCH3.HCl
N
O
CH3
LiAlH4
H
(CH3)2C(OH)CN
Et3N
OH
CN
AcCl, CH3OH
ClH3N
COOCH3
1. Boc2O
2. LiOH,
THF/H2O
COOH
NH4Cl, EDCl
HOOBt
CONH2
4M HCl/Dioxane
where R =
CF3
F
and

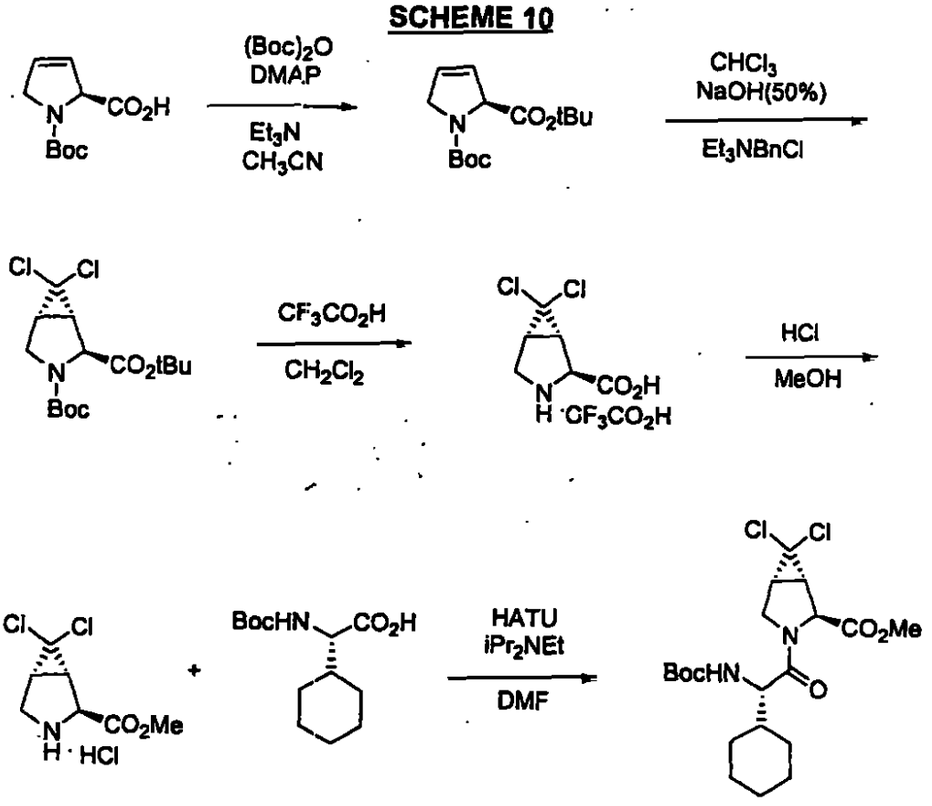
SCHEME 9



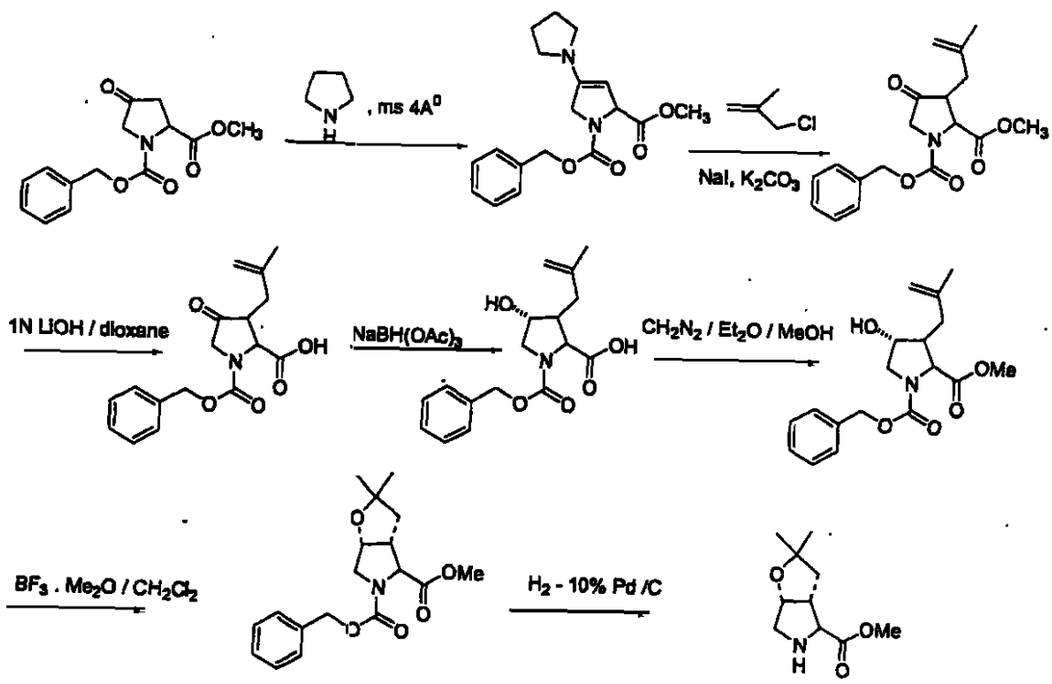
where R =



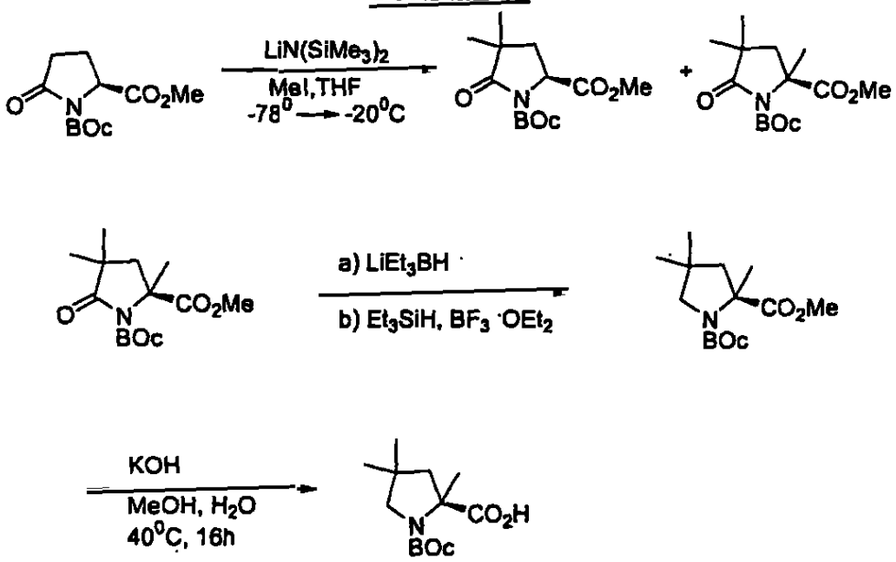
SCHEME 10


(Boc)2O
DMAP
Et3N
CH3CN
CO2H
Boc
CO2tBu
CHCl3
NaOH(50%)
Et3NBnCl
Cl
CF3CO2H
CH2Cl2
HCl
MeOH
CO2Me
HCl
BocHN
HATU
iPr2NEt
DMF
O

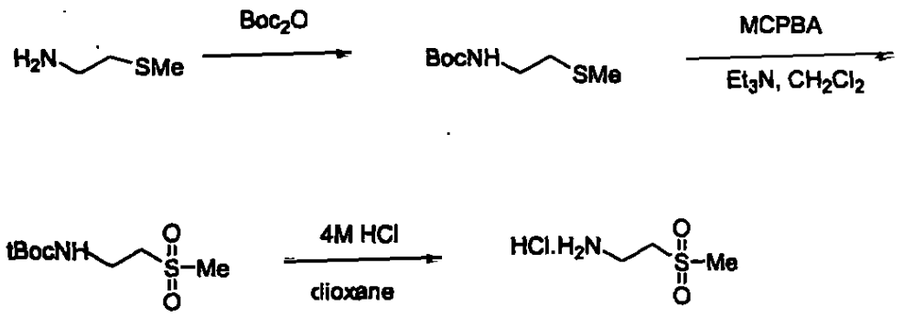
SCHEME 11


, ms 4A°
NaI, K2CO3
1N LiOH / dioxane
NaBH(OAc)3
CH2N2 / Et2O / MeOH
BF3 . Me2O / CH2Cl2
H2 - 10% Pd /C

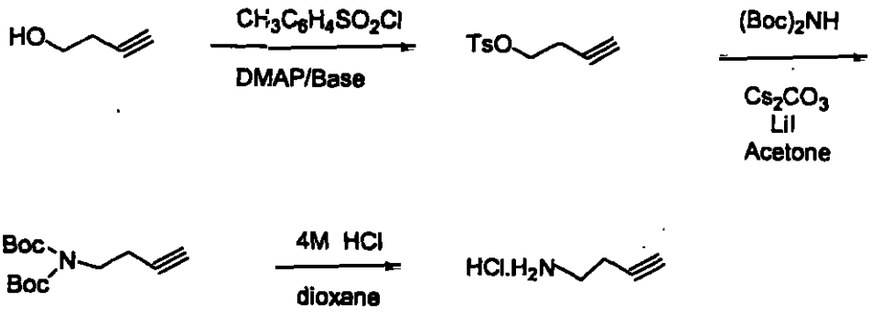
SCHEME 12



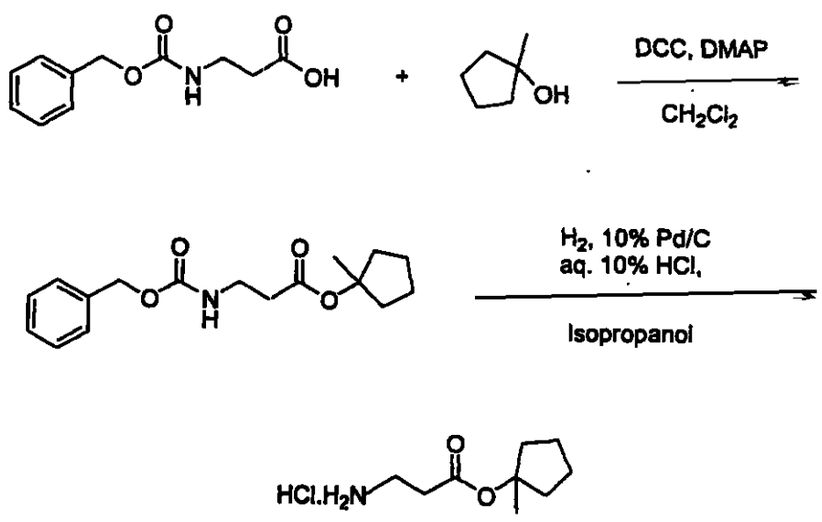
SCHEME 13



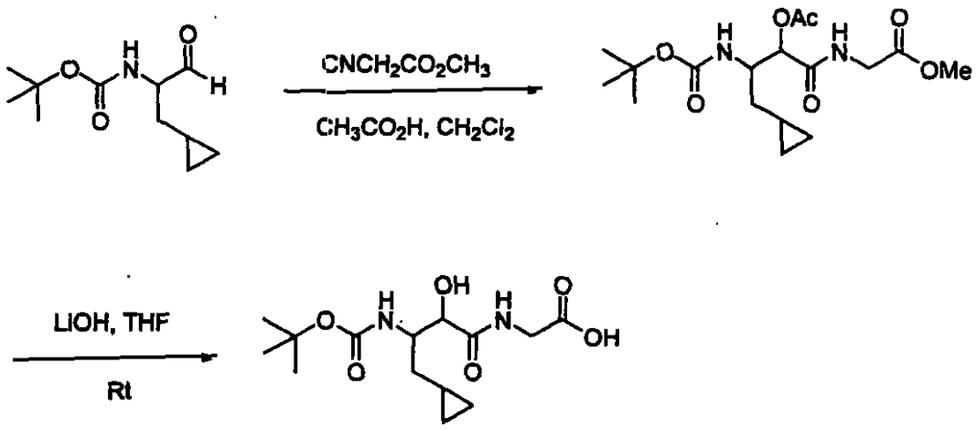
SCHEME 14



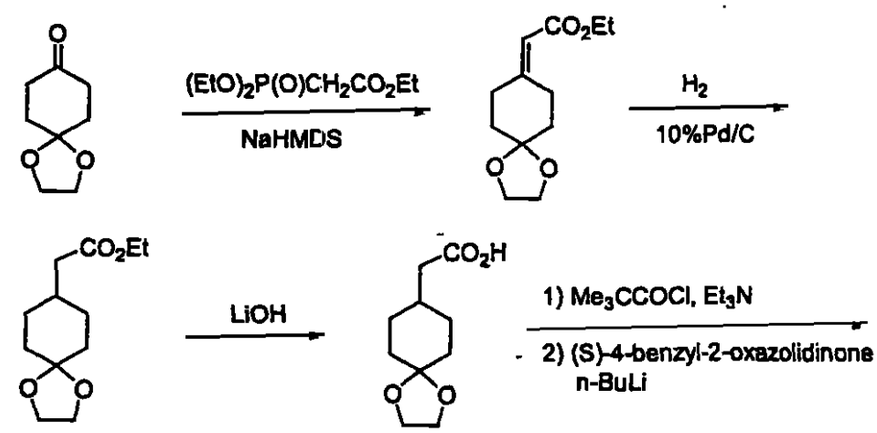
SCHEME 15

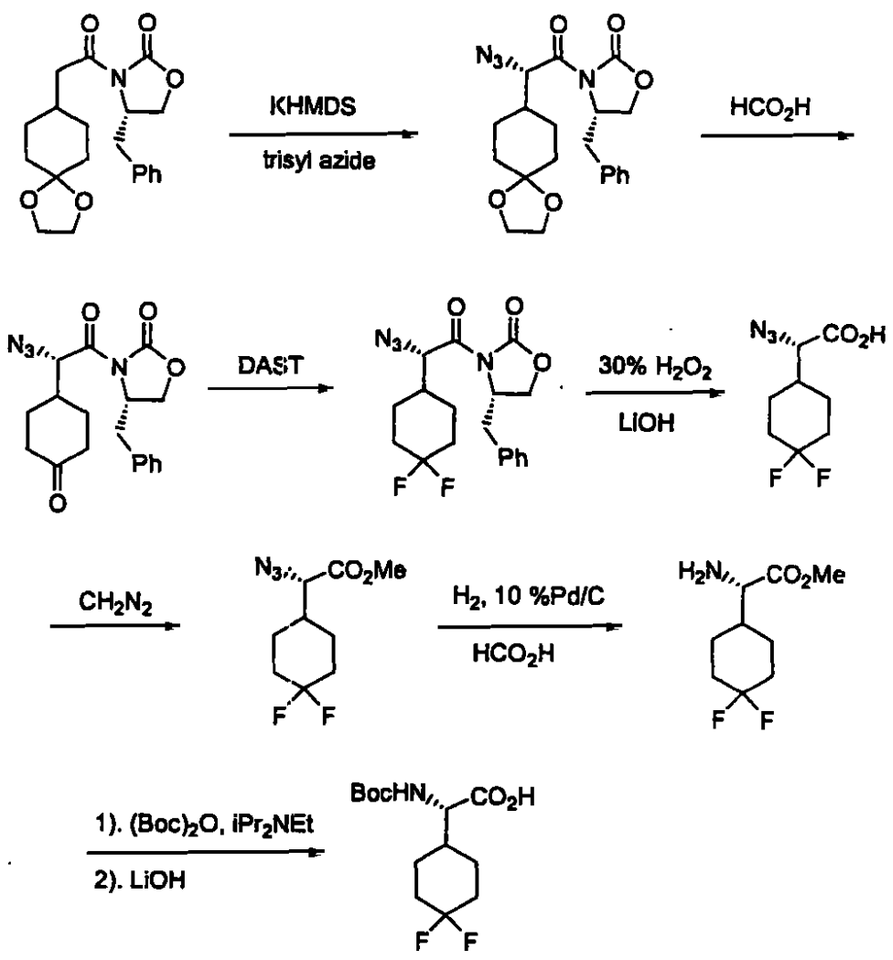


SCHEME 16

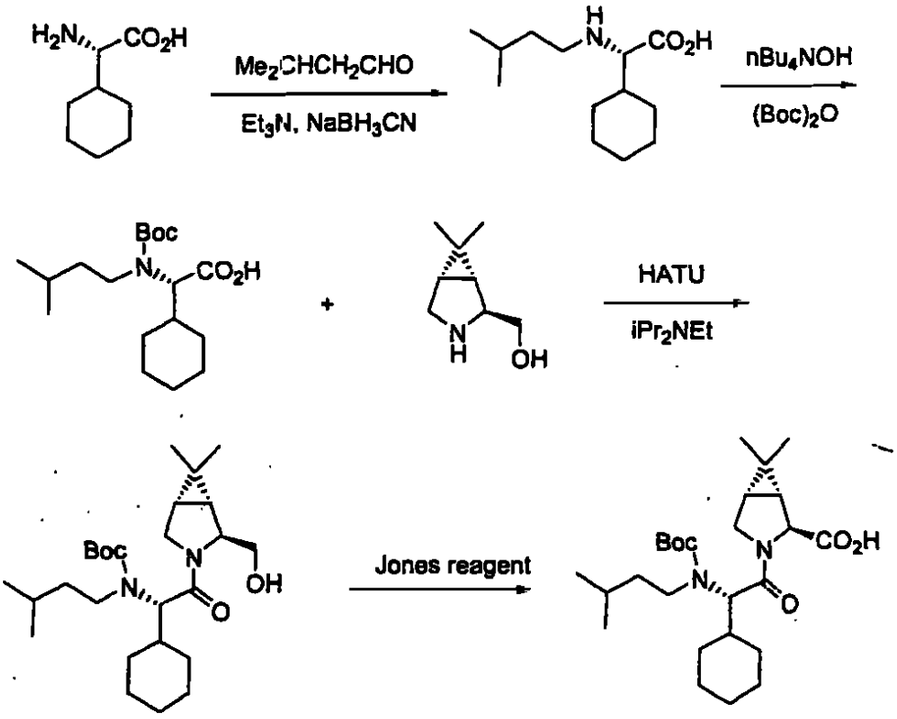


SCHEME 17

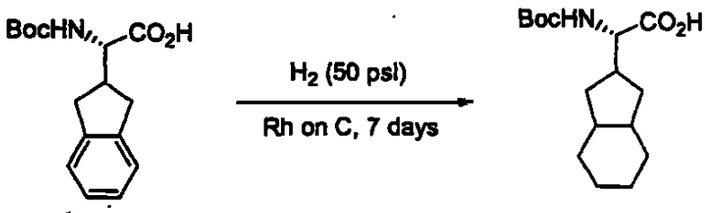



KHMDS
trisyl azide
HCO2H
DAST
30% H2O2
LIOH
CH2N2
H2, 10 %Pd/C
HCO2H
1). (Boc)2O, iPr2NEt
2). LiOH
Ph
F F

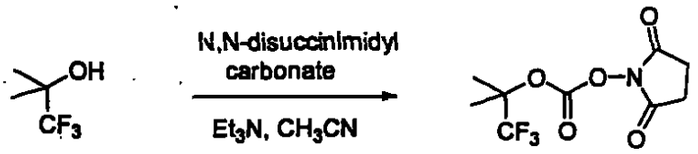
SCHEME 18



SCHEME 19



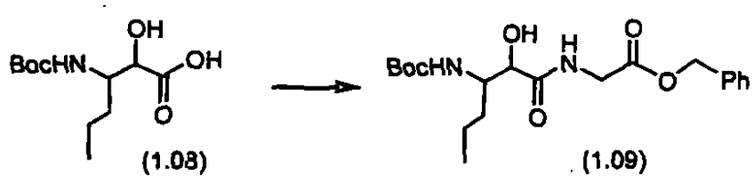
SCHEME 20



Preparation of Intermediates:

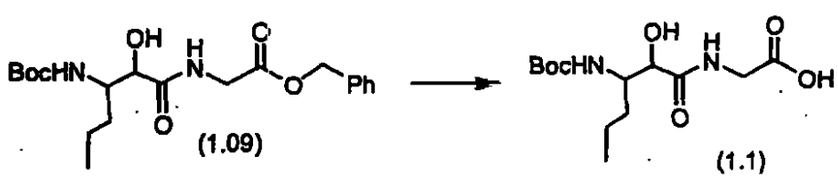
Preparative Example 1

Step A: Compound (1.1)



To a stirred solution of Compound (1.08)(3.00 g, 12.0 mmol (S. L. Harbeson *et al.* *J.Med.Chem.* 37 No.18 (1994) 2918-2929) in DMF (15 mL) and CH_2Cl_2 (15 mL) at -20°C was added HOOBt (1.97 g, 12.0 mmol), *N*-methyl morpholine (4.0 mL, 36.0 mmol) and EDCI (2.79 g, 14.5 mmol) and stirred for 10 minutes, followed by addition of HCl·H_2N-Gly-OBn (2.56 g, 13.0 mmol). The resulting solution was stirred at -20°C for 2 hrs, kept refrigerated overnight and then concentrated to dryness, followed by dilution with EtOAc (150 mL). The EtOAc solution was then washed twice with saturated $NaHCO_3$, H_2O, 5% H_3PO_4, brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the Compound (1.09) (4.5 g, 94%). LRMS *m/z* MH^+= 395.1.

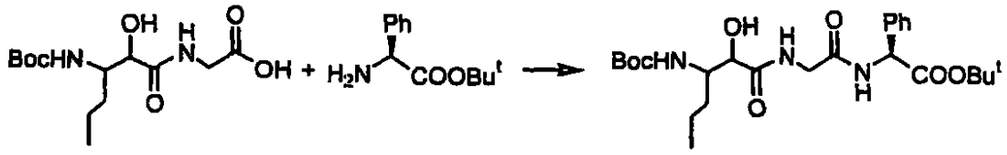
Step B: Compound (1.1)



A solution of Compound (1.09) (7.00 g, 17.8 mmol) in absolute ethanol (300 mL) was stirred at room temperature under a hydrogen atmosphere in the presence of Pd-C (300 mg, 10%). The reaction progress was monitored by tlc. After 2 h, the mixture was filtered through a celite pad and the resulting solution was concentrated in vacuo to give Compound (1.1) (5.40 g, quantitative). LRMS *m/z* MH^+= 305.1.

Preparative Example 2

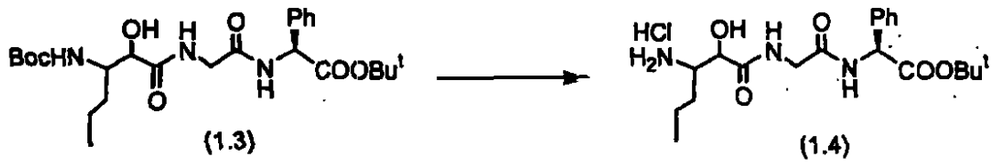
Step A Compound (1.3)



(1.1) (1.2) (1.3)

A mixture of Compound (1.1) from Preparative Example 1, Step B above (1 eq.), Compound (1.2) (from Novabiochem, Catalog No. 04-12-5147) (1.03 eq.), HOOBt (1.03 eq.), N-methylmorpholine (2.2 eq.), and dimethylformamide (70 mL/g) was stirred at -20°C. EDCI (1.04 eq.) was added and the reaction stirred for 48 hr. The reaction mixture was poured into 5% aqueous KH_2PO_4 and extracted with ethyl acetate (2 x). The combined organics were washed with cold 5% aqueous K_2CO_3, then 5% aqueous KH_2PO_4, then brine, and the organic layer was dried over anhydrous $MgSO_4$. The mixture was filtered, then evaporated and the filtrate dried under vacuum, the residue was triturated with Et_2O-hexane, and filtered to leave the title compound (1.3)(86% yield), $C_{25}H_{39}N_3O_7$ (493.60), mass spec. (FAB) M+1 = 494.3.

Step B Compound (1.4)



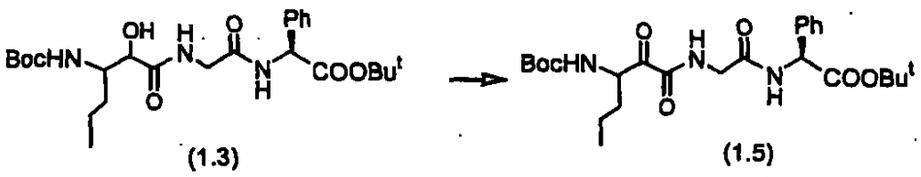
(1.3) (1.4)

Compound (1.3) from Preparative Example 2, Step A (3.0 g) was treated with 4 N HCl/dioxane (36 mL) and stirred at room temperature for 7 min. The mixture was poured into 1.5 L cold (5°C) hexane and stirred, then allowed to set cold for 0.5 hr. The mixture was suction-filtered in a dry atmosphere, and the collected solid was further dried to afford the title compound (1.4) (2.3 g, 88%

yield), $C_{20}H_{31}N_3O_5 \cdot HCl$, H^1 NMR (DMSO-d_6/NaOD) δ 7.38 (m, 5H), 5.25 (m, 1H), 4.3-4.1 (m, 1H), 3.8 (m, 2H), 3.4-3.3 (m, obscured by D_2O), 1.7-1.1 (m, 4H), 1.35 (s, 9H), 0.83 (m, 3H).

Preparative Example 3

Compound (1.5)

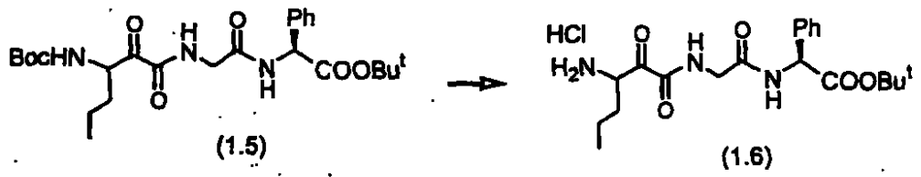


(1.3) (1.5)

Compound (1.3) from Preparative Example 2, Step A, was treated in essentially the same manner as in Preparative Example 7, Step A below to afford Compound (1.5).

Preparative Example 4

Compound (1.6)

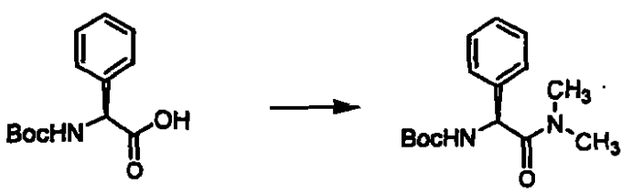


(1.5) (1.6)

Compound (1.5) from Preparative Example 3, was treated in essentially the same manner as in Preparative Example 2, Step B, to afford Compound (1.6).

Preparative Example 5

Step A Compound (2.09)



(2.08) (2.09)

To a solution of dimethylamine hydrochloride (1.61 g, 19.7 mmol), *N*-Boc-phenylglycine, Compound (2.08)(4.50 g, 17.9 mmol, Bachem Co. # A-2225), HOOBt (3.07 g, 18.8 mmol) and EDCI (4.12 g, 21.5 mmol) in anhydrous DMF (200 mL) and CH_2Cl_2 (150 mL) at -20°C was added NMM (5.90 mL, 53.7 mmol). After being stirred at this temperature for 30 min, the reaction mixture was kept in a freezer overnight (18 h). It was then allowed to warm to rt, and EtOAc (450 mL), brine (100 mL) and 5% H_3PO_4 (100 mL) were added. After the layers were separated, the organic layer was washed with 5% H_3PO_4 (100 mL), saturated aqueous sodium bicarbonate solution (2 X 150 mL), water (150 mL), and brine (150 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to afford Compound (2.09) (4.86 g) as a white solid, which was used without further purification.

Step B Compound (2.1)

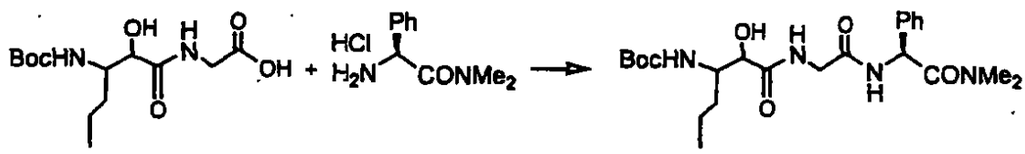


(2.09) (2.1)

Compound (2.09) from Preparative Example 5, Step A (4.70 g, crude) was dissolved in 4 N HCl (60 mL, 240 mmol) and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After 4 h, the solution was concentrated in vacuo to yield Compound (2.1) as a white solid which was used in the next reaction without further purification. LRMS *m/z* MH^+= 179.0.

Preparative Example 6

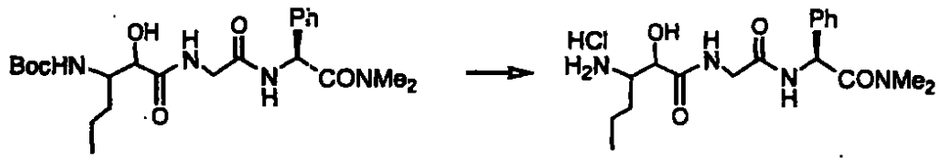
Step A Compound (2.2)



(1.1) (2.1) (2.2)

In essentially the same manner as Preparative Example 2, Step A. substituting phenylglycine N,N-dimethylamide hydrochloride in place of phenylglycine *t*-butyl ester hydrochloride, Compound (2.2) was prepared mass spec. (FAB) M+1 = 465.3.

Step B Compound (2.3)

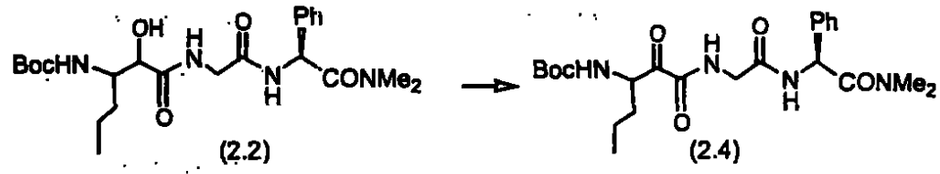


(2.2) (2.3)

Compound (2.2) from Step A (1.85 g) was reacted with 4 N HCl/dioxane (50 mL) at room temperature for 1 hr. The mixture was evaporated under vacuum in a 20°C water bath, triturated under isopropyl ether, filtered, and dried to afford Compound (2.3) (1.57 g, 98% yield), $C_{18}H_{28}N_4O_4 \cdot HCl$, mass spec. (FAB) M+1 = 365.3

Preparative Example 7

Step A Compound (2.4)

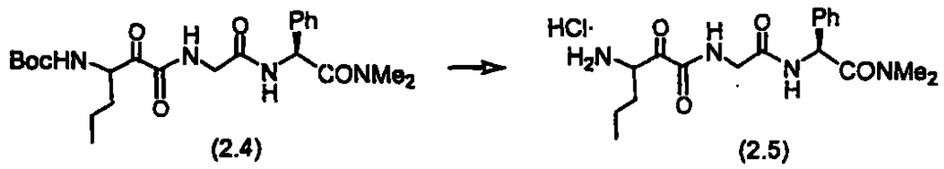


(2.2) (2.4)

A solution of Compound (2.2) from Preparative Example 5, Step A (2.0 g) in dichloromethane (60 mL) was treated with dimethylsulfoxide (3.0 mL) and 2,2-dichloroacetic acid (0.70 mL). The stirred mixture was cooled to 5°C and then added 1 M dicyclohexylcarbodiimide/ dichloromethane solution (8.5 mL). The cold

bath was removed and the mixture stirred for 22 hr. Then added 2-propanol (0.5 mL), and stirred for an additional 1 hr. The mixture was filtered then washed with ice-cold 0.1 N NaOH (50mL), then ice-cold 0.1 N HCl (50 mL), then 5% aqueous KH_2PO_4, then saturated brine. The organic solution was dried over anhydrous magnesium sulfate, then filtered. The filtrate was evaporated, and chromatographed on silica gel, eluting with ethyl acetate to afford Compound (2.3) (1.87 g, 94% yield), $C_{23}H_{34}N_4O_6$, mass spec. (FAB) M+1 = 463.3.

Step B Compound (2.5)



(2.4) (2.5)

In essentially the same manner as Preparative Example 2, Step B, Compound (2.5) was prepared.

Preparative Example 8

Step A Compound (3.1)

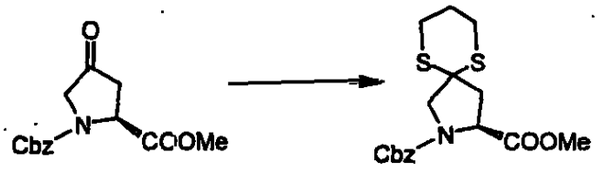


(3.01) (3.1)

In a flask were combined N-Cbz-hydroxyproline methyl ester (available from Bachem Biosciences, Incorporated, King of Prussia, Pennsylvania), compound (3.01) (3.0 g), toluene (30 mL), and ethyl acetate (30 mL). The mixture was stirred vigorously, and then a solution of NaBr/water (1.28 g /5 mL) was added. To this was added 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO, 17 mg, from Aldrich Chemicals, Milwaukee, Wisconsin). The stirred mixture was cooled to 5°C and then was added a prepared solution of oxidant [commercially available bleach, Clorox® (18 mL), $NaHCO_3$ (2.75 g) and water to make up 40

mL] dropwise over 0.5 hr. To this was added 2-propanol (0.2 mL). The organic layer was separated, and the aqueous layer extracted with ethyl acetate. The organic extracts were combined, washed with 2% sodium thiosulfate, then saturated brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated the filtrate under vacuum to leave a pale yellow gum suitable for subsequent reactions (2.9 g, 97% yield), $C_{14}H_{15}NO_5$ (277.28), mass spec. (FAB) M+1 = 278.1.

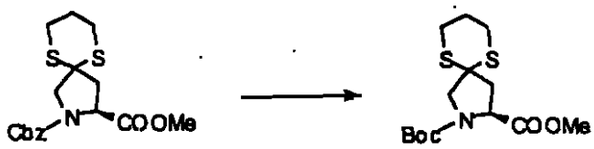
Step B Compound (3.2).



(3.1) (3.2)

Compound (3.1) from Step A above (7.8 g) was dissolved in dichloromethane (100 mL), and cooled to 15°C. To this mixture was first added 1,3-propanedithiol (3.1 mL), followed by freshly distilled boron trifluoride etherate (3.7 mL). The mixture was stirred at room temperature for 18 h. While stirring vigorously, a solution of K_2CO_3/water (2 g / 30 mL)was carefully added, followed by saturated $NaHCO_3$ (10 mL). The organic layer was separated from the aqueous layer (pH ~7.4), washed with water (10 mL), then brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum. The residue was chromatographed on silica gel, eluting with toluene, then a with a gradient of hexane-Et_2O (2:3 to 0:1) to afford a brown oil (7.0 g, 68% yield), $C_{17}H_{21}NO_4S_2$ (367.48), mass spec. (FAB) M+1 =368.1.

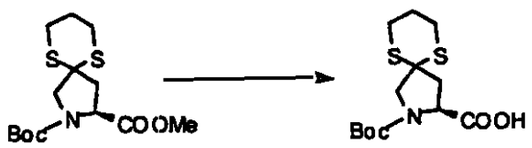
Step C Compound (3.3)



(3.2) (3.3)

A solution of compound (3.2) from Step B above (45 g) in acetonitrile (800 mL) at 20°C was treated with freshly distilled iodotrimethylsilane (53 mL) at once. The reaction was stirred for 30 min., then poured into a freshly prepared solution of di-t-butyldicarbonate (107 g), ethyl ether (150 mL), and diisopropylethylamine (66.5 mL). The mixture stirred for 30 min. more then was washed with hexane (2 x 500 mL). Ethyl acetate (1000 mL) was added to the lower acetonitrile layer, and then the layer was washed with 10% aqueous KH_2PO_4 (2 x 700 mL), and brine. The filtrate was evaporated under vacuum in a 25°C water bath, taken up in fresh ethyl acetate (1000 mL), and washed successively with 0.1 N HCl, 0.1 N NaOH, 10% aqueous KH_2PO_4, and brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum. The residue (66 g) was chromatographed on silica gel (2 kg), eluting with hexane (2 L), then Et_2O/hexane (55:45, 2 L), then Et_2O (2 L) to afford an orange gum which slowly crystallized on standing (28 g, 69% yield), $C_{14}H_{23}NO_4S_2$ (333.46), mass spec. (FAB) M+1 = 334.1.

Step D Compound (3.4)

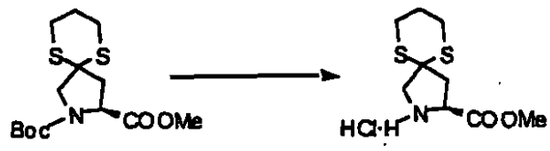


(3.3) (3.4)

A solution of compound (3.3) from Step C above (11 g) in dioxane (150 mL) at 20°C was treated with 1N aqueous LiOH (47 mL) and stirred for 30 h. The mixture was concentrated under vacuum in a 30°C water bath to half volume. The remainder was diluted with water (300 mL), extracted with Et_2O (2 x 200 mL).

The aqueous layer was acidified to pH ~4 with 12 N HCl (3-4 mL), extracted with ethyl acetate, and washed with brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum to leave Compound (3.4) (8.1 g, 78%), $C_{13}H_{21}NO_4S_2$ (319.44), mass spec. (FAB) M+1 = 320.1.

Step E Compound (3.5).

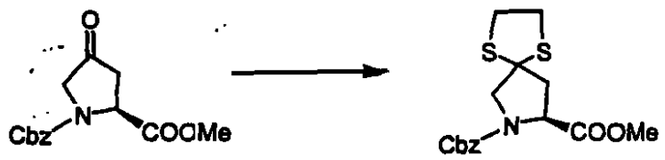


(3.3) (3.5)

To a solution of compound (3.3) from Step C above (1 g) in dioxane (5 mL), was added 4 N HCl-dioxane solution (50 mL). The mixture was stirred vigorously for 1 hr. The mixture was evaporated under vacuum in a 25°C water bath. The residue was triturated with Et_2O, and filtered to leave the title compound (0.76 g, 93% yield), $C_9H_{15}NO_2S_2 \cdot HCl$ (269.81), mass spec. (FAB) M+1 = 234.0.

Preparative Example 9

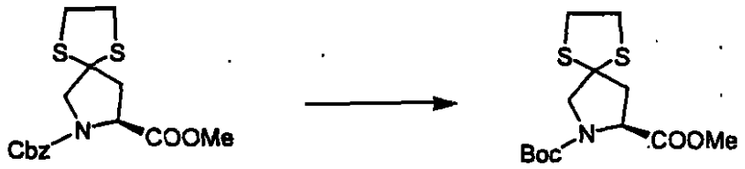
Step A Compound (3.6)



(3.1) (3.6)

Following essentially the same procedure of Preparative Example 8, Step B, substituting ethane dithiol for propane dithiol, compound (3.6) was obtained.

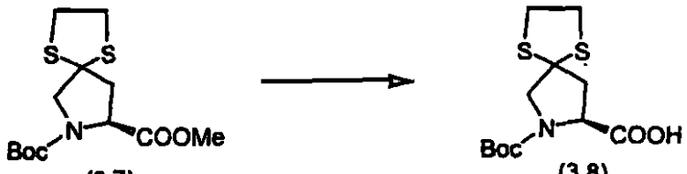
Step B Compound (3.7).



(3.6) (3.7)

Following essentially the same procedure of Preparative Example 8, Step C, substituting compound (3.6) for compound (3.2), the product compound (3.7) was obtained.

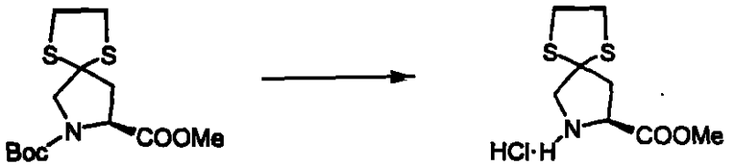
Step C Compound (3.8)



(3.7) (3.8)

Following essentially the same procedure of Preparative Example 8, Step D, substituting compound (3.7) for compound (3.3) the product compound (3.8) was obtained.

Step D Compound (3.9)

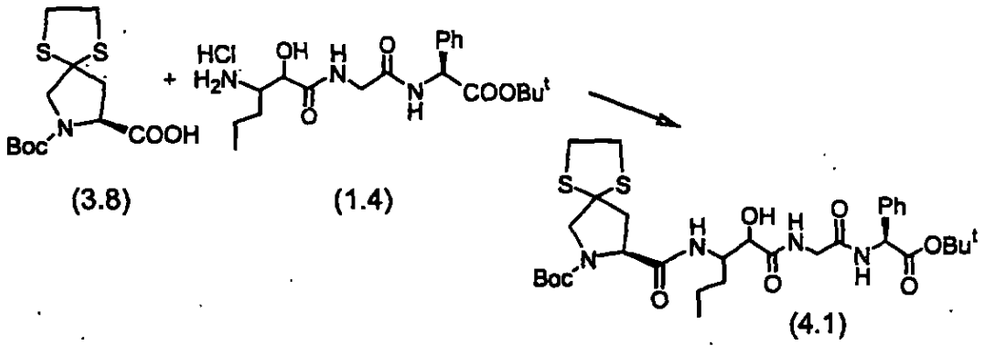


(3.7) (3.9)

Following essentially the same procedure of Preparative Example 8, Step E, substituting compound (3.7) for compound (3.3) the product compound (3.9) was obtained.

Preparative Example 10

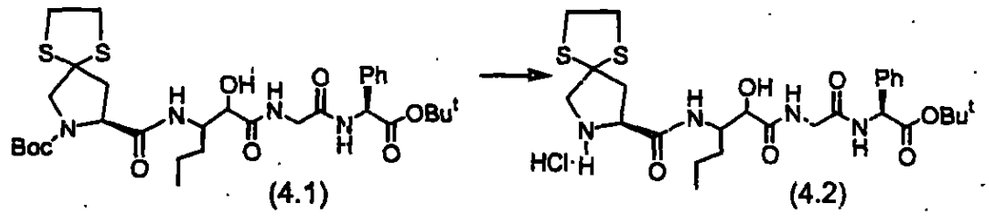
Step A Compound (4.1)



(3.8) (1.4) (4.1)

In essentially the same manner as Preparative Example 2, Step A, Compound (4.1) was prepared $C_{33}H_{48}N_4O_9S_2$ (708.89).

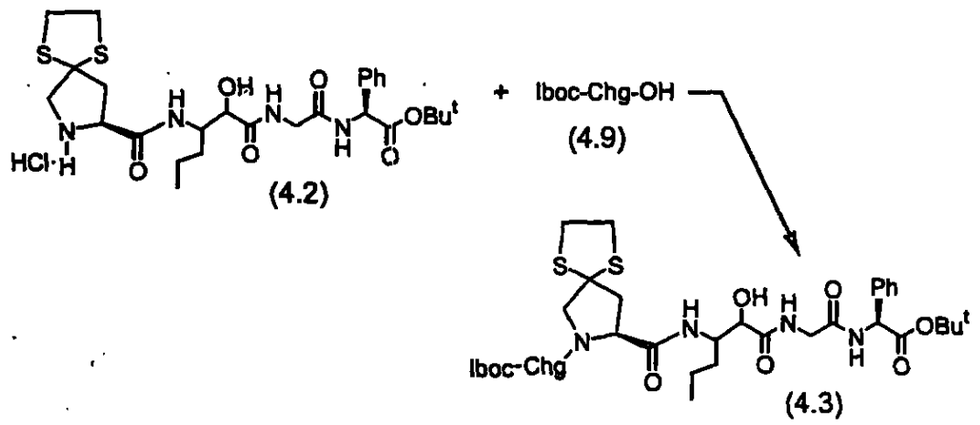
Step B Compound (4.2)



(4.1) (4.2)

In essentially the same manner as Preparative Example 2, Step B, Compound (4.2) was prepared mass spec. (FAB) M+1 = 609.3.

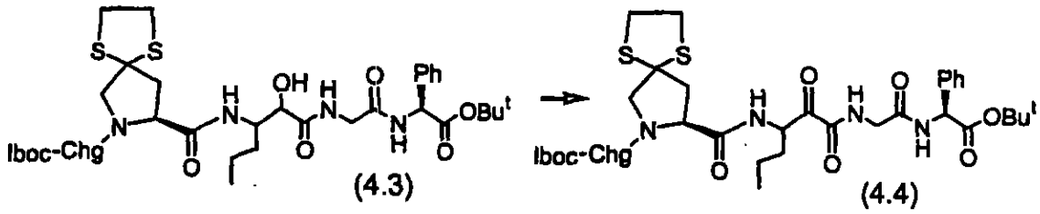
Step C Compound (4.3)



(4.2) (4.9) (4.3)

In essentially the same manner as Preparative Example 2, Step A, Compound (4.3) was prepared, $C_{41}H_{61}N_5O_{10}S_2$ (708.89), mass spec. (FAB) M+1 = 709.3.

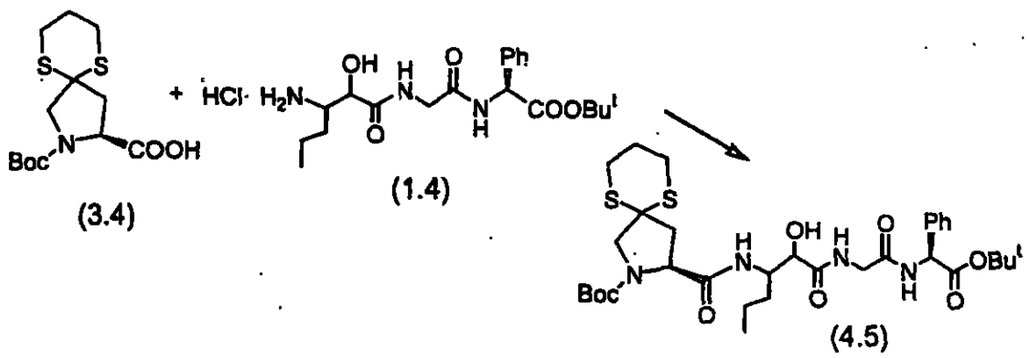
Step D Compound (4.4)



In essentially the same manner as Preparative Example 7, Step A, Compound (4.4) was prepared.

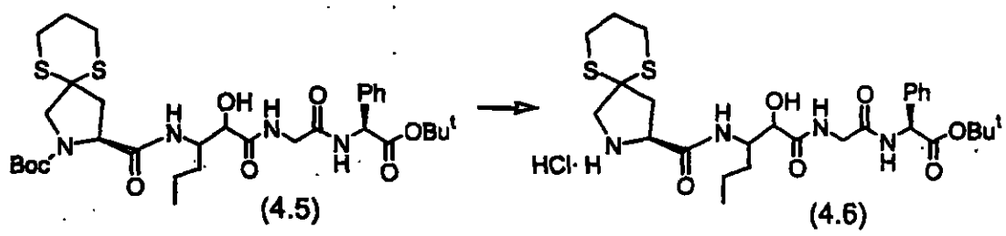
Preparative Example 11

Step A Compound (4.5)



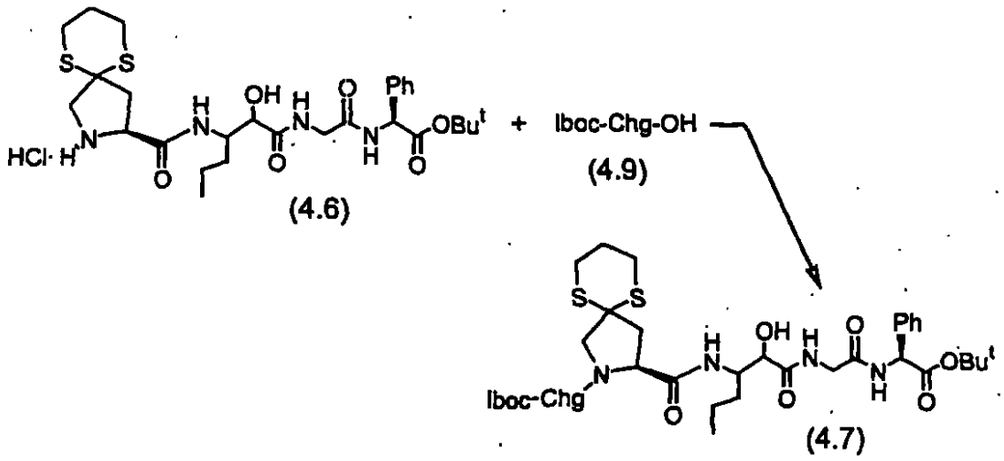
In essentially the same manner as Preparative Example 2, Step A, Compound (4.5) was prepared.

Step B. Compound (4.6)



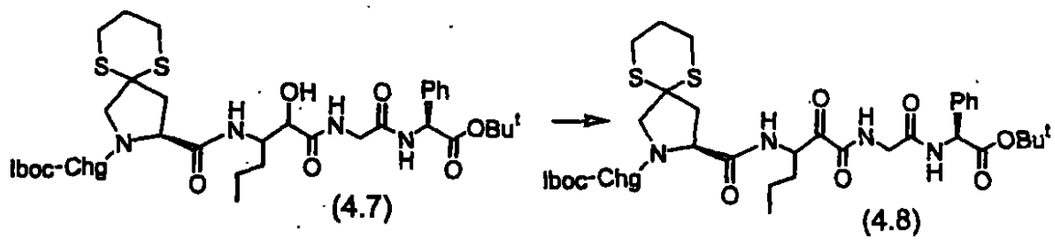
In essentially the same manner as Preparative Example 2, Step B, Compound (4.6) was prepared.

Step C. Compound (4.7)



Compound (4.9) from Preparative Example 12, was reacted with Compound (4.6) from Step B above, in essentially the same manner as Preparative Example 2, Step A, to afford Compound (4.7).

Step D. Compound (4.8)



In essentially the same manner as Preparative Example 7, Step A, Compound (4.8) was prepared.

Preparative Example 12

Compound (4.9)



(4.01) (4.02) (4.9)

A solution of L-cyclohexylglycine (4.02) (1.0 eq.), dimethylformamide (20 mL/g), and diisopropylethylamine (1.1 eq.) at 5°C is treated with isobutyl chloroformate (4.01) (1.1 eq.). The cold bath is removed and it is stirred for 6 hr. The reaction mixture is poured into 5% aqueous KH_2PO_4 and extracted with ethyl

acetate (2 x). The combined organics are washed with cold 5% aqueous K_2CO_3, then 5% aqueous KH_2PO_4, then brine, and the organics are dried over anhydrous $MgSO_4$. The mixture is filtered, the filtrate evaporated under vacuum, the residue chromatographed if necessary or else the residue triturated with Et_2O-hexane, and filtered to leave the title compound (4.9), $C_{13}H_{23}NO_4$ (257.33).

Preparative Example 13

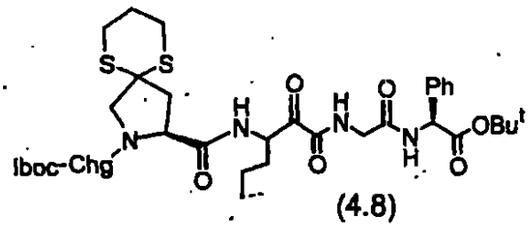
Compound (13.1)

i-BuOCOCl + H-Thr(Bzl)-OH ⟶ Iboc-Thr(Bzl)-OH

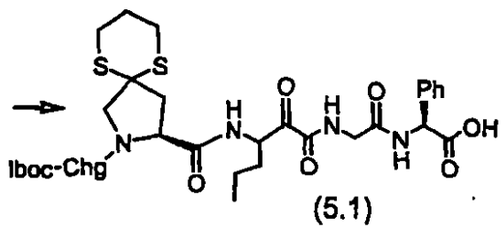
(4.01) (13.02) (13.1)

In essentially the same manner as Preparative Example 12, substituting L-O-benzylthreonine (13.02) (Wang *et al, J. Chem. Soc., Perkin Trans.* 1, (1997) No. 5, 621-624.) for L-cyclohexylglycine (4.02) Compound (13.1) is prepared $C_{16}H_{23}NO_5$ (309.36), mass spec. (FAB) M+1 = 310.2.

Preparative Example 14



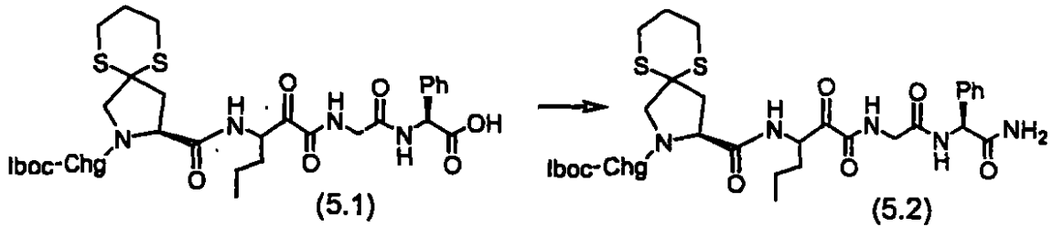
(4.8)



(5.1)

Compound (4.8) from Preparative Example 11, Step D (1.0 g) was reacted with a solution of anhydrous trifluoroacetic acid-dichloromethane (1:1, 50 mL) for 2 hr. The solution was diluted with xylene (100 mL) and evaporated under vacuum. The residue was triturated with Et_2O, and filtered to leave the title compound (5.1) (0.9 g), $C_{37}H_{53}N_5O_9S_2$ (775.98), mass spec. (FAB) M+1 =776.5.

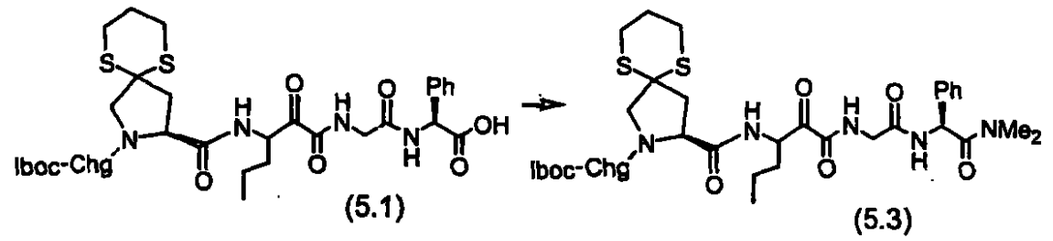
Step B Compound (5.2)



(5.1) (5.2)

In essentially the same manner as Preparative Example 2, Step A, Compound (5.1) was reacted with ammonia (0.5 M 1,4-dioxane solution), to obtain the title compound (5.2) $C_{37}H_{54}N_6O_8S_2$ (774.99), mass spec. (FAB) M+1 = 775.4.

Preparative Example 15

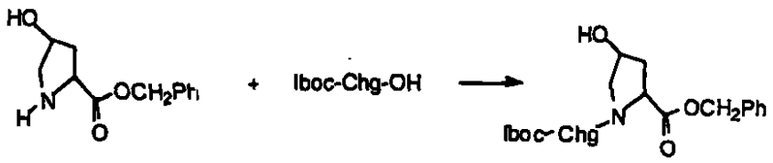


(5.1) (5.3)

A mixture of Compound (5.1) from Preparative Example 14, Step A (0.15 g), N,N-dimethylamine (0.12 mL of 2 M THF solution), dimethylformamide (10 mL), and PyBrOP coupling reagent (0.11 g) was cooled to 5°C, then diisopropylethylamine (DIEA or DIPEA, 0.12 mL) was added. The mixture was stirred cold for 1 min., then stirred at room temperature for 6 hr. The reaction mixture was poured into cold 5% aqueous H_3PO_4 (50 mL) and extracted with ethyl acetate (2 x). The combined organics were washed with cold 5% aqueous K_2CO_3, then 5% aqueous KH_2PO_4, then brine. The organic solution was dried over anhydrous $MgSO_4$, filtered, and evaporated under vacuum. The residue was chromatographed on silica gel, eluting with MeOH-CH_2Cl_2 to afford the title compound (5.3), $C_{39}H_{58}N_6O_8S_2$ (803.05), mass spec. (FAB) M+1 =803.5.

Preparative Example 16

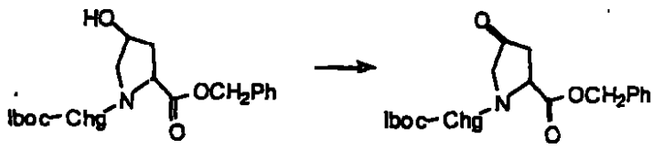
Step A Compound (6.2)



(6.1) 4.9) (6.2)

In essentially the same manner as Preparative Example 2, Step A, Compound (6.1) hydroxyproline benzyl ester hydrochloride was reacted with Compound (4.9) from Preparative Example 12, to obtain the title compound (6.2), $C_{25}H_{36}N_2O_6$ (460.56), mass spec. (FAB) M+1 = 461.2.

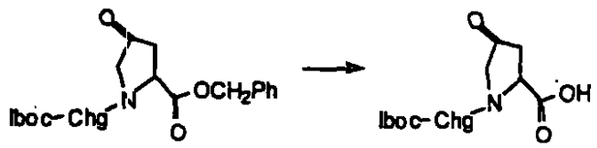
Step B Compound (6.3)



(6.2) (6.3)

In essentially the same manner as Preparative Example 8, Compound (6.3) was prepared, $C_{25}H_{34}N_2O_6$ (458.55), mass spec. (FAB) M+1 = 459.2.

Step C Compound (6.4)

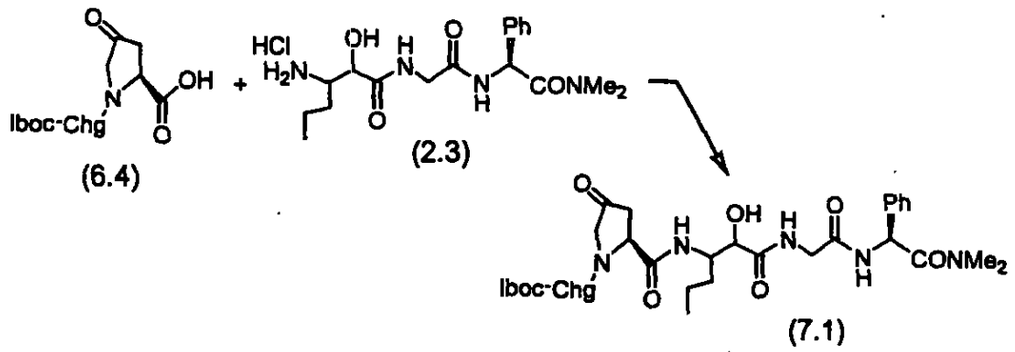


(6.3) (6.4)

A mixture of Compound (6.3) from Step B (1 g), 10% Pd/C (0.05 g), and EtOH (100 mL) was stirred under 1 atm. H_2 for 6 hr. The mixture was filtered, and evaporated to dryness under vacuum to leave the title compound (6.4) (0.77 g), $C_{18}H_{28}N_2O_6$ (368.42) mass spec. (FAB) M+1 = 369.2.

Preparative Example 17

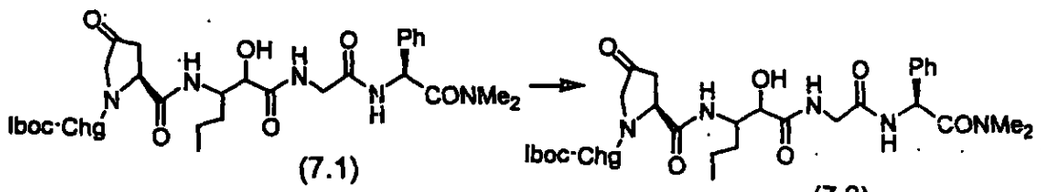
Step A Compound (7.1)



(6.4) (2.3) (7.1)

Compound (6.4) from Preparative Example 16, Step C, was reacted with Compound (2.3) from Preparative Example 6, Step B, in essentially the same manner as Preparative Example 2, Step A, to afford Compound (7.1), $C_{36}H_{54}N_6O_9$ (714.85), mass spec. (FAB) M+1 = 715.9.

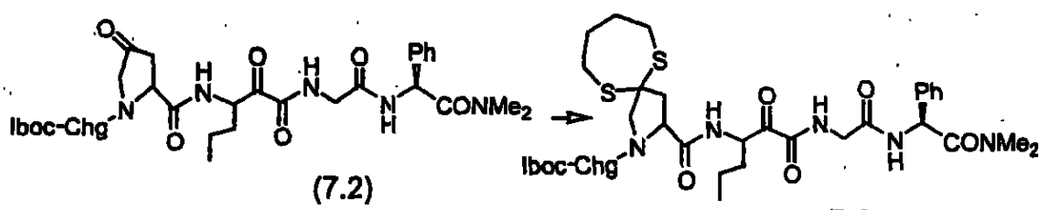
Step B Compound (7.2)



(7.1) (7.2)

Compound (7.1) was reacted in essentially the same manner as Preparative Example 7, Step A, to afford Compound (7.2), $C_{36}H_{52}N_6O_9$ (712.83), mass spec. (FAB) M+1 = 713.5.

Step C Compound (7.3)



(7.2) (7.3)

Compound (7.2) from Step B above, was reacted in essentially the same manner as Preparative Example 8, Step B, with 1,4-butanedithiol, to obtain the title compound (7.3), $C_{40}H_{60}N_6O_8S_2$ (817.07), mass spec. (FAB) M+1 = 817.5.

Using the above-noted and herein-described procedures, the compounds in the attached **Tables 2 through 6** were prepared. As a general note to all the Tables (1 through 6) that are attached hereto as well as to the Examples and Schemes in this specification, any open-ended nitrogen atom with unfulfilled valence in the chemical structures in the Examples and Tables refers to NH, or in the case of a terminal nitrogen, $-NH_2$. Similarly, any open-ended oxygen atom with unfulfilled valence in the chemical structures in the Examples and Tables refers to -OH and any open-ended carbon atom with unfilled valence is appropriately filled with -H.

Solid Phase Synthesis:

General procedure for solid-phase coupling reactions.

The synthesis was done in a reaction vessel which was constructed from a polypropylene syringe cartridge fitted with a polypropylene frit at the bottom. The Fmoc-protected amino acids were coupled under standard solid-phase techniques. Each reaction vessel was loaded with 100 mg of the starting Fmoc-Sieber resin (approximately 0.03 mmol). The resin was washed with 2 mL portions of DMF (2 times). The Fmoc protecting group was removed by treatment with 2 mL of a 20 % v/v solution of piperidine in DMF for 20 min. The resin was washed with 2 mL portions of DMF (4 times). The coupling was done in DMF (2 mL), using 0.1 mmol of Fmoc-amino acid, 0.1 mmol of HATU [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] and 0.2 mmol of DIPEA (N,N-diisopropylethylamine). After shaking for 2 h, the reaction vessel was drained and the resin was washed with 2 mL portions of DMF (4 times). The coupling cycle was repeated with the next Fmoc-amino acid or capping group.

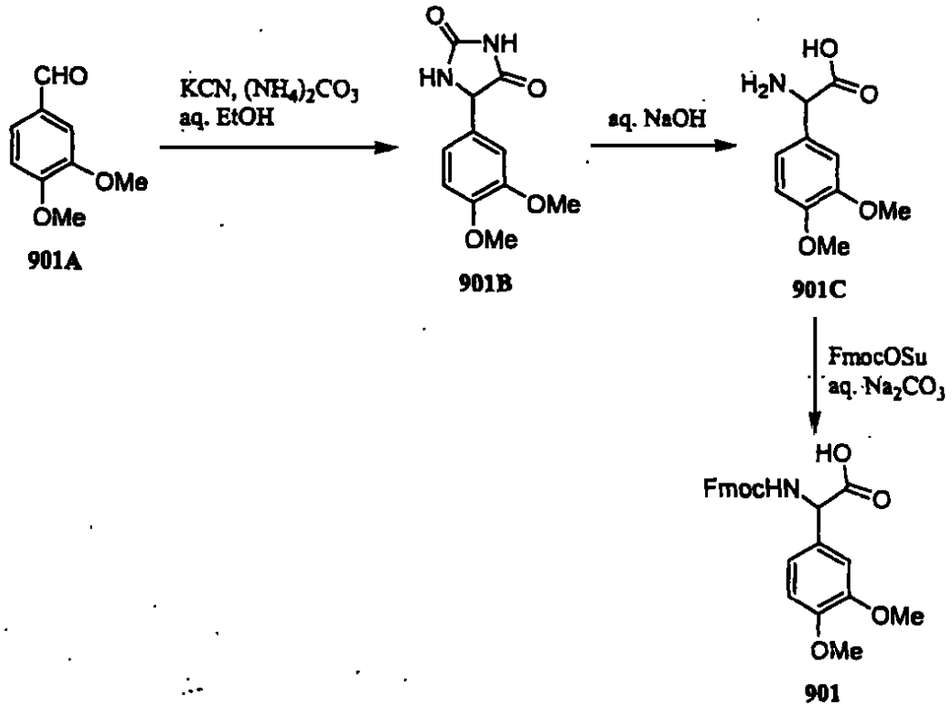
General procedure for solid-phase Dess-Martin oxidation.

The synthesis was conducted in a reaction vessel which was constructed from a polypropylene syringe cartridge fitted with a polypropylene frit at the bottom. Resin–bound hydroxy compound (approximately 0.03 mmol) was treated with a solution of 0.12 mmol of Dess-Martin periodinane and 0.12 mmol of t-BuOH

in 2 mL of DCM for 4 h. The resin was washed with 2 mL portions of a 20 % v/v solution of iPrOH in DCM, THF, a 50 % v/v solution of THF in water (4 times), THF (4 times) and DCM (4 times).

Preparative Example 18

Preparation of N-Fmoc-2',3'-dimethoxyphenylglycine Compound (901)

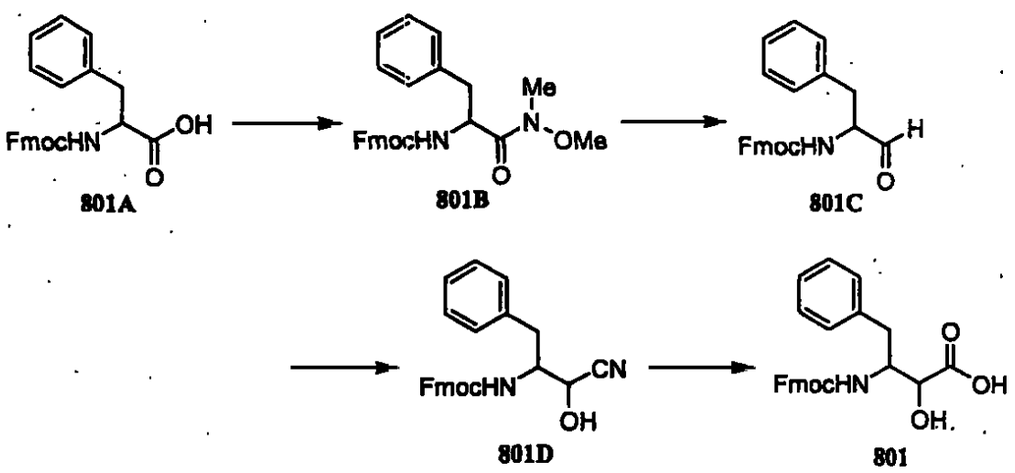


To a solution of potassium cyanide (1.465 g, 22.5 mmol) and ammonium carbonate (5.045 g, 52.5 mmol) in water (15 mL) was added a solution of 2,3-dimethoxybenzaldehye **901A** (2.5 g, 15 mmol) in ethanol (15 mL). The reaction mixture was heated at 40 °C for 24 h. The volume of the solution was reduced to 10 mL by evaporating under reduced pressure. Concentrated hydrochloric acid (15 mL) was added and compound **901B** was obtained as a white precipitate. Compound **901B** was isolated by filtration (2.2 g, 9.3 mmol). Compound **901B** was dissolved in 10 % w/w aqueous sodium hydroxide solution (15 mL) and the resulting solution was heated under reflux for 24 h. Concentrated hydrochloric acid was added and the pH was adjusted to neutral (pH 7). The resulting solution containing compound **901C** was evaporated under reduced pressure. The

residue was dissolved in 5 % w/w aqueous sodium bicarbonate solution (150 mL). The solution was cooled to 0 °C in an ice bath and 1,4-dioxane (30 mL) and a solution of 9-fluorenylmethyl succinimidyl carbonate (2.7 g, 8 mmol) in 1,4-dioxane (30 mL) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 24 h. 1,4-dioxane was evaporated under reduced pressure. The aqueous solution was washed with diethyl ether. Concentrated hydrochloric acid was added and the pH was adjusted to acidic (pH 1). Ethyl acetate was added the organic layer was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford the desired compound **901** as a white foamy solid (3.44 g, 7.9 mmol). MS (LCMS-Electrospray) 434.1 MH^+.

Preparative Example 19

Compound (801)



To a solution of N-Fmoc-phenylalanine **801A** (5 g, 12.9 mmol) in anhydrous DCM (22 mL) cooled to -30°C in a dry ice-acetone bath was added N-methylpyrrolidine (1.96 mL, 16.1 mmol) and methyl chloroformate (1.2 mL, 15.5 mmol) sequentially. The reaction mixture was stirred at -30°C for 1 h and a solution of N,O-dimethylhydroxylamine hydrochloride (1.51 g, 15.5 mol) and N-methylpyrrolidine (1.96 mL, 16.1 mmol) in anhydrous DCM (8 mL) was added.

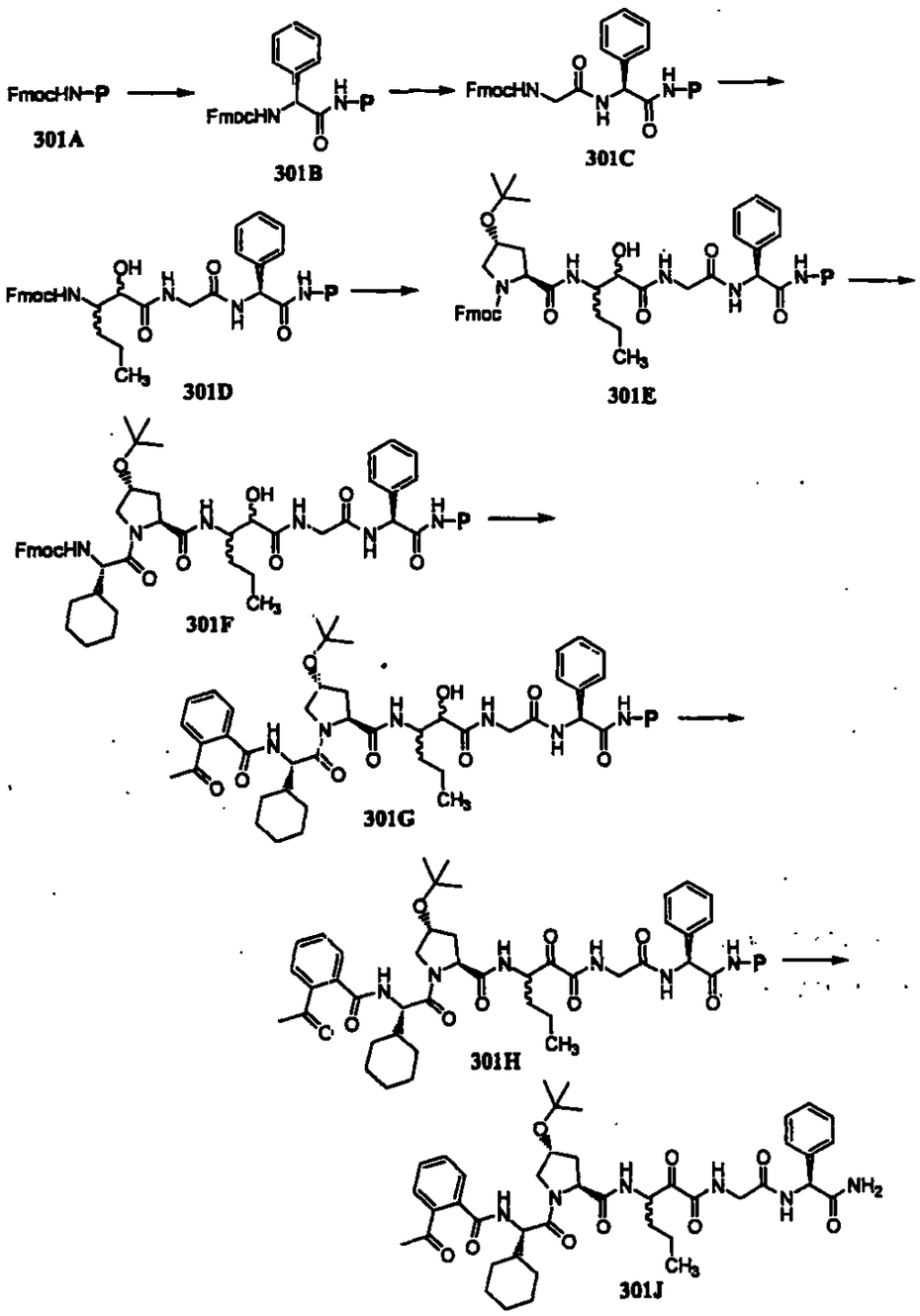
The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. Toluene was added and the organic layer was washed with dilute hydrochloric acid, aqueous sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afforded compound **801B** (4 g, 9.29 mmol).

To a solution of Red-Al (6.28 mL, 21.4 mmol) in anhydrous toluene (8 mL) cooled to -20°C in a dry ice-acetone bath was added a solution of compound **801B** (4 g, 9.29 mmol) in anhydrous toluene (12 mL). The reaction mixture was stirred at –20 °C for 1.5 h. The organic layer was washed with dilute hydrochloric acid, aqueous sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product **801C** was used in the next reaction without further purification.

To a solution of compound **801C** (approx. 9.29 mmol) in hexane (15 mL) was added a solution of potassium cyanide (24 mg, 0.37 mmol) and tetrabutylammonium iodide (34 mg, 0.092 mmol) in water (4 mL) and acetone cyanohydrin (1.27 mL, 13.9 mmol) sequentially. The reaction mixture was stirred at room temperature for 24 h. Ethyl acetate was added and the organic layer was washed with water and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford compound **801D** (2.4 g, 6.03 mmol).

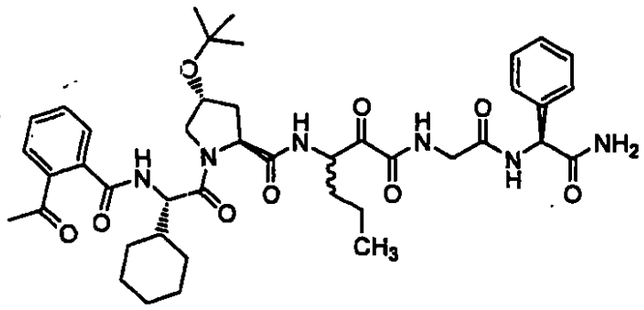
To a solution of compound **801D** (2.4 g, 6.03 mmol) in 1,4-dioxane (11 mL) was added concentrated hydrochloric acid (11 mL). The reaction mixture was heated at 80 °C for 3 h. Ethyl acetate (25 mL) and water (25 mL) was added. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afford the desired compound **801** as a white foamy solid (2 g, 4.8 mmol). MS (LCMS-Electrospray) 418.1 MH^+.

Scheme 8


FmocHN–P
301A
FmocHN
301B
FmocHN
301C
FmocHN
301D
Fmoc
301E
FmocHN
301F
301G
301H
NH2
301J

Example (301J):

Scheme 8 Compound (301J)

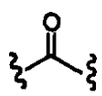


(301J)

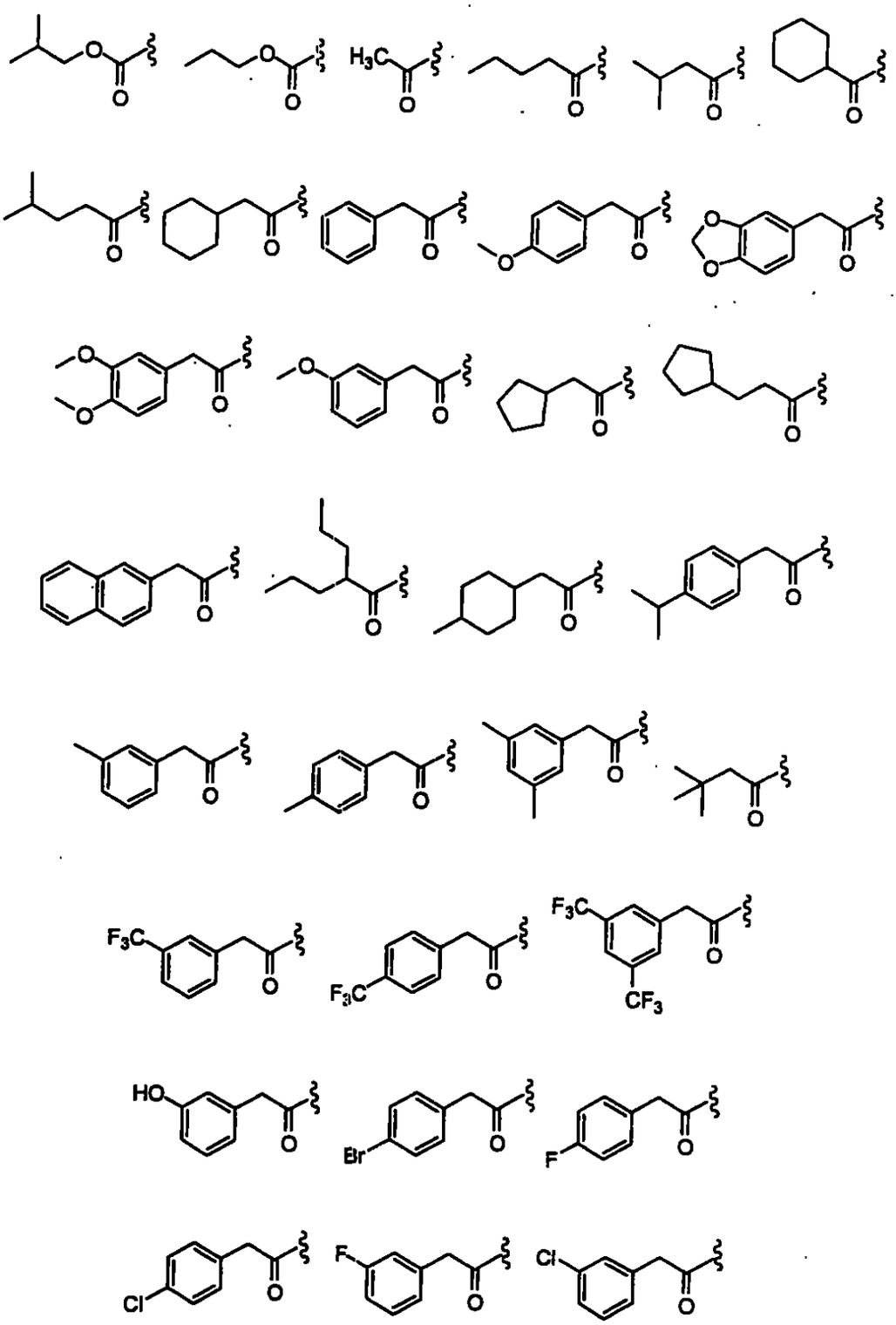
Resin-bound compound **301B**, **301C**, **301D**, **301E**, **301F** and **301G** were prepared according to the general procedure for solid-phase coupling reactions started with 100 mg of Fmoc-Sieber resin (0.03 mmol). Resin-bound compound **301G** was oxidized to resin-bound compound **301H** according to the general procedure for solid-phase Dess-Martin oxidation. The resin-bound compound **301H** was treated with 4 mL of a 2 % v/v solution of TFA in DCM for 5 min. The filtrate was added to 1 mL of AcOH and the solution was concentrated by vacuum centrifugation to provide compound **301J** (0.0069 g, 29 % yield). MS (LCMS-Electrospray) 771.2 MH^+.

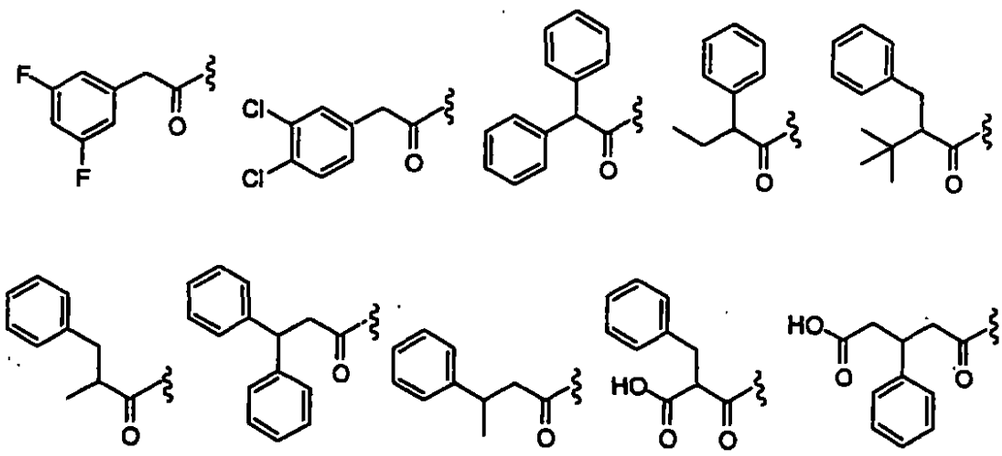
Using the solid phase synthesis techniques detailed above, and the following moieties for the various functionalities in the compound of Formula 1, the compounds in **Table 3** were prepared:

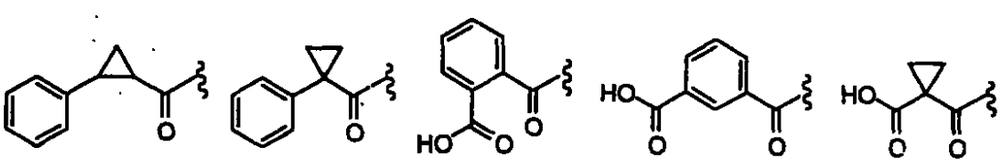
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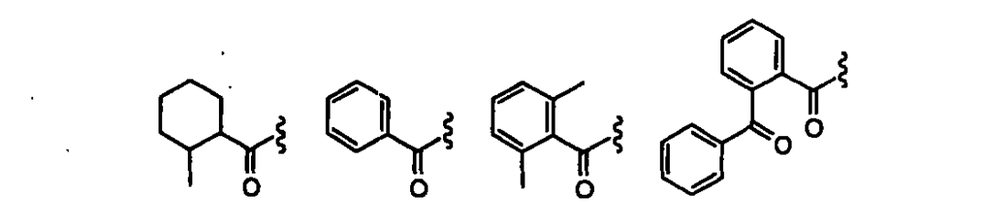


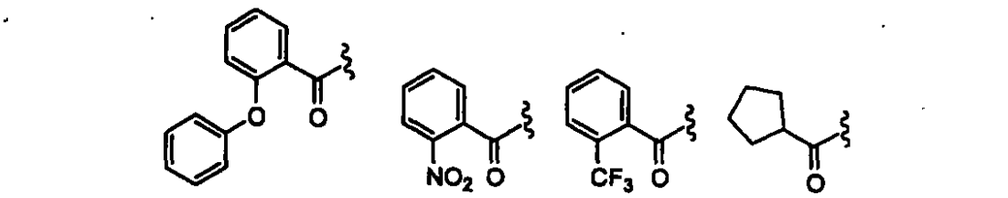
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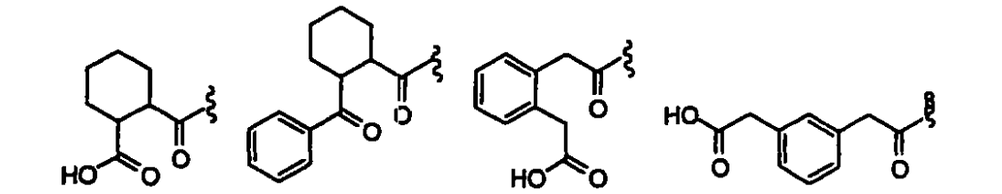


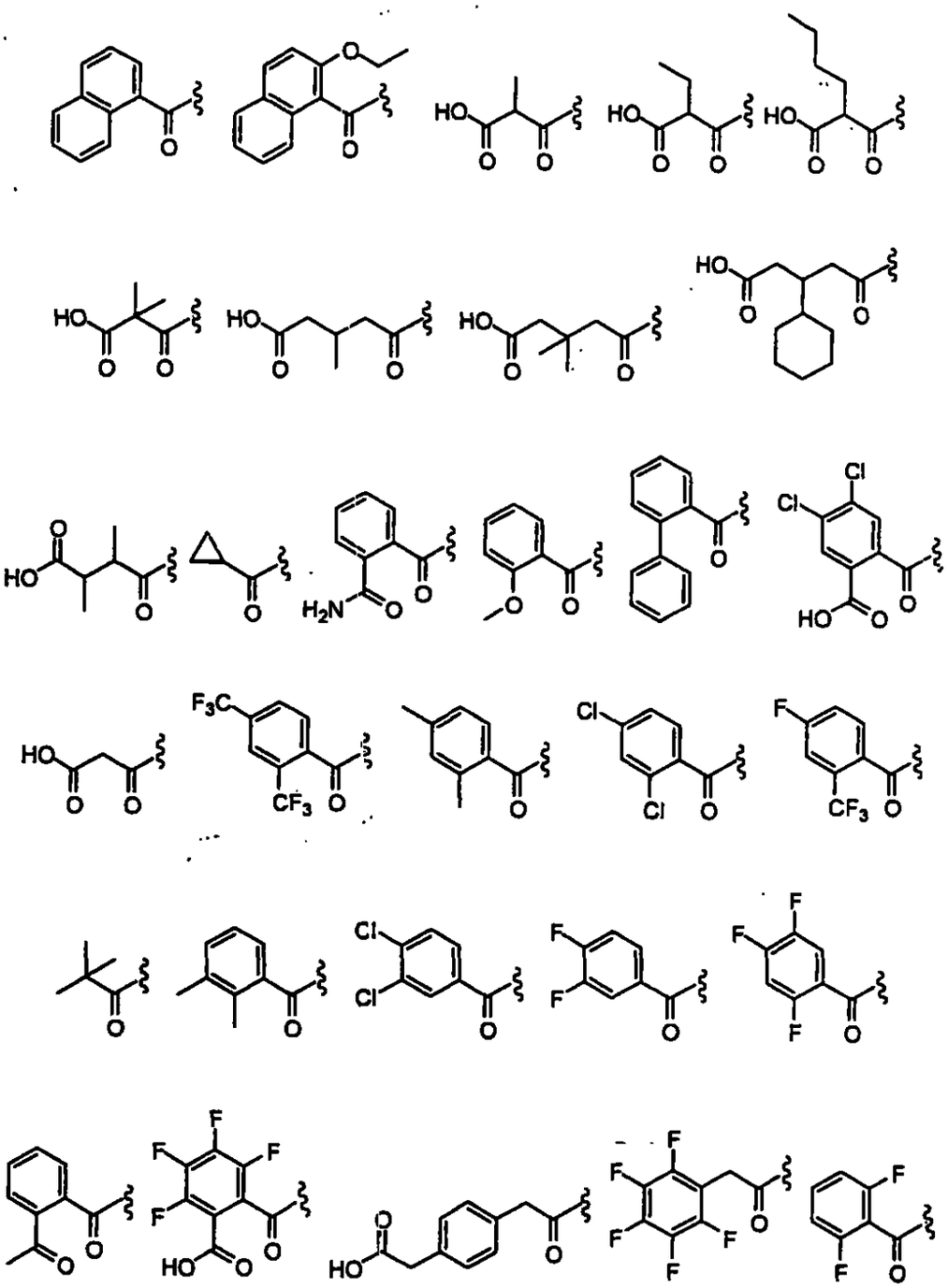


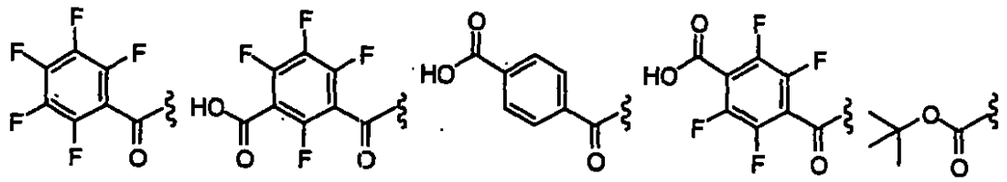


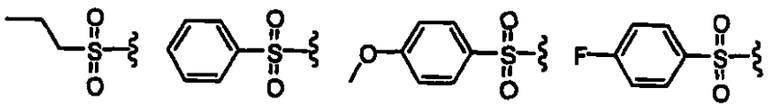












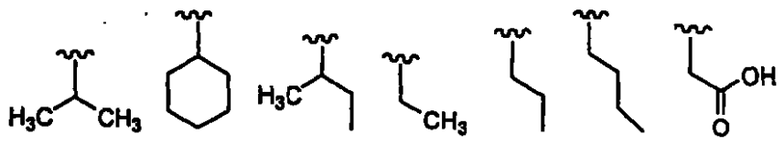
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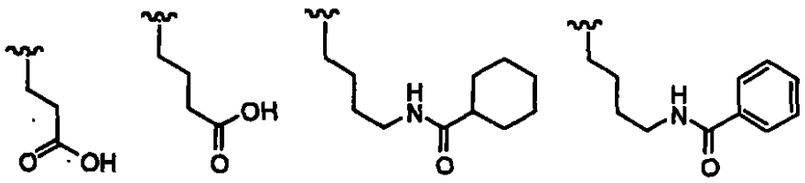


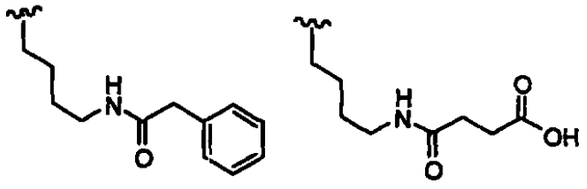
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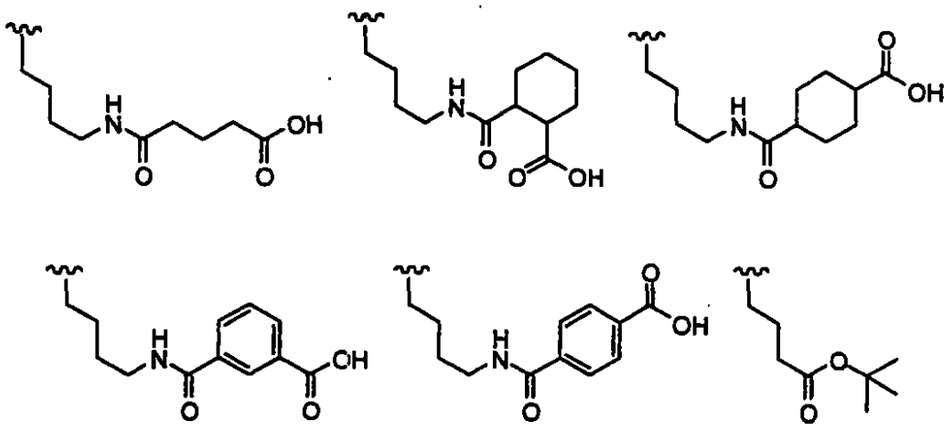


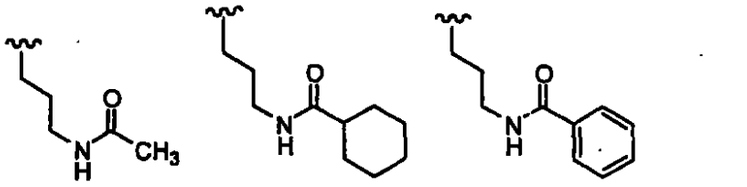
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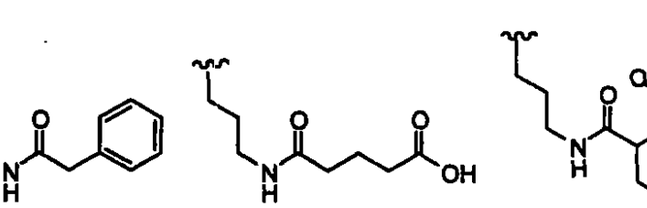


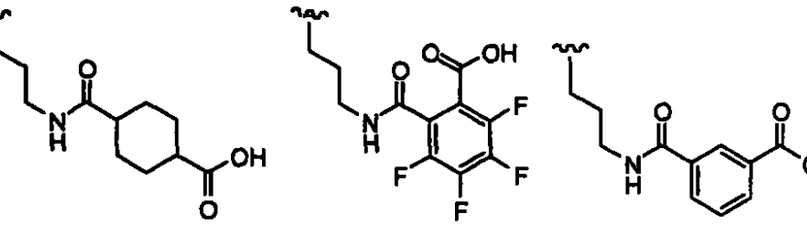


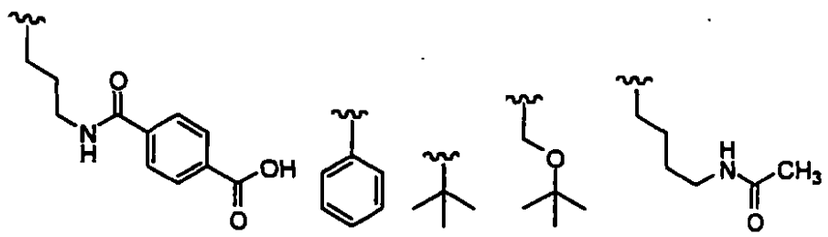




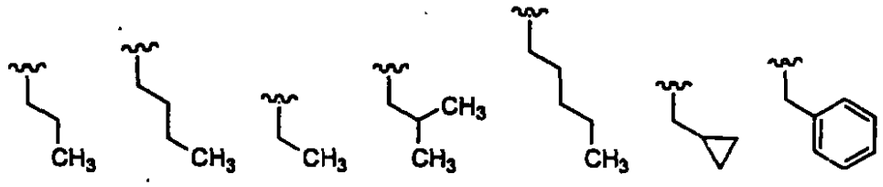




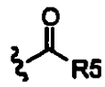




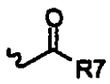
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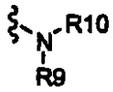
-R^1:



-R^5:



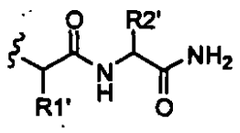
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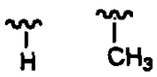
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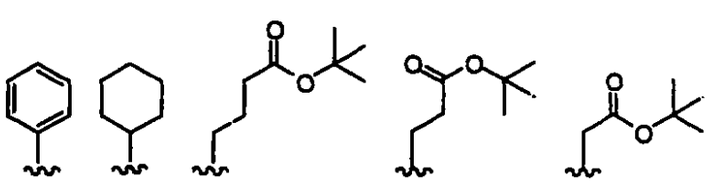
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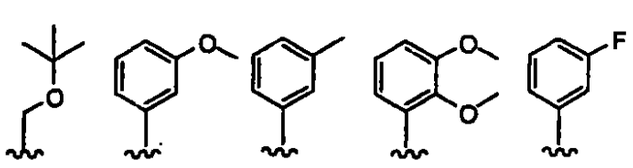


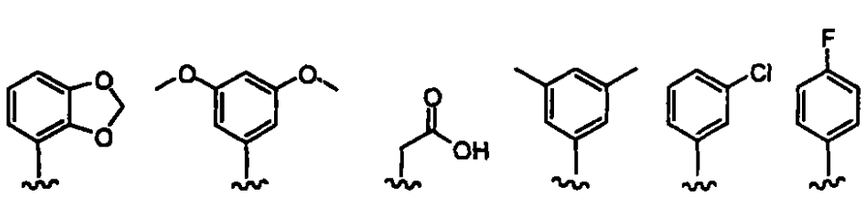
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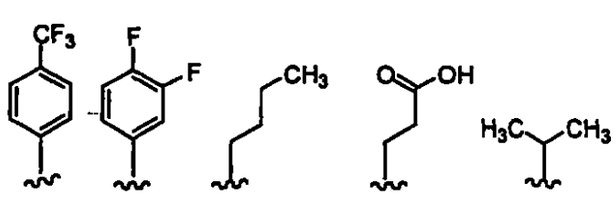


-$R^{2'}$:









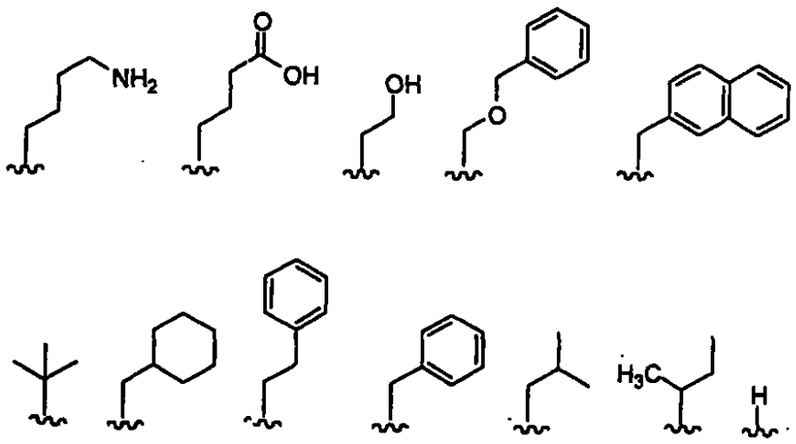
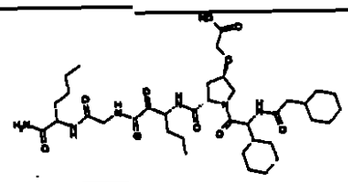
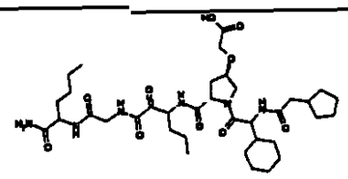
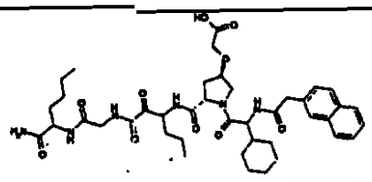
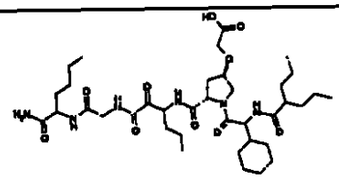
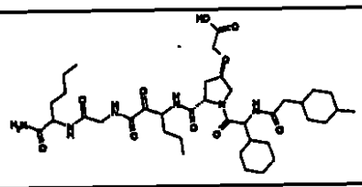
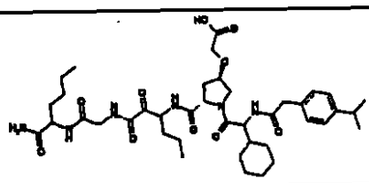
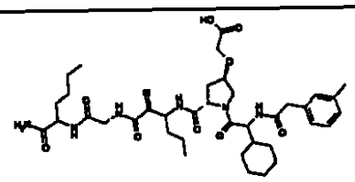
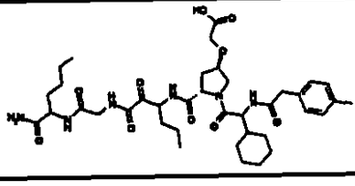
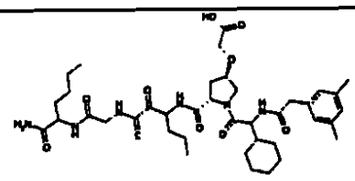
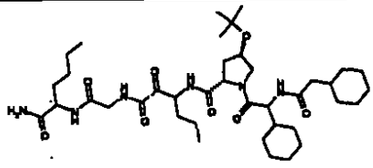
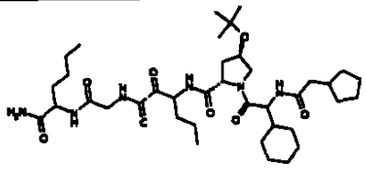
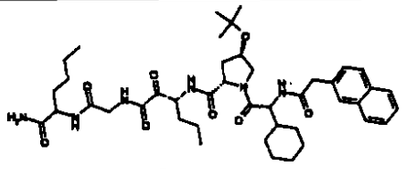
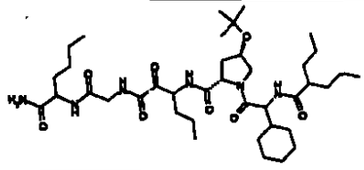
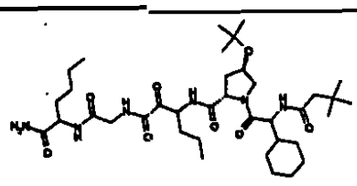
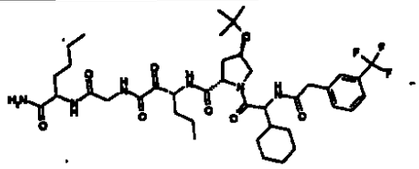
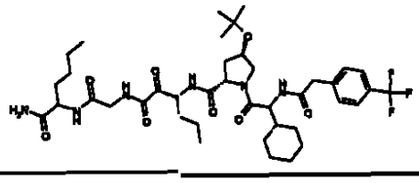
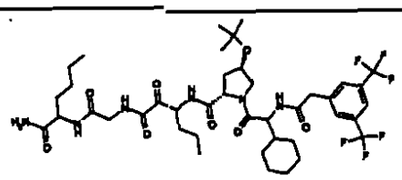
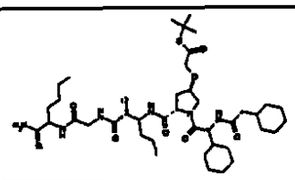
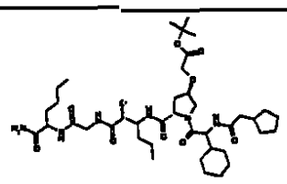
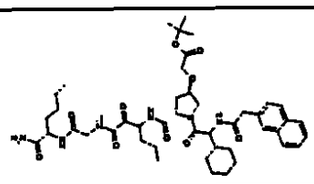
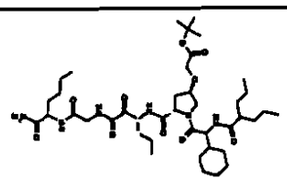
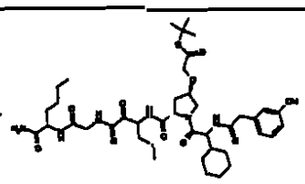
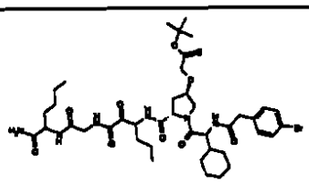
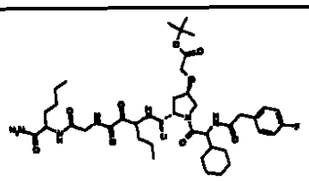
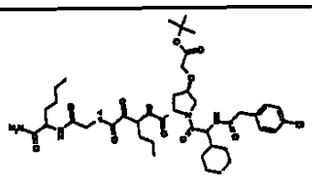
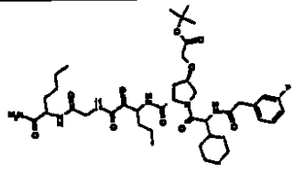
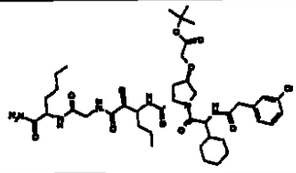
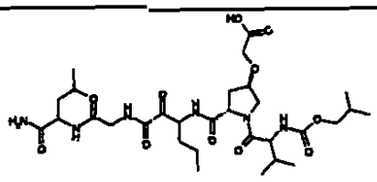
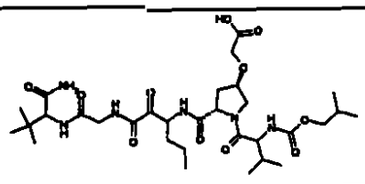
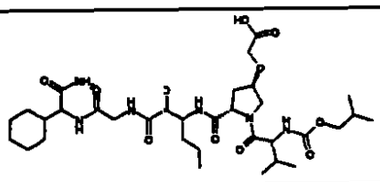
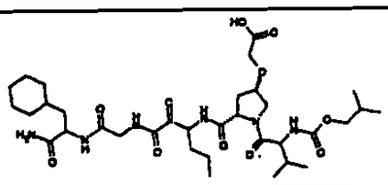
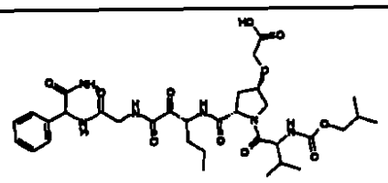


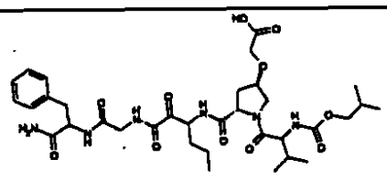
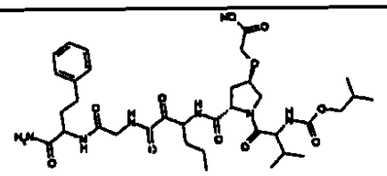
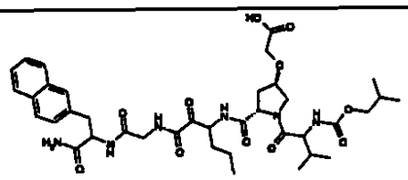
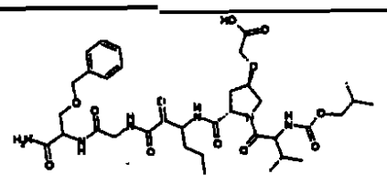
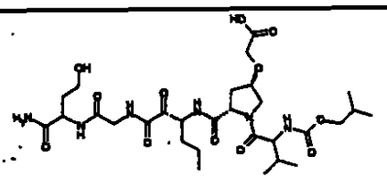
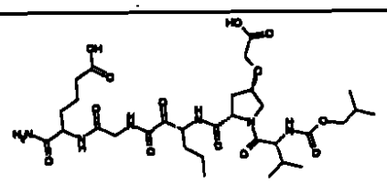
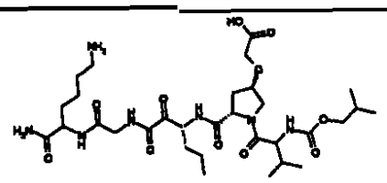
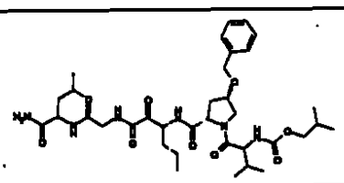
Table 3. Compounds prepared by Solid Phase Synthesis

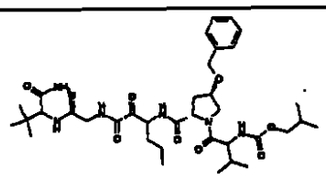
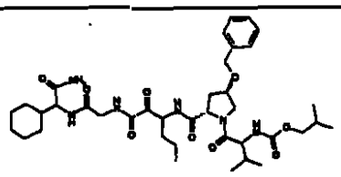
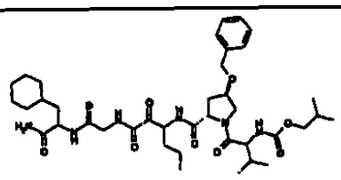
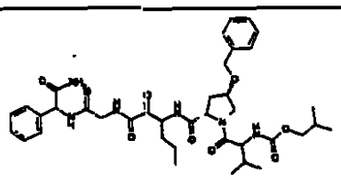
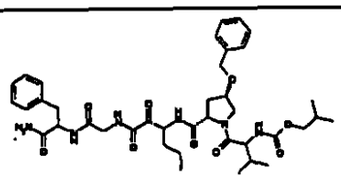
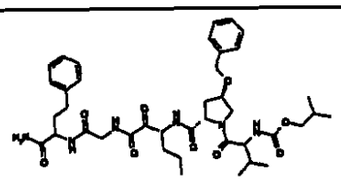
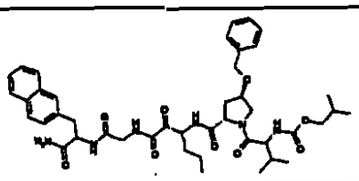
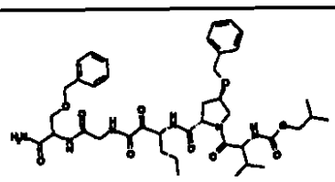
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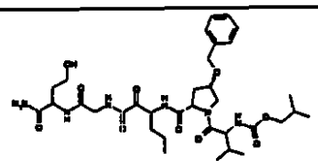
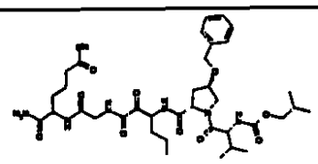
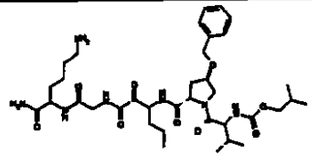
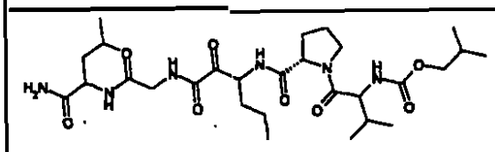
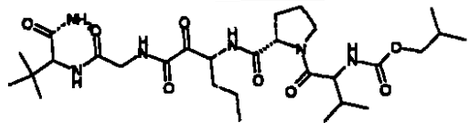
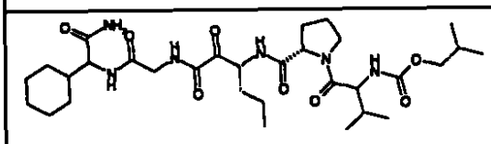
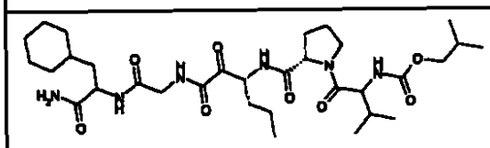
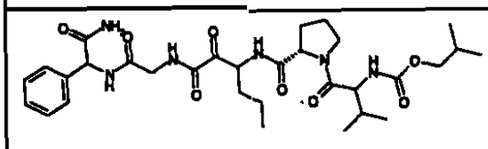
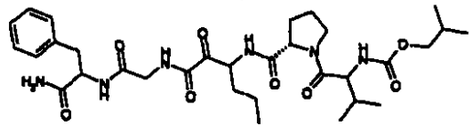
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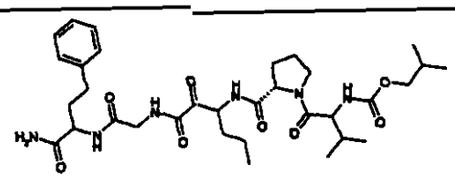
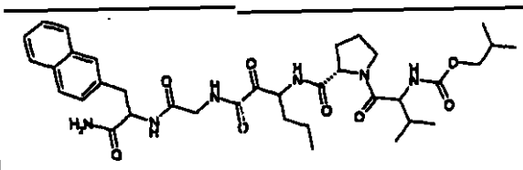
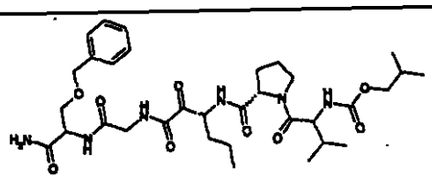
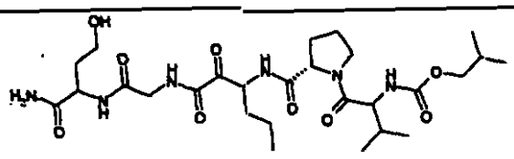
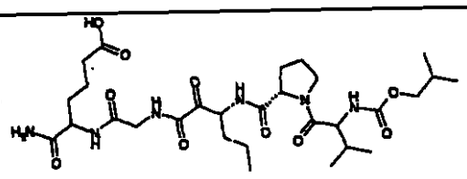
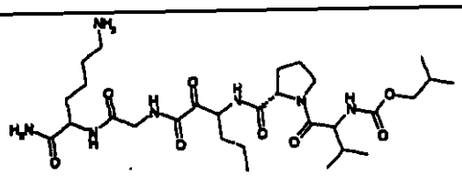
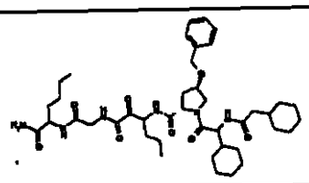
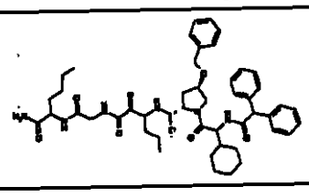
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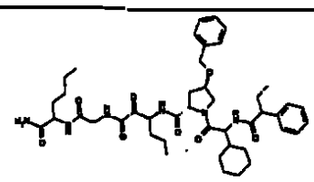
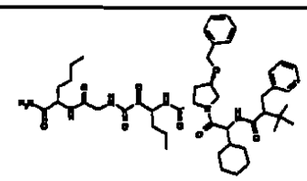
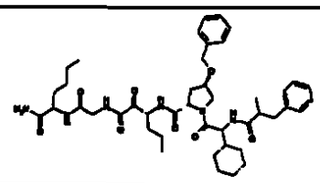
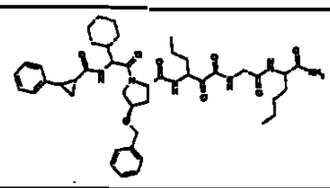
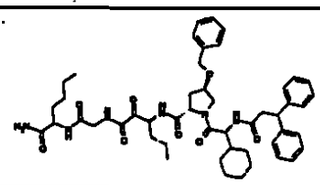
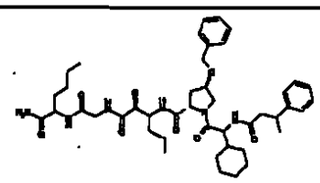
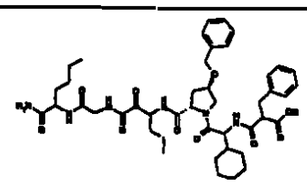
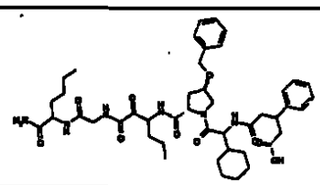
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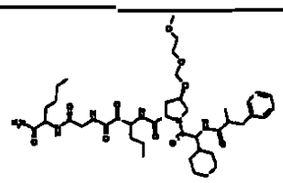
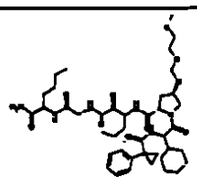
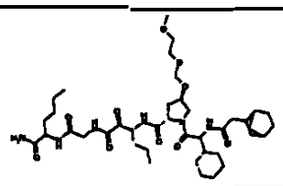
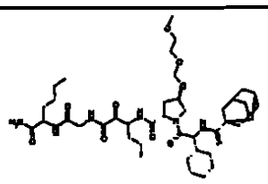
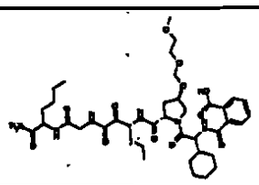
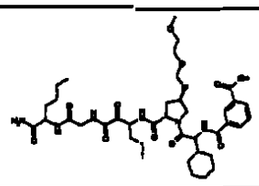
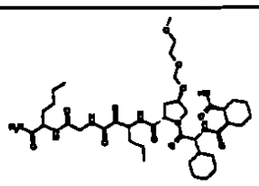
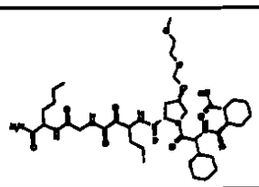
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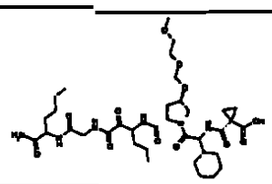
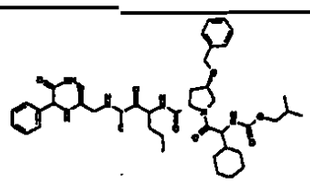
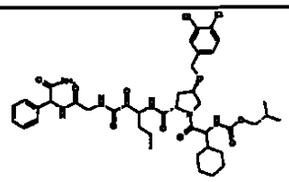
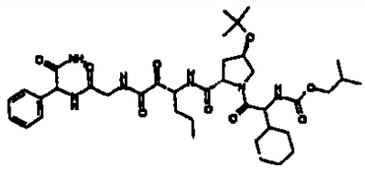
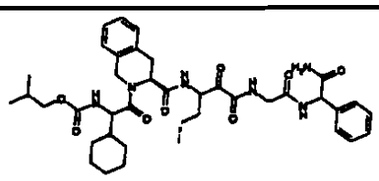
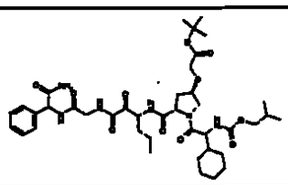
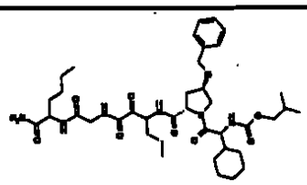
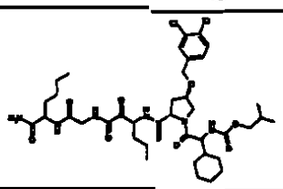
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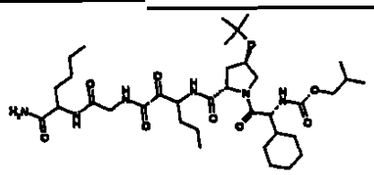
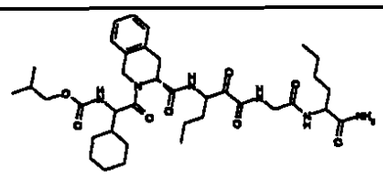
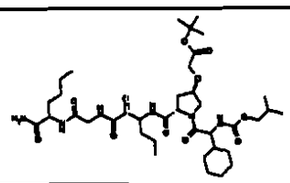
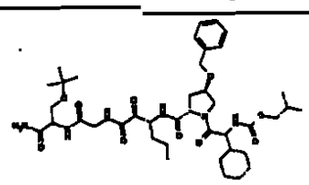
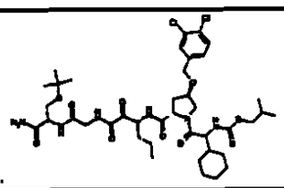
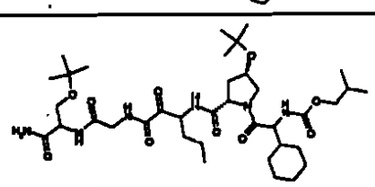
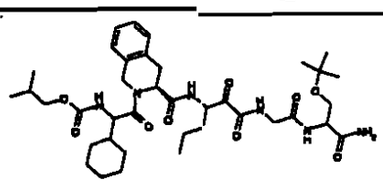
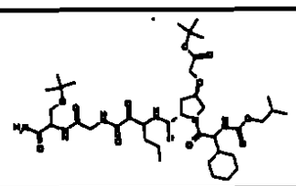
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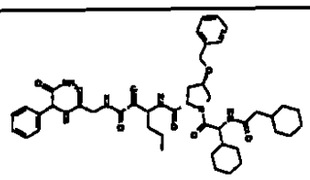
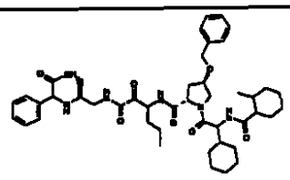
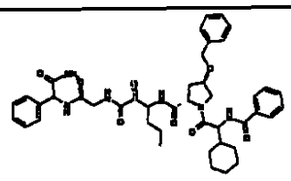
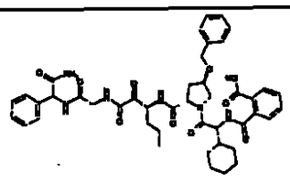
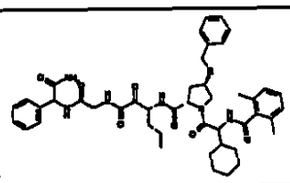
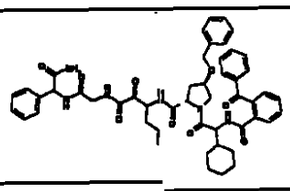
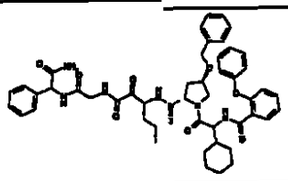
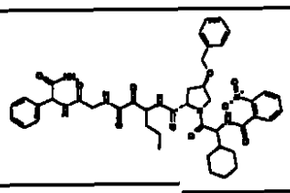
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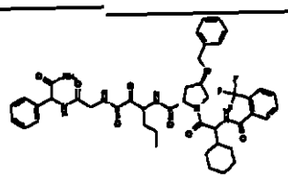
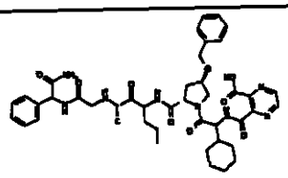
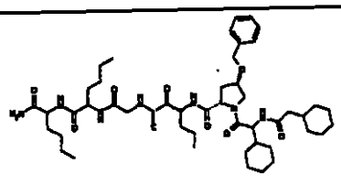
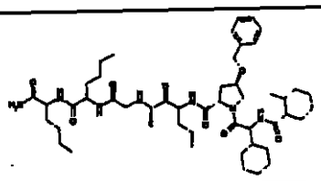
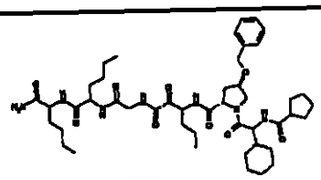
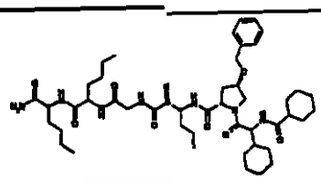
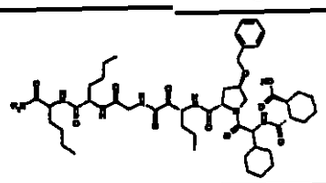
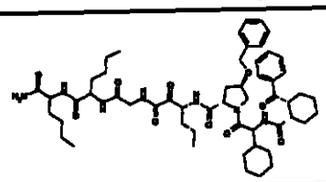
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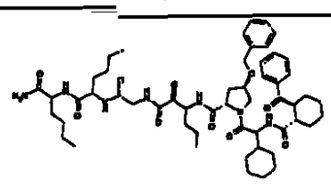
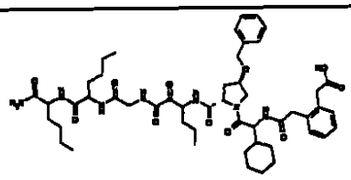
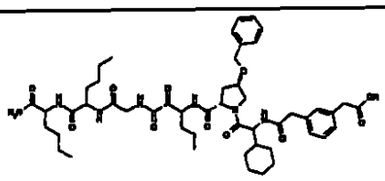
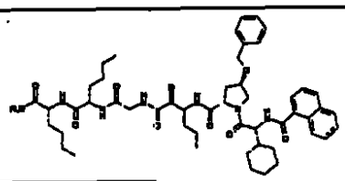
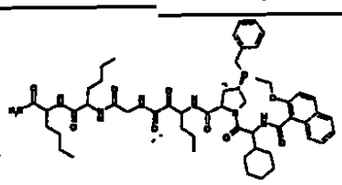
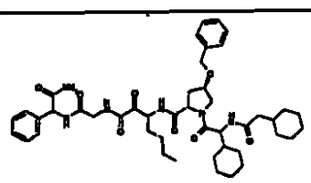
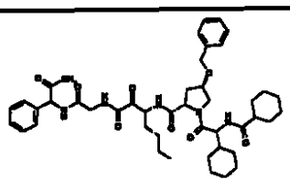
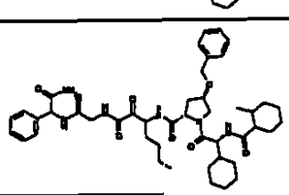
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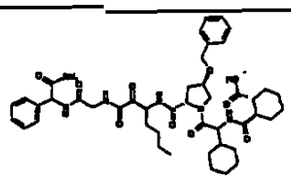
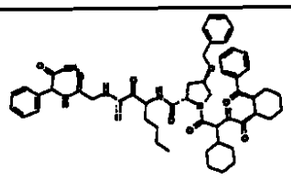
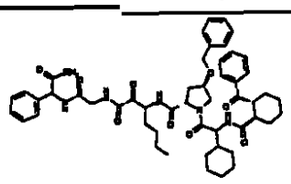
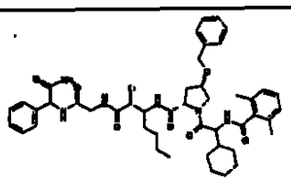
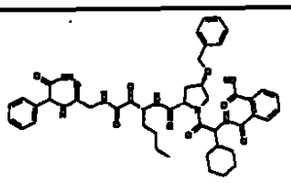
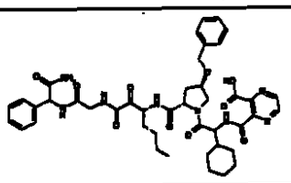
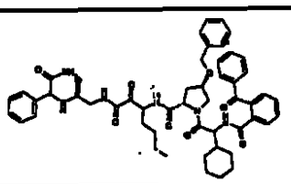
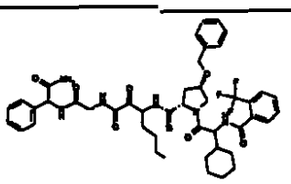
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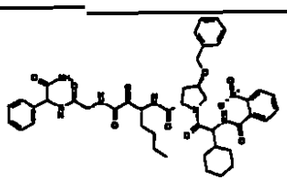
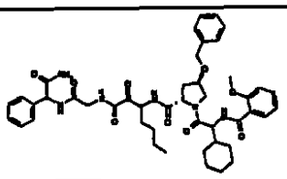
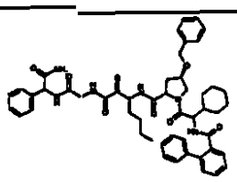
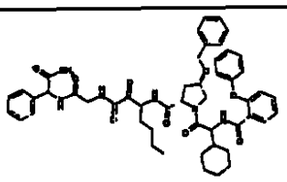
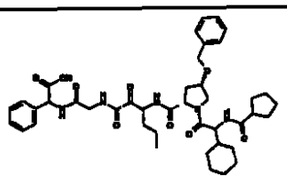
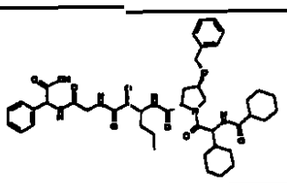
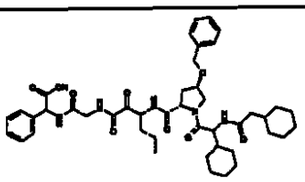
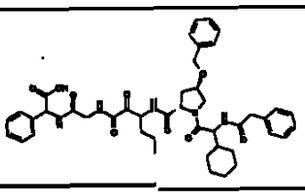
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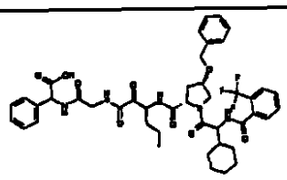
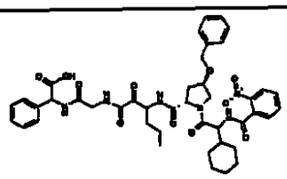
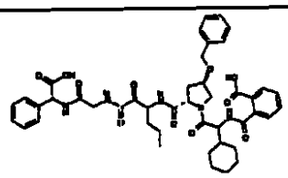
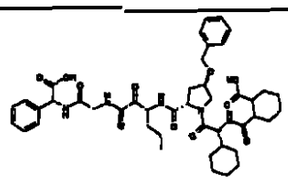
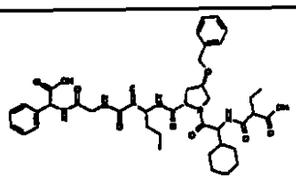
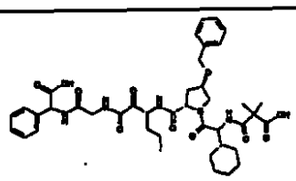
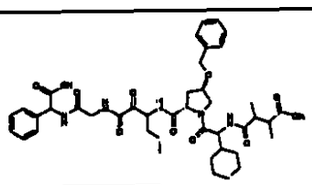
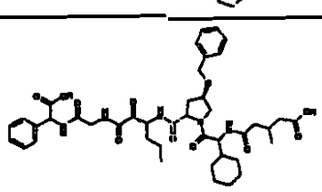
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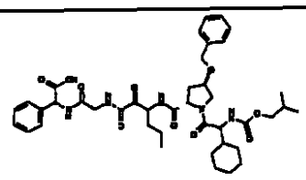
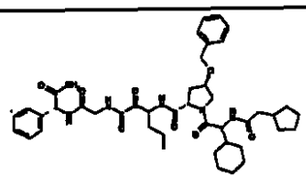
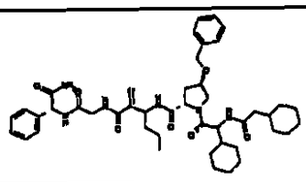
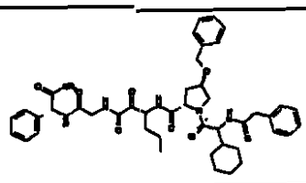
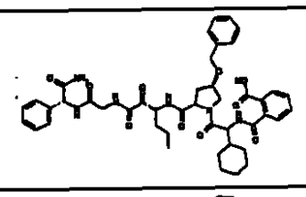
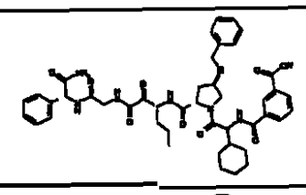
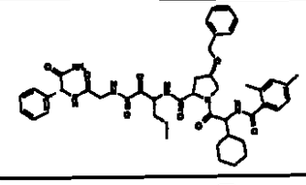
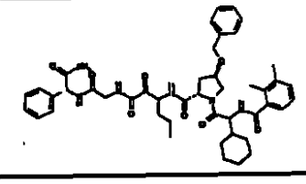
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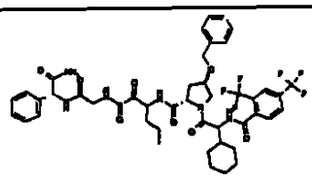
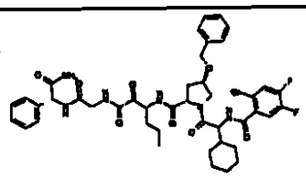
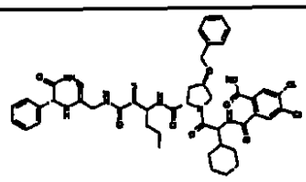
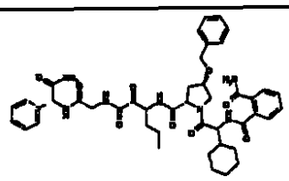
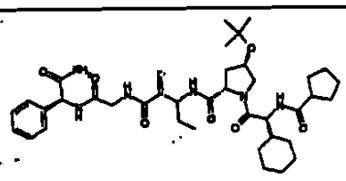
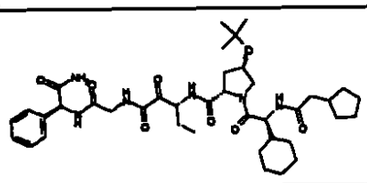
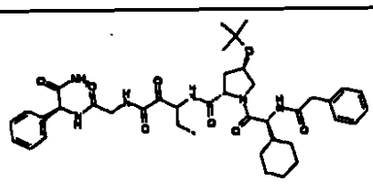
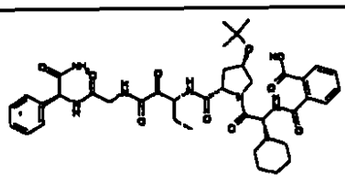
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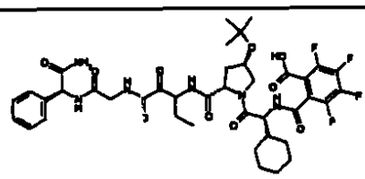
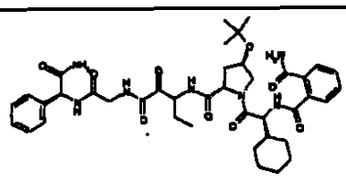
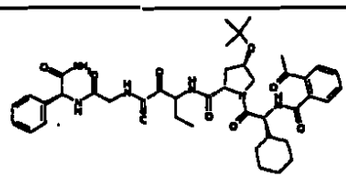
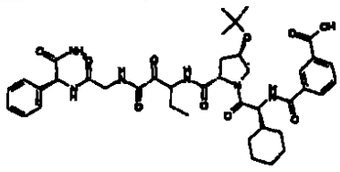
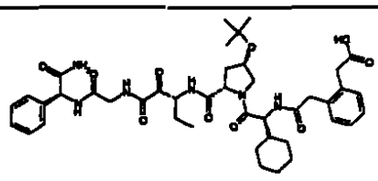
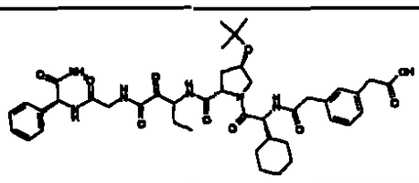
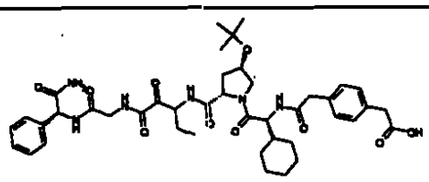
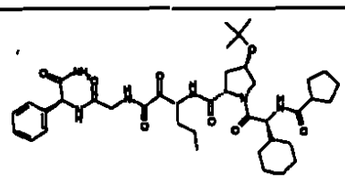
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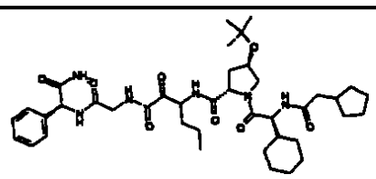
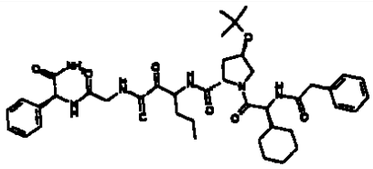
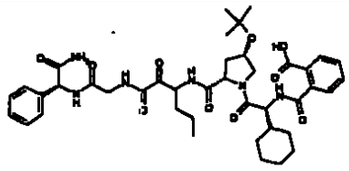
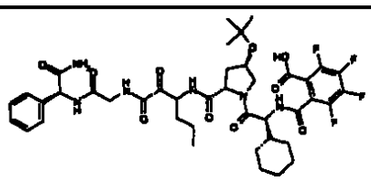
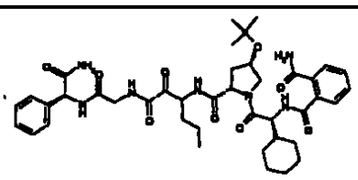
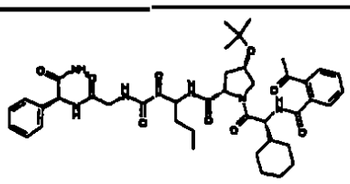
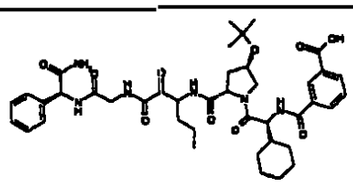
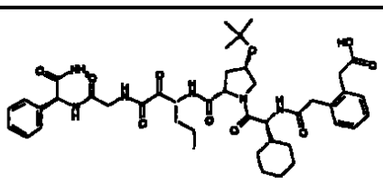
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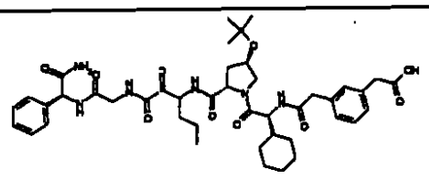
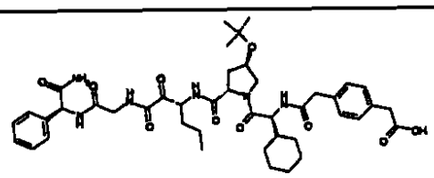
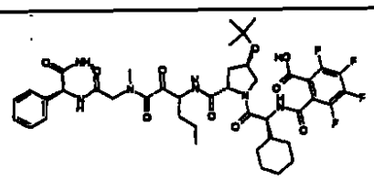
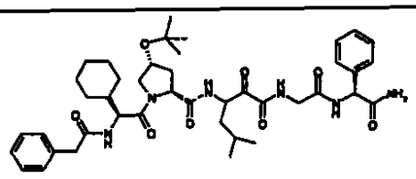
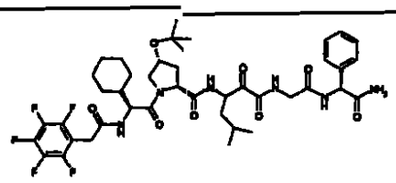
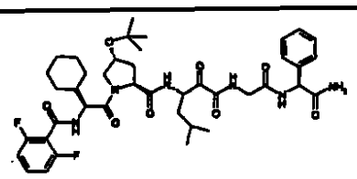
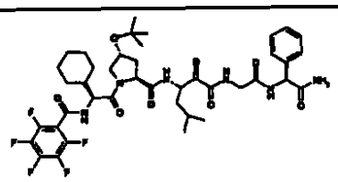
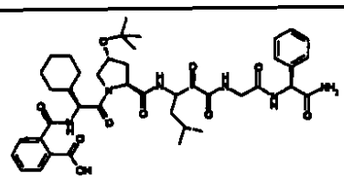
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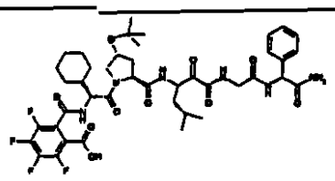
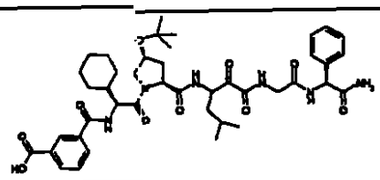
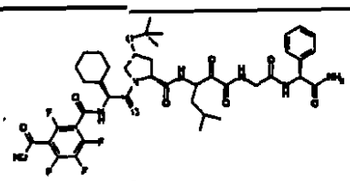
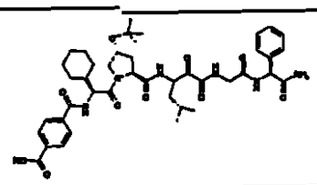
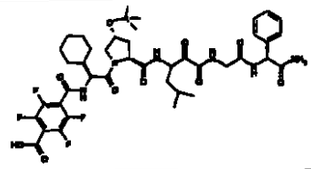
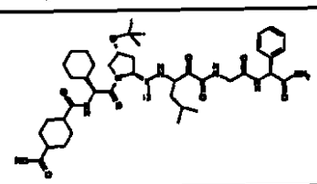
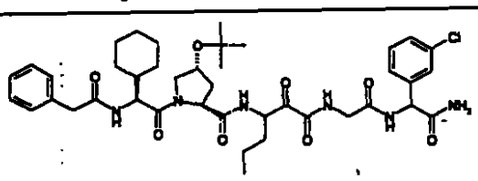
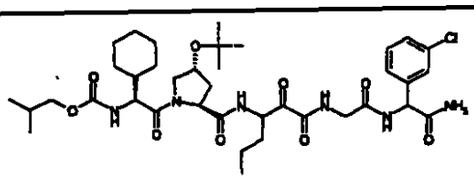
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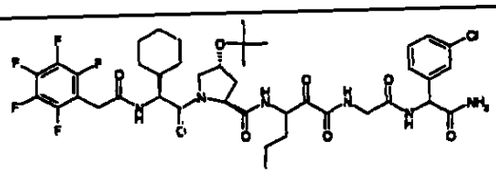
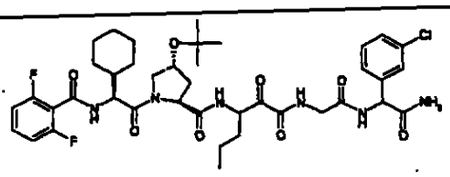
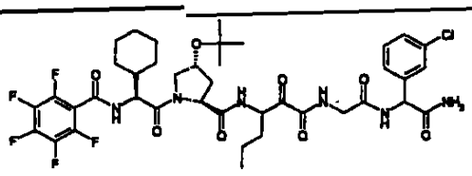
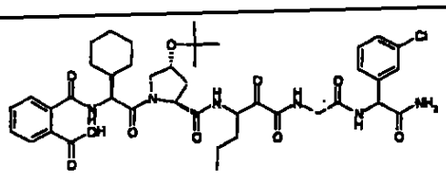
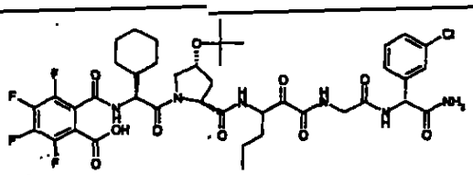
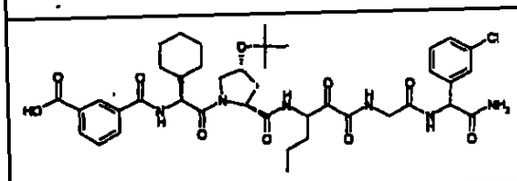
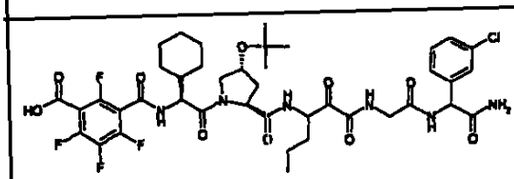
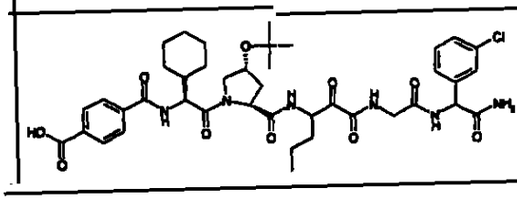
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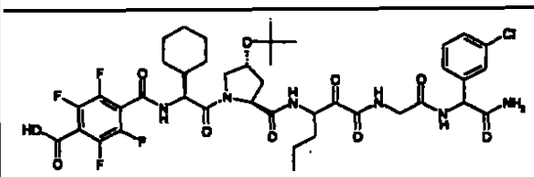
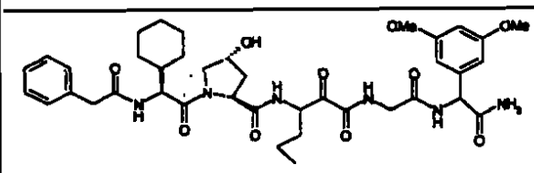
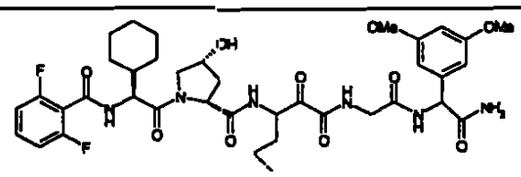
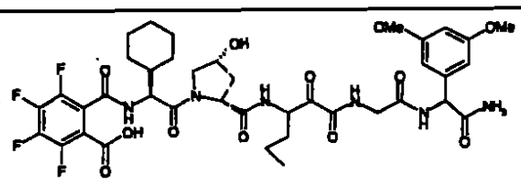
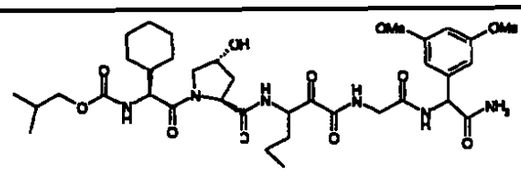
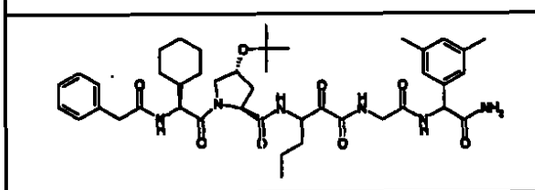
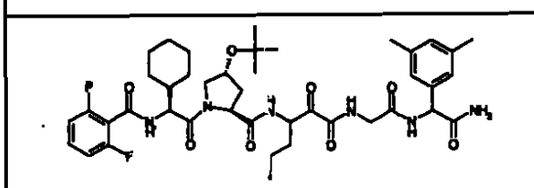
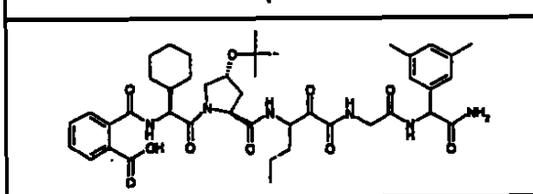
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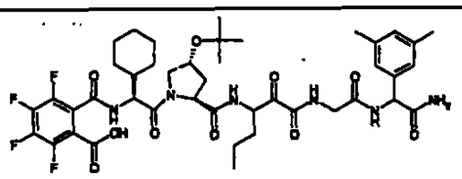
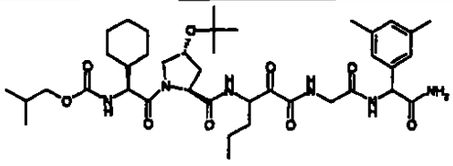
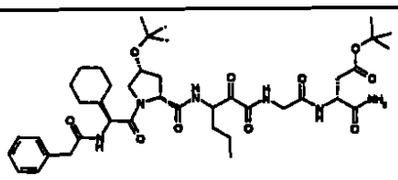
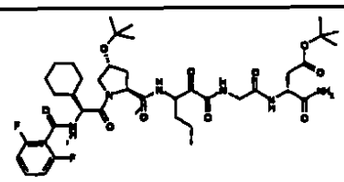
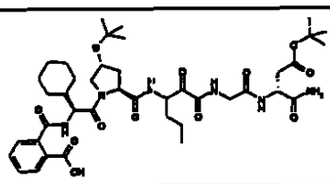
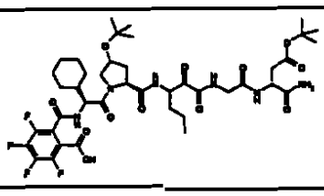
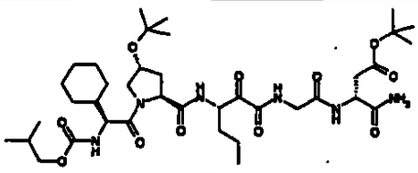
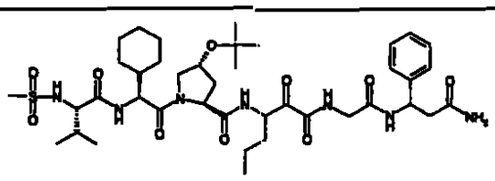
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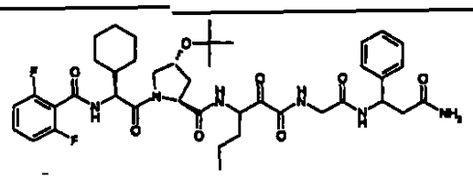
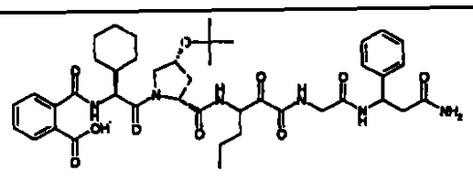
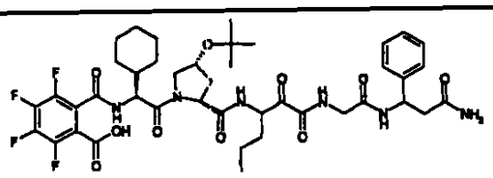
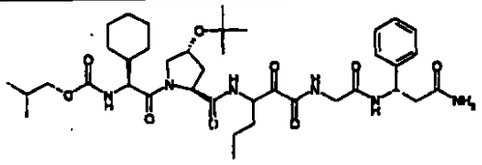
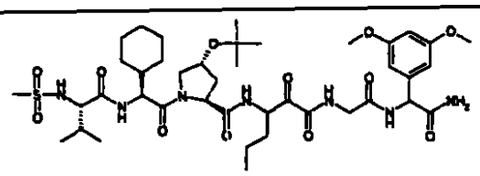
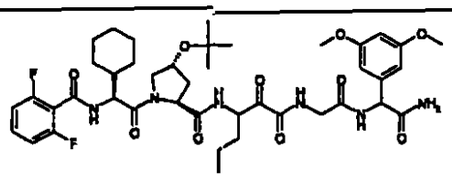
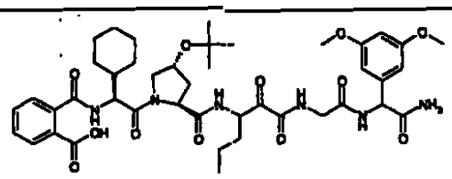
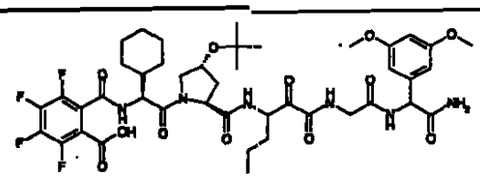
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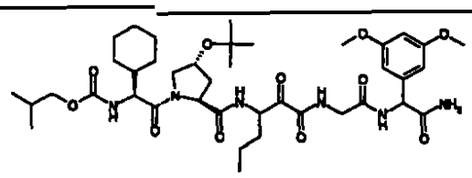
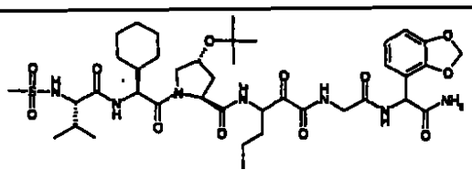
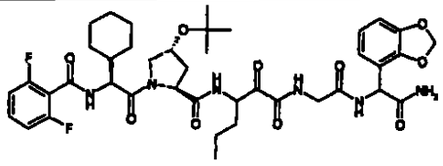
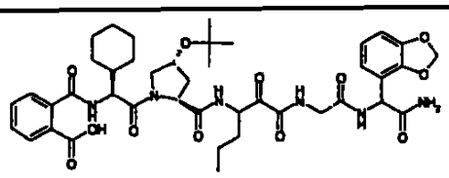
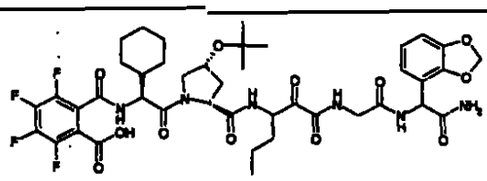
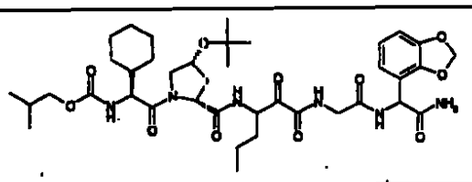
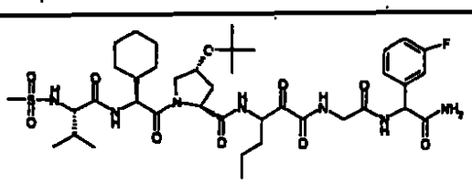
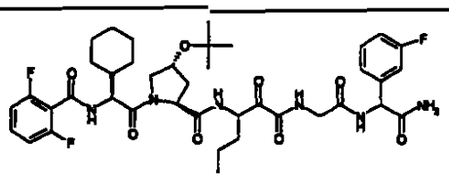
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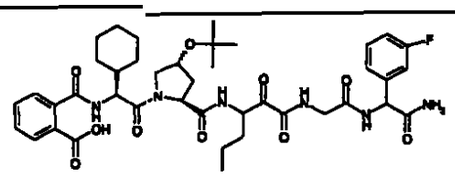
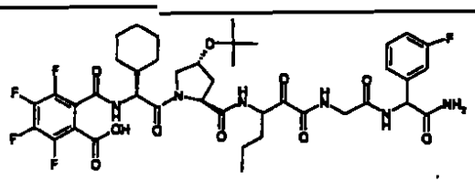
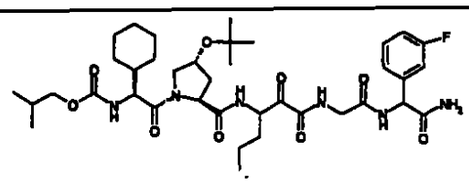
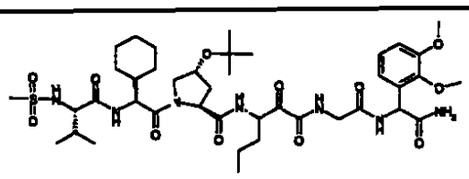
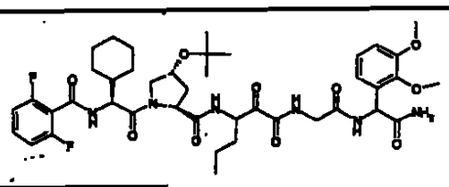
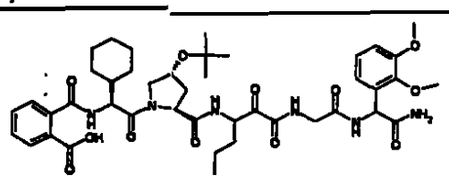
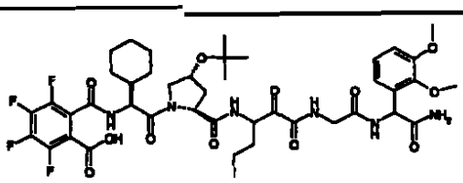
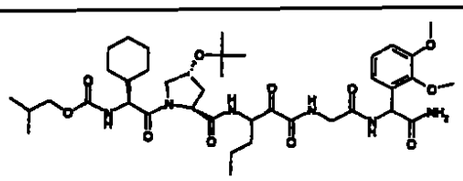
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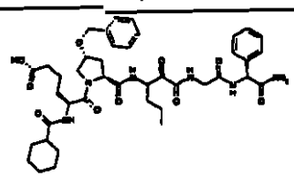
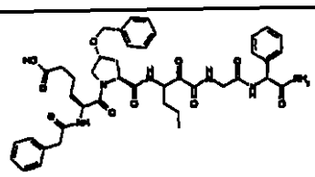
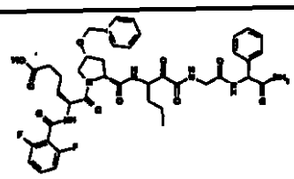
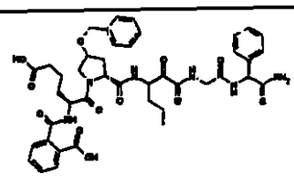
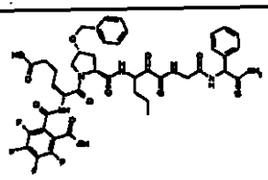
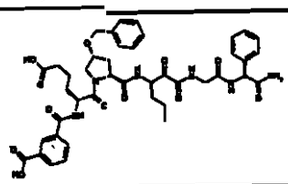
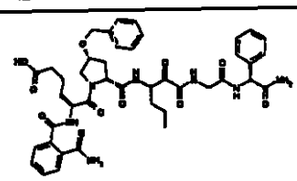
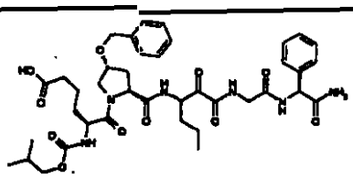
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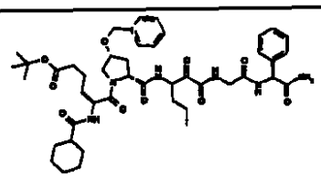
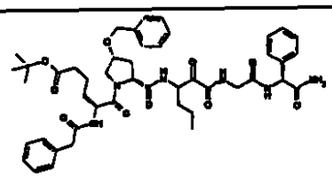
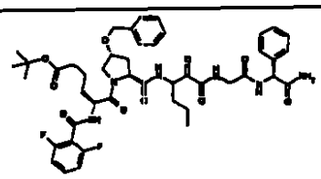
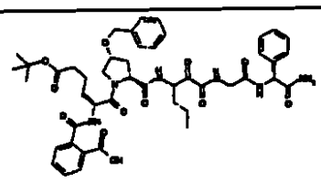
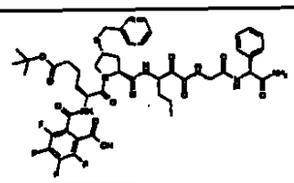
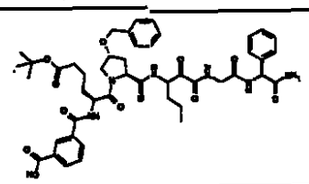
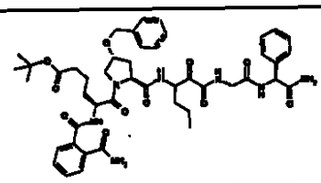
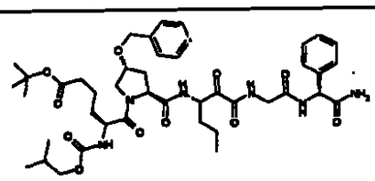
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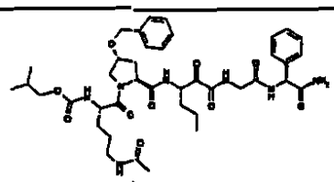
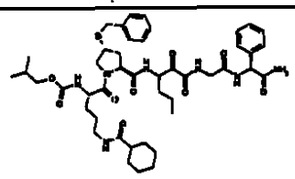
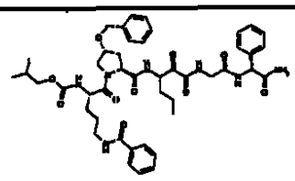
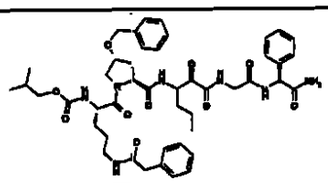
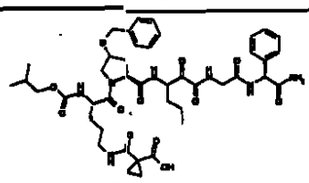
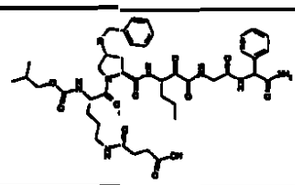
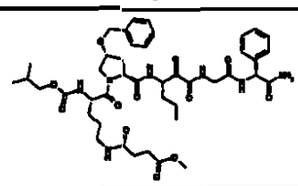
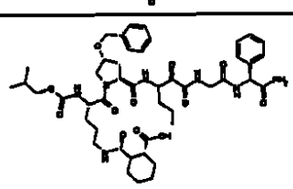
STRUCTURE	Ki* CLASS
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	B
	C
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	B
	B
	B

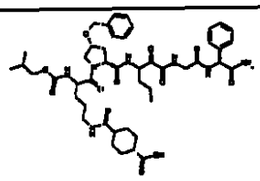
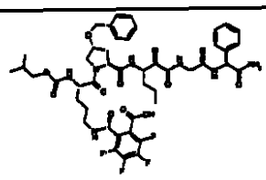
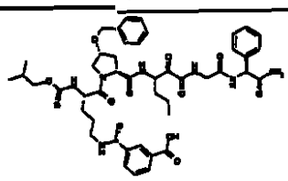
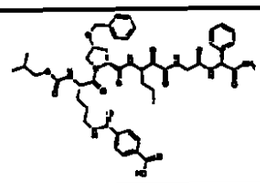
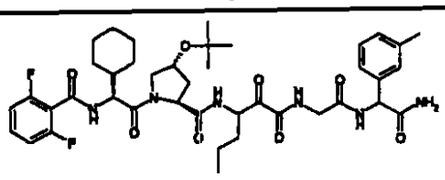
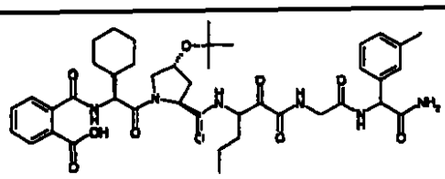
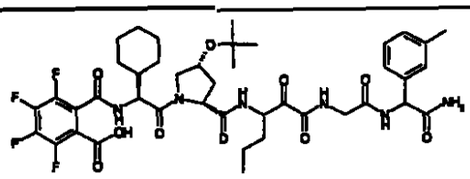
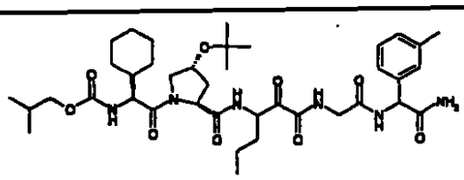
STRUCTURE	Ki* CLASS
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	B
	B

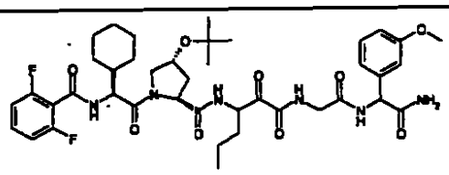
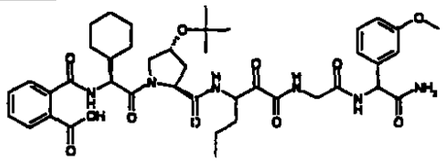
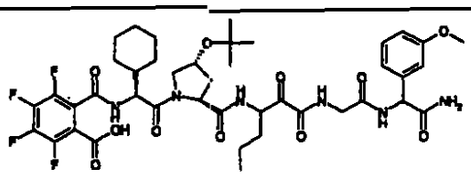
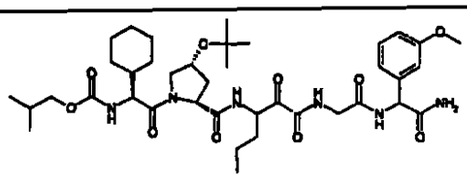
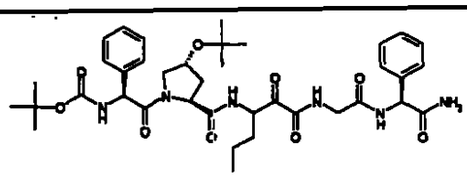
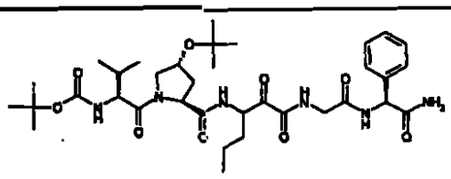
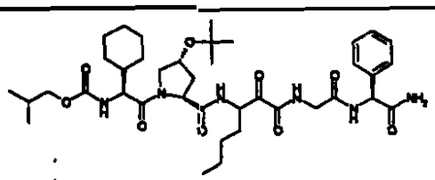
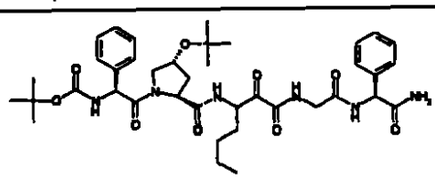
STRUCTURE	Ki* CLASS
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	B

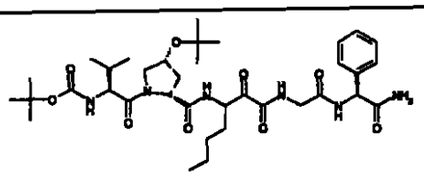
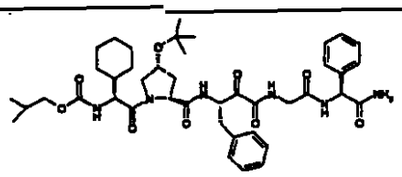
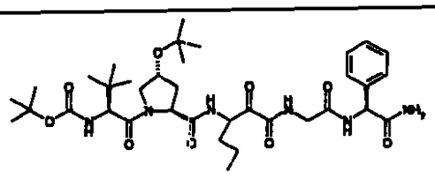
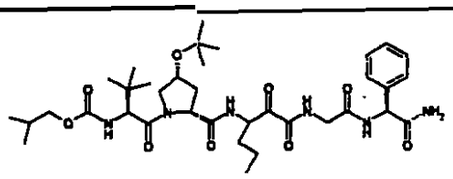
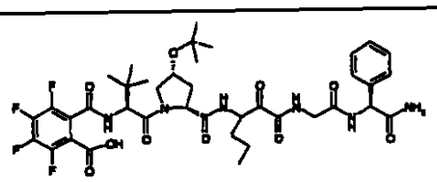
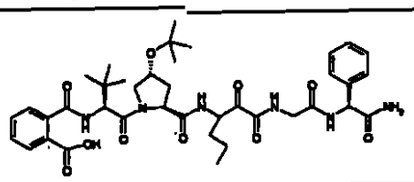
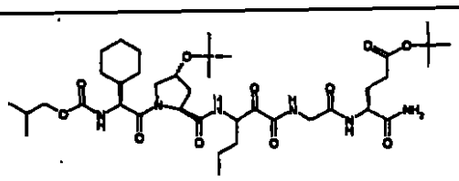
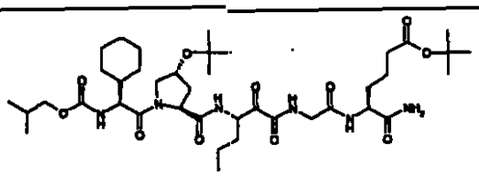
STRUCTURE	Ki* CLASS
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	B
	B
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	C
	B
	B

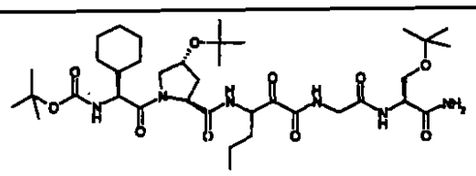
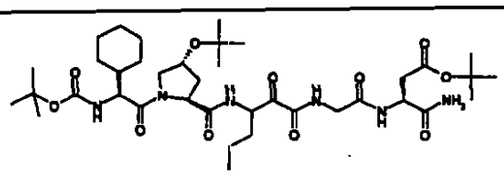
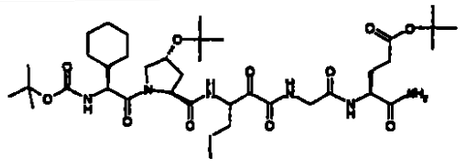
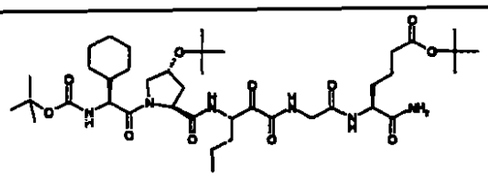
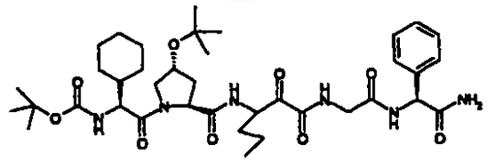
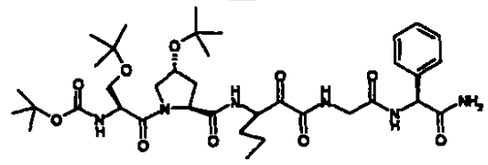
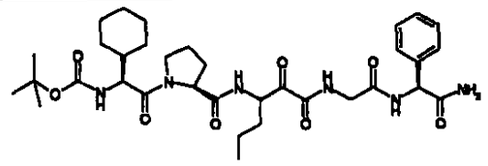
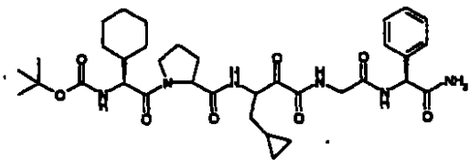
STRUCTURE	KI* CLASS
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	C
	C
	C
	B
	C
	C
	C

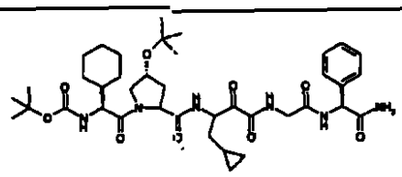
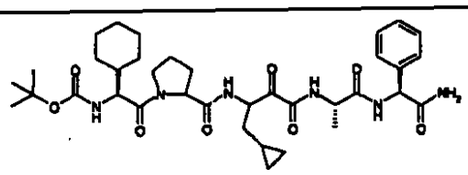
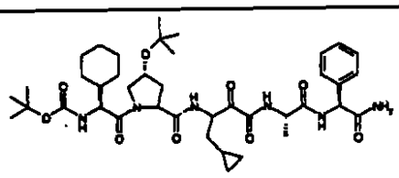
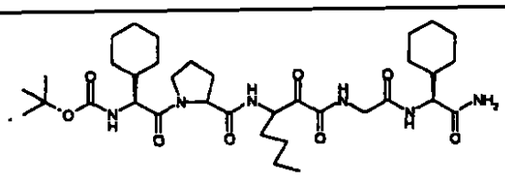
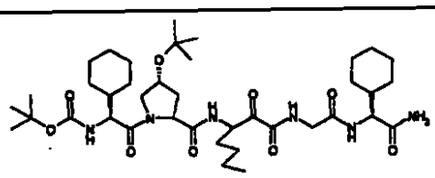
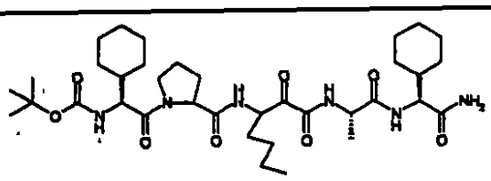
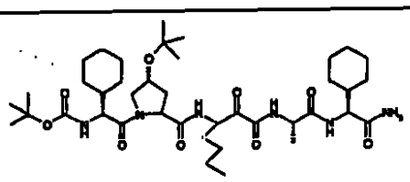
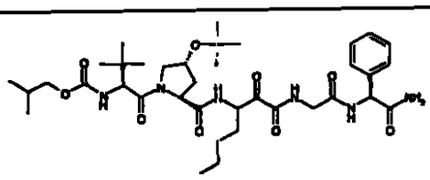
STRUCTURE	Ki* CLASS
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	C
	C
	C
	C
	C
	C
	C

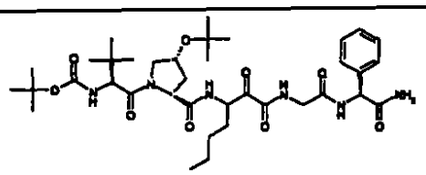
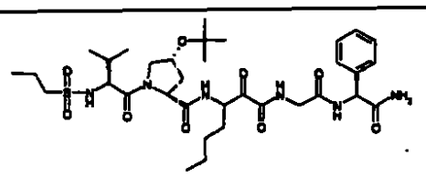
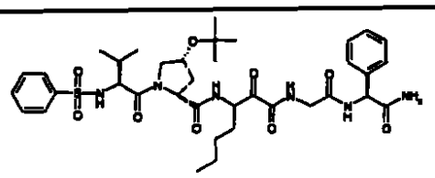
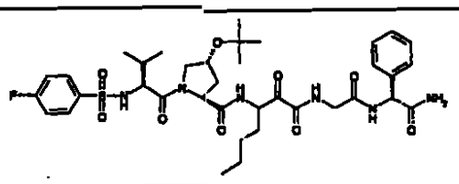
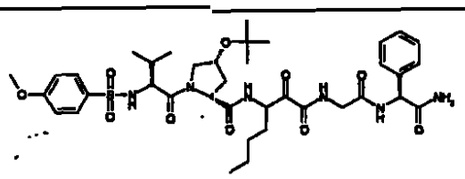
STRUCTURE	Ki* CLASS
	C
	C
	B
	B
	B
	B
	B
	B

STRUCTURE	Ki* CLASS
	B
	B
	B
	B
	C
	B
	B
	C

STRUCTURE	Ki* CLASS
	B
	C
	B
	B
	B
	B
	C
	C

STRUCTURE	Ki* CLASS
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	C
	C
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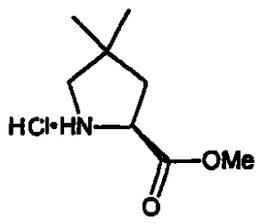
STRUCTURE	KI* CLASS
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	B

STRUCTURE	Ki* CLASS
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	C
	C
	C
	C

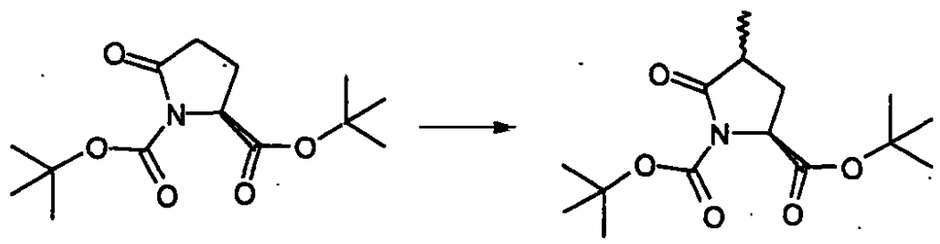
Additional compounds that were prepared and their activity (Ki*) ranges are given in the attached **Tables 4, 5 and 6.** The procedure used to prepare the compounds in **Tables 4, 5** and **6** is outlined below.

I) <u>Synthesis of Intermediates for the compounds in Tables 4, 5 and 6:</u>

Example I. Synthesis of 4,4-dimethyl proline methyl ester (H-Pro(4,4-diMe)-OMe)

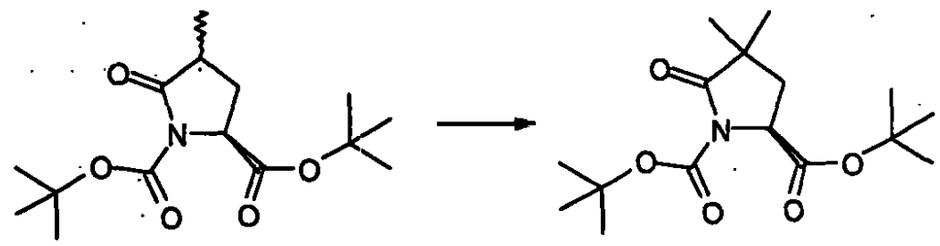


Step 1. Synthesis of tert-Butyl N-tert-butoxycarbonyl-4-methyl-L-pyroglutamate (Boc-PyroGlu(4-methyl)-OtBu):



To a solution of tert-butyl N-tert-butoxycarbonyl-pyroglutamate (11.5 g, 40 mmol) in THF (200 mL) stirring at -78 °C, was added a 1M solution of lithium hexamethyldisilazide in THF (42 mL, 42 mmol) dropwise over 5 minutes. After 30 minutes, methyliodide (3.11 mL, 50 mmol) was added. After an additional 2 hours at -78 °C, the cooling bath was removed and 50% saturated aqueous ammonium chloride (200 mL) was added. The solution was stirred for 20 minutes, then extracted with ether (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed with 1:1 ethylacetate/hexanes to give Boc-PyroGlu(4-methyl)-OtBu (10.6 grams, 35.4 mmol, 88%) as a mixture of isomers (2:1 cis to trans).

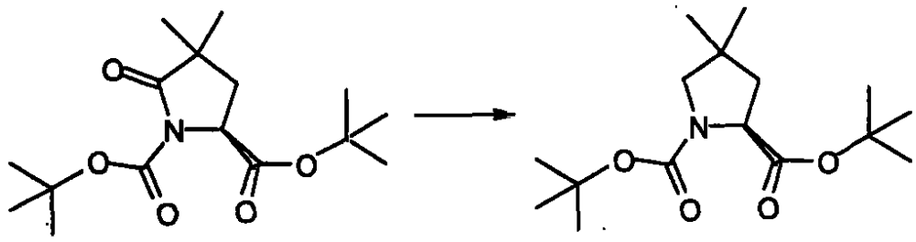
Step 2. Synthesis of tert-Butyl N-tert-butoxycarbonyl-4,4-dimethyl-L-pyroglutamate (Boc-PyroGlu(4,4-dimethyl)-OtBu):



To a solution of tert-butyl N-tert-butoxycarbonyl-4-methyl-L-pyroglutamate (1.2 g, 4.0 mmol) in tetrahydrofuran (20 mL) stirring at -78 °C, was added a 1M solution of lithium hexamethyldisilazide in tetrahydrofuran (4.4 mL, 4.4 mmol) dropwise over 5 minutes. After 30 minutes, methyliodide (0.33 mL, 5.2 mmol) was added. After an additional 3 hours at -78 °C, the cooling bath was removed and

50% saturated aqueous ammonium chloride (40 mL) was added. The solution was stirred for 20 minutes, then extracted with ether (2 x 50 mL). The combined organic layers were washed with water(2 × 25 mL), saturated sodium bicarbonate (2 × 25 mL), brine (50 mL), dried (Na_2SO_4), filtered and concentrated to give Boc-PyroGlu(4,4-dimethyl)-OtBu (0.673 g, 54%).

Step 3. Synthesis of tert-butyl N-tert-butoxycarbonyl-4,4-dimethylproline (Boc-Pro(4,4-dimethyl)-OtBu)

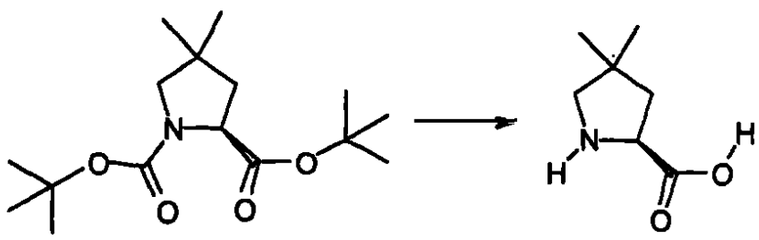


Modification of known procedure: Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron Letters* **1994**, 35(13), 2053-2056).

To a solution of tert-butyl N-tert-butoxycarbonyl-4,4-dimethylpyroglutamate (2.0 mmol) in tetrahydrofuran (5 mL) stirring at -78 °C, was added a 1M solution of lithium triethylborohydride in tetrahydrofuran (2.4 mL, 2.4 mmol) dropwise over 5 minutes. After 30 minutes, the cooling bath was removed and saturated aqueous sodium bicarbonate (5 mL) was added. The reaction mixture was immersed in an ice/water bath and 30% aqueous hydrogen peroxide (10 drops) was added. The solution was stirred for 20 minutes at 0 °C, then the reaction mixture was concentrated *in vacuo* to remove the tetrahydrofuran. The aqueous solution was diluted with water (10 mL) and extracted with dichloromethane (3 x 40 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was dissolved in dichloromethane (20 mL) and triethylsilane (310 µL, 2.0 mmol), then cooled to -78 °C and boron trifluoride diethyletherate (270 µL, 2.13 mmol) was added dropwise. Stirring was continued for 30 minutes, at which time additional triethylsilane (310 µL, 2.0 mmol) and boron trifluoride diethyletherate (270 µL,

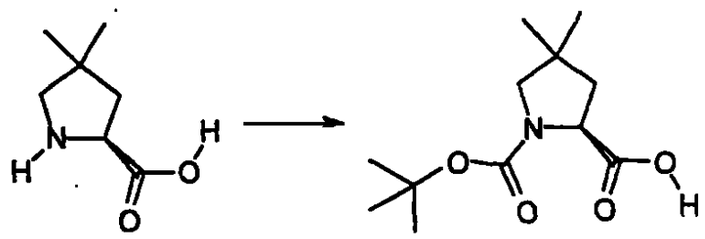
2.13 mmol) were added. After stirring at -78 °C for an additional two hours, the cooling bath was removed and saturated aqueous sodium bicarbonate (4 mL) was added. After 5 minutes the mixture was extracted with dichloromethane (3 x 40 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated to give Boc-Pro(4,4-dimethyl)-OtBu.

Step 4. Synthesis of 4,4-dimethylproline (H-Pro(4,4-dimethyl)-OH):



A solution of tert-butyl N-tert-butoxycarbonyl-4,4-dimethylproline in dichloromethane (5 mL) and trifluoroacetic (5 mL) was stirred at room temperature for five hours. The solution was concentrated, dried under high vacuum and taken to the next step without further purification.

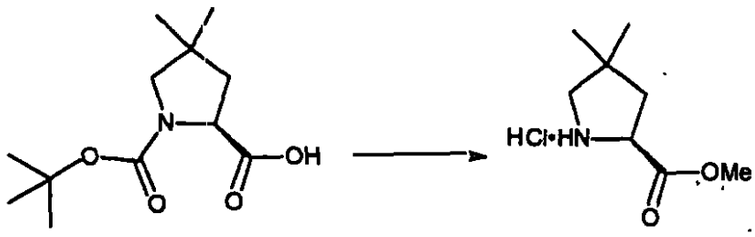
Step 5. Synthesis of N-tert-butoxycarbonyl 4,4-dimethylproline (Boc-Pro(4,4-dimethyl)-OH):



To a solution of 4,4-dimethylproline trifluoroacetic salt (1.5 mmol) in dioxane (7 mL), acetonitrile (12 mL) and diisopropylethylamine (700 µL, 4 mmol) was added a solution of di-tert-butyl-dicarbonate (475 mg, 2.18 mmol) in acetonitrile (5 mL). After stirring for 12 hours at room temperature the solution was concentrated in vacuo, dissolved in saturated aqueous sodium bicarbonate (50 mL) and washed with diethyl ether (3 x 40 mL). The aqueous layer was acidified to pH=3 with citric acid, then extracted with dichloromethane (3 x 40 mL).

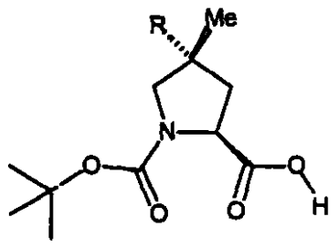
The combined organic layers were dried over sodium sulfate filtered and concentrated.

Step 6. Synthesis of 4,4-dimethylproline methylester hydrochloride salt (HCl•H-Pro(4,4-dimethyl)-OMe):



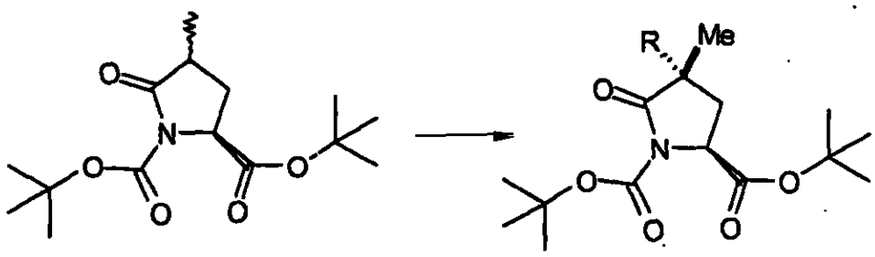
To a solution of Boc-Pro(4,4-diMe)-OH (0.5 g, 2.06 mmol) in anhydrous methanol (8 ml) was added dropwise thionylchloride (448 □l, 6.18 mmol) and the reaction was stirred for six hours at room temperature. The reaction mixture was concentrated to an amorphous solid (377 mg, 95%).

Example II. General procedure for the synthesis of N-tertbutoxycarbonyl-4-alkyl-4-methyl proline:



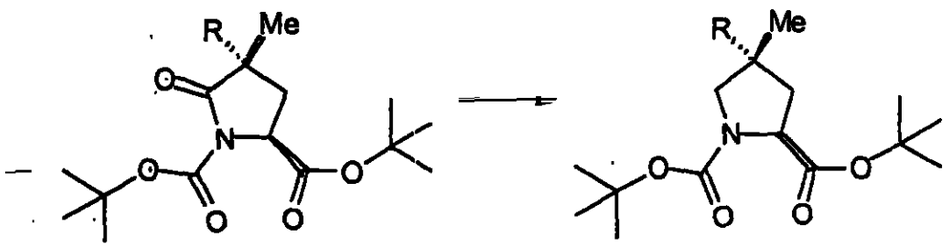
Compounds where R group is allyl and benzyl were synthesized following steps 1-4 below:

Step 1. Synthesis of tert-Butyl N-tert-butoxycarbonyl-4-alkyl-4-methyl-L-pyroglutamate:



To a solution of tert-butyl N-tert-butoxycarbonyl-4-methyl-L-pyroglutamate (10.2 g, mmol) (see Example I, step 1) in tetrahydrofuran (170 mL) stirring at -78 °C, was added a 1M solution of lithium hexamethyldisilazide in tetrahydrofuran (37.5 mL, 37.5 mmol) dropwise over 5 minutes. After 40 minutes, alkyl halide (61.4 mmol) was added. After an additional 3 hours at -78 °C, the cooling bath was removed and 50% saturated aqueous ammonium chloride (200 mL) was added. The solution was stirred for 20 minutes, then extracted with ether (2 x 200 mL). The combined organic layers were diluted with hexanes (150 mL) and washed with saturated sodium bicarbonate (100 mL), water (2 x 100 mL) and brine (100 mL), dried (Na_2SO_4), filtered and concentrated. The residue was flash chromatographed using 20% ethylacetate in hexanes to give the pure tert-Butyl N-tert-butoxycarbonyl-4-alkyl-4-methyl-L-pyroglutamate.

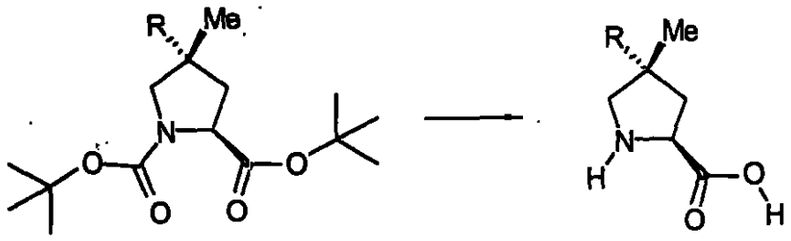
Step 2. Synthesis of tert-butyl N-tert-butoxycarbonyl-4-alkyl-4-methylproline:



Modification of known procedure: Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron Letters* (1994) 35(13), 2053-2056).

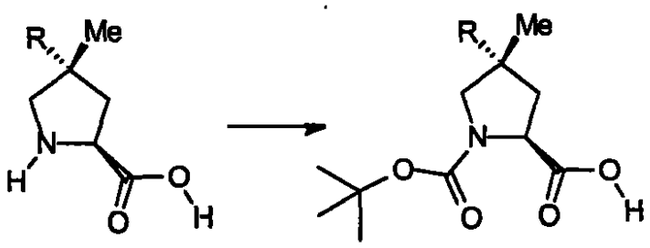
To a solution of tert-butyl N-tert-butoxycarbonyl-4-alkyl-4-methylpyroglutamate (16.6 mmol) in tetrahydrofuran (40 mL) stirring at -78 °C, was added a 1M solution of lithium triethylborohydride in tetrahydrofuran (20 mL, 20 mmol) dropwise over 10 minutes. After 120 minutes, the cooling bath was allowed to warm to –25 °C at which point saturated aqueous sodium bicarbonate (40 mL) was added. The reaction mixture was immersed in an ice/water bath and 30% aqueous hydrogen peroxide (4 mL) was added. The solution was stirred for 10 minutes at 0 °C, then the reaction mixture was concentrated in vacuo to remove the tetrahydrofuran. The aqueous solution was diluted with water (300 mL) and extracted with dichloromethane (3 x 200 mL). The organic layers were dried (sodium sulfate), filtered and concentrated. The residue was dissolved in dichloromethane (100 mL) and triethylsilane (2.6 mL, mmol), then cooled to -78 °C and boron trifluoride diethyletherate (2.2 mL, mmol) was added dropwise. Stirring was continued for 1 hour, at which time additional triethylsilane (2.6 mL, mmol) and boron trifluoride diethyletherate (2.2 mL, mmol) were added. After stirring at -78 °C for an additional 4 hours, the cooling bath was removed and saturated aqueous sodium bicarbonate (30 mL) and water (150 mL) were added. After 5 minutes the mixture was extracted with dichloromethane (3 x 200 mL). The organic layers were dried (Na_2SO_4), filtered and concentrated.

Step 3. Synthesis 4-alkyl-4-methylproline:



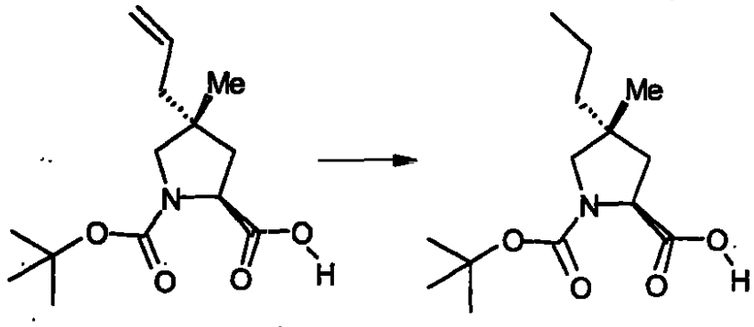
A solution of tert-butyl N-tert-butoxycarbonyl-4-alkyl-4-methylproline in dichloromethane (5 mL) and trifluoroacetic (5 mL) was stirred at room temperature for 5 hours. Toluene was added and the solution was concentrated and then dried under high vacuum.

Step 4. Synthesis of N-tert-butoxycarbonyl 4-alkyl-4-methylproline:



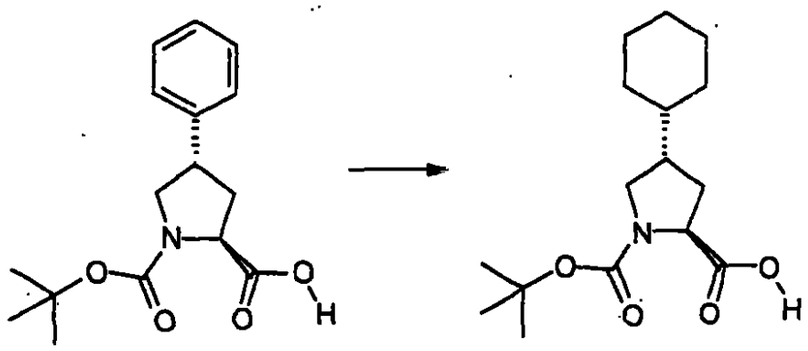
To a solution of 4-alkyl-4-methylproline trifluoroacetic salt (1.5 mmol) in dioxane (7 mL), acetonitrile (12 mL) and diisopropylethylamine (700 μL, 4 mmol) was added a solution of di-tert-butyl-dicarbonate (475 mg, 2.18 mmol) in acetonitrile(5 mL). After stirring for 12 hours at room temperature the solution was concentrated in vacuo, dissolved in saturated aqueous sodium bicarbonate (50 mL) and washed with diethyl ether (3 x 40 mL). The aqueous layer was acidified to pH=3 with 1N hydrochloric acid, then extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash chromatography using 1:1 ethylacetate/hexanes with 1% acetic acid.

Example III. Synthesis of N-tert-butoxycarbonyl 4-propyl-4-methylproline:



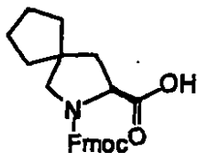
A solution of N-tertbutoxycarbonyl-4-allyl-4-methylproline (400 mg, 1.48 mmol) (see Example II Step 4) and 10% Pd on carbon (400 mg) in methanol (20 mL) was hydrogenated at 50 psi for 4 hours. The mixture was filtered and concentrated.

Example IV. Synthesis of Boc-4-cyclohexylproline:

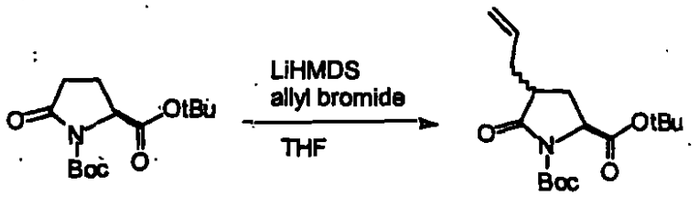


A solution of the commercially available Boc-4-phenylproline (750 mg) and 5% Rh on carbon (750 mg) in methanol (15 mL) was hydrogenated at 50 psi for 24 hours. The mixture was filtered and concentrated to give 730 mg of product.

Example V: Preparation of Fluorenylmethoxycarbonyl-Pro(4-spirocyclopentane)-carboxylic acid :



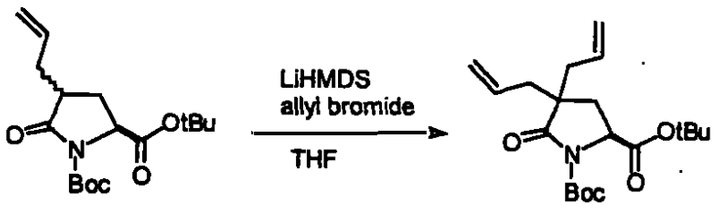
Step 1. Synthesis of Boc-pyroglutamic(4-allyl)-tert-butylester :



To a cooled (-78 °C) solution of the commercially available N^{α}-Boc-tert-butyl pyroglutamate (10.g, 35.1 mmol) in THF (175 ml) was added lithium hexamethyldisilazide (36.8 mL, 36.8 mmol) over five minutes. Stirring continued for thirty minutes. A solution of allyl bromide (6.1 ml, 70.2 mmol) in THF (39 mL) was added dropwise to the first solution. After two hours at -78 °C, the reaction was quenched by the slow addition of saturated ammonium chloride (50 mL) solution. The reaction mixture was then diluted with ethylacetate and the layers were separated. The organic layer dried over sodium sulfate and concentrated.

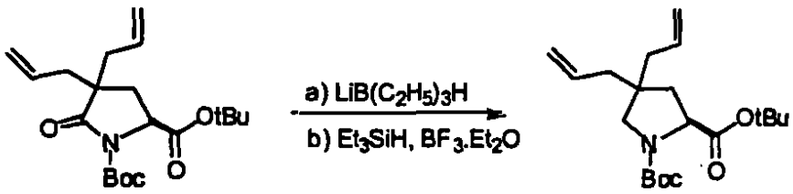
Flash column chromatography carried out in 2:8 ethylacetate: hexanes afforded the product (6 g, 53%). NMR δ ppm (CDCl3): 5.7 (m, 1H), 5.1 (dd, 2H), 4.4 (m, 1H), 2.6 (m, 2H), 2.4 (m, 1H), 1.8-2.2 (m, 1H), 1.45 (s, 9H), 1.4 (s, 9H).

Step 2. Synthesis of N-Boc-pyroglutamic(4,4-diallyl)-tert-butylester:



N-Boc-pyroglutamic(4-allyl)-tert-butylester obtained in the Step 1 above (2.68 g, 8.24 mmol) was subjected to a second alkylation with allyl bromide under similar conditions. Flash chromatography in 15:85 ethylacetate: hexanes provided 2.13 g product (71%) as a clear oil.

Step 3. Synthesis of Boc-Pro(4,4-diallyl)-tert-butylester:

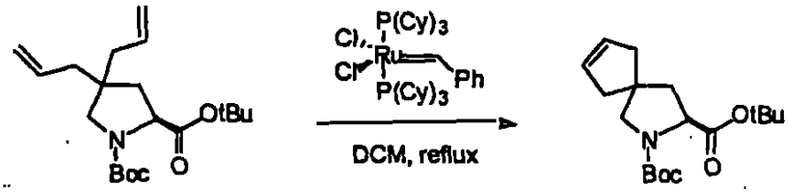


Part a: To a cooled (-78 °C) solution of Boc-PyroGlu(4,4-diallyl)-tert-butylester (2.13 g, 5.83 mmol) in tetrahydrofuran (14 ml) was added lithium triethylborohydride (1M in tetrahydrofuran, 7.29 ml, 7.29 mmol) over five minutes. After two hours at -78 °C, the reaction was warmed-up to 0 °C and quenched by the slow addition of saturated sodium bicarbonate solution (20 ml) and 30% hydrogen peroxide (20 drops). Stirring continued for 20 minutes. The tetrahydrofuran was removed under reduced pressure and the remaining thick white residue was diluted with water (80 ml) and extracted three times with dichloromethane. The organic layer was dried, filtered and concentrated and taken to the next step without further purification.

Part b): To the product obtained in part (a) in dichloromethane (14 ml) was added triethylsilane (931 µl, 5.83 mmol) followed by boron trifluoride diethyl

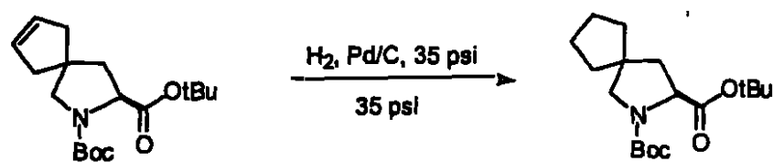
etherate (776 µl, 6.12 mmol). After thirty minutes more triethylsilane (931 µl; 5.83 mmol) and boron trifluoride diethyl etherate etherate (776 µl, 6.12 mmol) were added and the reaction was stirred at -78 °C for three hours at which time the reaction was quenched by the slow addition of saturated sodium bicarbonate solution and water. The reaction mixture was extracted with dichloromethane and the organic layer was dried, filtered and concentrated. Flash column chromatography in 15% ethylacetate in hexanes afforded 1.07 colorless oil (57%). NMR δ ppm (CDCl3): 5.7-5.8 (m, 2H), 5.1 (m, 4H), 4.1-4.2 (2 dd's, 1H rotamers), 3.5-3.3 (dd, 1H) and 3.2 (dd, 1H) rotamers, 2.2-2.0 (m, 5H), 1.7(m, 1H), 1.46 (s, 9H), 1.43 (s, 9H).

Step 4. Synthesis of Boc-Pro(4-spirocyclopentene)-tert-butylester:



To Boc-Pro(4,4-diallyl)-tert-butylester (1.07 g, 3.31 mmol) in dichloromethane (66 ml) was added 5% Bis(tricyclohexylphosphin)benzylidene ruthenium IV dichloride (Grubbs catalyst) and the mixture was heated at reflux for 1.5 hours. The reaction mixture was concentrated and the remaining residue was purified by flash column chromatography in 15% ethylacetate in hexanes. A yellow oil was obtained (0.57 g, 53%). NMR δ ppm (CDCl3): 5.56 (bs, 2H), 4.2 and 4.1 (t, 1H, rotamers), 3.2-3.5 (m, 2H), 2.2-2.5 (m, 5H), 1.9 (dd, 1H) 1.47 and 1.46 (2 s's, 9H, rotamers), 1.45 and 1.44 (2 s's, 9H, rotamers).

Step 5. Synthesis of Boc-Pro(4-spirocyclopentane)-tert-butylester:



A solution of Boc-Pro(4-spirocyclopentene)-tert-butylester (1.12 g) in methanol (18 ml), water (4 ml) and acetic acid (4 ml) was placed in the Parr

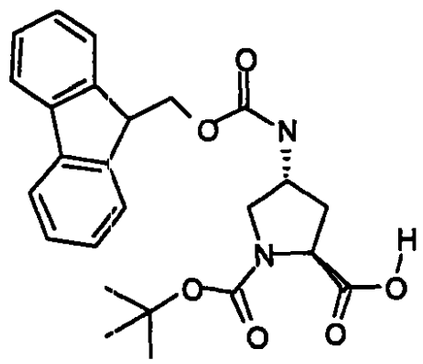
shaker and was hydrogenated for three hours at 35 psi in the presence of 10% palladium on carbon (300 mg). The catalyst was filtered off and the filtrate was concentrated to a colorless oil (1.26 g). NMR δ ppm (CDCl3): 4.1 and 4.2 (t, 1H, rotamers, 3.4 (d, 1H), 3.2 (d, 1H), 2.1 (m, 1H), 1.9 (m, 1H), 1.6-1.7 (m, 10H), 1.5 (3 s's, 18H, rotamers).

Step 6. Synthesis of Fmoc-Pro(4-spirocyclopentane)-carboxylic acid:

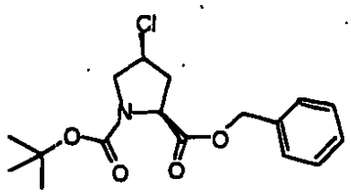


The Boc-Pro(4-spirocyclopentane)-tert-butylester (1.26, 3.9 mmol) was treated with dichloromethane (10 ml) and trifluoroacetic acid (15 ml) for three hours. The reaction mixture was concentrated and the yellow oil obtained was dissolved in water (6 ml). Fluorenylmethyl succinyl carbonate (1.45 g, 4.3 mmol) dissolved in dioxane (6 ml) was added portionwise followed by the addition of potassium carbonate (2.16 g, 15.6 mmol). The reaction was stirred for 18 hours and concentrated. The remaining residue was diluted with the saturated sodium bicarbonate solution (10 mL) and washed with diethylether (3 × 10 ml). The aqueous layer was then acidified to pH ~ 1 with 1N sodium bisulfate solution and extracted with ethylacetate. The organic layer was dried over sodium sulfate, filtered and concentrated to a beige foam (1.3 g, 100%).

Example VI. Synthesis of Boc-Pro(4t-NH(Fmoc))-OH:

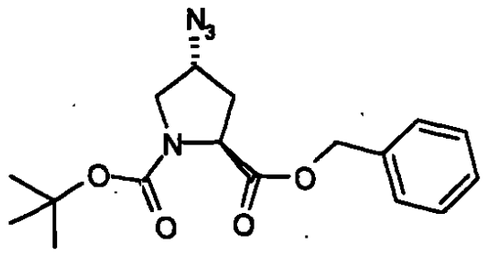


Step 1. Synthesis of N^{α}-tert-butoxycarbonyl-cis-4-chloro-L-proline benzyl ester:



A mixture of the commercially available N^{α}-tert-butoxycarbonyl-trans-4-hydroxy-proline (8.79 g, 38 mmol), potassium carbonate (13.0 g, 94 mmol); benzyl bromide (4.5 ml, 38 mmol) and dimethylformamide (150 mL) was stirred for 18 h. Addition of ethyl acetate (100 mL) was followed by filtration. The white cloudy filtrate was clarified by the addition of 1M HCl (100 mL). The layers were separated and the aqueous layer was extracted with additional ethyl acetate (2 x 100 mL). The combined organic layers were washed with water (2 x 50 mL), dried (sodium sulfate), filtered and concentrated. Toluene was added to the crude benzyl ester, and the solution was filtered and reconcentrated. Dichloromethane (70 mL) and carbon tetrachloride (70 mL) was added, followed by triphenylphosphine (21.11 g, 80 mmol). The reaction mixture was stirred for 10 h, quenched with ethanol (7 mL) and stirred for 5 more h. The solution was concentrated to approx. 100 ml, then dichloromethane (40 mL) was added, followed by the addition of ether (200 mL) while stirring. The solution was cooled for 4 h, filtered and concentrated to give a yellow-brown oil which was purified by flash chromatography using ether/hexane/dichloromethane 2:2:1 to give the title compound (9.13 g, 26.9 mmol, 71%) as a white solid.

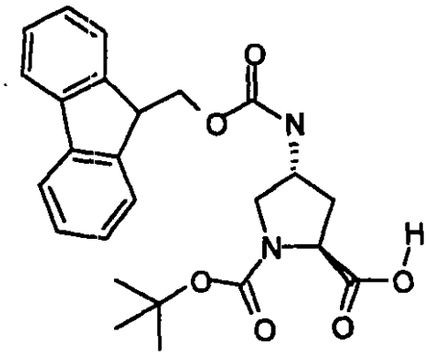
Step 2: Synthesis of N^{α}-tert-butoxycarbonyl-trans-4-azido-L-proline benzyl ester:



A solution of N^{α}-tert-butoxycarbonyl-cis-4-chloro-L-proline benzyl ester (9.0 g, 26.5 mmol) and sodium azide (7.36 g, 113 mmol) in dimethylformamide (270

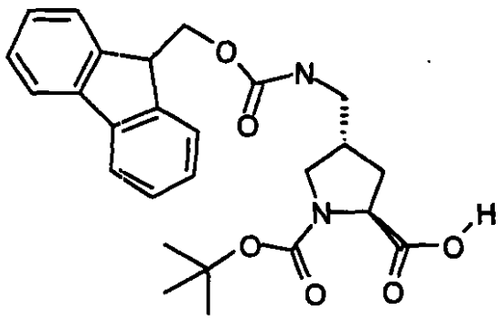
mL) was heated at 75°C for 2 days. Water (100 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with water (3 x 50 mL), dried (sodium sulfate), filtered and concentrated. The oil was purified by flash chromatography using ethyl acetate/hexanes 1:1 to give the title compound (8.59 g, 24.8 mmol, 94%).

Step 3. Synthesis of Boc-Pro(4t-NH(Fmoc))-OH:

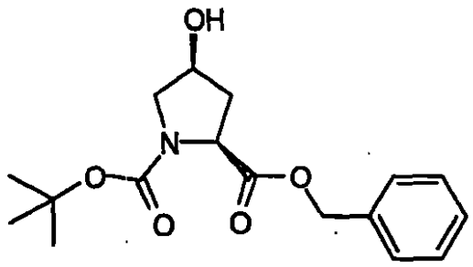


A mixture of N-α-t-butoxycarbonyl-trans-4-azido-L-proline benzyl ester (8.59 g, 24.8 mmol) and 10% palladium on carbon (900 mg) in ethanol (500 mL) was hydrogenated at 50 psi for 14 h using a Parr hydrogenation apparatus. The mixture was filtered, concentrated, dissolved in methanol (60 mL), refiltered and concentrated to give a colorless oil. The oil was dissolved in water (53 mL) containing sodium carbonate (5.31 g, 50.1 mmol) and a solution of fluorenylmethyl succinyl carbonate (8.37 g, 29.8 mmol) in dioxane (60 mL) was added over 40 min. The reaction mixture was stirred at room temperature for 17 h, then concentrated to remove the dioxane and diluted with water (200 mL). The solution was washed with ether (3 x 100 mL). The pH of the aqueous solution was adjusted to 2 by the addition of citric acid (caution! foaming!) and water (100 mL). The mixture was extracted with dichloromethane (400 mL, 100 mL, 100 mL) and the combined organic layers were dried (sodium sulfate), filtered and concentrated to give the title compound.

Example VII. Synthesis of N-t-butoxycarbonyl-4-trans-(N-fluorenylmethyloxycarbonyl aminomethyl)-L-proline (Boc-Pro(4t-MeNHFmoc)-OH):



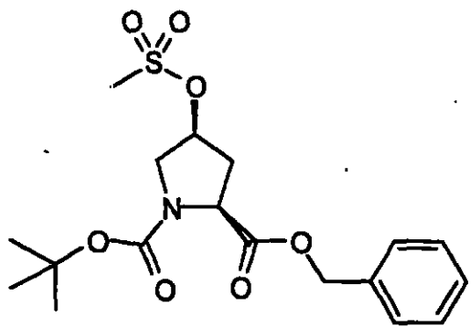
Step 1. Synthesis tert-butoxycarbonyl cis-4-hydroxy-L-proline benzyl ester (Boc-Pro(4-cis-OH)-OBn):



To a mixture of cis-hydroxy-L-proline (5 g, 38.1 mmol) in benzene (45 mL) and benzyl alcohol (45 mL) was added p-toluenesulfonic acid monohydrate (7.6 g, 40.0 mmol). The reaction mixture was heated at 125°C for 20 h while water (2ml) was removed using a Dean-Stark trap. The solution was filtered while still hot, and then ether (150 ml) was added. The solution was allowed to cool for three h at room temperature, then three h at 4 °C. The resulting solid was collected, washed with ether (100 mL) and dried in vacuo for 1 h to give 13.5 grams of white solid. The solid was dissolved in dioxane (40 mL) and diisopropylethylamine (7.6 mL), and then di-tert-butyl-dicarbonate (10 g, 45.8 mmol) was added over 5 min while using an ice bath to maintain a constant reaction temperature. After 10 h at room temperature the reaction mixture was poured into cold water (200 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (3 x 100 mL) and saturated aqueous sodium chloride (50 mL), dried (sodium sulfate), filtered and concentrated. The crude product was purified

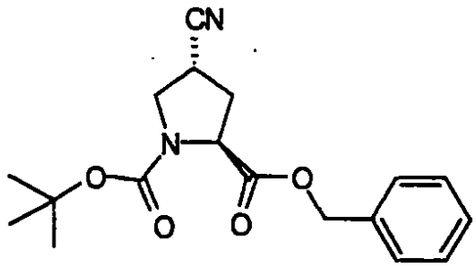
by flash chromatography using 40-60% ethyl acetate in hexanes to give the title compound (10.04 g, 31.24 mmol, 82%).

Step 2. Synthesis of N-t-butoxycarbonyl cis-4-mesyloxy-L-proline benzyl ester (Boc-Pro(4-cis-OMs)-OBn):



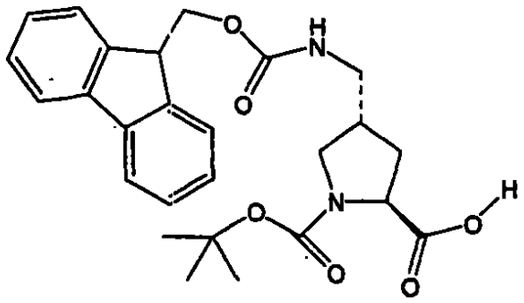
To a solution of Boc-Pro(4-cis-OH)-OBn (8.45 g, 26.3 mmol) in pyridine (65 mL) at 0°C, was added methanesulfonyl chloride (3.4 mL, 44 mmol) dropwise over 7 min. The reaction mixture was allowed to warm to room temperature over 2 h, then stirred overnight. A solution of 10% water in pyridine (20 mL) was added over 15 min and the reaction mixture was concentrated. The residue was dissolved in water and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were washed with water (2 x 50 mL) saturated aqueous sodium bicarbonate (50 mL) and saturated aqueous sodium chloride (50 mL), dried (sodium sulfate), filtered and concentrated. The resulting residue was dissolved in toluene (100 mL) and concentrated to remove traces of pyridine. The residue was dried in vacuo for 30 min to afford the title compound (10.7 g, 102%), then used in the next step without purification.

Step 3. N-t-butoxycarbonyl-trans-4R-cyano-L-proline benzylester (Boc-Pro(4-trans-CN)-OBn):



A solution of Boc-Pro(4-cis-OMs)-OBn (10.7 g, 26.3 mmol) and tetrabutylammonium cyanide (15.0 g, 56 mmol) in dimethylformamide (100 mL) was heated in an oil bath at 55°C for 28 h. After cooling, water (150 mL) was added and the mixture was extracted with ethyl acetate (3 x 200 mL). The combined organic layers were washed with water (3 x 100 mL) and saturated aqueous sodium chloride (100 mL), dried (sodium sulfate), filtered and concentrated. The resulting residue was purified by flash chromatography (1:1 ether/hexanes) and then recrystallized from ethyl acetate/hexanes to provide the title compound (2.40 g, 7.26 mmol, 28%).

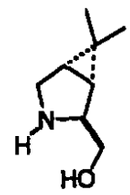
Step 4. N-t-butoxycarbonyl-4-trans-(N-fluorenylmethyloxycarbonyl aminomethyl)-L-proline (Boc-Pro(4t-MeNHFmoc)-OH) :



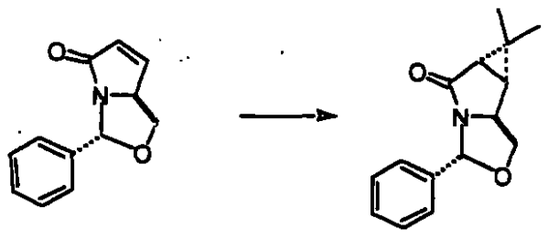
A mixture of the compound of Step 3 above (2.31 g, 7 mmol), water (10 mL), methanol (85 mL) and 10% palladium on carbon (700 mg) was hydrogenated at 50 psi for 11 h using a Parr hydrogenation apparatus. The mixture was filtered and concentrated. Water (15 mL) and sodium carbonate (1.5 g, 14.2 mmol) was added to the residue. A solution of fluorenylmethyl succinyl carbonate (2.36 g, 7.0 mmol) in dioxane (17 mL) was added over 5 min and stirring was continued for 28

h at room temperature. The reaction was concentrated in vacuo to a 15 mL volume, and water (100 mL) was added. The solution was washed with ether (3 x 75 mL). The pH of the aqueous solution was adjusted to 2 by the addition of citric acid (approx. 20 g, caution! foaming!) and water (100 mL). The mixture was extracted with dichloromethane (4 x 100 mL), and the combined organic layers were dried (sodium sulfate), filtered and concentrated. The crude product contained a major impurity which necessitated a three step purification. The crude product was dissolved in dichloromethane (50 mL) and trifluoroacetic acid (50 mL) and stirred for 5 h before being concentrated. The residue was purified by preparatory reverse-phase HPLC. The pure 4-(N-fluorenylmethyloxycarbonyl aminomethyl)proline trifluoroacetate salt (1.887 g, 3.93 mmol) was dissolved in dioxane (10 mL), acetonitrile (20 mL) and diisopropylethylamine (1.4 mL, 8 mmol). To the reaction mixture was added a solution of di-tert-butyldicarbonate (1.1g, 5 mmol) in dioxane (5 mL). After stirring for 18 h, the pH of the solution was adjusted to 2 by the addition of citric acid (caution: foaming!) and water (100 mL). The mixture was extracted with ethyl acetate (3 x 150 mL) and the combined organic layers were washed with saturated aqueous sodium chloride (100 mL), dried (sodium sulfate), filtered and concentrated. The crude product was dissolved in saturated aqueous sodium bicarbonate(100 mL) and washed with ether (3 x 75 mL). The aqueous layer was adjusted to pH = 3 by the addition of citric acid, then extracted with dichloromethane (4 x 100 mL). The combined organic layers were dried (sodium sulfate), filtered and concentrated to the title compound (1.373 g, 2.94 mmol, 42%).

Example VIII. Synthesis of 3,4-isopropylideneprolinol:

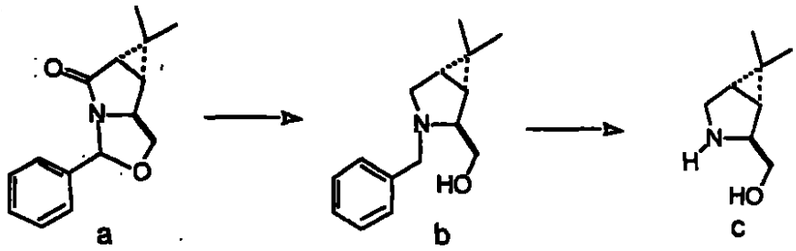


Step I. Cyclopropanation reaction (*Tetrahedron Lett.* 1993, 34(16), 2691 and 2695):



To a stirring solution of isopropyltriphenyl- phosphonium iodide (4.14 g, 9.58 mmol) in tetrahydrofuran (60 mL) at 0 °C, was added n-butyllithium (1.6 M in hexanes, 5.64 mL, 9.02 mmol) over 5 min. After 30 min, a solution of enamide ((5R, 7S)-5-phenyl-5,6,7,7a-tetrahydro-6-oxapyrrolizin-3-one) (1.206 grams, 6.0 mmol) (see *J. Org. Chem.* 1999, 64(2), 547 for the synthesis of the enamide starting material) in tetrahydrofuran (40 mL) was added over 10 min. After an additional 10 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 4 hours. The reaction was poured into water (400 mL) and extracted with diethyl ether (400 mL) and ethylacetate (2 x 400 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated to give the desired crude product. The residue was purified by flash chromatography eluting with 3:5:2 ethylacetate/hexanes/methylene chloride to give pure cyclopropanated product (750 mg, 3.08 mmol, 51%).

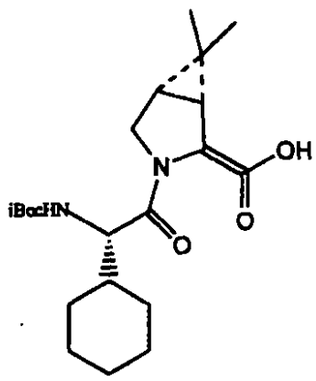
Step 2. Synthesis of 3,4-isopropylideneprolinol P[3,4-(diMe-cyclopropyl)]-alcohol) (*J. Org. Chem.* (1999) 64(2), 330):



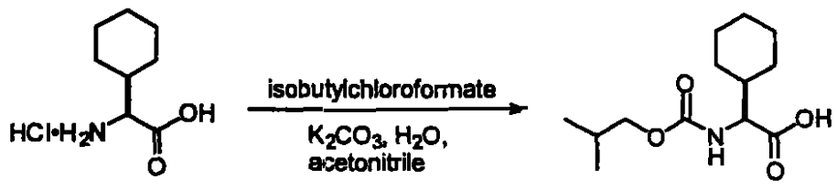
A mixture of the product obtained in step 1 above (1.23 grams, 5.06 mmol) and lithium aluminum hydride (1.0 M in THF, 15 mL, 15 mmol) was heated at reflux for 5 hours. After cooling to 0 °C, the remaining aluminum hydride was carefully quenched by the dropwise addition of saturated aqueous sodium sulfate

(1.5 mL) over 15 min. The mixture was diluted with ethylacetate (40 mL) and then filtered through celite. The filtrate was dried with sodium sulfate, filtered and concentrated to give crude N-benzyl aminoalcohol (1.25 grams), which was carried on to the next step without further purification. A solution of crude N-benzyl aminoalcohol (1.25 grams, 5.06 mmol) in 1:1 acetic acid/ethylacetate (30 mL) with 10% Pd/C (1 gram) was hydrogenated at 50 psi for 16 hours using a Parr hydrogenation apparatus. The reaction mixture was filtered to remove the carbon-based catalyst and the filtrate was concentrated. The residue was dissolved in water (30 mL) and the pH was adjusted to 13 with 50% NaOH. The mixture was extracted with ether (3 x 60 mL). The combined extract was dried with sodium sulfate, filtered and concentrated to give crude aminoalcohol (485 mg, 3.43 mmol). This material was taken to the next step without further purification.

Example IX. Synthesis of iBoc-G(Chx)-Pro(3,4-isopropylidene)- carboxylic acid :



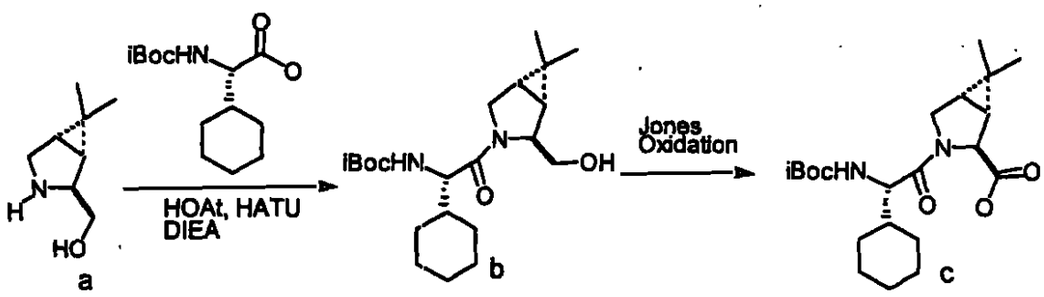
Step 1. Synthesis of isobutyloxycarbonyl- cyclohexylglycine (iBoc-G(Chx)-OH):



To a solution of the commercially available cyclohexylglycine hydrochloride (15 g, 77.4 mmol) in acetonitrile (320 ml) and water (320 ml) was added potassium carbonate. Isobutylchloroformate (11.1 ml, 85.1 mmol) was added to the clear solution over 15 minutes and the reaction was stirred for 17 hours. The

acetonitrile was removed under reduced pressure and the remaining aqueous layer was extracted twice with ether (100 ml). The aqueous layer was then acidified to pH 1 with 6N hydrochloric acid and extracted with dichloromethane (3 x 300 ml). The organic layer was dried over sodium sulfate, filtered and concentrated to yield 18.64 g (94%) product as a white solid.

Step 2. Synthesis of isobutyloxycarbonyl-cyclohexylglycyl-3,4-isopropylideneproline (iBoc-G(Chx)- P[3,4-(diMe-cyclopropyl)]-OH):



a) Coupling step

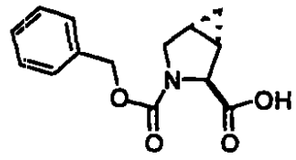
To a solution of iBoc-G(Chx)-OH (890 mg, 3.45 mmol) in acetonitrile (20 mL) was added HATU (1.33 g, 3.5 mmol), HOAt (476 mg, 3.5 grams) and then diisopropylethylamine (2.5 mL, 14 mmol). After a 2 minutes, 3,4-isopropylideneprolinol (485 mg, 3.43 mmol) was added and the reaction mixture was stirred overnight. Addition of saturated aqueous sodium bicarbonate was followed by extraction with ether and ethylacetate. The combined organic layers were dried, filtered and concentrated. The residue was purified by flash chromatography eluting with 1:1 ethylacetate/hexanes to give pure dipeptide alcohol iBoc-G(Chx)-3,4-isopropylideneprolinol (870 mg, 2.3 mmol, 67%)

b) Jones oxidation step

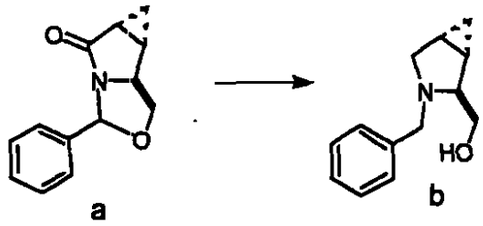
To a solution of dipeptide alcohol iBoc-G(Chx)-3,4-isopropylideneprolinol (100 mg, 0.26 mmol) in acetone (2 mL) stirring at 0 °C was added Jones reagent (300 µL) dropwise over 5 min. [Jones Reagent: Prepared from chromium trioxide (13.4 g) and concentrated sulfuric acid (11.5 mL) diluted with water to a total volume of 50 mL.] After stirring at 0 °C for 3 hours, isopropanol (500 µL) was added and stirring continued for an additional 10 minutes. The reaction mixture

was diluted with water (20 mL) and extracted with ethylacetate (3 x 70 mL). The combined organic layers were dried, filtered and concentrated to give the dipeptide iBoc-G(Chx)-3,4-isopropylideneproline (100 mg, 0.25 mmol, 96%).

Example X. Synthesis of N-Cbz-3,4-methanoproline:



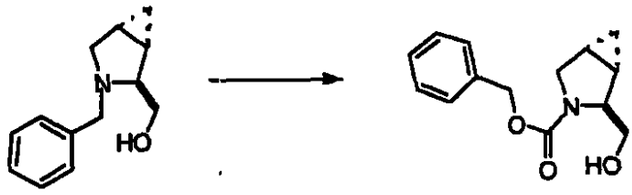
Step 1. Synthesis of N-benzyl-3,4-methanoprolinol:



a b

A mixture of the benzylidene starting material (J. Org. Chem. 1999, 64(2), 547) (4.6 grams, 21.4 mmol) and lithium aluminum hydride (1.0 M in THF, 64 mL, 64 mmol) was heated at reflux for 5 hours. After cooling to 0 °C, the remaining aluminum hydride was carefully quenched by the dropwise addition of saturated aqueous sodium sulfate (5 mL) over 15 min. The mixture was diluted with ethylacetate (200 mL) and then filtered through celite. The filtrate was dried with sodium sulfate, filtered and concentrated to give crude N-benzyl aminoalcohol (3.45 grams), which was carried on to the next step without further purification.

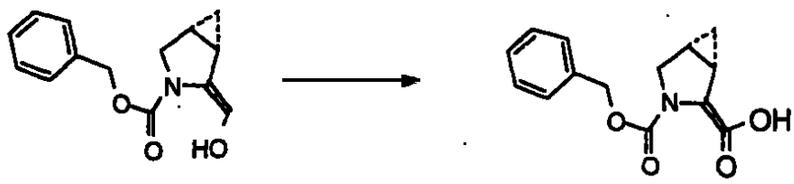
Step 2. Synthesis of N-benzyloxycarbonyl-3,4-methanoprolinol (CBz-P(3,4-CH2)-ol):



A solution of crude N-benzyl aminoalcohol (3 grams, 14.76 mmol) in methanol (120 mL) and concentrated HCl (1.5 mL) with 10% Pd/C (300 mg) was

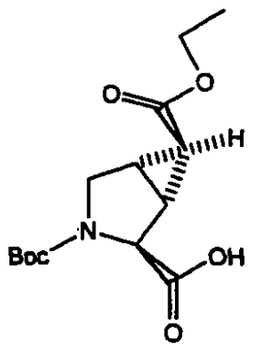
hydrogenated at 50 psi for 16 hours. The reaction mixture was filtered to remove the carbon-based catalyst and the filtrate was concentrated. The residue was dissolved in water/dioxane (100 mL) and diisopropylethylamine (3.2 mL) was added. Benzyl chloroformate (2.76 mL, 16.2 mmol) was added and the reaction was stirred overnight. The reaction mixture was concentrated, dissolved in 1M HCl (100 mL) and extracted with ethylacetate (3 x 200 mL). The combined organic layers were dried with magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography using 1:3 ethylacetate/hexanes to give the N-Cbz-3,4-methanoprolinol (2.4 g)

Step 3. Synthesis of N-benzyloxycarbonyl-3,4-methanoproline (CBz-P(3,4-CH2)-OH):



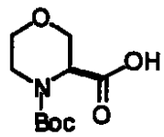
To a solution of N-Cbz-3,4-methanoprolinol (2.2 g, 8.90 mmol) in acetone (68 mL) stirring at 0 °C, was added Jones reagent (6.6 mL) dropwise over 5 min. [Jones Reagent: Prepared from chromium trioxide (13.4 g) and concentrated sulfuric acid (11.5 mL) diluted with water to a total volume of 50 mL.] After stirring at 0 °C for 3 hours, isopropanol (11 mL) was added and stirring continued for an additional 10 minutes. The reaction mixture was diluted with water (400 mL) and extracted with ethylacetate (3 x 500 mL). The combined organic layers were dried over magnesium sulfate, filtered and concentrated to give N-Cbz-3,4-methanoproline (2.25 g, 96%)

Example XI. Synthesis of Boc-(6S-carboethoxymethano) proline:



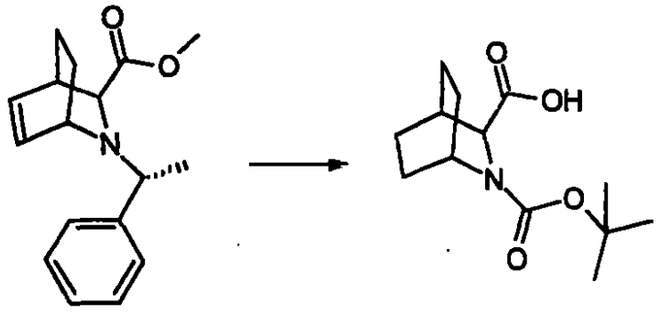
The synthesis of the title compound was carried out according to the published procedure: Marinozzi, M.; Nataini, B.; Ni, M.H.; Costantino, G.; Pellicciari R. *IL Farmaco (*1995*)* 50 (5), 327-331.

Example XII. Synthesis of Boc-3-morpholine carboxylic acid :



The synthesis of the title compound was carried out according to the published procedure: Kogami Y., Okawa, K. *Bull. Chem. Soc. Jpn.* (1987) 60, 2963-2965.

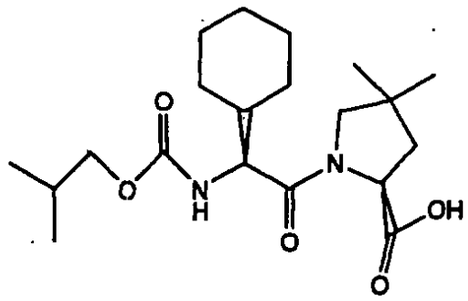
Example XIII. Synthesis of N-tert-butoxycarbonyl 2-aza-3S-hydroxycarbonyl-[2.2.2]-bicyclooctane:



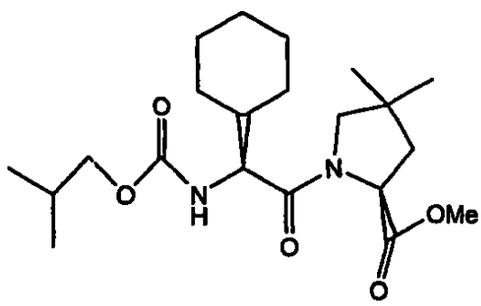
A solution of crude 2-aza-2-(1-phenylethyl)-3S-methoxycarbonyl-[2,2,2]-bicyclooct-5-ene (10 mmol) (Tetrahedron (1992) 48(44) 9707-9718) and 10% Pd on carbon (1 g) in methanol (30 mL) was acidified with 12N HCl then hydrogenated at 50 psi for 16 hours using a Parr hydrogenation apparatus. The

reaction mixture was filtered to remove the carbon-based catalyst and the filtrate was concentrated. The residue was dissolved in concentrated HCl and stirred overnight. The solution was concentrated and redissolved in acetonitrile (50 mL). Diisopropylethylamine (3.5 mL) and di-tert-butyldicarbonate (1 g) were added. The reaction mixture was stirred for 24 hours and then concentrated. The residue was dissolved in CH_2Cl_2 and 5% aqueous sulfuric acid. The reaction mixture was extracted with CH_2Cl_2 and the combined organic layers were concentrated. The residue was dissolved in 10% saturated sodium bicarbonate, washed with diethyl ether (2x) and acidified with 5% aqueous sulfuric acid. The aqueous layer was extracted with ethylacetate (2x). The combined ethylacetate layers were dried filtered and concentrated to give N-tert-butoxycarbonyl 2-aza-3S-hydroxycarbonyl-[2,2,2]-bicyclooctane (650 mg).

Example XIV. Synthesis of isobutyloxycarbonyl-cyclohexylglycyl-4,4-dimethyl proline (iBoc-G(Chx)-P(4,4-dimethyl)-OH):



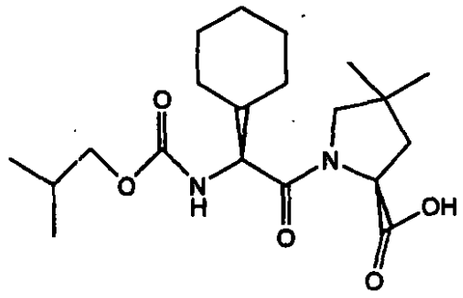
Step I. Synthesis of iBoc-G(Chx)-P(4,4-dimethyl)-OMe:



To a solution of iBoc-G(Chx)-OH (Example IX, Step 1.)(377 mg, 1.95 mmol) in acetonitrile (7 mL) was added successively HCl•HN-Pro(4,4-dimethyl)-OMe (Example I, step 6)(377 mg, 1.95 mmol), N-hydroxybenzotriazole (239 mg,

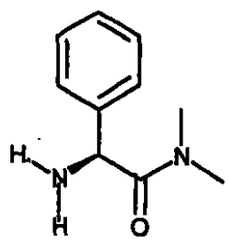
1.75 mmol), TBTU (845 mg, 2.63 mmol) and diisopropylethylamine (1.35 mL, 7.8 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated and the remaining residue was dissolved in ethylacetate. The organic layer was washed twice with 10 ml portions of saturated sodium bicarbonate solution, 1N hydrochloric solution, and brine. The organic layer was dried over sodium sulfate, filtered and concentrated to a white solid (612 mg, 79%).

Step 2. Synthesis of iBoc-G(Chx)-P(4,4-dimethyl)-OH:

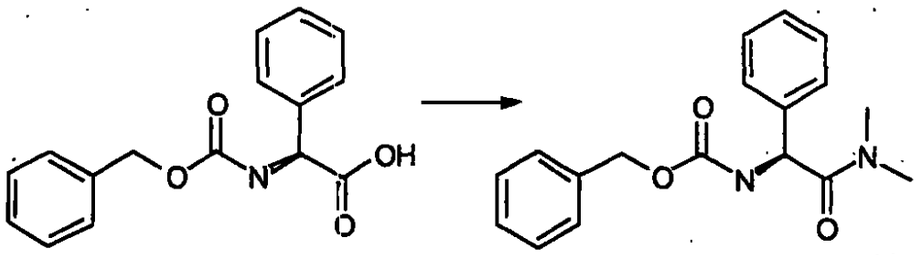


The methyl ester obtained in Step 1 above (612 mg, 1.54 mmol) in methanol (6 ml) was saponified in the presence of 2M lithium hydroxide (1.16 ml) for three hours. The methanol was removed under reduced pressure and the remaining residue was diluted with ethylacetate and acidified to pH=2 with 1N hydrochloric acid. The layers were separated and the organic layer was washed with water and brine, dried over sodium sulfate, filtered and concentrated.

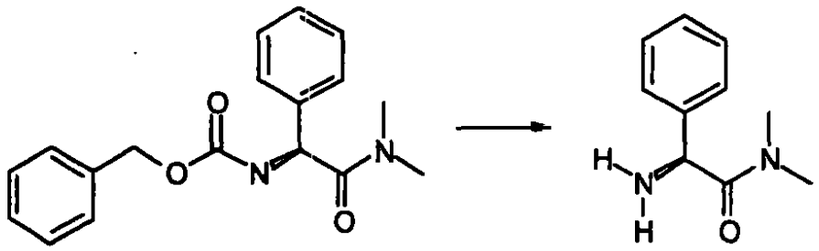
Example XV. Synthesis of L-phenylglycine dimethylamide



Step 1. Synthesis of N-benzyloxycabonyl –L-phenylglycine dimethylamide (CBz-Phg-NMe2):



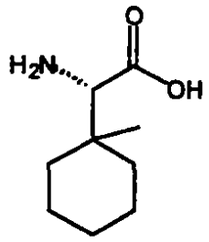
N-benzyloxycarbonyl-L-phenylglycine (25g, 88 mmols) was dissolved in THF (800mL) and cooled to -10 °C. N-methylmorpholine (9.7 mL, 88 mmols) and isobutylchloroformate (11.4 mL, 88.0 mmols) were added and the mixture allowed to stir for 1 minute. Dimethylamine (100 mL, 2M in THF) was added and the reaction was allowed to warm to room temperature. The mixture was filtered and the filtrate concentrated in *vacuo* to afford N-benzyloxycabonyl –L-phenylglycine dimethylamide (32.5 g) as a yellow oil.



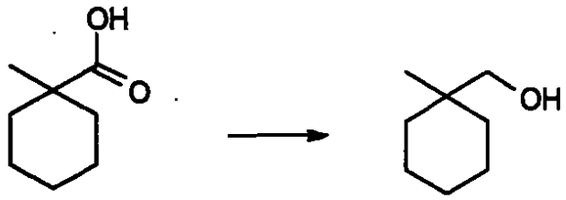
Step 2. Synthesis of L-phenylglycine dimethylamide (H-Phg-NMe2):

The N-benzyloxycarbonyl-L-phenylglycine dimethylamide (32.5 g) obtained above was dissolved in methanol (750 ml) and 10% palladium on activated carbon (3.3 g) was added. This mixture was hydrogenated on a Parr apparatus under 35 psi hydrogen for 2 hours. The reaction mixture was filtered and the solvent removed in *vacuo* and the residue recrystallized from methanol-hexanes to afford phenylglycine dimethylamide (26g) as an off white solid. The ee of this material was determined to be >99% by HPLC analysis of the 2,3,4,6-tetra-O-acetylglucopyranosylthioisocyanate derivative.

Example XVI. Synthesis of (1-methylcyclohexyl) glycine:



Step 1. 1-methyl-1-hydroxymethylcyclohexane



To a solution of 1-methyl-1-hydroxycarbonylcyclohexane (10 g, 70 mmol) in tetrahydrofuran(300 mL) at 0 °C was added 1M diborane in tetrahydrofuran (200 mL, 200 mmol) over 90 minutes. The cooling bath was removed and the reaction mixture was stirred at room temperature for two days. The remaining borane was quenched by the slow addition of saturated sodium bisulfate (10 mL) over 90 min with cooling. Additional saturated sodium bisulfate (200 mL) was added and after 20 min of stirring the aqueous layer was removed. The organic layer was washed with water and saturated sodium chloride, dried, filtered and concentrated. The

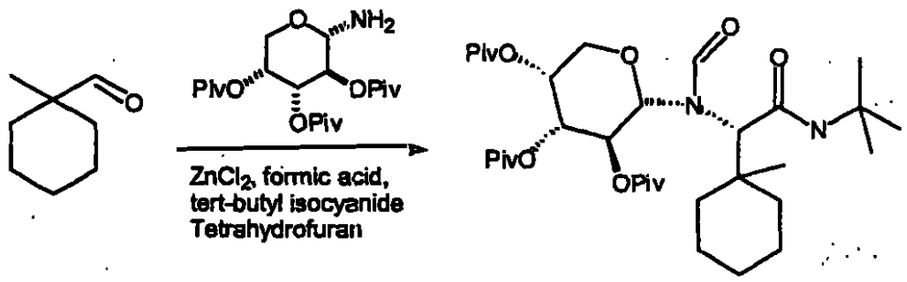
residue was purified by flash chromatography using 20% diethylether in hexanes to give 1-methyl-1-hydroxymethylcyclohexane (6.17 g, 48 mmol, 69%).

Step 2. 1-methylcyclohexylcarboxaldehyde:



To a solution of 1-methyl-1-hydroxymethylcyclohexane (6.17 g, 48 mmol) and triethylamine (20.1 mL, 144 mmol) in dichloromethane (150 mL) at 0 °C, was added a solution of pyridine sulfur trioxide complex (22.9 g, 144 mmol) in dimethylsulfoxide (150 mL) over 15 min. The cooling bath was allowed to warm to room temperature over two hours, at which time the reaction mixture was poured into brine with ice (400 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (200 mL). The combined organic layers were diluted with hexanes (600 mL) and washed with 1M HCl (2 x 150 mL), saturated sodium chloride (2 x 100 mL), dried, filtered and concentrated. The residue was purified by flash chromatography to give 1-methylcyclohexylcarboxaldehyde (1.77 g, 13.8 mmol, 29%).

Step 3. Synthesis of N-formyl-N-glycosyl- 1-methylcyclohexyl- tert-butylamide :

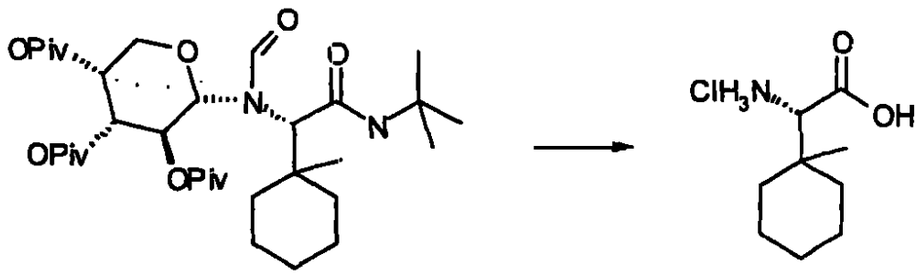


The synthesis of the 2,3,4-tri-O-pivaloyl-□-D-arabinosylamine was carried out according to the published procedure (Kunz. H.; Pfrengle, W.; Ruck, K.; Wilfried, S. *Synthesis* (1991) 1039-1042).

To a solution of 1-methylcyclohexylcarboxaldehyde (1.17 g, 8.34 mmol), 2,3,4-tri-O-pivaloyl-□-D-arabinosylamine (8.3 g, 20.7 mmol), formic acid (850 µL, 22.2 mmol) and tert-butylisocyanide (2.4 mL, 21.2 mmol) in tetrahydrofuran (170

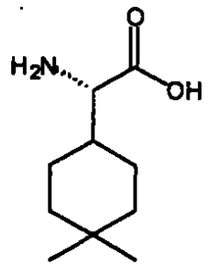
mL) at –30 °C was added 0.5M zinc chloride in tetrahydrofuran (41 mL, 20.57 mmol). The solution was stirred at –20 °C for 3 days, then concentrated. The residue was diluted with CH_2Cl_2 (500 mL), washed with saturated sodium bicarbonate (2 x 500 mL), water (500 mL). The organic layer was dried, filtered and concentrated to give a clear oil. Flash chromatography (20% ethylacetate in hexanes) provided pure product (4.3 g, 6.6 mmol, 33%)

Step 4. Synthesis of (1-methylcyclohexyl)glycine:

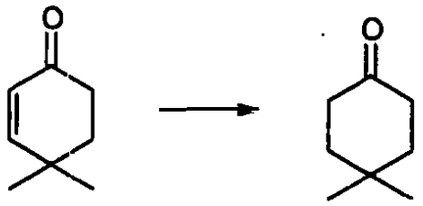


A solution of the product obtained in step 3 above (4.3 g, 6.6 mmol) in dichloromethane (30 mL) and saturated anhydrous methanolic HCl (30 mL) was stirred overnight. The solution was concentrated and the residue was dissolved in water (100 mL) and washed with pentane (2 x 100 mL). The aqueous layer was concentrated and the residue was dissolved in 6N HCl (50 mL) and heated at reflux for 30 hours. The solution was concentrated to give the crude (1-methylcyclohexyl)glycine hydrochloride (790 mg, 3.82 mmol, 58%).

Example XVII. Synthesis of (4,4-dimethylcyclohexyl)glycine:

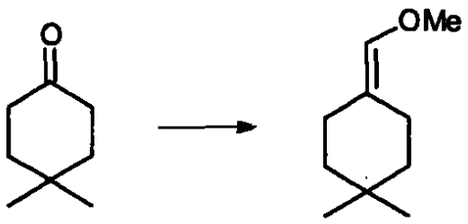


Step 1. Synthesis of 4,4-dimethylcyclohexanone:



A mixture of 4,4-dimethylcyclohex-2-en-1-one (12 mL, 91.2 mmol) and Degussa type 10% Pd on carbon (2 g) was hydrogenated at 40 psi for 18 hours. The mixture was filtered and concentrated (^{1}H NMR showed a mixture of ketone and alcohol in a 5:3 ratio). The mixture was dissolved in acetone (400 mL) and cooled to 0 °C. Jones reagent (40 mL) was added over 30 min and the cooling bath was removed. After 2 days the excess acetone was evaporated and the resulting residue was dissolved in water and diethylether. The ether layer was washed with water until colorless, dried, filtered and concentrated to give 4,4-dimethylcyclohexanone (7.4 g, 58.6 mmol, 64%).

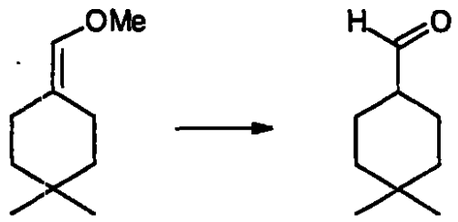
Step 2. Synthesis of the methyl enol ether of 4,4-dimethylcyclohexylcarboxaldehyde:



To a solution of methoxymethyl triphenylphosphonium chloride (8.6 g) in tetrahydrofuran (125 mL) at 0 °C was added n-butyllithium (1.6M in hexanes, 14.3

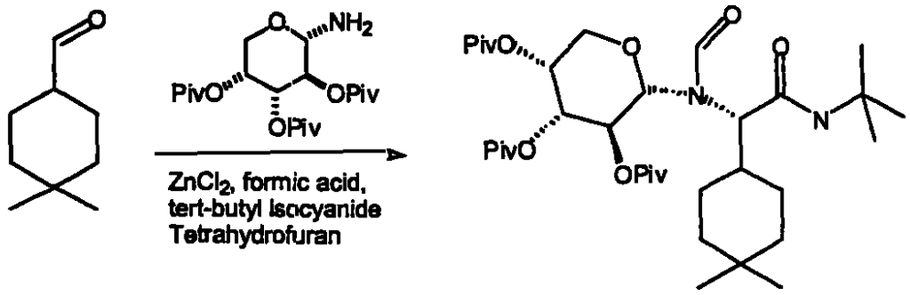
mL) over 10 min. After 30 min the reaction mixture was cooled to –78 °C and a solution of 4,4-dimethylcyclohexanone (2.45 g, 19.1 mmol) in tetrahydrofuran (50 mL) was added over 20 min. After 1 hour the cooling bath was remove and the reaction was warmed slowly to 0 °C. The reaction was diluted with saturated ammonium chloride (50 mL), ethylacetate (100 mL) and hexanes (100 mL). The organic layer was washed with water and brine, dried filtered and concentrated. The residue was stirred with hexanes (70 mL) for 10 min and filtered. The filtrate was concentrated and chromatographed using 25% ethylacetate in hexanes to give the title compound (1.925 g, 12.5 mmol, 65%).

Step 3: 4,4-dimethylcyclohexylcarboxaldehyde:



A solution of the methyl enol ether of 4,4-dimethylcyclohexylcarboxaldehyde (1.925 g, 12.5 mmol) (Step II above), tetrahydrofuran (100 mL) and 6M HCl (20 mL) was stirred at room temperature for 4 hours. The reaction mixture was diluted with hexanes, diethylether, brine and water. The organic layer was dried, filtered and concentrated to give 4,4-dimethylcyclohexylcarboxaldehyde (1.0 g, 7.1 mmol, 57%).

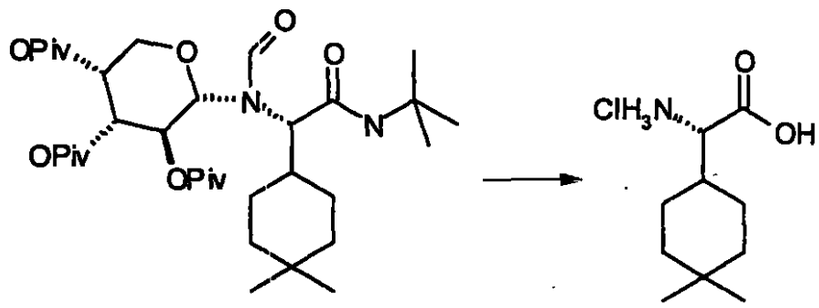
Step 4. Synthesis of N-formyl-N-glycosyl- 4,4-dimethylcyclohexyl- tert-butylamide :



To a solution of 4,4-dimethylcyclohexylcarboxaldehyde (1.17 g, 8.34 mmol), 2,3,4-tri-O-pivaloyl-α-D-arabinosylamine (3.43 g, 8.55 mmol), formic acid

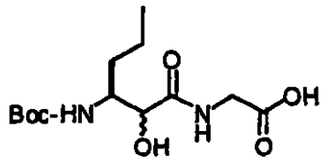
(350 µL, 9.17 mmol) and tert-butylisocyanide (990 µL, 8.76 mmol) in THF (70 mL) at –30 °C was added 0.5M zinc chloride in tetrahydrofuran (17 mL, 8.5 mmol). The solution was stirred at –20 °C for 2 days, then concentrated. The residue was diluted with dichloromethane (200 mL), washed with saturated sodium bicarbonate (2 x 200 mL), water (200 mL). The organic layer was dried, filtered and concentrated to give a clear oil. Flash chromatography (20% ethylacetate in hexanes) provided pure product (2.1 g, 3.3 mmol, 39%)

Step 5. Synthesis of (4,4-dimethylcyclohexyl)glycine:

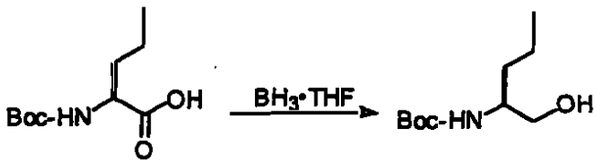


A solution of the Ugi product obtained in step 4 above (2.1 g, 3.3 mmol) in dichloromethane (20 mL) and saturated anhydrous methanolic HCl (20 mL) was stirred overnight. The solution was concentrated and the residue was dissolved in water (100 mL) and washed with pentane (2 x 100 mL). The aqueous layer was concentrated and the residue was dissolved in 6N HCl (40 mL) and heated at reflux for 30 hours. The solution was concentrated to give the crude (1-methylcyclohexyl)glycine hydrochloride (300 mg, 1.36 mmol, 41%).

Example XVIII. Synthesis of Boc-nVal-(CHOH)-Gly-OH:

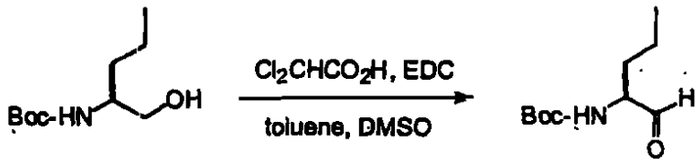


Step 1. Preparation of Boc-norvalinol:



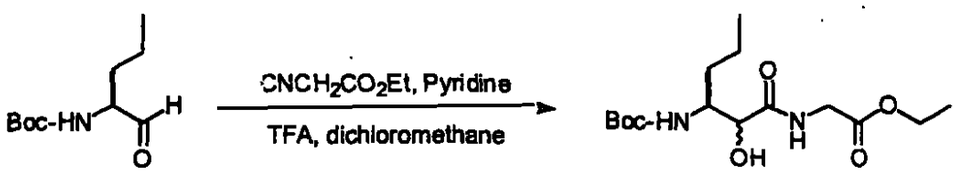
To a solution of Boc-norvaline (25.0 g, 0.115 mol) in tetrahydrofuran (461 mL), cooled to 0°C, was added borane/tetrahydrofuran complex (461 mL of a 1.0M solution in tetrahydrofuran) dropwise. After 1h at 0°C, the solution was warmed to room temperature over a period of 1.5h. TLC indicated that the reaction was complete. Methanol was added to quench the reaction. The solution was concentrated to yield the title compound (22.56 g, 96%) as a foamy syrup. TLC of the products indicated satisfactory purity. R_f = 0.34 (40% ethyl acetate/hexanes).

Step 2. Preparation Boc-norvalinal:



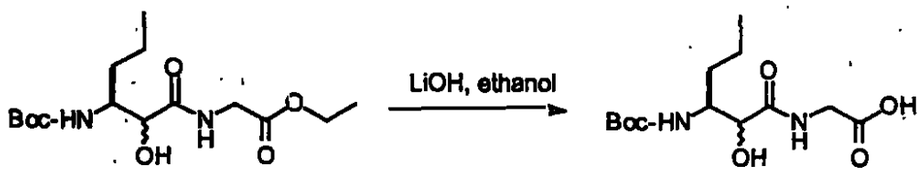
To Boc-norvalinol (7.77 g, 38 mmol), in anhydrous dimethylsulfoxide (153 mL) and toluene (153 mL) was added EDC (73.32g, 382 mmol). After the solution was cooled to 0°C, dichloroacetic acid (15.8 mL, 191 mmol) was added dropwise. After addition was complete, the reaction was stirred for 15 min. The solution was allowed to warm to room temperature over a period of 2h. The reaction mixture was concentrated to remove the toluene, then dissolved in ethyl acetate. The solution was washed successively with 1N sodium bisulfate, saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered and concentrated to afford crude Boc-norvalinal which was used directly in the next step. TLC R_f = 0.84 (40% ethyl acetate/hexanes).

Step 3. Synthesis of Boc-nVal-(CHOH)-Gly-OEt:



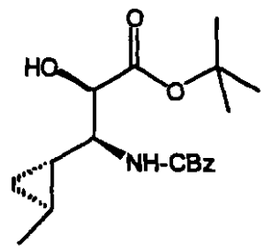
To a solution of the crude Boc-norvalinal (4.18 g, 20.77 mmol) in dichloromethane (83 mL) was added ethylisocyanoacetate (2.72 ml, 24.93 mmol) and pyridine (6.72 ml, 83.09 mmol). After the solution was cooled to 0°C, trifluoroacetic acid (4.15 ml, 41.54 mmol) was added dropwise. After stirring for 1h, the solution was stirred at room temperature for 18 hours while allowing the solvent from the reaction mixture in an uncovered vessel to evaporate under ambient conditions. The reaction mixture was concentrated, then dissolved in ethyl acetate. The solution was washed successively with 1N sodium bisulfate, saturated sodium bicarbonate and brine, dried over sodium sulfate, filtered and then concentrated. The residue was purified by flash chromatography eluting with 20% to 40% ethylacetate/hexanes to afford 2.8 g of the title compound as a yellow syrup. Low resolution mass spectroscopy confirmed the presence of the desired product (MH^+ 333).

Step 4. Synthesis of Boc-nVal-(CHOH)-Gly-OH:

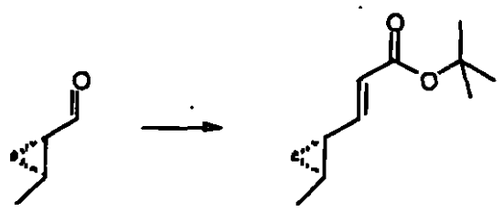


The product obtained (Boc-nVal-(CHOH)-Gly-OEt) (1.52 g, 4.70 mmol) dissolved in ethanol (23 ml) was saponified with 1N lithium hydroxide (18.81 ml) for two hours at room temperature. The reaction mixture was acidified to pH ≅ 2 with Dowex® 50 WX8 ion exchange resin, stirred for 20 minutes and then filtered. The resin was washed well with ethanol and water and the combined filtrates were concentrated to a white foam (0.48 g, 33%).

Example XVIV. Synthesis of (2R,3S,4S,5S)-tert-Butyl N-CBz-3-amino-2-hydroxy-4,5 methylene-hexanoate:

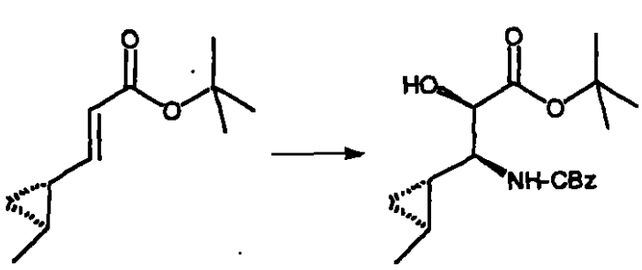


Step 1:



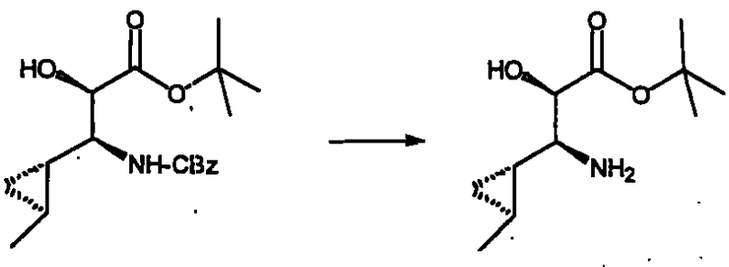
To a solution of tert-Butyl diethylphosphonoacetate (4.7 mL, 20 mmol) dissolved in THF (50 mL) at -78° C was added 1.6M n-butyl lithium in hexanes (12.4 mL). After 30 minutes (1S, 2S)-2-methylcyclopropylcarboxaldehyde (1 g, 12 mmol) (Barrett, A. G. M.; Doubleday, W. W.; Kasdorf, K.; Tustin, G. J., *J. Org. Chem.* (1996) *61*, 3280) in diethyl ether (100 mL) was added over 10 min. The reaction was warmed to 0° C for 2 hours and to 6 °C for 12 hours. The reaction was quenched with saturated ammonium chloride (20 mL) and the organic layer was separated, washed with 50 mL brine and dried over sodium sulfate, filtered and concentrated to afford 3.5 g of a clear oil. Flash chromatography (20% ethylacetate in hexanes) afforded pure unsaturated tert-butylester (1.4 g).

Step 2:



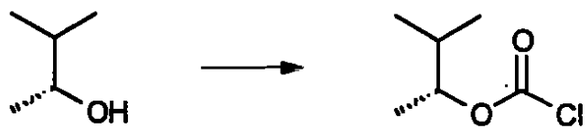
To a solution of benzyl carbamate (3.55g, 23.5 mmols) in n-propanol (24 mL) was added a solution of sodium hydroxide (900 mg ,22.7 mmol)in water (48 mL), followed by tert-butylhypochlorite (2.57 mL, 22.7 mmol). After 15 minutes the reaction was cooled to 0 ^{o}C and $(DHQ)_2PHAL$ (350 mg, 0.45 mmol) was added in n-propanol (24 mL), followed by unsaturated tert-butyl ester (1.4 g) from above in n-propanol (48 mL). Finally potassium osmate (110 mg, 0.30 mmol) in water (2 mL) was added and the solution very rapidly developed a dark green color which persisted for 4 hours. After 6 hours saturated sodium sulfate (50 mL) was added and the mixture extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate, filtered and concentrated. Flash chromatography with 20% ethylacetate in hexanes afforded the desired cBz protected amino tert-butylester as a white solid (316 mg).

Step 3:



A mixture of CBz protected amino tert-butylester (316 mg, 0.9 mmol) and 32mg 10% palladium on carbon in 9 mL methanol was hydrogenated for 8 hours. The mixture was filtered and concentrated to afford the free amine as a clear oil (195 mg).

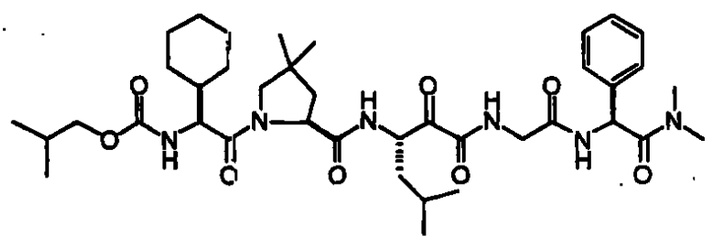
Example XX. Synthesis of 1R,2-dimethylPropyl chloroformate:



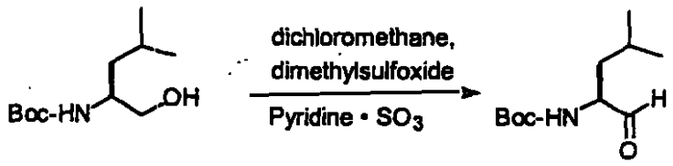
To the commercially available 2R-hydroxy-3-methylbutane (410 mg, 4.65 mmol) was added a solution of 20% phosgene in toluene (1 mL, 2 mmol). The solution was stirred for 6 hours to generate the chloroformate (2 mmol) which was reacted directly and immediately with the desired amine. The S-isomer was synthesized by the same procedure.

II) Representative solution phase synthesis of HCV inhibitors

Example XXI. Solution phase synthesis of iBoc-G(Chx)-Pro(4,4-dimethyl)-Leu-(CO)-Gly-Phg-dimethylamide:

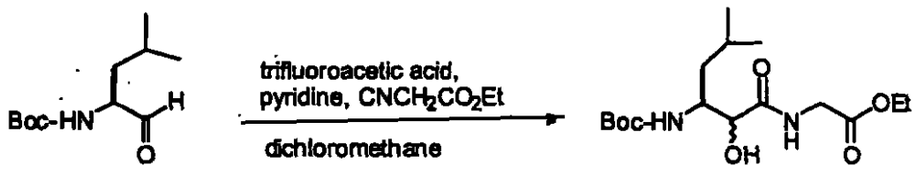


Step 1. Synthesis of tert-butyloxycarbonyl-leucinal (Boc-Leu-CHO):



To a solution of the commercially available (Advanced Chem Tech) Boc-L-leucinol (0.78 g, 3.6 mmol) in anhydrous dichloromethane (17.5 ml) was added triethyl amine (2 ml, 14.36 mmol) and the mixture was cooled to 0 °C. Dimethyl sulfoxide (17.5 ml) was added followed by sulfur trioxide pyridine complex (2.3 g, 14.36 mmol) and the reaction was stirred for two hours. TLC in 1:1 ethylacetate: hexanes confirmed the completion of the reaction. The reaction mixture was concentrated and the remaining residue diluted with ethylacetate. The ethylacetate layer was washed with 1M hydrochloric acid (2 x 75 ml) followed by saturated sodium bicarbonate solution (2 x 75 ml) and brine (75 ml). The organic layer was dried (sodium sulfate), filtered and concentrated to yield 775 mg of product.

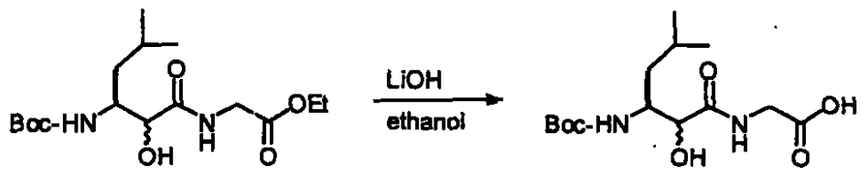
Step 2. Synthesis of Boc-2-hydroxy-3-amino-5-methyl hexanoyl-glycine ethyl ester (Boc-Leu-(CHOH)-Gly-OEt):



To a solution of Boc-Leucine aldehyde (0.77 g, 3.59 mmol) in anhydrous dichloromethane (24 ml) was added anhydrous pyridine (1.16 ml, 14.36 mmol) and ethylisocyanoacetate (0.4 ml, 4.66 mmol). The reaction mixture was cooled to 0 °C and trifluoroacetic acid (0.55 ml, 7/18 mmol) was added over two minutes. The reaction mixture was capped and stirred at 4 °C for four days, and at room temperature for one day. The reaction mixture was diluted with dichloromethane (350 ml) and washed twice each with 75 ml portions of 1M hydrochloric acid, saturated sodium bicarbonate and brine. The organic layer was dried, filtered and concentrated. The residue obtained was subjected to flash chromatography in a

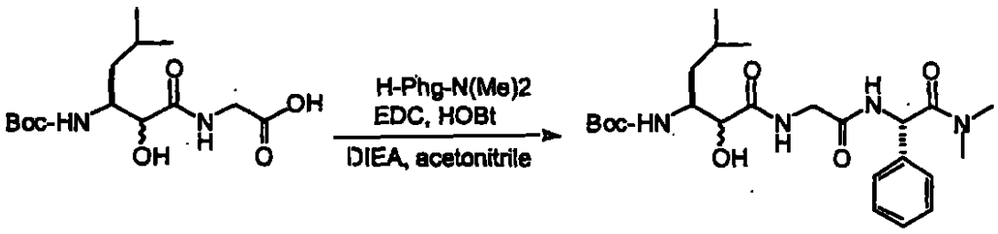
2" x 6" silica gel column using 10% ethylacetate in hexanes (800 ml) followed by 1:1 ethylacetate in hexanes (800 ml). The fractions corresponding to the product were pooled and concentrated to yield 980 mg (79%) product.

Step 3. Synthesis of Boc-Leu-(CHOH)-Gly-OH:



To a solution of Boc-Leu-(CHOH)-Gly-Oet (0.98 g, 2.83 mmol) in ethanol (11.3 ml) was added 2M lithium hydroxide (4.25 ml) and the reaction was stirred for five hours at room temperature. The ethanol was removed under reduced pressure and the aqueous layer was diluted with ethylacetate. The organic layer was washed with 1M hydrochloric acid followed by brine, dried, filtered and concentrated to yield 775 mg (86%) product as a white solid.

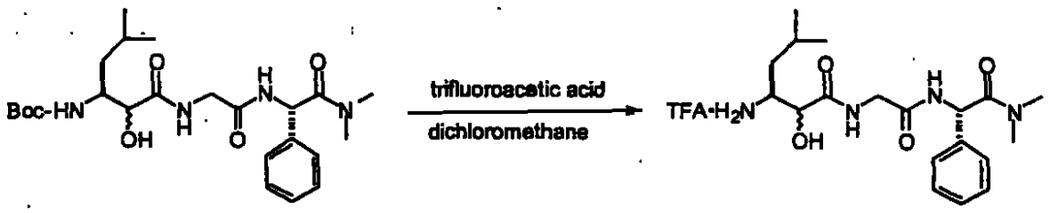
Step 4. Synthesis of Boc-Leu-(CHOH)-Gly-Phg-dimethylamide:



To a solution of Boc-Leu-(CHOH)-Gly-OH (0.37 g, 1.18 mmol) in acetonitrile (23 ml) was added successively phenylglycine dimethylamide (obtained in Example XV, Step 2), EDC (0.34 g, 1.76 mmol), N-hydroxybenzotriazole (HOBt)(0.18 g, 1.18 mmol) and diisopropylethylamine (DIEA) (0.82 ml, 4.7 mmol) and the reaction was stirred for 18 hours at room temperature. The reaction mixture was concentrated and the remaining residue was diluted with ethylacetate and washed successively with two 75 ml portions of 1M hydrochloric acid, saturated sodium bicarbonate and brine. The organic layer was then dried filtered and concentrated. The crude product was subjected to

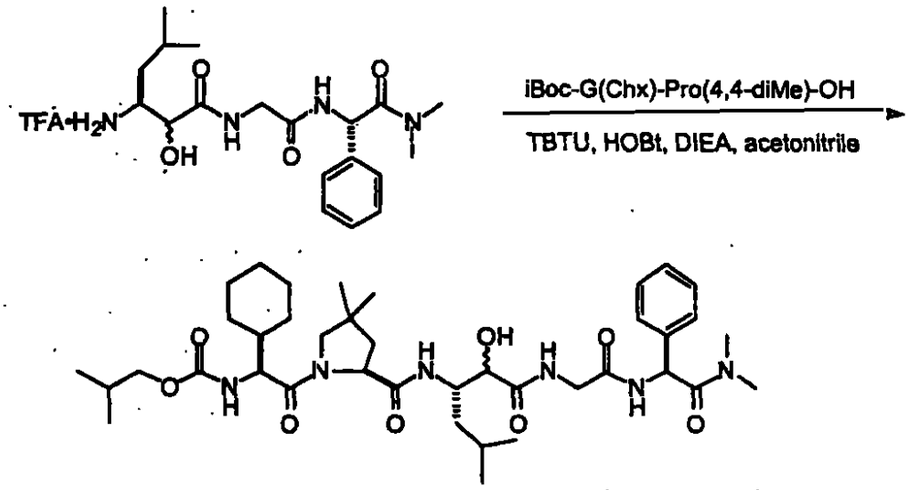
flash chromatography in a 2" x 6" silica gel column using 4:1 ethylacetate: hexanes (700 ml) followed by ethylacetate (1000 ml) and 10% methanol in dichloromethane (600 ml). The fractions corresponding to the product were pooled and concentrated to yield 445 mg (80%) white solid.

Step 5. Synthesis of H-Leu-(CHOH)-Gly-Phg-dimethylamide trifluoroacetate salt:



To a solution Boc-Leu-(CHOH)-Gly-Phg-dimethylamide (70 mg, 0.146 mmol) in dichloromethane (1 ml) was added trifluoroacetic acid (1 ml) and the reaction was stirred at room temperature for 1 hour. The reaction mixture was concentrated and taken to the next step without further purification.

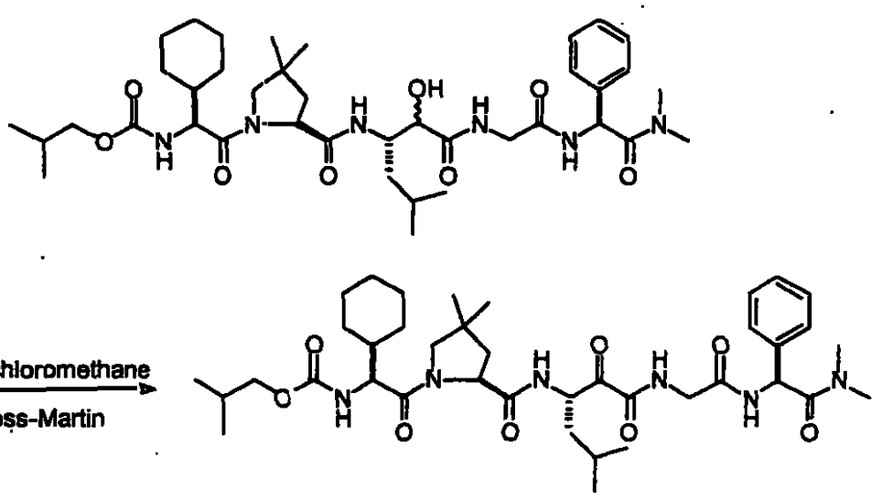
Step 6. Synthesis of iBoc-G(Chx)-Pro(4,4-dimethyl)-Leu-(CHOH)-Gly-Phg-dimethylamide:



To a solution of iBoc-G(Chx)-P(4,4-diMe)-OH (Example XIV, step 2)(53 mg, 0.148 mmol) in acetonitrile (3 ml) was added successively TFA•2HN-Leu(CHOH)-Gly-Phg-NMe2 (61 mg, 0.148 mmol), N-Hydroxybenzotriazole (HOBt) (23 mg, 0.148 mmol), TBTU (71.5 mg, 0.222 mmol and diisopropylethyl amine (103 □l,

0.593 mmol). The reaction was stirred at room temperature for 18 hours and concentrated. The remaining residue was dissolved in ethylacetate and washed with 1M hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate solution (2 x 5 ml), and brine (2 x 5 ml). The organic layer was dried, filtered and concentrated. The product (100 mg) was taken to the next step without further purification.

Step 7. Synthesis of iBoc-G(Chx)-Pro(4,4-dimethyl)-Leu-(CO)-Gly-Phg-dimethylamide:



To a solution of iBoc-G(Chx)-Pro(4,4-dimethyl)-Leu-(CHOH)-Gly-Phg-dimethylamide (30 mg, 0.04 mmol) in dichloromethane (1 ml) was added the commercially available Dess-Martin reagent (Omega Chemical Company Inc.)(67.8 mg, 0.16 mmol) and the reaction was stirred at room temperature for 90 minutes. The reaction mixture was concentrated and the remaining residue was stirred in 5% sodium thiosulfate. It was then diluted with dichloromethane and the layers were separated. The organic layer was washed with sodium thiosulfate (4 x 3 ml), followed by water and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The crude product was dissolved in hexanes and isopropyl alcohol and was subjected to HPLC purification using a normal phase Kromasil 5 silica column (Phenomenex, 250 x 21.20 mm, 100 angstrom pore size, 5 µm gel particles) eluting with a 30 minutes gradient consisting of 0 to

25% isopropyl alcohol in hexanes (25 ml/minutes). The fractions corresponding to the product were pooled and concentrated. Lyophilization from water yielded 6.7 mg white powder. Low resolution mass spectra confirmed the desired mass (MH^+ = 741.4).

III) Solid Phase Synthesis:

Solid-phase synthesis is useful for the production of small amounts of certain compounds of the present invention. As with the conventional solid-phase synthesis of peptides, reactors for the solid-phase synthesis of peptidyl ketoamides are comprised of a reactor vessel with at least one surface permeable to solvent and dissolved reagents, but not permeable to synthesis resin of the selected mesh size. Such reactors include glass solid phase reaction vessels with a sintered glass frit, polypropylene tubes or columns with frits, or reactor Kans™ made by Irori Inc., San Diego CA. The type of reactor chosen depends on volume of solid-phase resin needed, and different reactor types might be used at different stages of a synthesis. The following procedures will be referenced in the subsequent examples:

Procedure A: *Coupling reaction*: To the resin suspended in N-methylpyrrolidine (NMP) (10-15 mL/ gram resin) was added Fmoc-amino acid (2 eq), HOAt (2 eq), HATU (2 eq) and diisopropylethylamine (4 eq). The mixture was let to react for 4-48 hours. The reactants were drained and the resin was washed successively with dimethylformamide, dichloromethane, methanol, dichloromethane and diethylether (use 10-15 mL solvent/ gram resin). The resin was then dried in vacuo.

Procedure B: *Fmoc deprotection*: The Fmoc-protected resin was treated with 20% piperidine in dimethylformamide (10 mL reagent/ g resin) for 30 minutes. The reagents were drained and the resin was washed successively with

dimethylformamide, dichloromethane, methanol, dichloromethane and diethyl ether (10 mL solvent/ gram resin):

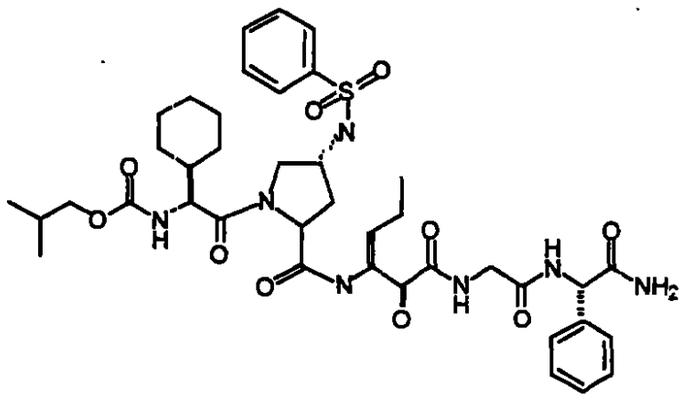
Procedure C: *Boc deprotection*: The Boc-protected resin was treated with a 1:1 mixture of dichloromethane and trifluoroacetic acid for 20-60 minutes (10 mL solvent/ gram resin). The reagents were drained and the resin was washed successively with dichloromethane, dimethylformamide, 5% diisopropylethylamine in dimethylformamide, dimethylformamide, dichloromethane and dimethylformamide (10 mL solvent/ gram resin).

Procedure D: *Semicarbazone hydrolysis*: The resin was suspended in the cleavage cocktail (10 mL/ g resin) consisting of trifluoroacetic acid: pyruvic acid: dichloromethane: water 9:2:2:1 for 2 hours. The reactants were drained and the procedure was repeated three more times. The resin was washed successively with dichloromethane, water and dichloromethane and dried under vacuum.

Procedure E: *HF cleavage*: The dried peptide-nVal(CO)-G-O-PAM resin (50 mg) was placed in an HF vessel containing a small stir bar. Anisole (10% of total volume) was added as a scavenger. In the presence of glutamic acid and cysteine amino acids, thioanisole (10%) and 1,2-ethanedithiol (0.2%) were also added. The HF vessel was then hooked up to the HF apparatus (Immuno Dynamics) and the system was flushed with nitrogen for five minutes. It was then cooled down to -70°C with a dry ice/ isopropanol bath. After 20 minutes, HF was distilled to the desired volume (10 mL HF/ g resin). The reaction was let to proceed for one and a half hour at 0°C. Work up consisted of removing all the HF using nitrogen. Dichloromethane was then added to the resin and the mixture was stirred for five minutes. This was followed by the addition of 20% acetic acid in water (4 mL). After stirring for 20 minutes, the resin was filtered using a fritted funnel and the dichloromethane was removed under reduced pressure. The remaining residue and the mixture was washed with hexanes (2x) to remove scavengers. Meanwhile, the resin was soaked in 1 mL methanol. The aqueous

layer (20% HOAc) was added back to the resin and the mixture was agitated for five minutes and then filtered. The methanol was removed under reduced pressure and the aqueous layer was lyophilized. The peptide was then dissolved in 10-25% methanol (containing 0.1% trifluoroacetic acid) and purified by reverse phase HPLC.

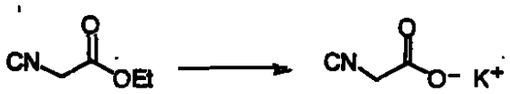
Example XXII: Representative solid phase Synthesis of Hep C inhibitors: (iBoc-G(Chx)-P(4t-NHSO2Ph)-nV-(CO)-G-G(Ph)-NH2)



Step 1. Synthesis of Fmoc-nV-(dpsc)-Gly-OH:

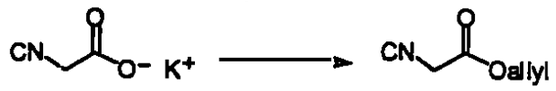
A) Synthesis of allyl isocyanoacetate (steps a-b below):

a) Synthesis of isocyanoacetic acid potassium salt:



Ethyl isocyanoacetate (96.6 ml, 0.88 mol) was added dropwise to a chilled solution of ethanol (1.5 L) and potassium hydroxide (59.52 g, 1.0 mol). The reaction was slowly warmed to room temperature. After two hours the precipitated product was filtered on a glass funnel and washed with several portions of chilled ethanol. The potassium salt of isocyanoacetic acid thus obtained was dried in vacuo to a golden-brown solid (99.92 g, 91.8%).

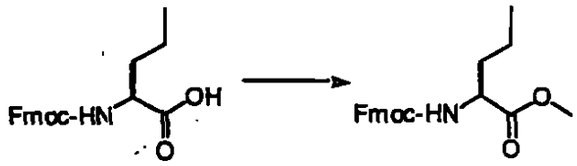
b) Synthesis of allyl isocyanoacetate:



To the product of part a (99.92 g, 0.81 mol) dissolved in acetonitrile (810 ml) was added allyl bromide (92 ml, 1.05 mol). After heating at reflux for four hours a dark brown solution was obtained. The reaction mixture was concentrated and the remaining residue was dissolved in ether (1.5 L) and washed three times with water (500 ml). The organic layer was dried, filtered and concentrated to a dark brown syrup. The crude was purified by vacuum distillation at 7 mm Hg (98°C) to a clear oil (78.92 g, 78%). NMR δ ppm ($CDCl_3$): 5.9 (m, 1 H), 5.3 (m, 2H), 4.7 (d, 2H), 4.25 (s, 2H).

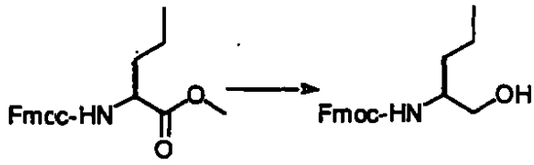
B) Synthesis of 9-fluorenylmethoxycarbonyl-norvalinal (steps a-c below):

a) Synthesis of 9-fluorenylmethoxycarbonyl-L-norvaline methyl ester (Fmoc-nVal-OMe):



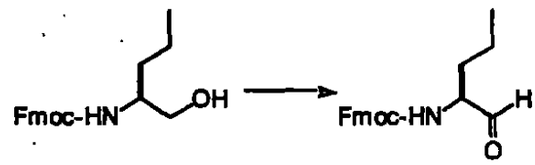
To a chilled solution of the commercially available Fmoc-norvaline (25 g, 73.75 mmol) in anhydrous methanol (469 ml) was added thionyl chloride (53.76 ml, 737.5 mmol) over one hour. TLC in ethylacetate taken an hour later confirmed the completion of the reaction (R_f = 0.85). The reaction mixture was concentrated and the remaining residue was dissolved in ethylacetate. The organic layer was washed with several 200 ml portions of saturated sodium bicarbonate followed by brine. The organic layer was dried, filtered and concentrated to afford Fmoc-norVal-OMe) as a white solid (26.03 g) in quantitative yield. NMR δ ppm (CD_3OD): 7.7 (m, 2H), 7.6 (m, 2H), 7.4 (m, 2H), 7.3 (m, 2H), 4.3 (m, 2H), 4.1 (m, 2H), 3.7 (s, 3H), 1.7 (m, 1H), 1.6 (m, 1H), 1.4 (m, 2H), 0.95 (t, 3H).

b) Synthesis of 9-fluorenylmethoxycarbonyl-norvalinol (Fmoc-nValinol):



To Fmoc-nVal-OMe (26.03 g, 73.75 mmol) in tetrahydrofuran (123 ml) and methanol (246 ml) was added calcium chloride (16.37 g, 147.49 mmol). The reaction mixture was cooled to 0°C and sodium borohydride (11.16 g, 294.98 mmol) was added in several batches. To the thick paste obtained, methanol (500 ml) was added and the reaction was let to stir at room temperature for 90 minutes. TLC in 2:3 ethylacetate: hexanes confirmed the completion of the reaction (R_f = 0.25). The reaction was quenched with the slow addition of water (100 ml) at 0°C. The methanol was removed under reduced pressure and the remaining aqueous phase was diluted with ethylacetate. The organic layer was washed with water (3 x 500 ml), saturated sodium bicarbonate (3 x 500 ml) and brine (500 ml). The organic layer was dried over sodium sulfate, filtered and concentrated to a white solid (21.70 g, 90.5%). NMR δ ppm (CD_3OD): 7.8 (m, 2H), 7.7 (m, 2H), 7.4 (m, 2H), 7.3 (m, 2H), 4.3-4.5 (m, 2H), 4.2 (m, 1H), 3.6 (s, 1H), 3.5 (s, 2H), 1.5 (m, 1H), 1.3-1.4 (m, 3H), 0.99 (m, 3H).

c) Synthesis of 9-fluorenylmethoxycarbonyl-norvalinal (Fmoc-nVal-CHO):

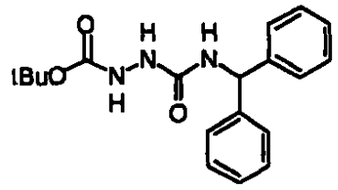


To a solution of Fmoc-norValinol (21.70 g, 66.77 mmol) in dichloromethane (668 ml) was added triethylamine (37.23 ml, 267 mmol) and the solution was cooled to 0°C. A suspension of pyridine sulfur trioxide complex (42.51 g, 267 mmol) in dimethylsulfoxide (96 ml) was added to the chilled solution. After one hour, TLC in 2:3 ethylacetate: hexanes confirmed the completion of the reaction. The dichloromethane was removed under reduced pressure and the remaining residue was dissolved in ethylacetate and washed with water (2 x 50 ml), 1N

saturated sodium bisulfate (2 x 50 ml), saturated sodium bicarbonate (2 x 50 ml) and brine (50 ml). The organic layer was concentrated to yield a white solid. Theoretical yield (21.57 g) was assumed and the reaction was taken to the next step without further purification.

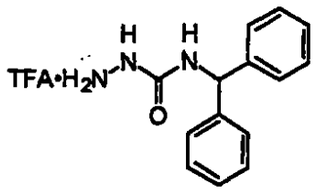
C) Synthesis of diphenylmethyl semicarbazide (dpsc) trifluoroacetate salt (steps a-b below):

a) Synthesis of Boc-semicarbazid-4-yl diphenylmethane



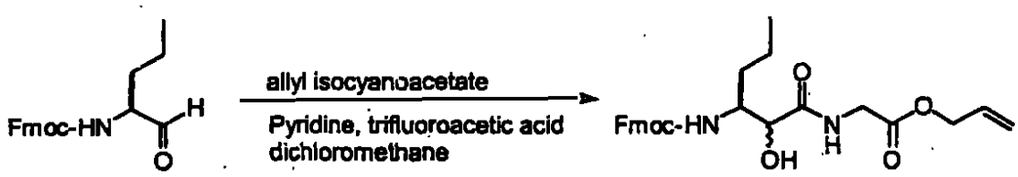
To a solution of carbonyldiimidazole (16.2 g, 0.10 mole) in dimethylformamide (225 ml) was added a solution of t-butyl carbazate (13.2 g, 0.100 mol) in dimethylformamide (225 ml) dropwise over 30 minutes. Diphenylmethylamine (18.3 g, 0.10 mol) was added next over 30 minutes. The reaction was allowed to stir at room temperature for one hour. Water (10 mL) was added and the mixture was concentrated to about 150 mL under reduced pressure. This solution was poured into water (500 mL) and extracted with ethyl acetate (400 mL). The ethylacetate phase was washed two times each with 75 mL 1N HCl, water, saturated sodium bicarbonate solution and sodium chloride, and dried with magnesium sulfate. The mixture was filtered and the solution was concentrated to give 29.5 g (85% yield) of a white foam. This material could be purified by recrystallization from ethyl acetate/hexane, but was pure enough to use directly in the next step: mp 142-143°C. ^{1}H NMR ($CDCl_3$) d 1.45 (s, 9H), 6.10 (dd, 2H), 6.42 (s, 1H), 6.67 (bs, 1H), 7.21-7.31 (m, 10H). Anal calculated for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 66.46; H, 6.75; N; 12.90.

b) Synthesis of diphenylmethyl semicarbazide (dpsc) trifluoroacetate salt



A solution of Boc-semicarbazid-4-yl diphenylmethane (3.43 g, 10 mmol) in dichloromethane (12.5 mL) was treated with 12.5 mL of trifluoroacetic acid at room temperature and stirred for 30 min. The solution was added dropwise to 75 mL of ether and the resulting solid (2.7 g, 80%) was collected by filtration. mp 182-184°C. ^{1}H NMR (CD_3OD) d 6.05 (s, 1H), 7.21-7.35 (m, 10H). ^{13}C NMR (CD_3OD) d 57.6, 118.3 (q, CF_3), 126.7, 127.9, 141.6, 156.9, 160.9 (q, $CF_3\underline{C}O_2H$).

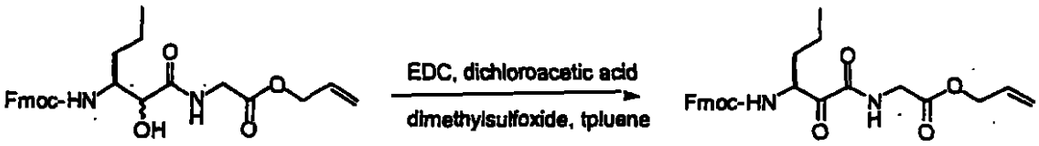
D) Synthesis of Fmoc-nVal-(CHOH)-Gly-Oallyl:



To a solution of Fmoc-nVal-CHO (Step IB) (5.47 g, 16.90 mmol) in dichloromethane (170 ml) was added allyl isocyanoacetate (Step IA) (2.46 ml, 20.28 mmol) and pyridine (5.47 ml, 67.61 mmol). The reaction mixture was cooled to 0°C and trifluoroacetic acid (3.38 ml, 33.80 mmol) was added dropwise. The reaction was stirred at 0°C for 1h, and then at room temperature for 48 hours. TLC taken in ethylacetate confirmed the completion of the reaction. The reaction mixture was concentrated and subjected to flash chromatography using 20% to 70% ethylacetate in hexanes. Fractions containing the desired product were pooled and concentrated to a white foam (6.88 g, 87.3%). TLC in 50:50 ethylacetate shows one spot (R_f = 0.37). NMR δ ppm (CD_3OD): 7.8 (m, 2H), 7.65 (m, 2H), 7.4 (m, 2H), 7.3 (m, 2H), 5.9 (m, 1H), 5.1-5.4 (m, 2H), 4.55-4.65 (m, 2H),

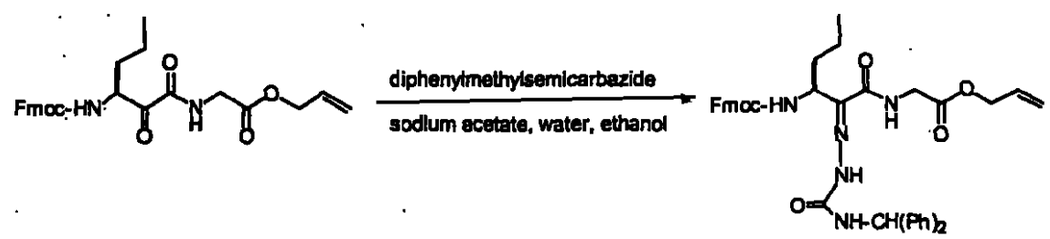
4.3-4.4 (m, 2H), 4.15-4.25 (m, 1H), 4.01 (s, 1H), 3.9-4.0 (m, 3H), 1.5-1.6 (m, 2H), 1.35-1.45 (m, 3H), 0.9 (m, 3H).

E) Synthesis of Fmoc-nVal-(CO)-Gly-Oallyl:



to a solution of Fmoc-nVal-(CHOH)-Gly-Oallyl (Step D) (5.01 g, 10.77 mmol) in dimethylsulfoxide (100 ml) and toluene (100 ml) was added EDC (20.6 g, 107.7 mmol). The reaction mixture was cooled to 0 °C and dichloroacetic acid (4.44 ml, 53.83 mmol) was added dropwise. The reaction was stirred for 15 minutes at 0 °C and 1h at room temperature. After cooling back to 0 °C, water (70 ml) was added and the toluene was removed under reduced pressure. The remaining residue was diluted with ethylacetate and washed several times with a saturated sodium bicarbonate solution followed by 1N sodium bisulfate and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The theoretical yield of 4.99 g was assumed and the reaction was taken to the next step without further purification. TLC in 50:50 ethylacetate shows one spot (R_f = 0.73).

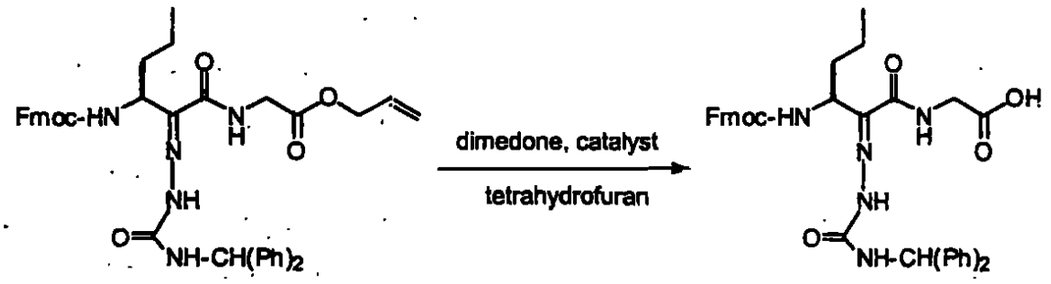
F) Synthesis of Fmoc-nVal-(dpsc)-Gly-Oallyl:



To a solution of Fmoc-nVal-(CO)-Gly-Oallyl (Step E) (4.99 g, 10.75 mmol) in ethanol (130 ml) and water (42 ml) was added diphenylmethyl semicarbazide (dpsc) trifluoroacetate salt (Step IC) (7.6 g, 21.5 mmol) and sodium acetate $\cdot 3H_2O$ (1.76 g, 12.9 mmol), successively . The reaction mixture was heated at

reflux for 90 minutes. The completion of reaction was confirmed by TLC taken in 1:1 ethylacetate: hexane. Ethanol was removed under reduced pressure and the remaining residue was dissolved in ethylacetate and washed with 1N sodium bisulfate (2 x 10 ml), saturated sodium bicarbonate (2 x 10 ml), followed by brine (10 ml). The organic layer was dried, filtered and concentrated. The resulting residue was purified by flash chromatography in 20% to 50% ethylacetate in hexanes to give a white solid (5.76g, 78%). TLC in 50:50 ethylacetate: hexanes showed two spots (cis and trans isomers) with R_f = 0.42 and 0.5.

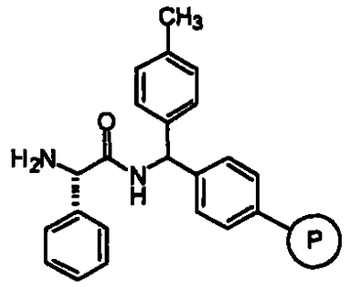
G) Synthesis of Fmoc-nVal-(dpsc)-Gly-OH:



To a solution of Fmoc-nVal-(dpsc)-Gly-Oallyl (Step IG) (4.53 g, 6.59 mmol) in tetrahydrofuran (300 ml) was added dimedone (4.62 g, 32.97 mmol) followed by tetrakis(triphenylphosphine) palladium(0) catalyst (0.76 g, 0.66 mmol). The completion of the reaction was confirmed by TLC after 90 minutes using 9:1 dichloromethane: methanol. The reaction mixture was concentrated and the remaining residue was dissolved in ethylacetate and washed three times with 50 ml portions of 0.1M potassium biphosphate. The organic layer was then treated with 50 ml sodium bisulfite and the two phase system was stirred for 15 minutes. The phases were separated and the procedure was repeated twice more. The organic layer was dried and concentrated and subjected to flash chromatography with 20% to 100% ethylacetate in hexanes. This was followed with 9:1 dichloromethane: methanol solution. The fractions corresponding to the pure product were pooled and concentrated to obtain a white solid (3.99 g, 94%). TLC

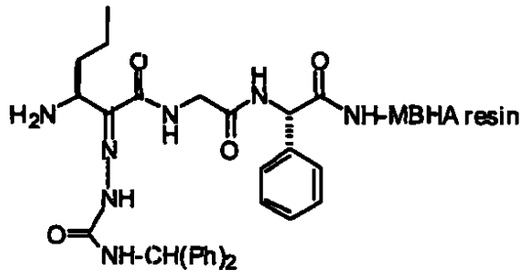
in 9:1 dichloromethane: methanol showed two spots (cis and trans isomers). NMR δ ppm (CD_3OD): 7.75 (m, 2H), 7.6 (m, 3H), 7.2-7.4 (m, 14H), 6.1-6.2 (m, 1H), 4.25-4.4 (m, 2H), 4.1-4.2 (m, 2H), 3.85 (s, 2H), 1.6-1.8 (m, 2H), 1.3-1.5 (m, 2H), 0.95 (t, 3H).

Step 2. Synthesis H-Phg-MBHA resin:



The commercially available MBHA resin (2.6 g, 1.12 mmol/g, 2.91 mmol) was transferred to a 250 mL fritted solid phase reaction vessel equipped with a nitrogen inlet. It was then washed thoroughly with 30 ml portions of dichloromethane, methanol, dimethylformamide and dichloromethane and coupled over 18 hours to the commercially available Fmoc-Phg-OH (2.17 g, 5.82 mmol) according Procedure A with 99.82% efficiency. The resin was then subjected to Fmoc deprotection according to procedure B. A qualitative ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction.

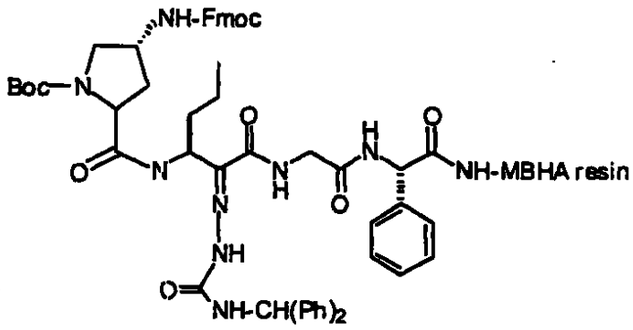
Step 3. Synthesis of H-nVal(dpsc)-Gly-Phg-MBHA resin:



The resin obtained in step II (2.6 g, 0.8 mmol/g, 2.91 mmol) was reacted with Fmoc-nVal-(dpsc)-Gly-Oallyl (Step IG) (5.82 mmol, 3.77 g) according to

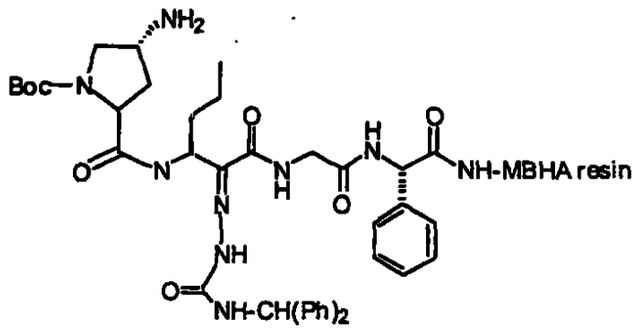
Procedure A. After 18 hours, quantitative ninhydrin analysis indicated 99.91% coupling efficiency. The resin was subjected to Fmoc deprotection according to procedure B. A qualitative ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction.

Step 4. Synthesis of Boc-Pro(4t-NHFmoc)-nVal(dpsc)-Gly-Phg-MBHA resin:



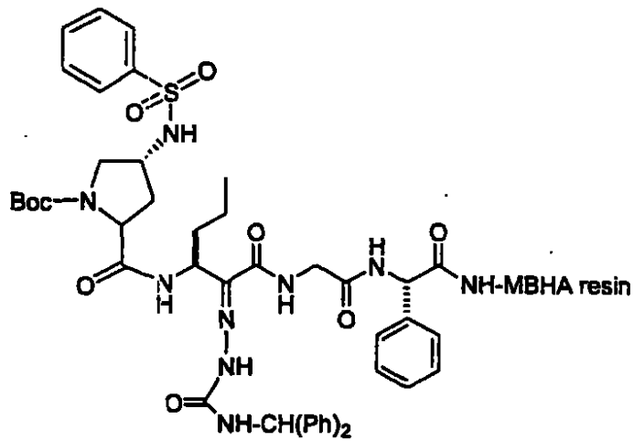
The compound H-nVal(dpsc)-Gly-Phg-MBHA resin (Step 3 above) (600 mg, 0.8 mmol/g, 0.67 mmol) was transferred to a fritted polypropylene tube and was coupled to Boc-Pro(4t-NHFmoc)-OH (Example VI, Step 3) (610 mg, 1.34 mmol) according to procedure A. After 18 hours, quantitative ninhydrin analysis indicated 99.96% coupling efficiency.

Step 5. Synthesis of Boc-Pro(4t-NH_2)-nVal(dpsc)-Gly-Phg-MBHA resin:



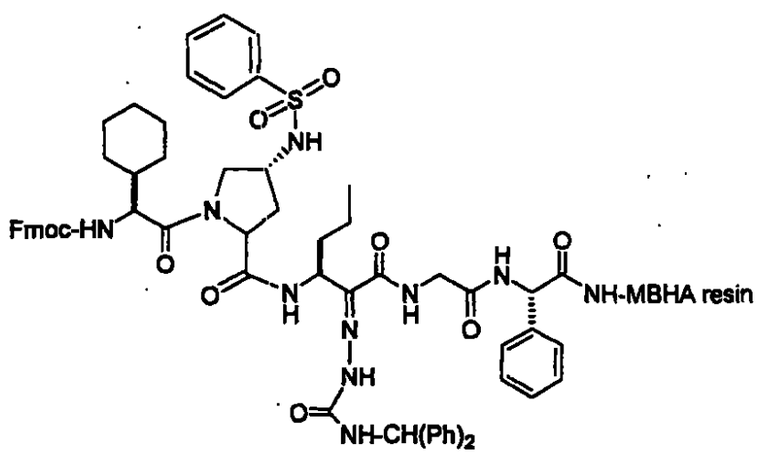
The resin from the previous step (Boc-Pro(4t-NHFmoc)-nVal(dpsc)-Gly-Phg-MBHA resin) was subjected to Fmoc deprotection according to procedure B. A qualitative ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction.

Step 6. Synthesis of Boc-Pro(4t-$NHSO_2Bn$)-nVal(dpsc)-Gly-Phg-MBHA resin:



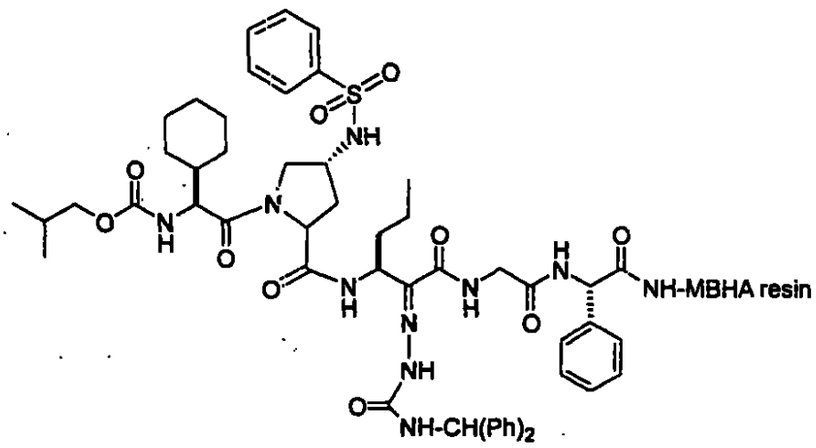
To the resin obtained from the previous step (Boc-Pro(4t-NH_2)-nVal(dpsc)-Gly-Phg-MBHA resin) (0.2 g, 0.22 mmol) suspended in NMP (2 ml) was added 2,4,6-collidine (0.24 ml, 1.79 mmol) and benzenesulfonyl chloride and the reaction was shaken for 18 hours. The solvent was drained and the resin was washed thoroughly with 2 ml portions of dichloromethane, methanol, dimethylformamide and dichloromethane. Qualitative ninhydrin analysis showed colorless beads and solution indicating a successful reaction.

Step 7. Synthesis of Fmoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal(dpsc)-Gly-Phg-MBHA resin:



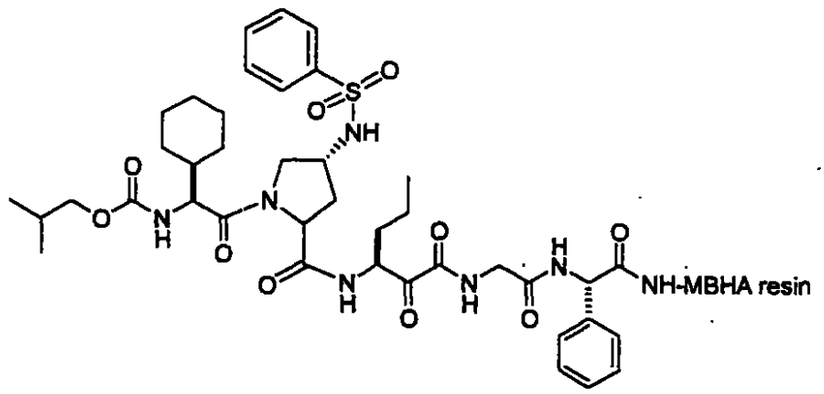
The resin obtained in the previous step (Boc-Pro(4t-NHSO$_2$Bn)-nVal(dpsc)-Gly-Phg-MBHA resin) was subjected to the Boc deprotection procedure according to Procedure C. Fmoc-G(Chx) (0.17 g, 0.45 mmol) was then coupled according to procedure A. After 18 hours qualitative ninhydrin analysis showed colorless beads and the quantitative ninhydrin analysis indicated 99.79% coupling efficiency.

Step 8. Synthesis of iBoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(dpsc)-Gly-Phg-MBHA resin:



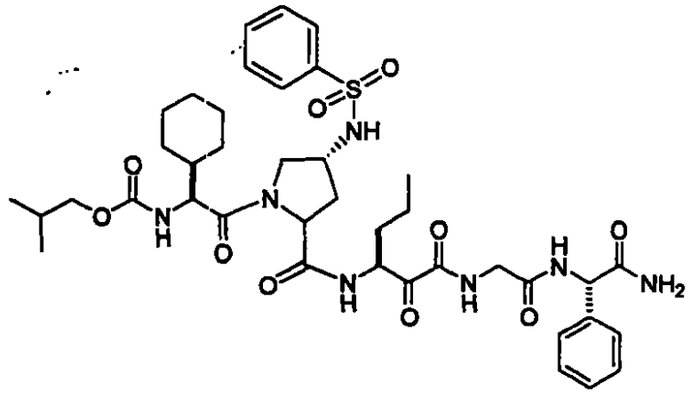
The resin obtained in the previous step (Fmoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(dpsc)-Gly-Phg-MBHA resin) was subjected to Fmoc deprotection according to procedure B. A ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction. To the resin (0.2 g, 0.22 mmol) suspended in 2 ml NMP was added isobutylchloroformate (0.12 ml, 0.90 mmol) followed by diisopropylethylamine (0.31 ml, 1.79 mmol), and the reaction mixture was shaken for 18 hours at room temperature. Qualitative ninhydrin analysis showed colorless beads and solution indicating a successful reaction.

Step 9. Synthesis of iBoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(CO)-Gly-Phg-MBHA resin:



The compound of the previous step (iBoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(dpsc)-Gly-Phg-MBHA resin) (200 mg) was subjected to semicarbazone hydrolysis Procedure D.

Step 10. Synthesis of Synthesis of iBoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(CO)-Gly-Phg-NH_2:



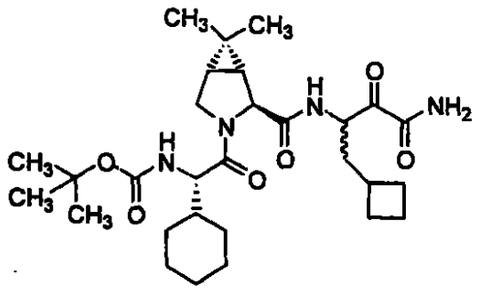
The resin of the previous step (iBoc-G(Chx)-Pro(4t-NHSO$_2$Bn)-nVal(CO)-Gly-Phg-MBHA resin) (100 mg) was subjected to HF cleavage condition (Procedure E) to yield the desired crude product. The material was purified by HPLC using a 2.2 x 25 cm reverse phase column, containing a C-18 resin comprised of 10 micron size gel particles with a 300 angstrom pore size, eluting

with a gradient using 20-50% acetonitrile in water. Analytical HPLC using a 4.6 × 250 mm reverse phase column, containing a C-18 resin comprised of 5 micron size gel particles with a 300 angstrom pore size, eluting with 25-75% acetonitrile (containing 0.1% trifluoroacetic acid) showed one peak at 13.5 minutes. Low resolution mass spectrum confirmed the desired mass (MH^+ 826.4).

IV. Additional Compounds Prepared by Solution Phase Synthesis:

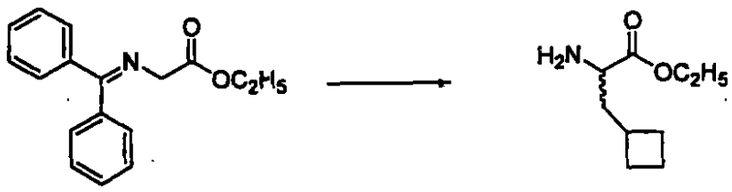
Representative procedures to prepare additional inventive compounds are shown below, and the compounds prepared by such procedures are listed in **Tables 5 and 6.**

Example XXIII : Preparation of a Compound of Formula XXIII:



XXIII

Step 1.

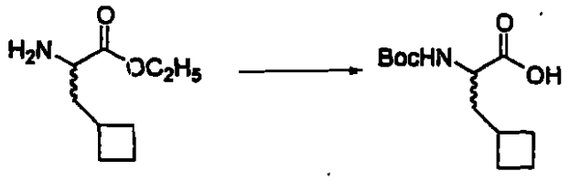


XXIIIa **XXXIIIb**

A stirred solution of ketimime **XXIIIa** (50 g, 187.1 mmol) under N_2 in dry THF (400 mL) was cooled to –78 ^{0}C and treated with 1 M solution of K-^{t}BuO (220 mL, 1.15 equiv.) in THF. The reaction mixture was warmed to 0 ^{0}C and stirred for 1 h and treated with bromomethyl cyclobutane (28 mL, 249 mmol). The reaction

mixture was stirred at room temperature for 48 h and concentrated *in vacuo*. The residue was dissolved in Et_2O (300 mL) and treated with aq. HCl (2 M, 300 mL) The resulting solution was stirred at room temperature for 5 h and extracted with Et_2O (1 L). The aqueous layer was made basic to pH ~12-14 with NaOH (50 % aq.) and extracted with CH_2Cl_2 (3x300 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give pure amine (**XXIIIb**, 18 g) as a colorless oil.

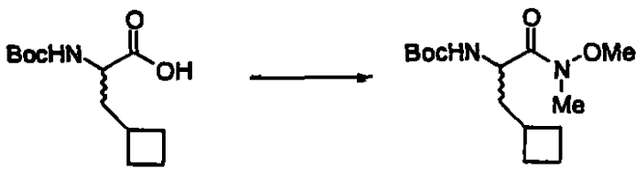
Step 2.



XXIIIb XXIIIc

A solution of amine **XXIIIb** (18g, 105.2 mmol) at 0 ^{0}C in CH_2Cl_2 (350 mL) was treated with di-*tert*-butyldicarbonate (23 g, 105.4 mmol) and stirred at rt. for 12 h. After the completion of the reaction (TLC), the reaction mixture was concentrated in *vacuo* and the residue was dissolved in THF/H_2O (200 ml, 1:1) and treated with $LiOH{\cdot}H_2O$ (6.5 g, 158.5 mmol) and stirred at room temperature for 3 h. The reaction mixture was concentrated and the basic aqueous layer was extracted with Et_2O. The aqueous layer was acidified with conc. HCl to pH~1-2 and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in *vacuo* to yield **XXIIIc** as a colorless viscous oil which was used for next step without any further purification.

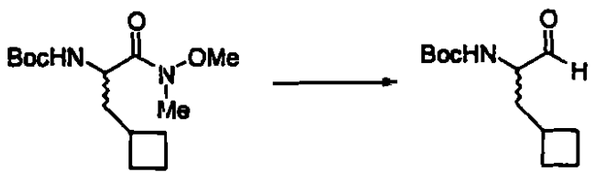
Step 3.



XXIIIc XXIIId

A solution of acid **XXIIIc** (15.0 g, 62 mmol) in CH_2Cl_2 (250 mL) was treated with BOP reagent (41.1 g, 93 mmol), N-methyl morpholine (27 mL), N,O-dimethyl hydroxylamine hydrochloride (9.07 g, 93 mmol) and stirred overnight at rt. The reaction mixture was diluted with 1 N aq. HCl (250 mL), and the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3x300 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 2:3) to yield the amide **XXIIId** (15.0 g) as a colorless solid.

Step 4.



XXIIId **XXIIIe**

A solution of amide **XXIIId** (15 g, 52.1 mmol) in dry THF (200 mL) was treated dropwisely with a solution of $LiAlH_4$ (1M, 93 mL, 93 mmol) at 0 ^{0}C. The reaction mixture was stirred at room temperature for 1 h and carefully quenched at 0 °C with a solution of $KHSO_4$ (10% aq.) and stirred for 0.5 h. The reaction mixture was diluted with aq. HCl (1 M, 150 mL) and extracted with CH_2Cl_2 (3x200 mL), The combined organic layers were washed with aq. HCl (1 M), saturated $NaHCO_3$, brine, and dried ($MgSO_4$). The mixture was filtered and concentrated in *vacuo* to yield **XXIIIe** as a viscous colorless oil (14 g).

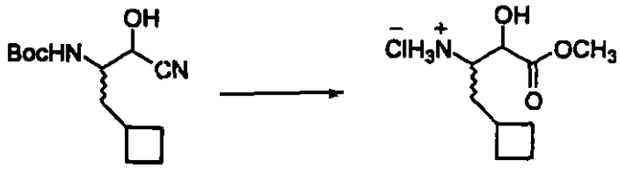
Step 5.



XXIIIe XXIIIf

A solution of the aldehyde **XXIIIe** (14 g, 61.6 mmol) in CH_2Cl_2 (50 mL), was treated with Et_3N (10.73 mL, 74.4 mmol), and acetone cyanohydrin (10.86 g, 127.57 mmol) and stirred at room temperature for 24 hrs. The reaction mixture was concentrated in *vacuo* and diluted with aq. HCl (1 M, 200 mL) and extracted into CH_2Cl_2 (3x200 mL). The combined organic layer were washed with H_2O, brine, dried ($MgSO_4$), filtered, concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 1:4) to yield **XXIIIf** (10.3 g) as a colorless liquid

Step 6.

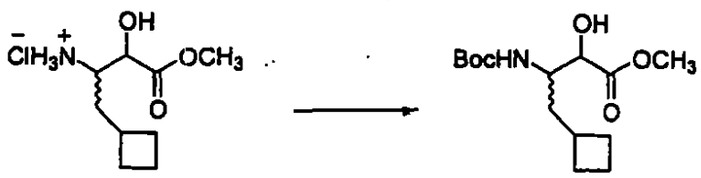


XXIIIf XXIIIg

Methanol saturated with HCl*, prepared by bubbling HCl gas to CH_3OH (700 ml) at 0 °C, was treated with cyanohydrin **XXIIIf** and heated to reflux for 24 h. The reaction was concentrated in *vacuo* to yield **XXIIIg**, which was used in the next step without purification.

* Alternatively 6M HCl prepared by addition of AcCl to dry methanol can also be used.

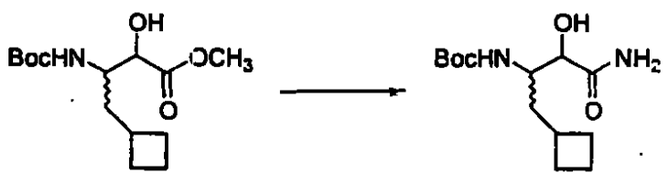
Step 7.



XXIIIg XXIIIh

A solution of the amine hydrochloride **XXIIIg** in CH_2Cl_2 (200 mL) was treated with Et_3N (45.0 mL, 315 mmol) and Boc_2O (45.7g, 209 mmol) at –78 °C. The reaction mixture was then stirred at room temperature overnight and diluted with HCl (2 M, 200 mL) and extracted into CH_2Cl_2. The combined organic layer were dried ($MgSO_4$) filtered, concentrated in *vacuo* and purified by chromatography (EtOAc/Hex 1:4) to yield hydroxy ester **XXIIIh**.

Step 8.



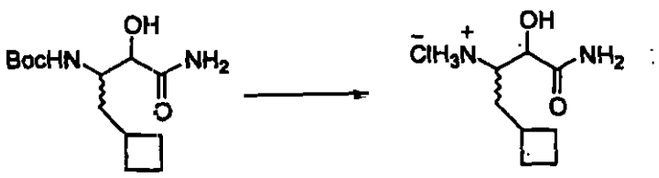
XXIIIh XXIIIi

A solution of methyl ester **XXIIIh** (3g, 10.5 mmol) in THF/H_2O (1:1) was treated with $LiOH \cdot H_2O$ (645 mg, 15.75 mmol) and stirred at rt. for 2 h. The reaction mixture was acidfied with aq HCl (1 M, 15 mL) and concentrated in *vacuo*. The residue was dried in vacuum.

A solution of the acid in CH_2Cl_2 (50 mL) and DMF (25 mL) was treated with NH_4Cl (2.94 g, 55.5 mmol), EDCI (3.15 g, 16.5 mmol), HOOBt (2.69 g, 16.5 mmol), and NMM (4.4 g, 44 mmol). The reaction mixture was stirred at room temperature for 3 d. The solvents were removed under *vacuo* and the residue was diluted with aq. HCl (250 mL) and extracted with CH_2Cl_2. The combined organic layers were washed with aq. Sat'd. $NaHCO_3$, dried ($MgSO_4$) filtered concentrated

in vacuo to obtain **XXIIIi**, which was used as it is in the following steps. (Alternatively **XXIIIi** can also be obtained directly by the reaction of **XXIIIf** (4.5 g, 17.7 mmol) with aq. H_2O_2 (10 mL), $LiOH{\bullet}H_2O$ (820 mg, 20.8 mmol) at 0 °C in 50 mL of CH_3OH for 0.5 h.)

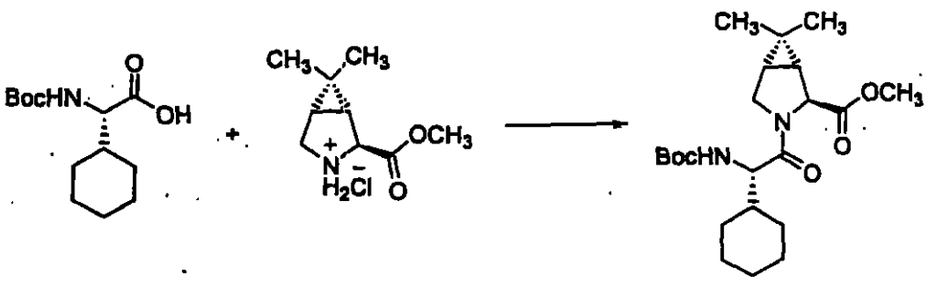
Step 9.



XXIIIi **XXIIIj**

A solution of **XXIIIi** obtained in the previous step was dissolved in 4 N HCl in dioxane and stirred at rt. for 2 h. The reaction mixture was concentrated in *vacuo* to give **XXIIIj** as a solid, which was used without further purification.

Step 10.

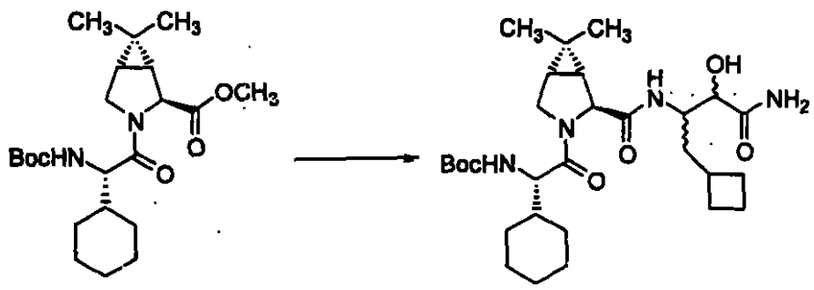


XXIIIk **XXIIIl** **XXIIIm**

The amino ester **XXIIIl** was prepared following the method of R. Zhang and J. S. Madalengoitia (*J. Org. Chem.* **1999**, *64*, 330), with the exeception that the Boc group was cleved by the reaction of the Boc-protected amino acid with methanolic HCl.

A solution of commercial amino acid Boc-Chg-OH, **XXIIIk** (Senn chemicals, 6.64 g, 24.1 mmol) and amine hydrochloride **XXIIII** (4.5 g, 22 mmol) in CH_2Cl_2 (100 mL) at 0 °C was treated with BOP reagent and stirred at rt. for 15 h. The reaction mixture was concentrated *in vacuo*, then it was diluted with aq. 1 M HCl and extracted into EtOAc (3x200 mL). The combined organic layers were washed with sat'd. $NaHCO_3$ (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*, and chromatographed (SiO_2, EtOAc/Hex 3:7) to obtain **XXIIIm** (6.0 g) as a colorless solid.

Step 11.

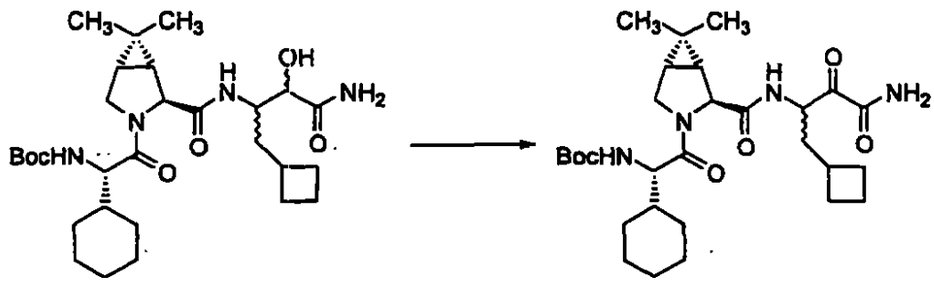


XXIIIm **XXIIIn**

A solution of methyl ester **XXIIIm** (4.0 g, 9.79 mmol) in THF/H_2O (1:1) was treated with $LiOH \cdot H_2O$ (401 mg, 9.79 mmol) and stirred at rt. for 3 h. The reaction mixture was acidified with aq. HCl and concentrated in *vacuo* to obtain the free acid.

A solution of acid (1.5 g, 3.74 mmol) in DMF/CH_2Cl_2 (1:1 50mL) was treated with amine **XXIIIj** (772 mg, 3.74 mmol), EDCI (1.07 g, 5.61 mmol), HOOBt (959 mg , 5.61 mmol) and NMM (2.15 mL, 14.96 mmol) at -10 °C. The reaction mixture was stirred at 0 °C for 48 h and concentrated in vacuo. The residue was diluted with aq. 1M HCl and extracted with CH_2Cl_2, The combined organic layers were extracted with aq. $NaHCO_3$, aq. HCl, brine, dried ($MgSO_4$), filtered and concentrated in vacuo to obtain **XXIIIn** (2.08 g) as a tan colored solid.

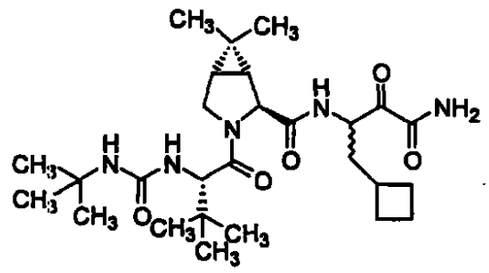
Step12.



XXIIIn XXIII

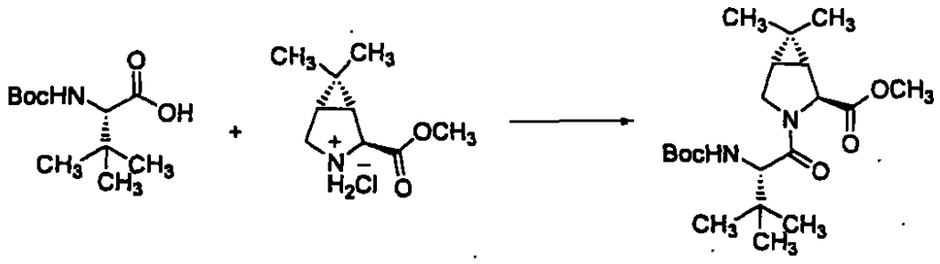
A solution of amide **XXIIIn** (2.08 g, 3.79 mmol) in toluene and DMSO (1:1 20 mL) at 0 °C was treated with EDCI (7.24 g, 37.9 mmol) and dichloroacetic acid (2.42 g, 19.9 mmol) and stirred at rt. for 4 h. The reaction mixture was diluted with CH_2Cl_2, washed with sat'd. $NaHCO_3$, and brine. The organic layer were dried ($MgSO_4$) filtered, concentrated, in vacuo and purified by chromatography (SiO_2, Acetone/Hexanes 3:7) to yield **XXIII** as a colorless solid.

Example XXIV Preparation of a Compound of Formula XXIV:



XXIV

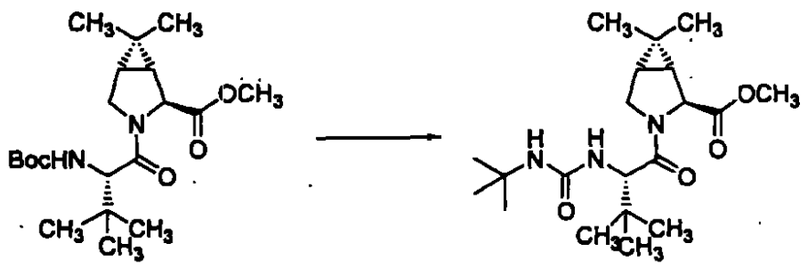
Step 1.



XXIVa XXIIII XXIVb

A solution of Boc-tert-Lue **XXIVa** (Fluka, 5.0 g 21.6 mmol) in dry CH_2Cl_2/DMF (50 mL, 1:1) was cooled to 0 °C and treated with the amine **XXIIII** (5.3 g, 25.7 mmol), NMM (6.5 g, 64.8 mmol) and BOP reagent (11.6 g, 25.7 mmol). The reaction was stirred at rt. for 24h, diluted with aq. HCl (1 M) and extracted with CH_2Cl_2. The combined organic layers were washed with HCL (aq, 1 M), sat'd. $NaHCO_3$, brine, dried ($MgSO_4$), filtered and concentrated in vacuo and purified by chromatography (SiO2, Acetone/Hexane 1:5) to yield **XXIVb** as a colorless solid.

Step 2.

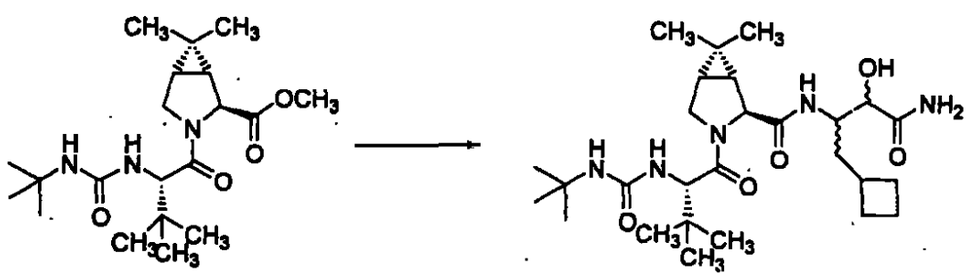


XXIVb XXIVc

A solution of methyl ester **XXIVb** (4.0 g, 10.46 mmol) was dissolved in HCl (4 M soln. dioxane) and stirred at rt. for 3 h. The reaction mixture was concentrated in *vacuo* to obtain the amine hydrochloride salt used in the next step.

A solution of the amine hydrochloride salt (397 mg, 1.24 mmol) in CH_2Cl_2 (10 mL) was cooled to –78 °C and treated with *tert*-butyl isocyanate (250 mg, 2.5 mmol) and stirred at rt. overnight. The reaction mixture was concentrated in vacuo and the residue was diluted with aq. HCl (1M) and extracted with CH_2Cl_2. The combined organic layers were washed with aq. HCl (1M), sat'd. $NaHCO_3$ and brine. The organic layers were dried, filtered and concentrated in vacuo and the residue was purified by chromatography (SiO_2, acetone/Hex 1:4) to yield **XXIVc** as a colorless solid.

Step 3.

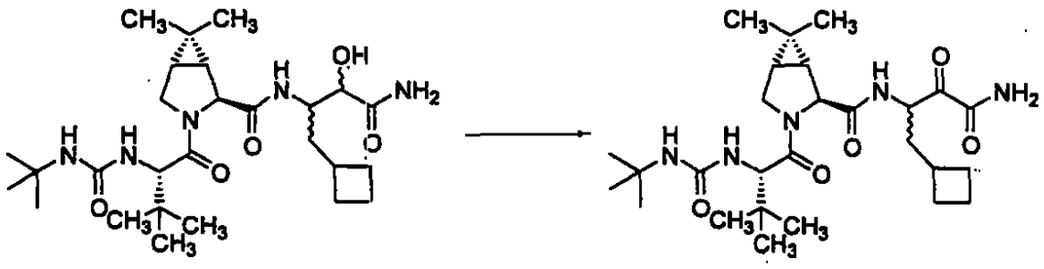


XXIVc **XXIVd**

A solution of methyl ester **XXIVc** (381 mg, 1.0 mmol) in THF/H_2O (1:1, 5 mL) was treated with $LiOH \cdot H_2O$ (62 mg, 1.5 mmol) and stirred at rt. for 3 h. The reaction mixture was acidified with aq. HCl and concentrated in *vacuo* to obtain the free acid.

A solution of acid (254.9 mg, 0.69 mmol) in DMF/CH_2Cl_2 (1:1, 5.0 mL) was treated with amine **XXIIIj** (159 mg, 0.763 mmol), EDCI (199 mg, 1.04 mmol), HOOBt (169.5 mg , 1.04 mmol) and NMM (280 mg, 2.77 mmol) at -20 °C. The reaction mixture was stirred at -20 °C for 48 h and concentrated in *vacuo*. The residue was diluted with aq. 1M HCl and extracted with EtOAc, The combined organic layers were extracted with aq. $NaHCO_3$, aq. HCl, brine, dried ($MgSO_4$) filtered concentrated in *vacuo* to obtain **XXIVd** (470 mg) as a tan colored solid.

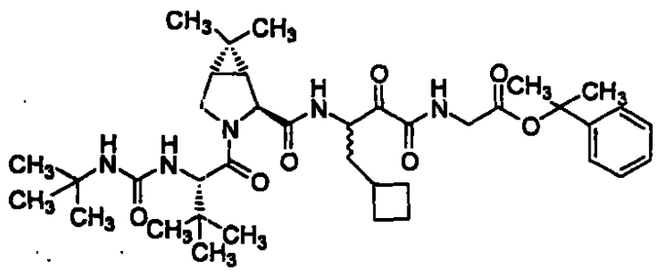
Step 4.



XXIVd XXIV

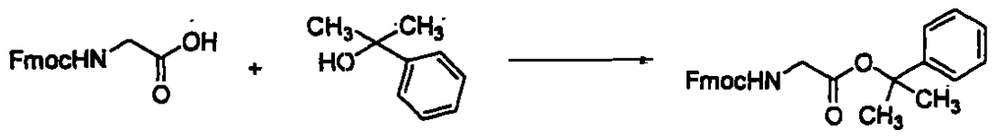
A solution of amide **XXIVd** (470 mg, 0.9 mmol) in toluene and DMSO (1:1 20 mL) at 0 °C was treated with EDCI (1.72 g, 9.0 mmol) and dichloroacetic acid (0.37 mL, 4.5 mmol) and stirred at 0 °C for 4h. The reaction mixture was diluted with CH_2Cl_2, and washed with satd. $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, concentrated, in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 3:7) to yield **XXIV** as a colorless solid.

Example XXV Preparation of a compound of Formula XXV:



XXV

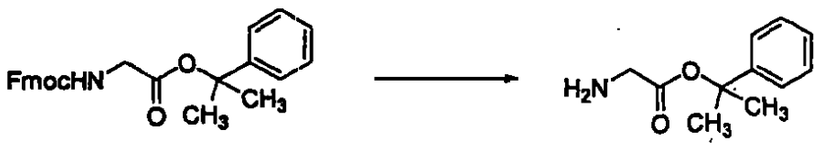
Step 1.



XXVa XXVb XXVc

A solution of Fmoc–glycine (Bachem, 2.0 g, 6.87 mmol) in CH_2Cl_2 (20 mL) was treated with 2-phenyl-2-propanol (Aldrich, 3.36 g, 24.7 mmol), DCC (1M soln CH_2Cl_2, 8.24 mL), DMAP (167 mg, 1.37 mmol) and stirred at rt. for 24 h. The reaction mixture was concentrated in *vacuo* and diluted with Et_2O (100 mL). The solid seperating out was filtered and the filterate was washed with satd. $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, concentrated in vacuo, and purified by chromatography (SiO_2, EtOAc/Hex 1:5) to yield ester XXVc (1.1 g) as a colorless viscous liquid.

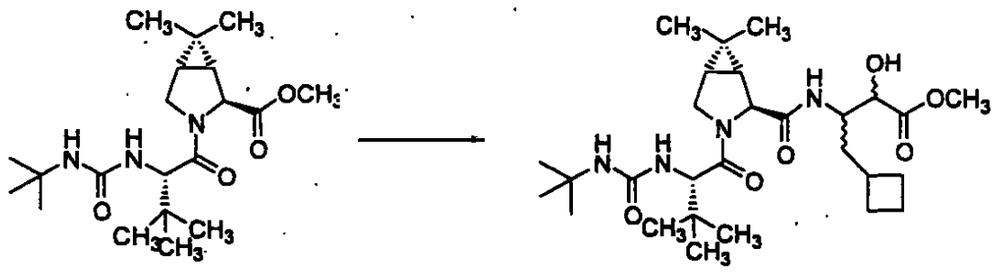
Step 2.



XXVc XXVd

A solution of XXVc in CH_2Cl_2 (16.0 mL) was treated with piperidine (4.0 mL) and stirred at rt. for 0.5 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, Acetone/Hexanes 1:10 to 1:1) to yield the amine XXVd (420 mg) as a colorless liquid.

Step 3.

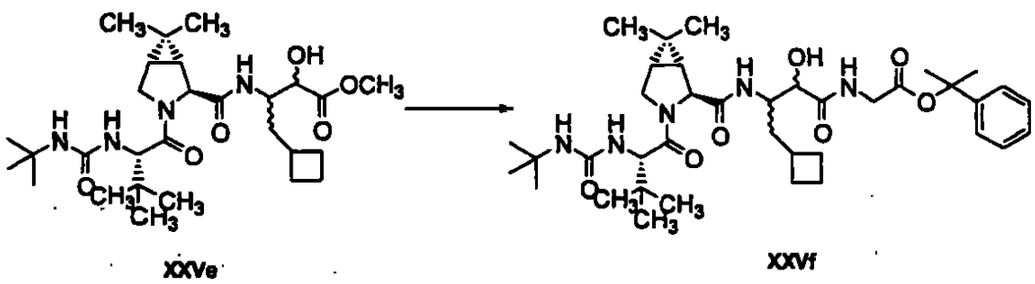


XXIVc XXVe

A solution of methyl ester **XXIVc** (381 mg, 1.0 mmol) in THF/H_2O (1:1, 5 mL) was treated with $LiOH \cdot H_2O$ (62 mg, 1.5 mmol) and stirred at rt. for 3 h. The reaction mixture was acidified with aq. HCl and concentrated in *vacuo* to obtain the free acid.

A solution of acid (2.0 g, 5.5 mmol) in DMF/CH_2Cl_2 (1:1, 40.0 mL) at -10 °C was treated with amine XXIIIg (1.51 g, 6.8 mmol), EDCI (1.57 g, 8.25 mmol), HOOBt (1.41 g, 8.25 mmol) and NMM (2.5 g, 24.7 mmol). The reaction mixture was stirred at 0 °C for 48 h and concentrated in vacuo. The residue was diluted with aq. 1M HCl (100 mL) and extracted with CH_2Cl_2 (3x100 mL). The combined organic layers were extracted with aq. $NaHCO_3$, aq. HCl, brine, dried ($MgSO_4$) filtered, concentrated in *vacuo* to obtain XXVe (3.17 g) as a tan colored solid used further without any purification.

Step 4.

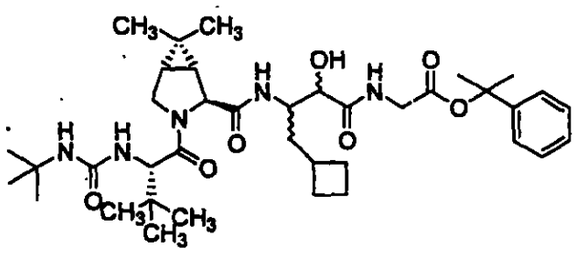


XXVe XXVf

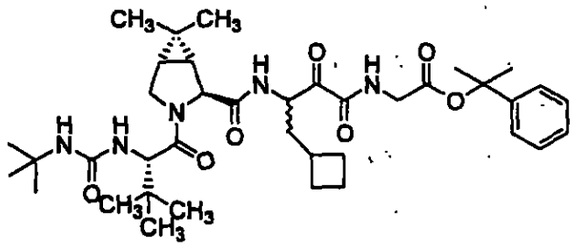
A solution of methyl ester **XXVe** (2.5 g, 4.66 mmol) in THF/H_2O/CH_3OH (1:1:1, 60 mL) was treated with LiOH•H_2O (200 mg, 4.87 mmol) and stirred at rt. for 4 h. The reaction mixture was acidified with aq. HCl and concentrated in *vacuo* to obtain the free acid.

A solution of acid (200.0 mg, 0.38 mmol) in DMF/CH_2Cl_2 (1:1, 6.0 mL) at -10 °C was treated with amine XXVd (78 mg, 0.4 mmol), EDCI (105 mg, 0.55 mmol), HOOBt (95 mg, 0.55 mmol) and NMM (150 mg, 1.48 mmol). The reaction mixture was stirred at 0 °C for 48 h and concentrated in vacuo. The residue was diluted with aq. 1M HCl (30 mL) and extracted with CH_2Cl_2 (3x30 mL). The combined organic layers were extracted with aq. $NaHCO_3$ (2x30 mL), aq. HCl, brine (30 mL), dried ($MgSO_4$) filtered, concentrated in *vacuo* to obtain XXVf (240 mg) as a tan colored solid.

Step 5.



XXVf

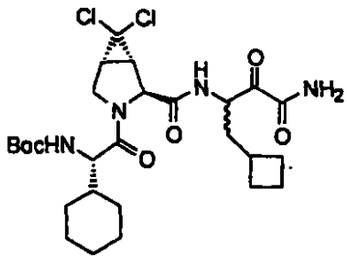


XXV

A solution of XXVf (240 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) was treated with Dess-Martin reagent (Omega, 242 mg, 0.56 mmol) and stirred at rt. for 2 h. After the oxidation was complete (TLC, Acetone/Hex 1:4) the reaction mixture was diluted with satd. $NaHCO_3$ (20 mL) and $Na_2S_2O_3$ (10% aq soln, 20 mL). The

reaction mixture was stirred for 30 min and extractred with CH_2Cl_2 (3x30 mL). The combined organic layers were extracted with satd. NaHCO3, brine, dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/Hexanes 1:5) to yield XXV (122 mg) as a colorless solid.

Example XXVI Preparation of a compound of Formula XXVI:



XXVI

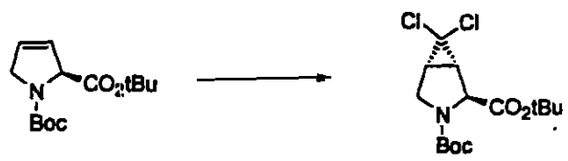
Step 1:



XXVIa XXVIb

To a stirred solution of *N*-Boc-3,4-dehydroproline **XXVIa** (5.0 g, 23.5 mmol), di-*tert*-butyl dicarbonate (7.5 g, 34.4 mmol), and 4-*N,N*-dimethylaminopyridine (0.40 g, 3.33 mmol) in acetonitrile (100 mL) at room temperature was added triethylamine (5.0 mL, 35.6 mmol). The resulting solution was stirred at this temperature for 18 h before it was concentrated *in vacuo*. The dark brown residue was purified by flash column chromatography eluting with 10-25% EtOAc/hexane to give the product **XXVIb** as a pale yellow oil (5.29 g, 84%).

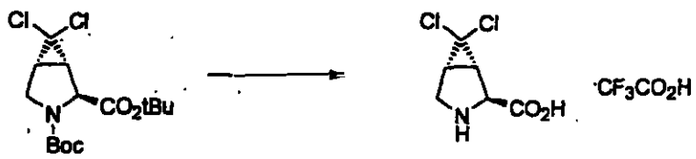
Step 2:



XXVIb XXVIc

To a stirred solution of dehydroproline **XXVIb** (10.1 g, 37.4 mmol), benzyltriethylammonium chloride (1.60 g, 7.02 mmol) in chloroform (120 mL) at room temperature was added 50% aqueous sodium hydroxide (120 g). After vigorously stirred at this temperature for 24 h, the black mixture was diluted with CH_2Cl_2 (200 mL) and diethyl ether (600 mL). After the layers were separated, the aqueous solution was extracted with CH_2Cl_2/Et_2O (1:2, 3x600 mL). The organic solution was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography using 5-20% EtOAc/hexane to afford 9.34 g (71%) of **XXVIc** as an off-white solid.

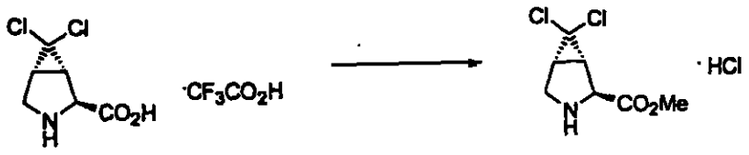
Step 3:



XXVIc XXVId

The solution of **XXVIc** (9.34 g, 26.5 mmol) in CH_2Cl_2 (25 mL) and CF_3CO_2H (50 mL) was stirred at room temperature for 4.5 h before it was concentrated *in vacuo* to give a brown residue which was used in Step 4 without further purification.

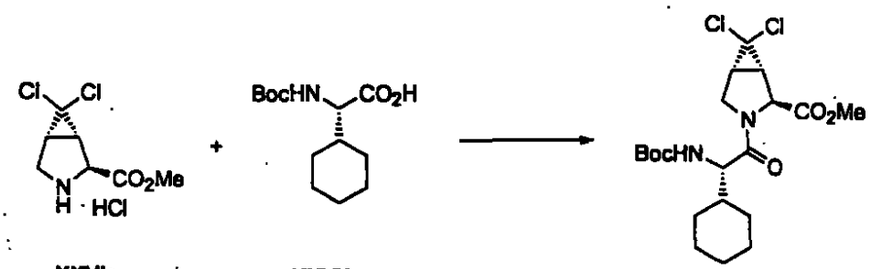
Step 4



XXIIId XXIIIe

Commercial concentrated hydrochloric acid (4.5 mL) was added to a solution of the residue from Step 3 in methanol (70 mL) and the resulting mixture was warmed to 65°C in an oil bath. After 18 h, the mixture was concentrated *in vacuo* to give a brown oil **XXVIe**, which was used in Step 5 without further purification.

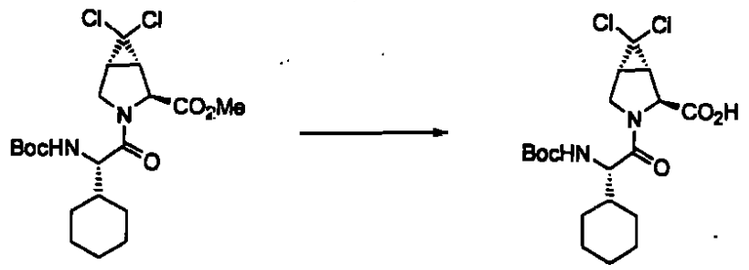
Step 5:



XXVIe **XXVIf** **XXVIg**

To a stirred solution of proline methyl ester **XXVIe** from Step 4, commercial N-Boc-cyclohexylglycine **XXVIf** (10.2 g, 40.0 mmol) and [O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate] (HATU) (16.0 g, 42.1 mmol) in DMF (200 mL) at 0°C was added diisopropylethylamine (18.0 mL, 104 mmol). After allowed to warm to room temperature along with the ice bath over night (18 h), the reaction mixture was diluted with EtOAc (600 mL), 5% H_3PO_4 (150 mL) and brine (150 mL). The organic solution was washed with 5% H_3PO_4 (150 mL), saturated $NaHCO_3$ (2x200 mL) before it was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography using 5-20% EtOAc/hexane to afford 3.84 g (32%, three steps) of **XXVIg** as an off-white solid.

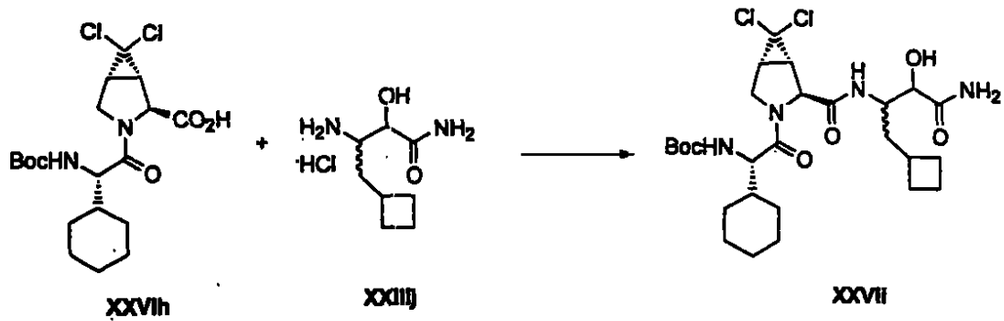
Step 6:



XXVIg XXVIh

The solution of methyl ester **XXVIg** (5.87g, 13.1 mmol) and LiOH (1.65 g, 39.3 mmol) in THF/MeOH/H_2O (1:1:1, 90 mL) was stirred at room temperature for 4 h. Methanol and THF were removed under reduced pressure. The aqueous solution was acidified to PH~2 using 1 N aqueous HCl solution (50 mL) and saturated with solid sodium chloride before it was extracted with EtOAc (3x150 mL). The organic solutions were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a white solid **XXVIh** (5.8 g, quantitative).

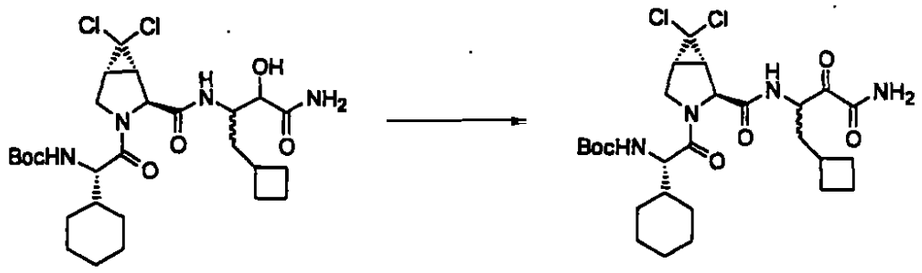
Step 7:



XXVIh XXIIIj XXVII

The desired product **XXIIII** was prepared according to the procedure in Example XXIII, Step 11.

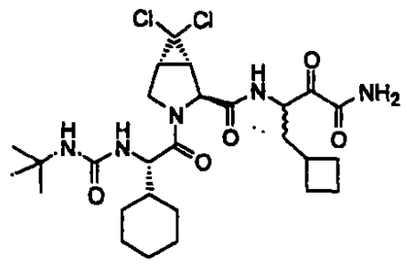
Step 8:



XXVII XXVI

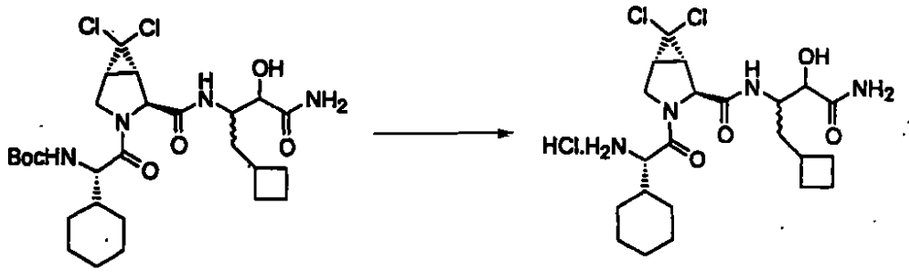
The desired product **XXVI** was prepared according to the procedure in Example XXIII, Step 12.

Example XXVII: Preparation of compound of formula XXVII:



XXVII

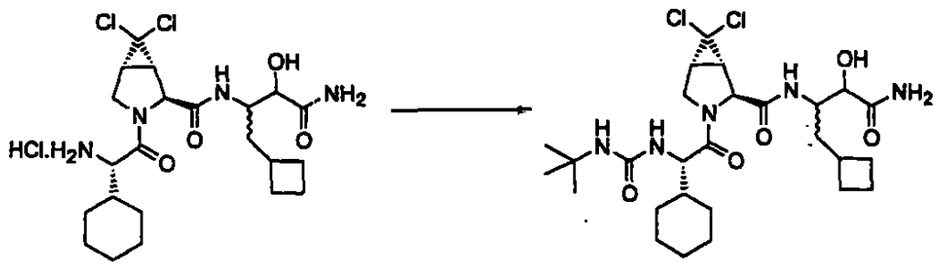
Step 1



XXVII XXVIIa

The desired product **XXVIIa** was prepared according to the procedure in Example XXIII, Step 9.

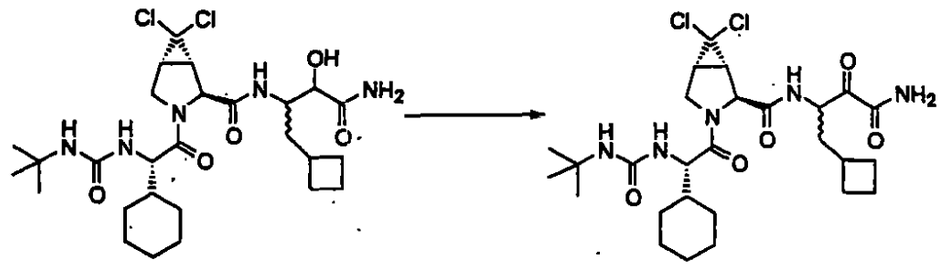
Step 2



XXVIIa **XXVIIb**

The desired product **XXVIIb** was prepared according to the procedure in Example XXIV, Step 2.

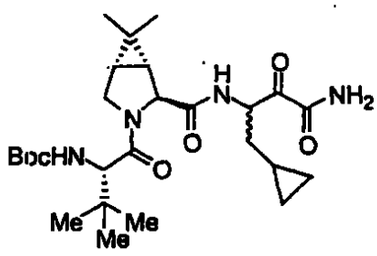
Step 3



XXVIIb **XXVII**

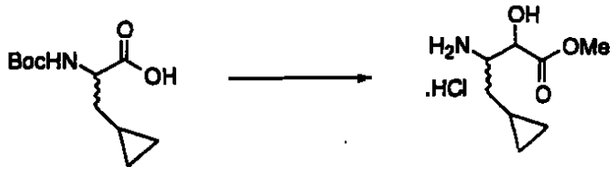
The desired product **XXVII** was prepared according to the procedure in Example XXIII, Step 12.

Example XXVIII: Preparation of a compound of formula XXVIII:



XXVIII

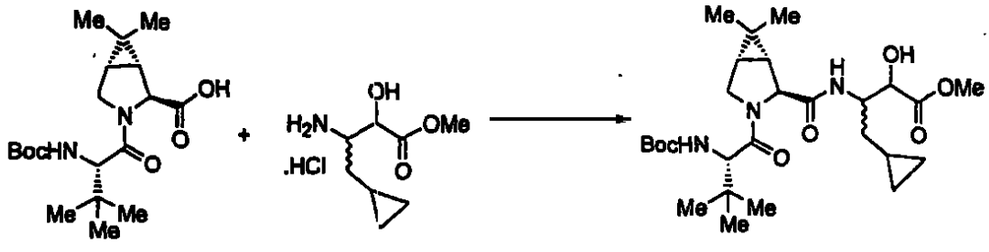
Step 1:



XXVIIIa XXVIIIb

The intermediate **XXVIIIb** was prepared according to the procedure in Example XXIII, Steps 3-6.

Step 2:

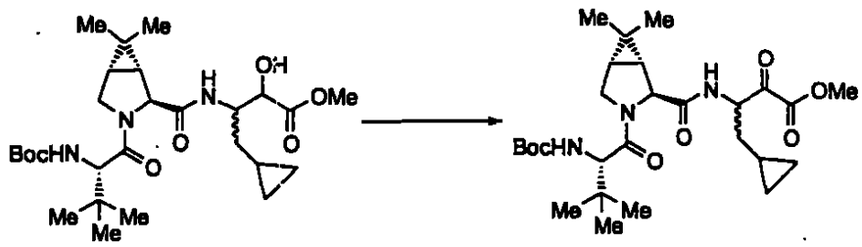


XXVIIIc XXVIIIb XXVIIId

The acid from Example XXIV, Step 2 (**XXVIIIc**) (0.7g) was reacted with product from Step 1 above (0.436g), HATU (0.934g) and DIPEA (1.64 mL) in the

manner previously described in Example IX, Step 2a to afford 0.66 g of the desired product **XXVIIId.**

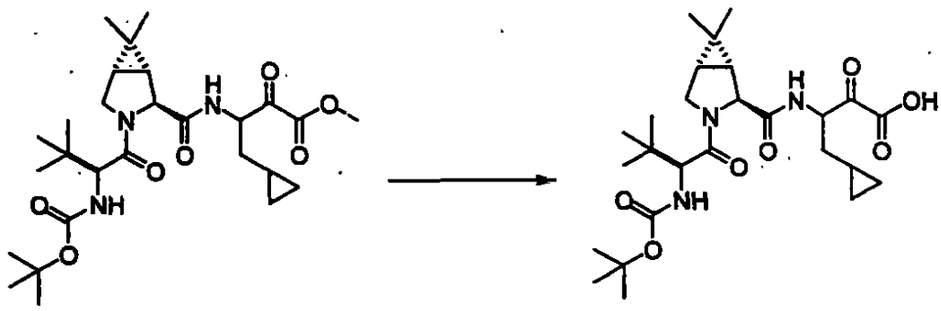
Step 3:



XXVIIId **XXVIIIe**

The product of Step 2 (0.5g) was reacted with Dess-Martin reagent (1g) in the manner previously described in Example XX, Step 7. Purification by flash column chromatography (40% EtOAc, Hexane, silica) furnished 0.35g of product **XXVIIIe.** Mass spectrum (LCMS) 522 ($M+H^+$).

Step 4:

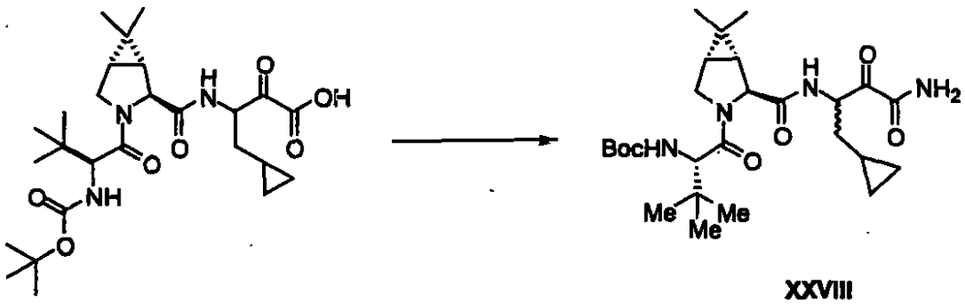


XXVIIIe **XXVIIIf**

The product of Step 4 (0.3g) was added a 1/1 H_2O/MeOH solution (20 mL) and NaHCO3 solid (242 mg, 5equiv.). After being stirred for 18 hours at room temperature, the reaction was diluted with EtOAc and layers were separated. The aqueous layer was acidified to pH 2 with HCl 1.0 N and extracted with EtOAc. The EtOAc layer was washed with brine then dried over $MgSO_4$, filtered and

concentrated in vacuo to afford product **XXVIIIf** as a white powder (0.26g). Mass spectrum (LCMS) 508 ($M+H^+$).

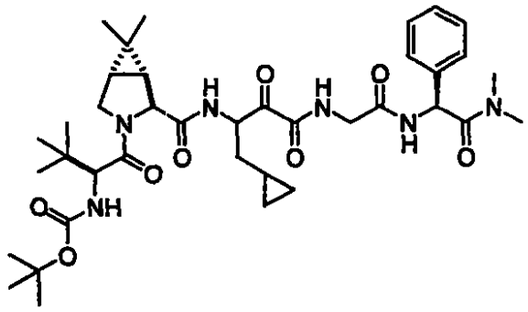
Step 5:



XXVIIIf **XXVIII**

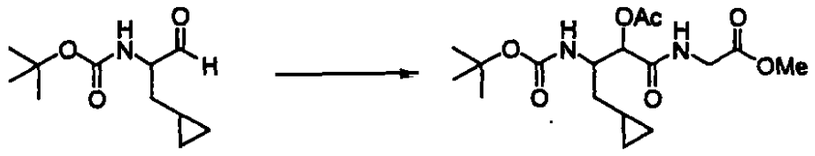
The product of Step 5 (0.15g) was dissolved in CH_2Cl_2 and reacted with HATU (0.137g), NH_4Cl (0.08g, 5equiv.) and DIPEA (0.53 mL). After 2 hours at room temperature, the reaction was diluted with EtOAc, washed with a 10% citric acid solution, then a saturated $NaHCO_3$ solution. The EtOAc layer was washed with brine then dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. Purification by flash column chromatography (30% Acetone, Hexane, silica) furnished the desired product **XXVIII** (0.096g). Mass spectrum (LCMS) 507 ($M+H^+$).

Example XXIX: Preparation of a compound of formula XXIX:



XXIX

Step1:



XXIXa

To a 0 °C solution of the starting aldehyde (4.0g) in CH_2Cl_2 (75 mL) was added acetic acid (2.0 equiv., 2.15 mL) followed by methylisocyanoacetate (1.1 equiv., 1.9 mL). The reaction was then gradually warmed-up to room temperature. After 18 hours (overnight), the reaction was diluted with EtOAc and washed with a saturated $NaHCO_3$ solution. The EtOAc layer was washed with brine then dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. Purification by flash column chromatography (30 to 40% EtOAc, Hexane, silica) furnished the product **XXIXa** (4.5g).

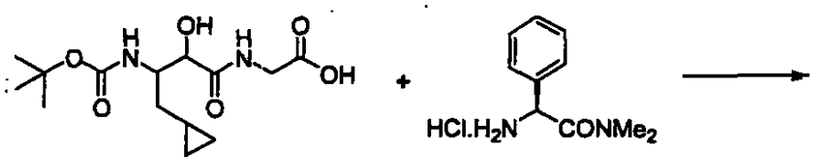
Step2:



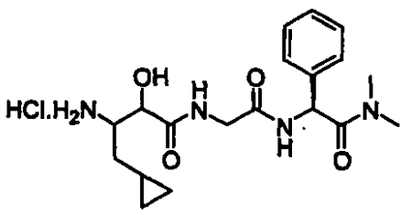
XXIXa XXIXb

To a 0 °C solution of **XXIXa** (4.4g) in THF (100 mL) was added 26 mL (2.2 equiv.) of a 1.0 N LiOH solution. The reaction was stirred at this temperature for 2 hours then warmed-up to room temperature. After 2 hours, reaction mixture was acidified to pH 2 with a 1.0 N HCl solution. EtOAc was added and layers were separated. The EtOAc layer was washed with brine then dried over $MgSO_4$, filtered and concentrated in vacuo to afford product **XXIXb** (3.7g).

Step3:



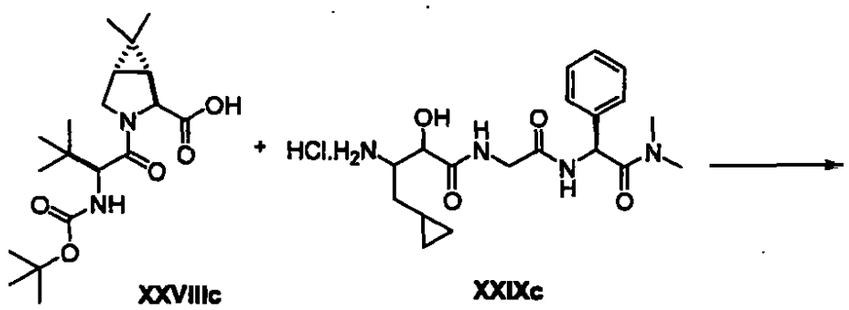
XXIXb XV



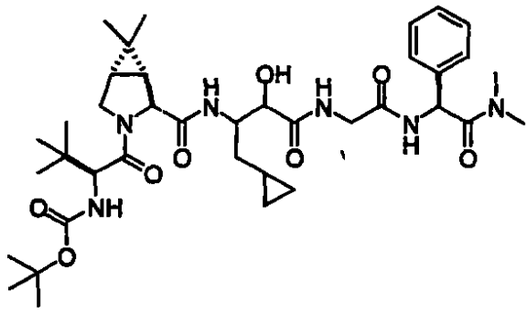
XXIXc

The acid **XXIXb** was reacted with the amine from Example XV in the manner previously described in Example XXI, Step 4. The resulting intermediate was then treated with HCl in the manner previously described in Example XXIII, Step 9 to afford product **XXIXc**.

Step4:



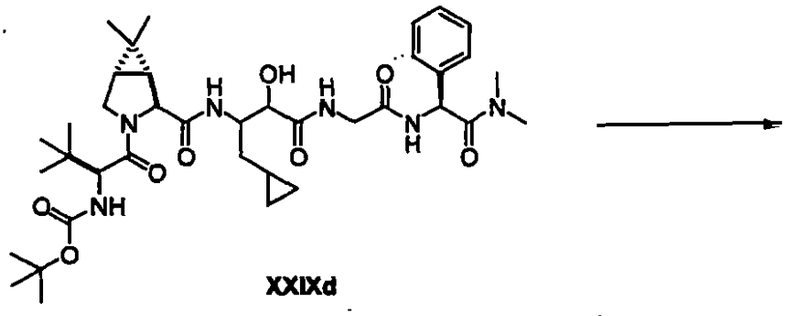
XXVIIIc XXIXc



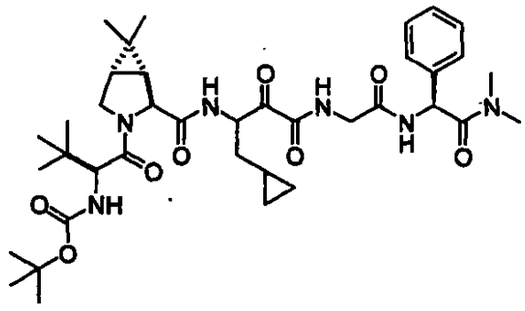
XXIXd

The acid **XXVIIIc** (2.43g) was dissolved in CH_2Cl_2 and was reacted with amine **XXIXc** (2.47g), HATU (2.5g) and DIPEA (5.8 mL) in the manner previously described in Example IX, Step 2a to afford, after purification by flash column chromatography (4% MeOH, CH_2Cl_2, silica), the desired product **XXIXd** (4.35g). Mass spectrum (LCMS) 727 ($M+H^+$).

Step 5:



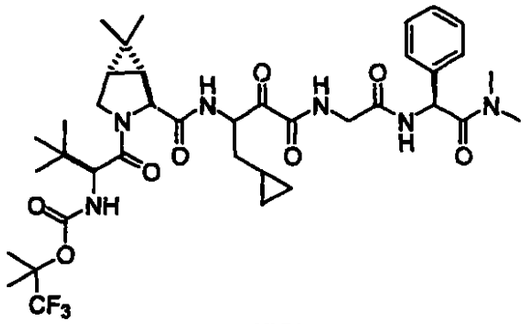
XXIXd



XXIX

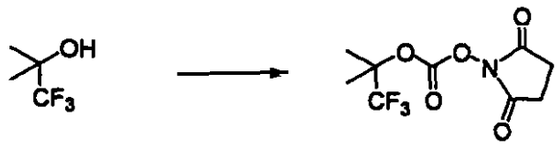
The product of Step 4 (4.2g) was reacted with Dess-Martin reagent (6.4g) in the manner previously described in preparative Example XX, Step 7. Purification by flash column chromatography (100% EtOAc, silica) furnished 3 g of the final product **XXIX**. Mass spectrum (LCMS) 725 ($M+H^+$).

Example XXX: Preparation of a compound of formula XXX:



XXX

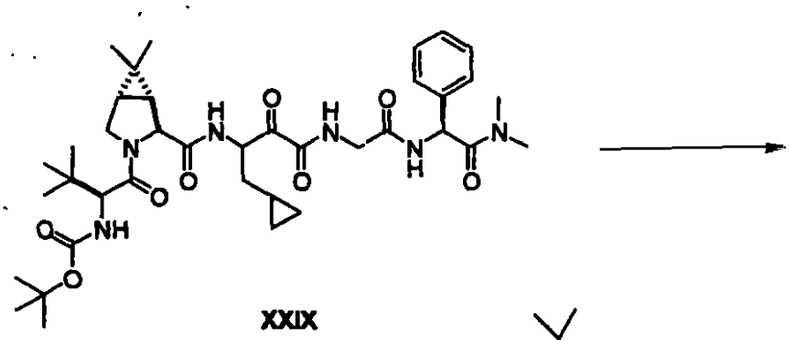
Step 1:



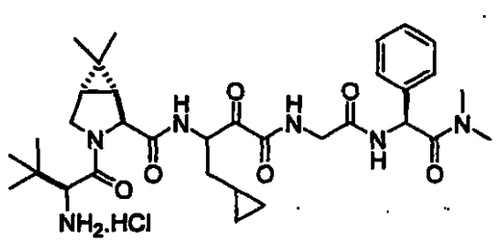
XXXa

The alcohol 2-(trifluoromethyl)propan-2-ol (1.28g) was reacted with N,N-disucciminidyl carbonate (3.84g) and Et_3N (4.2 mL) in dry CH_3CN (50 mL) for 18 hours. The mixture was diluted with EtOAc (200 mL) and filtered. The filtrate was washed with $NaHCO_3$, brine then dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. Purification by flash column chromatography (50% EtOAc, Hexane, silica) furnished the desired product **XXXa** (0.3g).

Step 2:



XXIX

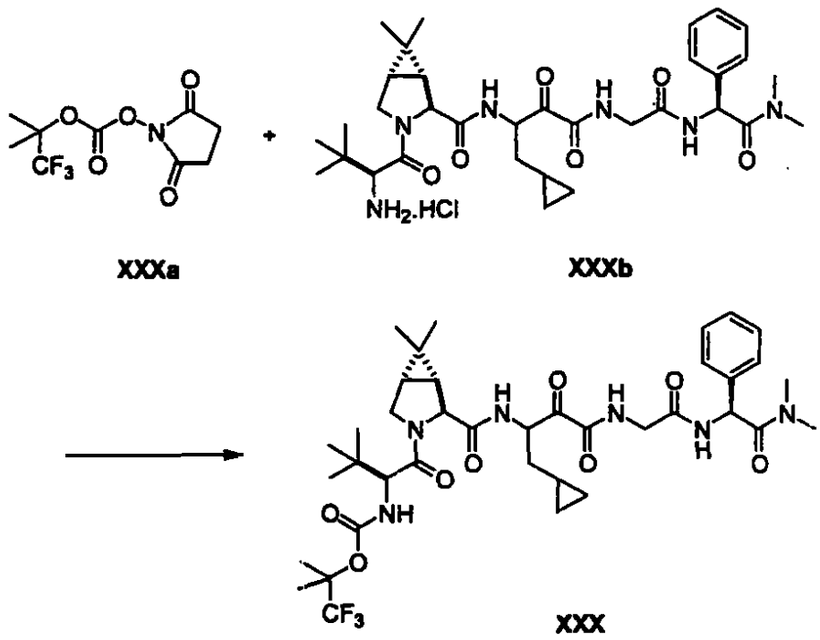


XXXb

The product from Example XXIX (0.3g) was treated with 100 mL of 4.0 N HCl in dioxane. After 1 h, 200 mL of Et_2O were added and the resulting precipitate

was filtered off and dried under vacuo to afford the product **XXXb** (0.27g) as a white powder. Mass spectrum (LCMS) 625 (M – HCl +H^+).

Step 3:

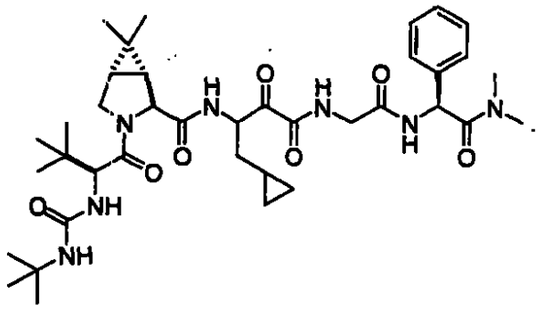


XXXa **XXXb**

XXX

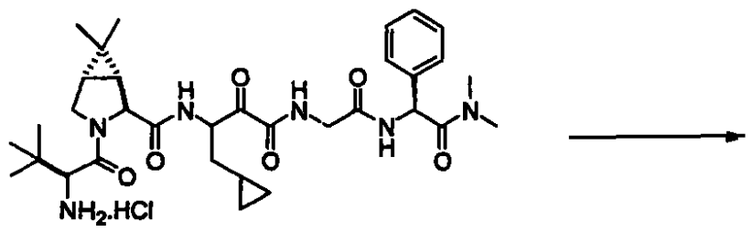
To a room temperature solution of **XXXb** (0.05g) in CH_2Cl_2 (5 mL) was added DIPEA (0.040 mL) **XXXa** (1.5 equiv., 0.030g), followed by 1 crystal of DMAP. After 30 minutes, reaction was diluted with EtOAc (20 mL) and washed with HCl 1.5 N then $NaHCO_3$ then brine. EtOAc layer was dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. Purification by preparative chromatography (40% Acetone, Hexane, silica) furnished the desired product **XXX** (0.044g). Mass spectrum (LCMS) 779 (M+H^+).

Example XXXI: Preparation of a compound of formula XXXI:

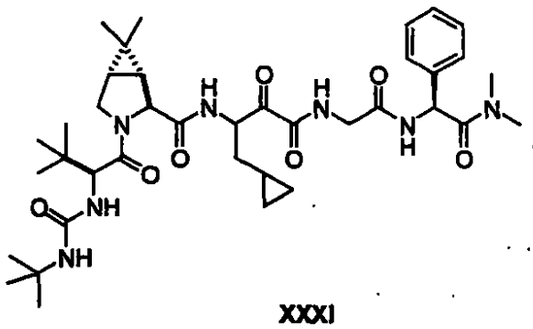


XXXI

Step 1:



XXXb

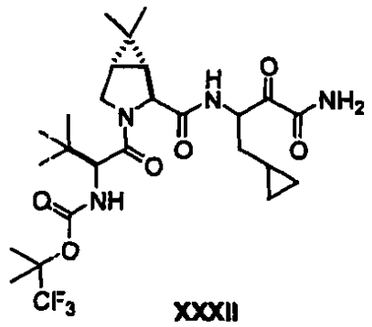


XXXI

To a solution of **XXXb** (0.05g) in CH_2Cl_2 (5 mL) at room temperature was added DIPEA (0.040 mL) and *tert*-butylisocyanate (1.2 equiv., 0.01 mL). After 18 hours, reaction was diluted with EtOAc (20 mL) and washed with HCl 1.5 N, $NaHCO_3$ and brine. EtOAc layer was dried over $MgSO_4$, filtered and concentrated in vacuo to afford a crude mixture. Purification by preparative chromatography

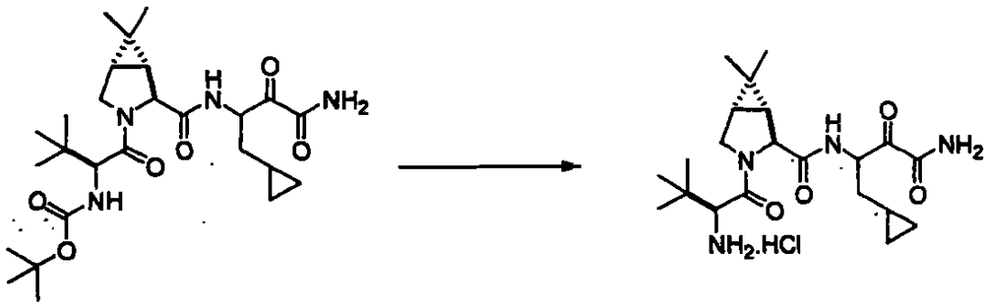
(100% EtOAc, silica) furnished the final product **XXXI** (0.021g). Mass spectrum (LCMS) 724 ($M+H^+$).

Example XXXII: Preparation of a compound of formula XXXII:



XXXII

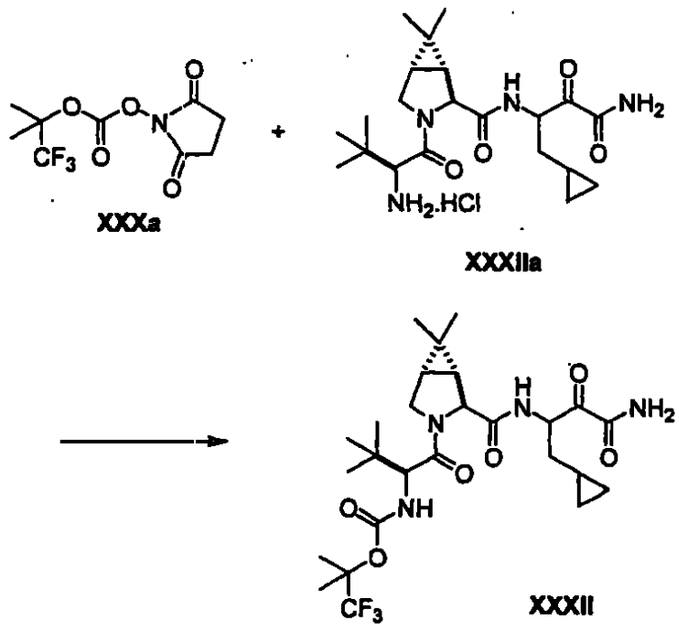
Step 1:



XXVIII **XXXIIa**

The product from Example XXVIII was treated in the manner previously described in preparative Example XXX, Step 2 to afford product **XXXIIa**. Mass spectrum (LCMS) 407 ($M - HCl + H^+$).

Step 2:



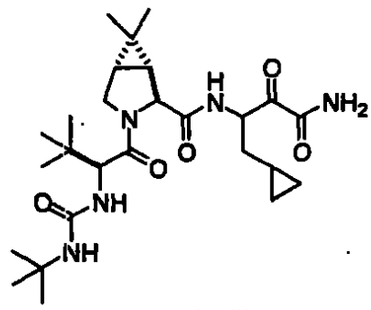
XXXa

XXXIIa

XXXII

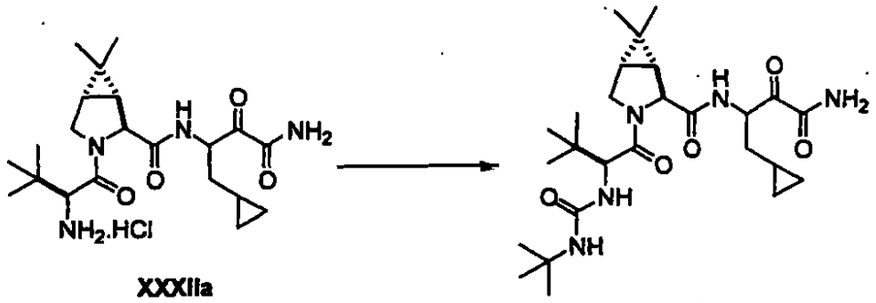
The amine **XXXIIa** was reacted with **XXXa** in the manner previously described in preparative Example XXX, Step 3 to afford the desired product **XXXII**. Mass spectrum (LCMS) 508 ($M+H^+$).

Example XXXIII: Preparation of a compound of formula XXXIII:



XXXIII

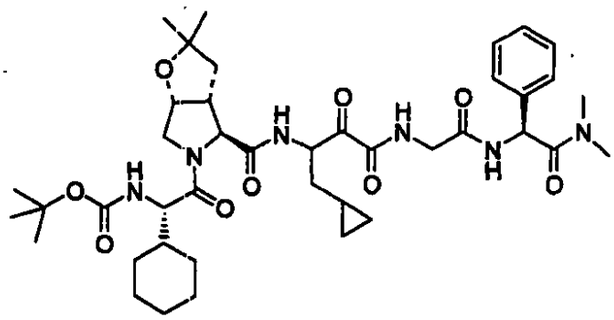
Step 1:



XXXIIa XXXIII

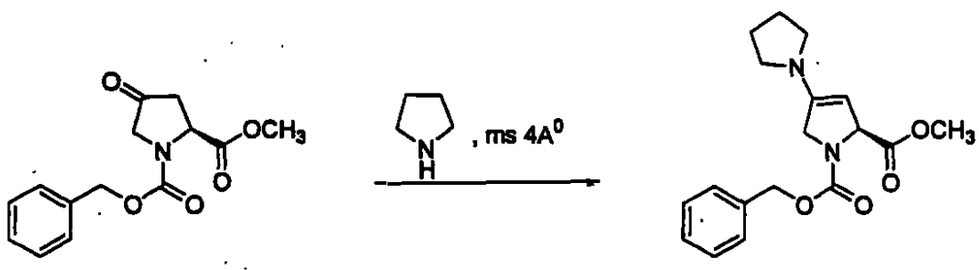
The amine **XXXIIa** was reacted with *tert*-butylisocyanate in the manner previously described in Example XXXI, Step 1, to afford the product **XXXIII**. Mass spectrum (LCMS) 561 ($M+H^+$).

Example XXXIV: Preparation of a compound of formula XXXIV:



XXXIV

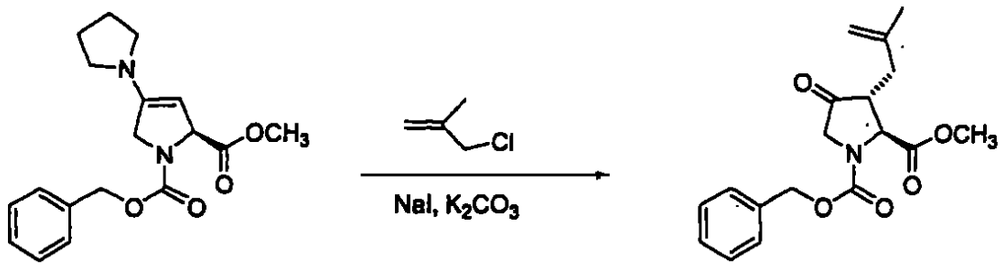
Step 1:



To the mixture of ester (6.0g) and molecular sieve (5.2g) in anhydrous methylene chloride (35 mL) was aded pyrrolidine (5.7 mL, 66.36 mmoL). The resulting brown slurry was stirred at room temperature under N_2 for 24 h, filtered

and washed with anhydrous CH_3CN. The combined filtrate was concentrated to yield the desired product.

Step 2:



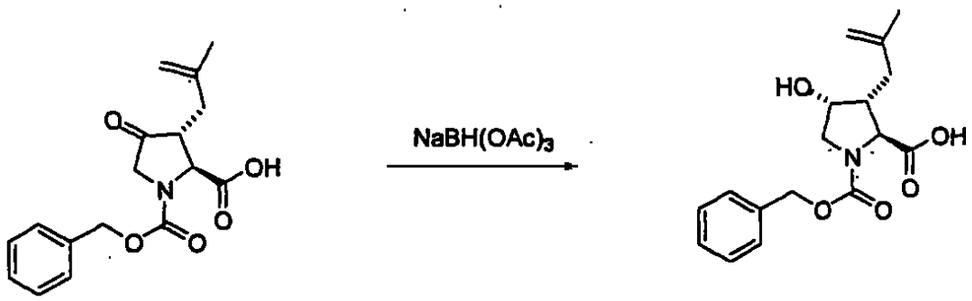
To a solution of the product from proceeding step in CH_3CN (35 mL) was added anhydrous K_2CO_3, methallyl chloride (2.77g, 30.5 mmoL), NaI (1.07g, 6.7 mmoL). The resulting slurry was stirred at ambient temperature under N_2 for 24 h. 50 mL of ice-cold water was added followed by 2N $KHSO_4$ solution until pH was 1. EtOAc (100 mL) was added and the mixture was stirred for 0.75h. Combined organic layer was collected and washed with brine, dried over $MgSO_4$, and evaporated to yield the desired product.

Step 3:



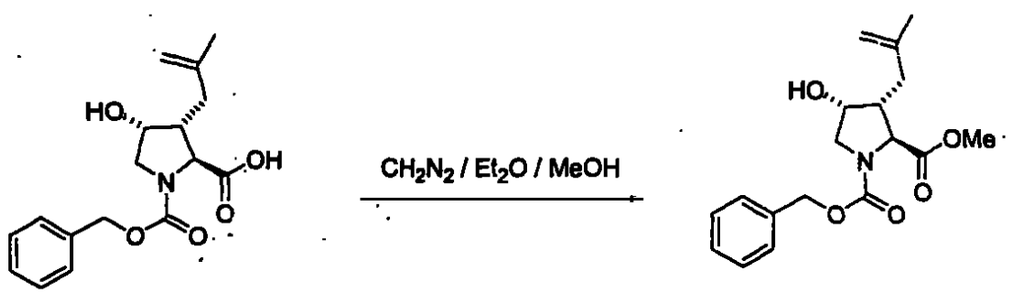
The product from preceding step (2.7 g, 8.16 mmoL) was dissolved in dioxane (20 mL) and treated with freshly prepared 1N LiOH (9 mL). The reaction mixture was stirred at ambient temperature under N_2 for 20 h. The reaction mixture was taken in EtOAc and washed with H_2O. The combined aqueous phase was cooled to 0^0C and acidifed to pH 1.65 using 1N HCl. The turbid mixture was extracted with EtOAc (2 x 100 mL). Combined organic layer was washed with brine, dried over $MgSO_4$, concentrated to give the desired acid (3.40 g).

Step 4:



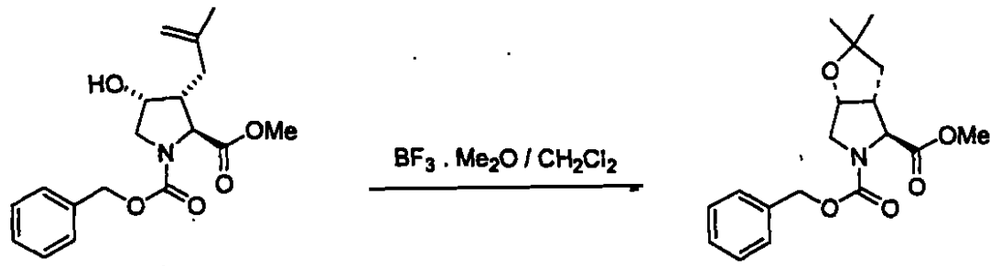
To a suspension of $NaBH(OAc)_3$ (3.93g, 18.5 mmoL) in CH_2Cl_2 (55 mL) was added a solution of product from preceding step in anhydrous CH_2Cl_2 (20 mL) and acetic acid (2 mL). The slurry was stirred at ambient temperature for 20 h . Ice cold water (100 mL) was added to the slurry and stirred for 1/2 hr. Organic layer was separated, filtered, dried and evaporated to yield the desired product.

Step 5:



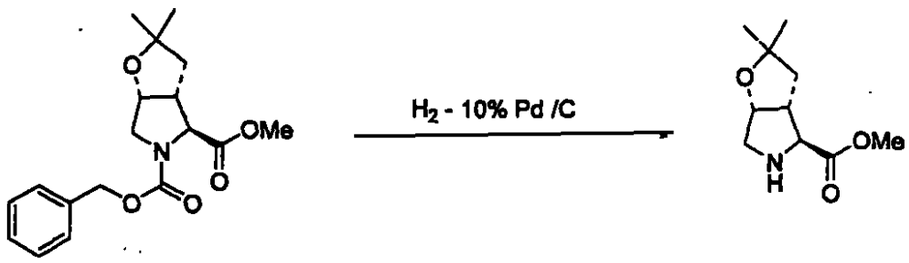
To a solution of the product from preceding step (1.9g) in MeOH (40 mL) was treated with excess of CH_2N_2 / Et_2O solution and stirred for overnight. The reaction mixture was concentrated to dryness to yield a crude residue. The residue was chromatographed on silica gel, eluting with a gradient of EtOAc / hexane to afford 1.07 g of the pure desired product.

Step 6:



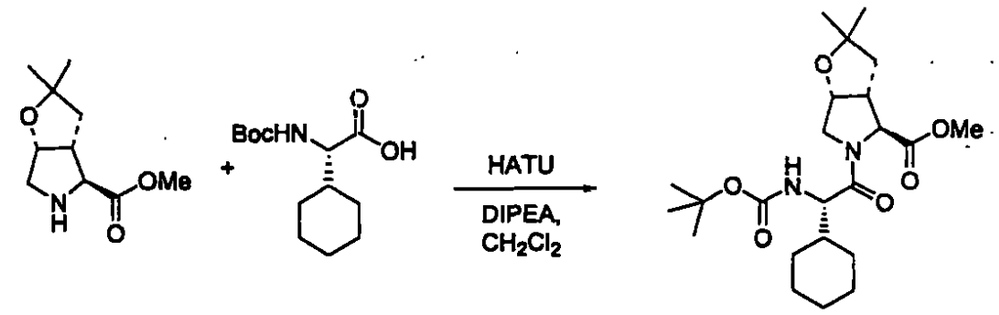
To a solution of product from preceding step (1.36 g) in anhydrous CH_2Cl_2 (40 mL) was treated with BF_3. Me_2O (0.7 mL). The reaction mixture was stirred at ambient temperature for 20 h and quenched with sat. $NaHCO_3$ (30 mL) ad stirred for 1/2 hr. Organic layer was separated and combined organic layer was washed with brine, dried over $MgSO_4$, concentrated to give crude residue. The residue was chromotagraphed on silica gel eluting with a gradient of EtOAc / hexane to afford 0.88 g of the desired compound.

Step 7:



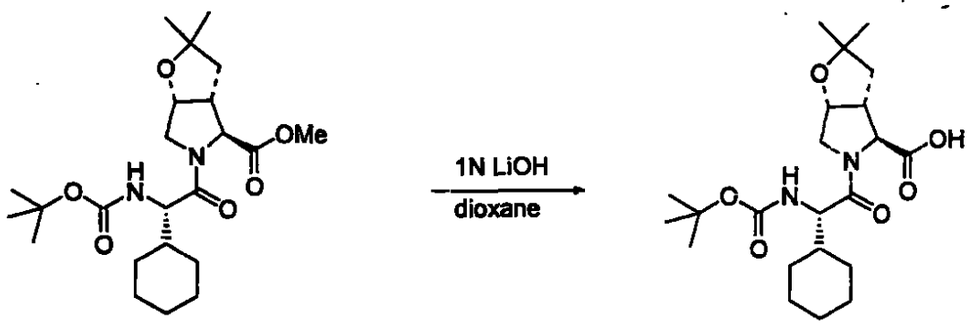
To a solution of the product (0.92 g) from preceding step in MeOH (30 mL) was added 10 % Pd/C (0.16 g) at room temperature and hydrogenated at ambient temperature under 1 atm. Pressure. The reaction mixture was stirred for 4 h and concentrated to dryness to yelld the desired compound.

Step 8:



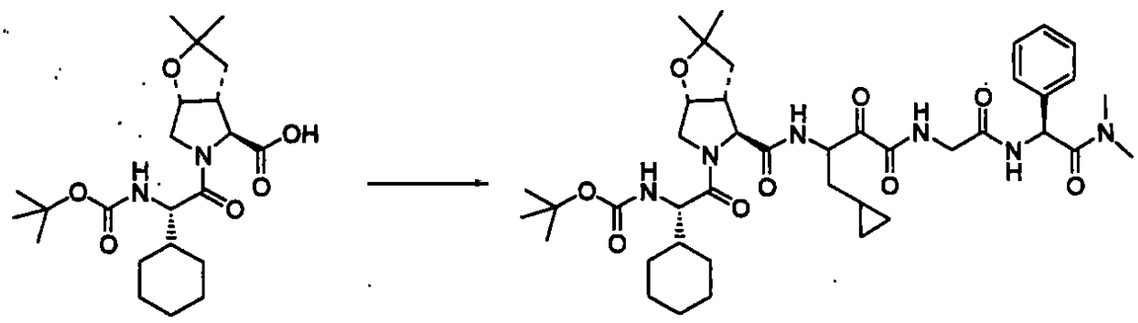
The desired product was prepared according to the procedure in Example XXIII, Step 10.

Step 9:



The desired acid product was prepared according to the procedure in Example XXIV, Step 3.

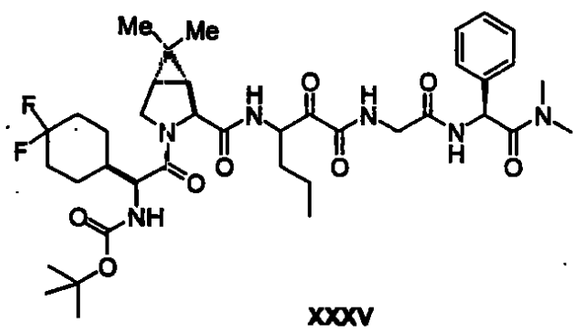
Step 10:



XXXIV

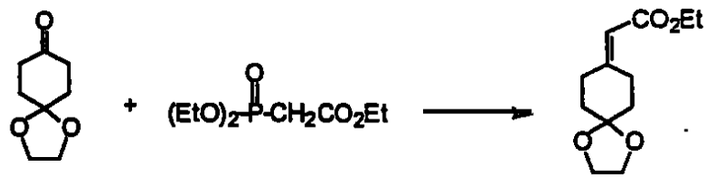
The desired product **XXXIV** was prepared according to the procedure in Example XXIX, Steps 4-5.

Example XXXV: Preparation of a compound of formula XXXV:



XXXV

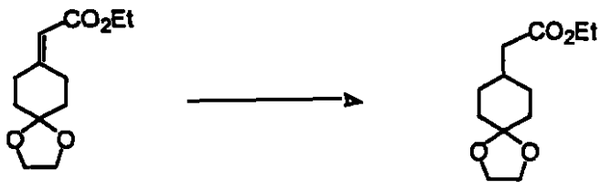
Step 1:



A solution of triethyl phosphonate (44.8 g) in THF (30 mL) at 0°C was treated with a 1M solution (200 mL) of sodium bis(trimethylsilylamide) in THF. The resulting mixture was stirred at RT for 0.5 hour, and then cooled to 0°C. A solution of 1,4-cyclohexanedione ethylene ketal (15.6 g) in THF (50 mL) was

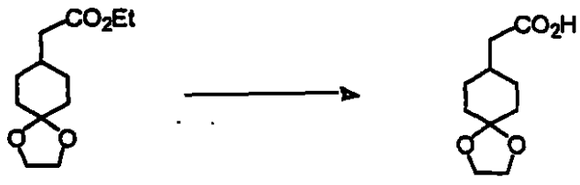
added dropwise, and the resulting solution was stirred at RT for 18 hours. The reaction mixture was then cooled to 0°C, treated with cold aqueous citric acid, and the mixture was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$, then brine; then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with a gradient of CH_2Cl_2/EtOAc to afford the title compound (21 g), 92% yield. Mass spectrum (FAB) 227.3 ($M+H^+$).

Step 2:



The product of the preceding step (20 g) was dissolved in EtOH (150 mL) and treated with 10% Pd/C under 1 atm of hydrogen for 3 days. The mixture was filtered and the filtrate evaporated to afford the title compound (20.3 g), 100 % yield. Mass spectrum (FAB) 229.2 ($M+H^+$).

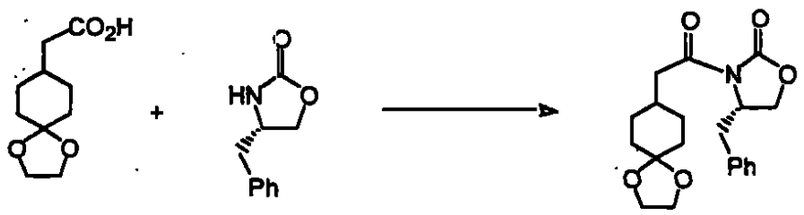
Step 3:



The product of the preceding step (20 g) was dissolved in MeOH (150 mL) and treated with a solution of LiOH (3.6 g) in water (50 mL). The mixture was stirred for 18 hours, and concentrated under vacuum. The residue was dissolved in cold water (100 mL), the solution was acidified to pH 2-3 with 5N HCl, and the resulting mixture was extracted with EtOAc. The extract was dried over

anhydrous Na_2SO_4, filtered, and the filtrate evaporated to afford the title compound (17.1 g), 97% yield. Mass spectrum (FAB) 201.2 ($M+H^+$).

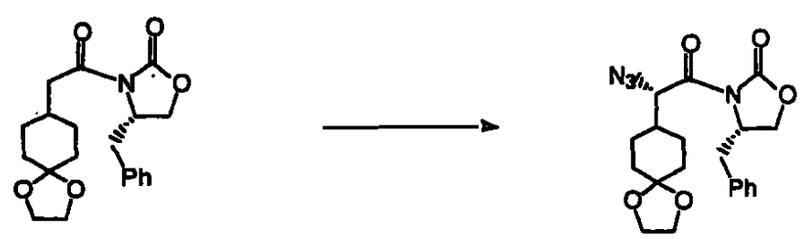
Step 4:



1. The product of the preceding step (3.0 g) was dissolved in Et_2O (150 mL), treated with Et_3N (2.1 mL), and the solution cooled to -78°C. Pivaloyl chloride (1.85 mL) was added dropwise, and after 0.25 hour additional stirring, the reaction was allowed to warm to 0°C over 0.75 hour, and then cooled again to -78°C to afford a solution of mixed anhydride for reaction in part 2.

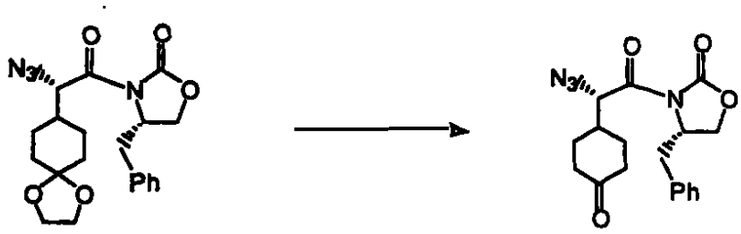
2. A solution of (S)-4-benzyl-2-oxazolidinone (2.66 g) in THF (22 mL) was cooled to -78°C, and a 1.6 M solution (9.38 mL) of n-butyllithium in hexane was added dropwise. After an additional 0.33 hour stirring at this temperature, the solution was transferred via canula to the cold solution of part 1. The mixture was stirred at -78°C , then warmed to 0°C, and stirred at this temperature for 0.5 hour. The organic layer was separated, the aqueous layer was extracted with Et_2O, the combined organics were washed with brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with a gradient of hexane/EtOAc (9:1) to afford the title compound (5.0 g), 93% yield. Mass spectrum (FAB) 360.4 ($M+H^+$).

Step 5:



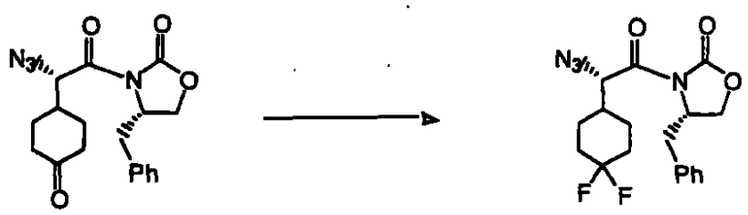
The product of the preceding step (2.7 g) was dissolved in THF (25 mL), cooled to -78°C, transferred by canula to a solution of 0.5 M potassium bis(trimethylsilyl)amide/toluene (16.5 mL) in THF (25 mL) at -78°C, and the resulting solution was stirred at -78°C for 0.75 hour. To this solution was added via canula a solution of trisyl azide (3.01 g) in THF (25 mL) pre-cooled to -78°C. After 1.5 minutes, the reaction was quenched with acetic acid (1.99 mL), the reaction was warmed to RT, and then stirred for 16 hours. The reaction was diluted with EtOAc (300 mL), and washed with 5% aqueous NaCl. The aqueous phase was extracted with EtOAc, the combined organic phases were washed with saturated aqueous $NaHCO_3$, then brine; then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with EtOAc/hexane (1:3) to afford the title compound (2.65 g), 88% yield.

Step 6:



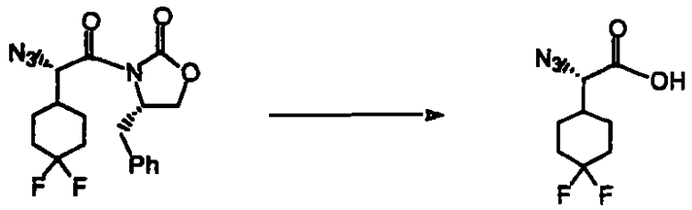
The product of the preceding step (11.4 g) was dissolved in 95% formic acid (70 mL) and heated at 70°C for 0.5 hour while stirring. The solution was evaporated under vacuum, and the residue was taken up in EtOAc. The solution was washed with saturated aqueous $NaHCO_3$, then brine; then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel to afford the title compound (8.2 g).

Step 7:



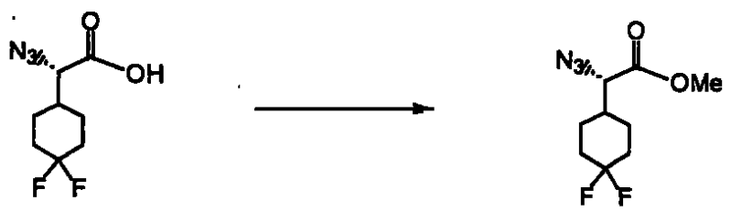
The product of the preceding step (8.2 g) was dissolved in CH_2Cl_2 (16 mL) and treated with diethylaminosulfur trifluoride (DAST, 7.00 mL) at RT for 3 hours. The reaction was poured over ice/water (200 cc), and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$, then brine; then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with EtOAc/hexane (15:85) to afford the title compound (4.5 g), 52% yield.

Step 8:



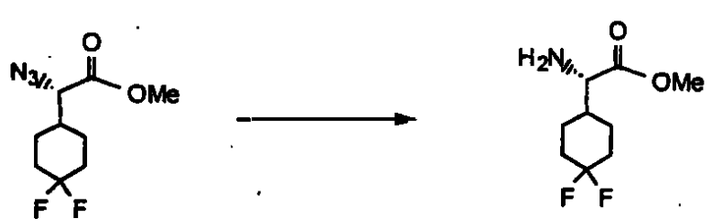
The product of the preceding step (3.7 g) was dissolved in a mixture of THF (150 mL) and water (48 mL), cooled to 0°C, treated with 30% H_2O_2 (3.95 mL), and then with $LiOH \cdot H_2O$ (0.86 g). The mixture was stirred for 1 hour at 0°C, then quenched with a solution of Na_2SO_3 (5.6 g) in water (30 mL), followed by a solution of 0.5 N $NaHCO_3$ (100 mL). The mixture was concentrated under vacuum to 1/2 volume, diluted with water (to 500 mL), and extracted with CH_2Cl_2 (4 x 200 mL). The aqueous phase was acidified to pH 1-2 with 5N HCl, and extracted with EtOAc (4 x 200 mL). The extract was washed brine; then dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated to afford the title compound (1.95 g), 91% yield, which was used directly in the next step.

Step 9:



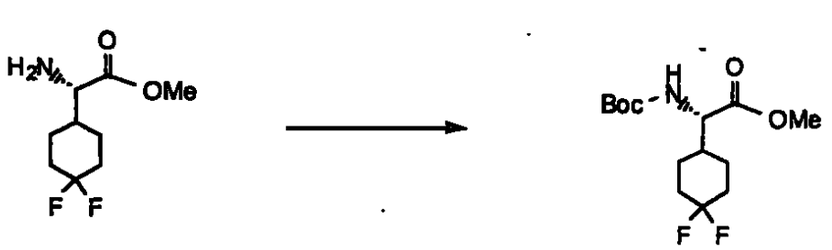
The product of the preceding example (2.6 g) was dissolved in Et_2O (50 mL) and treated dropwise with a solution of $CH2N_2$ in Et_2O until the solution remained yellow. The solution was stirred for 18 hours, then evaporated under vacuum to afford the title compound (2.8), which was used directly in the next step.

Step 10:



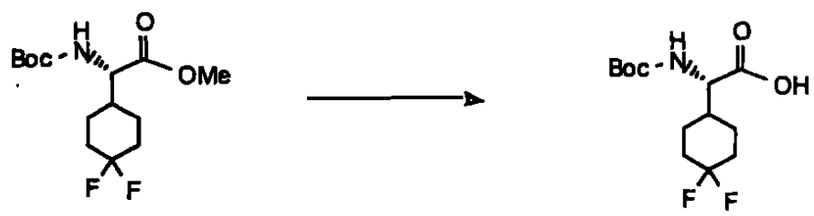
The product of the preceding step (1.95 g) was dissolved in MeOH (150 mL), treated with formic acid (1.7 mL), then treated with 10% Pd/C (3.3 g, Degussa type E101) under 1 atm of hydrogen for 1.5 hours. The mixture was filtered and the filtrate evaporated to afford the title compound (2.1 g) as the formic acid salt, which was used directly in the next step.

Step 11:



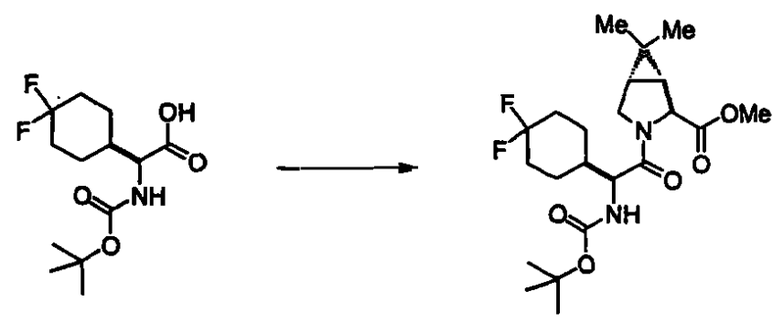
The product of the preceding step (2.1 g) was dissolved in 1,4-dioxane (100 mL) and di-*tert*-butyl dicarbonate (1.9 g) was added, followed by diisopropylethylamine (2.9 mL). The solution was stirred for 18 hours, and concentrated under vacuum. The residue was treated with aqueous 5% KH_2PO_4 and the mixture extracted with EtOAc. The extract was washed with brine; then dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated. The residue was chromatographed on silica gel, eluting with a gradient of CH_2Cl_2/Et_2O to afford the title compound (2.5 g), 99% yield. Mass spectrum (FAB) 307.9 ($M+H^+$).

Step 12:



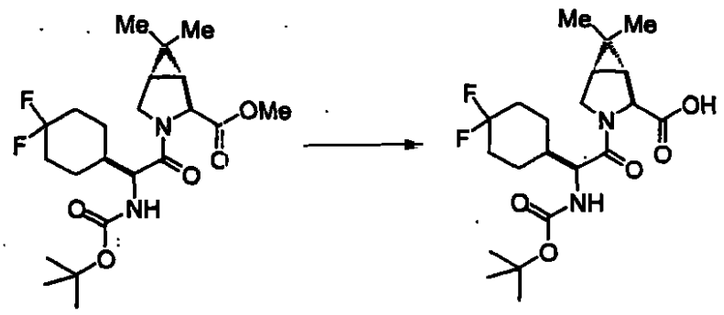
The product of the preceding step (2.5 g) was dissolved in 1,4-dioxane (35 mL), treated with aqueous 1M LiOH (17 mL), and stirred for 2 hours. The mixture was quenched with ice/water (125 cc), the mixture was acidified to pH 3-4 with 3N HCl, and extracted with EtOAc. The extract was dried over anhydrous $MgSO_4$, filtered, and the filtrate evaporated to afford the title compound (2.3 g), 96% yield. Mass spectrum (FAB) 294.0 ($M+H^+$).

Step 13:



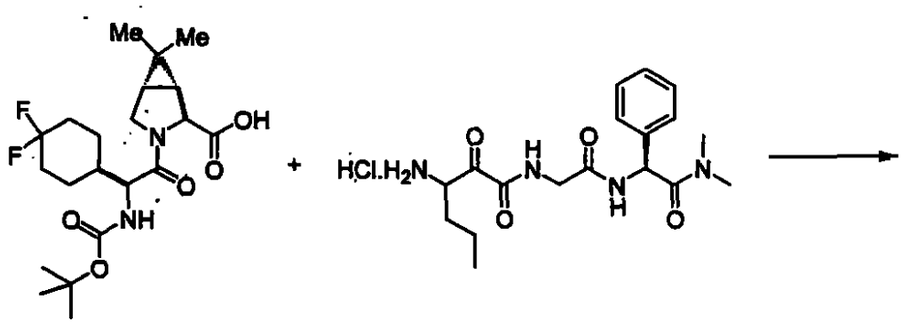
The desired product was prepared according to the procedure in Example XXIII, Step 10.

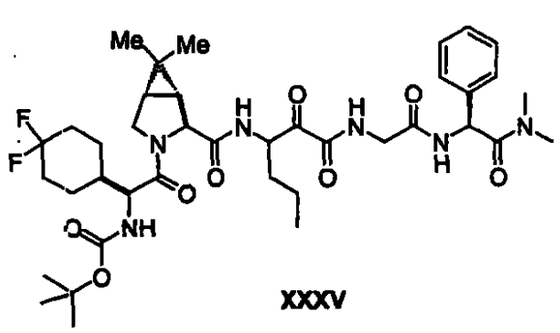
Step 14:



The desired acid product was prepared according to the procedure in Example XXIV, Step 3.

Step 15:



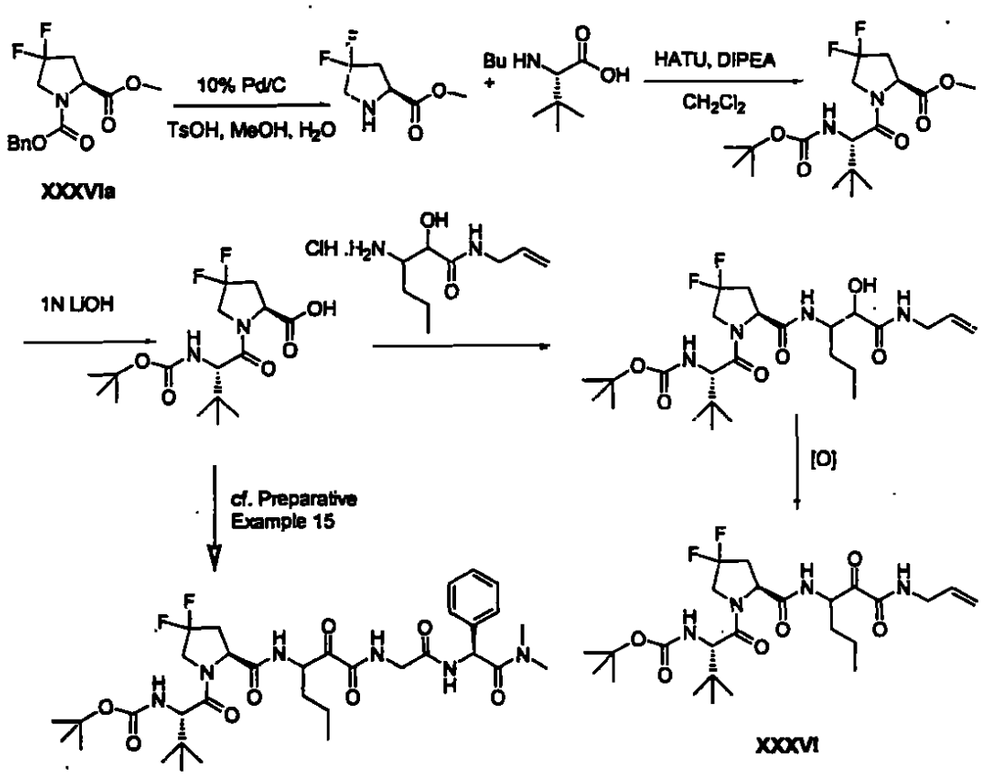


XXXV

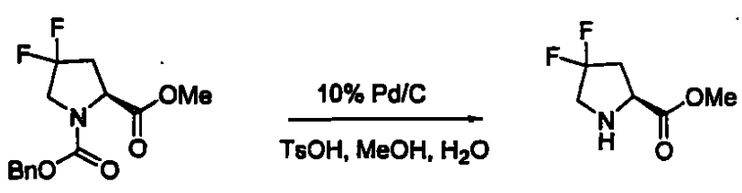
The desired acid product was prepared according to the procedure in Example XXIX, Step 4.

Example XXXVI. Preparation of compounds of Formulas XXXVI and XXXVIII:

Compounds of formulas XXXVI and XXXVIII were prepared according to the scheme below and utilizing preparative Examples 11 through 15 discussed above.



The compound of formula XXXVIb was prepared from a compound of formula XXXVIa as follows by known procedures:

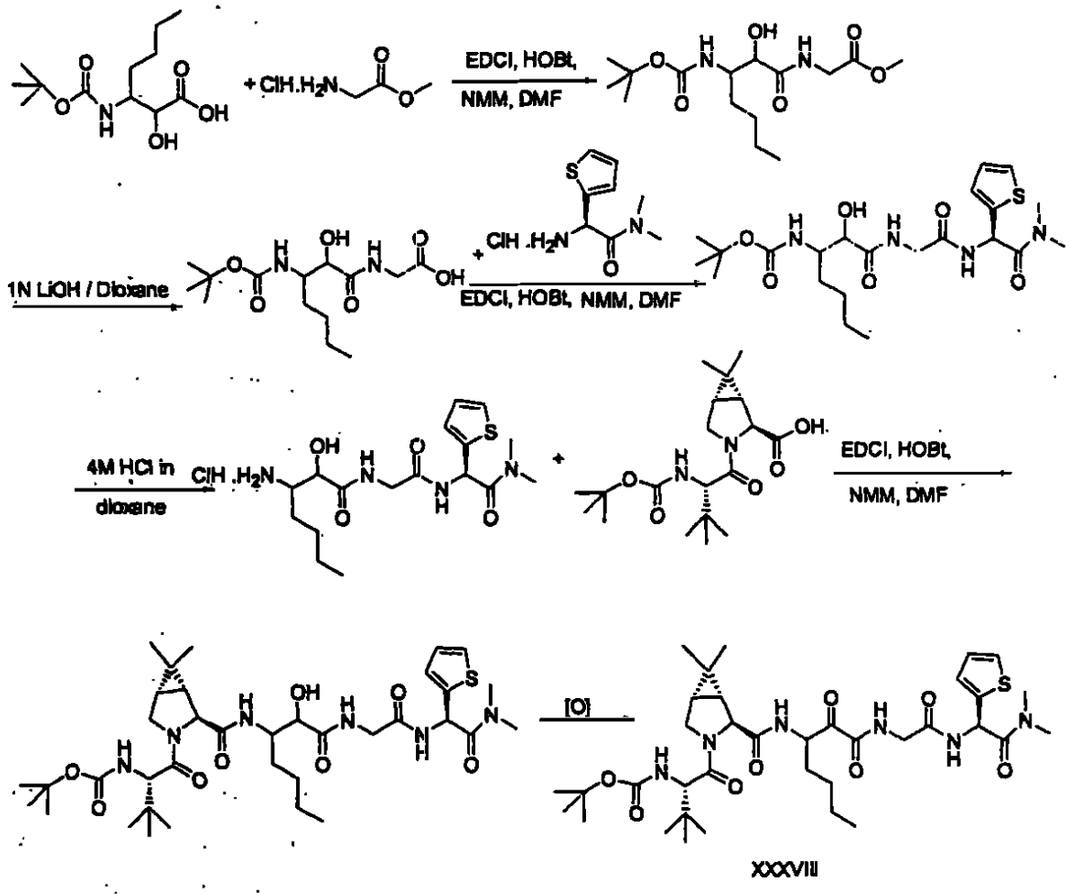


XXXVIa XXXVIb

To a solution of Compound XXXVIa (6.58g, 22 mmol) in 100 mL of MeOH was added 10% Pd/C (0.8 g) and *p*-toluene sulfonic acid (4.2 g). The reaction mixture was subjected to hydrogenation at room temperature overnight. The reaction mixture was filtered through celite and washed with excess MeOH. The combined filtrate was concentrated in-vacuo to provide the title compound XXXVIb as a gummy. Conversion of XXXVIb to XXXVI and XXXVII followed the route as shown in the scheme above and according to preparative examples 11-15.

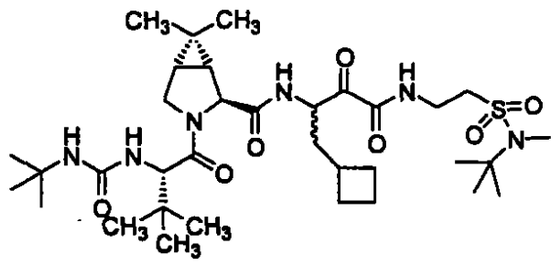
Example XXXVIII. Preparation of a compound of formula XXXVIII:

A compound of the formula XXXVIII was prepared utilizing the following scheme and following preparative Examples 11 through 15 discussed earlier.



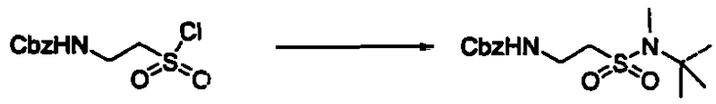
XXXVIII

Example XXXIX. Synthesis of the compound of Formula XXXIX:



XXXIX

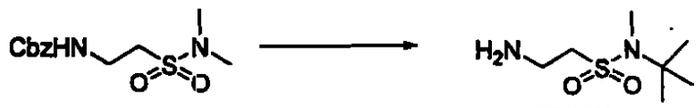
Step 1:



XXXIXa XXXIXb

A solution of the sulfonyl chloride XXXIXa prepared by the procedure of H. Mcklwain (*J. Chem. Soc* 1941, 75) was added dropwise to a mixture of 1.1. equiv of t-butylmethylamine and triethylamine at –78 °C and stirred at rt for 2h. The reaction mixture was concentrated in vacuo and purified by chromatography (SiO_2, Hex/Acetone 4:1) to yield sulfonamide XXXIXb as a colorless oil.

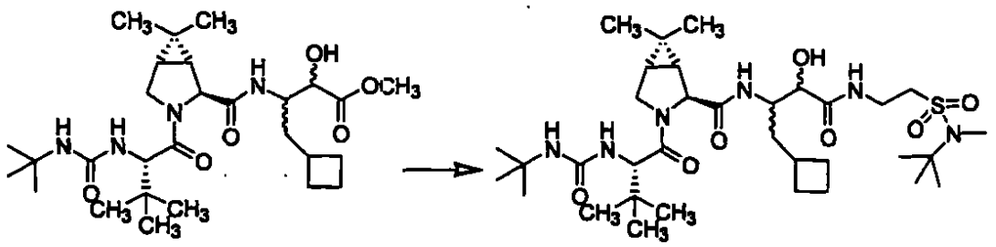
Step 2:



XXXIXb XXXIXc

A solution of the Cbz-protected amine XXXIXb was dissolved in methanol and treated with 5 mol% of Pd /C (5%w/w) and hydrogenated at 60 psi. The reaction mixture was filtered through a plug of celite and concentrated in vacuo to obtain the free amine XXXIXc which solidfied on standing.

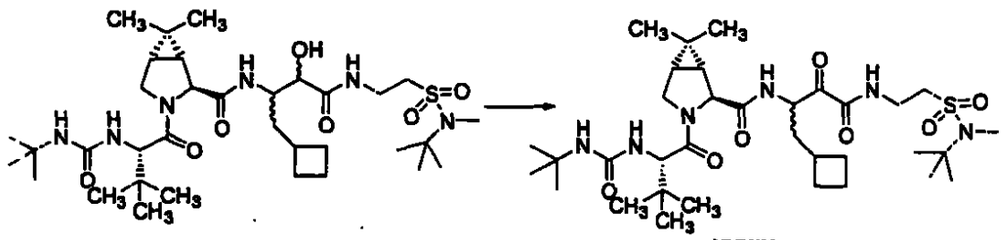
Step 3:



XXVe XXXIXd

The hydroxy sulfonamide XXXIXd was synthesized similar to the procedure for the synthesis of XXVf except replacing the amine XXVd with XXXIXc. The crude reaction mixture directly used for the next reaction.

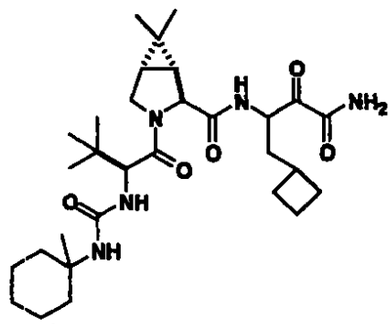
Step 4:



XXXIXd XXXIX

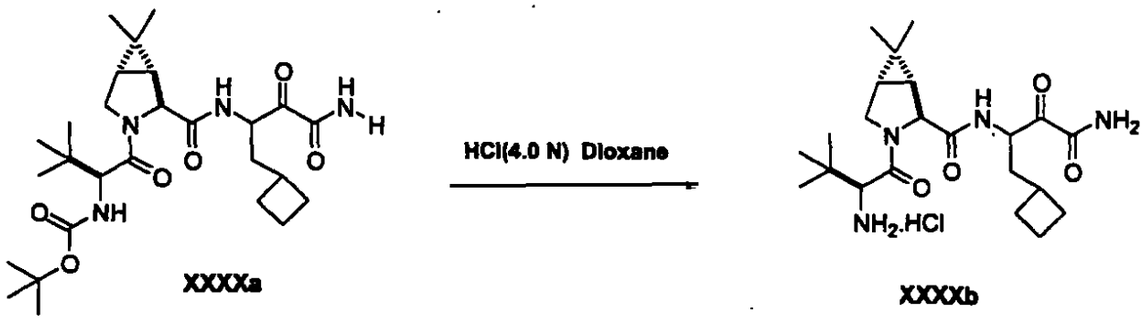
The hydroxy amide XXXIXd was oxidized to compound XXXIX using the Dess Martin reagent following the procedure for the synthesis of XXV (step 5). The crude mixture was purified by chromatography (SiO_2, Acetone/Hexane 3:7) to obtain XXXIX as a colorless solid.

Example XXXX Preparation of Compound of Formula XXXX



XXXX

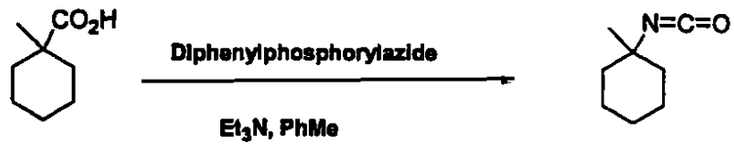
Step1



XXXXa XXXXb

XXXXa was reacted in the manner previously described XXXII step 1 to afford **XXXXb** product product of step 1 Mass spectrum (LCMS) 421 ($M - HCl + H^+$).

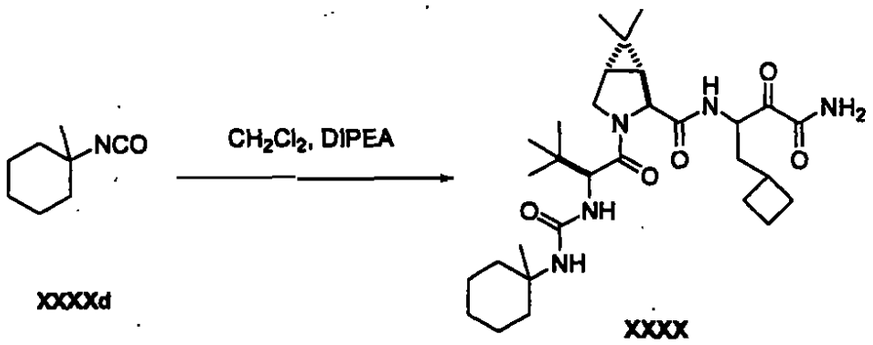
Step2



XXXXc XXXXd

Et_3N(1.4 mL) and Diphenylphosphorylazide(2.2 mL) were added to a solution of carboxylic acid **XXXXc** in toluene (13 mL). Reaction was stirred at RT for 30 min then refluxed overnight. After 18 h, reaction is cooled to RT and **XXXXd** product of step2, which was used directly 0as a 0.7 M solution in Toluene.

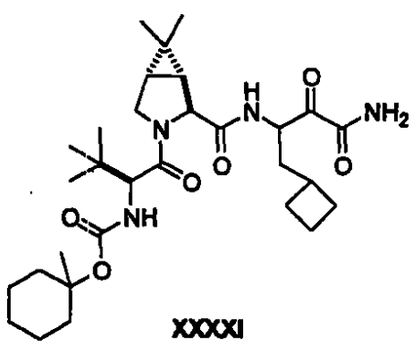
Step 3



XXXXd **XXXX**

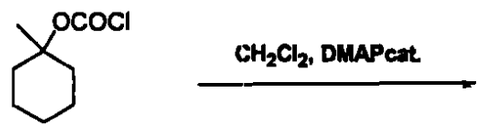
XXXXb, Product of step 1 of preparative example **XXXX** was reacted with **XXXXd** product of step 2 of preparative example **XXXX** in the manner previously described in example XXXIII to afford **XXXX**. Mass spectrum (LCMS) 560 ($M+H^+$).

Example XXXXI Preparation of Compound of Formula XXXXI



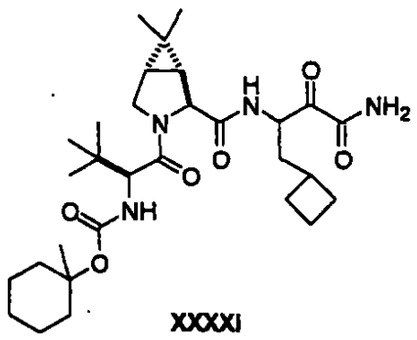
XXXXI

Step4



Prepared cf J.Org.Chem., 1977,42,143

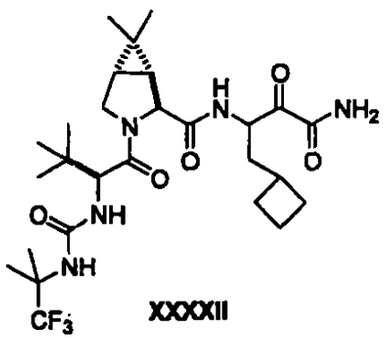
XXXXIa



XXXXI

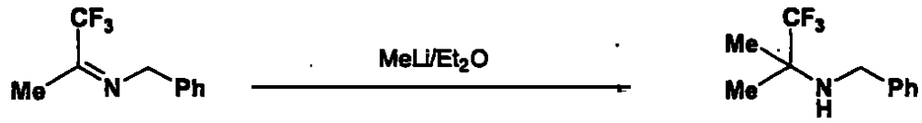
XXXXb, product of step 1 of preparative example **XXXX** was reacted with chloroformate **XXXXIa** prepared as ***J.Org.Chem.***,1977,42,143 in the manner previously preparative example 12 compound 4.1 described to afford **XXXXI**. Mass spectrum (LCMS) 561 ($M+H^+$).

Example XXXXII Preparation of Compound of Formula XXXXII



XXXXII

Step1



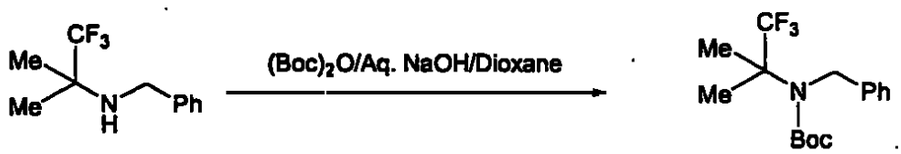
Prepared cf J.Org.Chem., 1996 p 6567

XXXXIIa

XXXXIIb

To a stirred and cooled (acetone/dry ice bath) solution of the starting imine **XXXXII a** (3.679 g) in diethyl ether (50 ml) was added 1.6M methyl lithium in diethyl ether (12.6 ml). The reaction mixture was allowed to warm up to room temperature over 2 hrs. Saturated $NaHCO_3$ was added and after stirring for ~30 min the organic phase was separated. It was then washed with brine, dried over anhydrous Na_2SO_4 and concentrated to dryness under vacuum. The crude product was subjected to chromatography over silica gel (2% ethyl acetate in n-hexane) to provide the desired product **XXXXIIb** (0.3 g).

Step 2

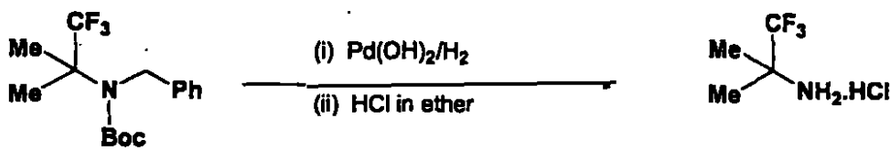


XXXXIIb

XXXXIIc

To a stirred and cooled (ice bath) solution of **XXXXIIb** the product from step 1 (0.3 g) was added 1.0N NaOH (1.38 ml) followed by $(Boc)_2O$. The reaction mixture was stirred at room temperature for ~20 hrs after which it was distributed between ethyl acetate (50 ml) and water (10 ml). The ethyl acetate phase was separated, washed with brine and dried over anhydrous Na_2SO_4. Evaporation under vacuum to dryness provided the desired NBoc derivative **XXXXIIc** (0.660 g), which was used without further purification in the following step.

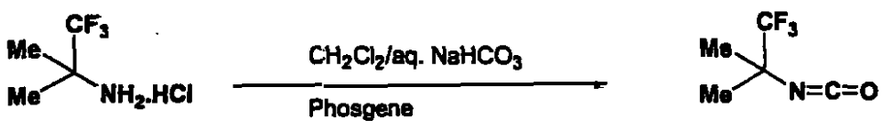
Step 3



XXXXIIc XXXXIId

A solution of the **XXXXIIc** product from step 2 in methanol (10 ml) was hydrogenated in the presence of $Pd(OH)_2$ until thin layer chromatography showed the absence of the starting material. $Pd(OH)_2$ was removed by filtration and washed with methanol. The combined filtrate and washings were concentrated to dryness under vacuum to provide a solid which was dissolved in methanol and treated with 1.0N HCl in diethyl ether. After ~2 hr the reaction mixture was evaporated to dryness under vacuum to provide **XXXXIId** the desired amine hydrochloride as a white solid (0.2 g).

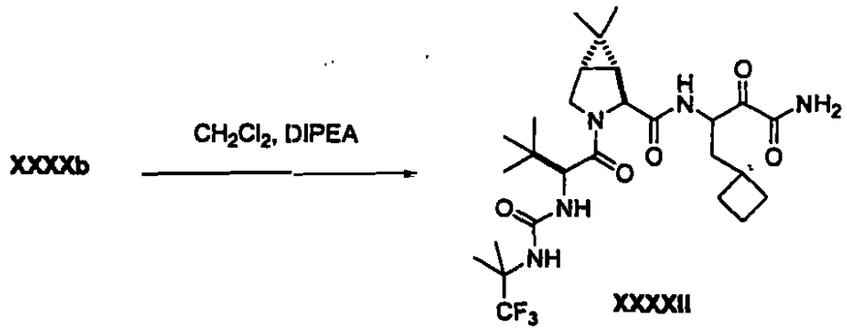
Step 4



XXXXIId XXXXIIe

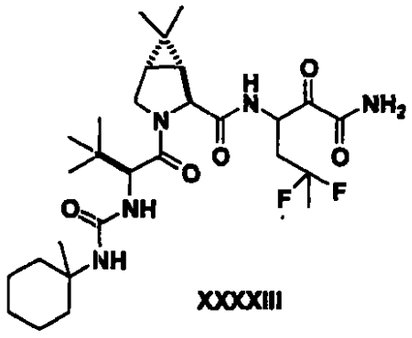
To a stirred and cooled (ice bath) solution of **XXXXIId** the product from step C (0.1 g) in CH_2Cl_2 (6 ml) was added saturated $NaHCO_3$ solution (4 ml) followed by phosgene (0.64 ml). The reaction mixture was stirred at 0°C for 30 min and at room temperature for 1 hr. The organic phase was separated, dried over anhydrous $MgSO_4$ and concentrated to dryness in vacuum to provide the desired isocyanate **XXXXIIe** (0.0611 g).

Step 5

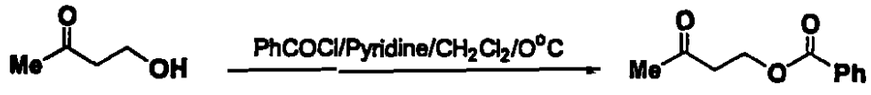


XXXXIIe, product of step 5 was reacted with **XXXXb** of preparative example **XXXX** in the manner previously in example **XXXIII** described to afford **XXXXII**. Mass spectrum (LCMS) 574 ($M+H^+$).

Example XXXXIII Preparation of Compound of Formula XXXXIII



Step 1

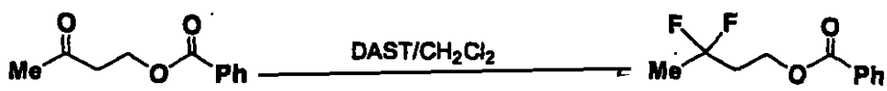


XXXXIIIa **XXXXIIIb**

To a cooled solution (ice bath) of 4-hydroxy-2-butanone (8.81 g) **XXXXIIIa** in CH_2Cl_2 (100 ml) was added with stirring, benzoyl chloride (14.76 g) followed by pyridine (16.15 ml) and DMAP (0.01 g). The reaction mixture was stirred at room temperature overnight then diluted with ethyl acetate (~200 ml). The solution was

washed with aqueous $CuSO_4$, aqueous NH_4Cl and brine. The organic phase was then dried over anhydrous $MgSO_4$ and evaporated to dryness. The product was purified by column chromatography over silica gel (5%-15% ethyl acetate in n-hexane) to provide **XXXXIIIb** (16.3 g; 84.9%).

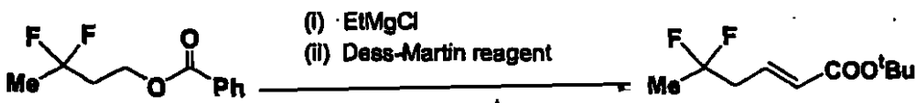
Step 2



XXXXIIIb XXXXIIIc

To a solution of **XXXXIIIb**, the product from step 1 (16.3 g) in CH_2Cl_2 (150 ml), was added DAST (26.1 ml) and the reaction mixture stirred at room temperature for ~72 hrs. The mixture was then added dropwise to a cold saturated solution of Na_2CO_3 (150 ml). The mixture was diluted with ethyl acetate (~200 ml) and after stirring for ~30 min the organic phase was separated; washed with brine and dried over anhydrous $MgSO_4$. Concentration in-vacuo and purification by chromatography over silica gel (4% ethyl acetate in n-hexane) provided **XXXXIIIc** (14.6 g; 80.4%).

Step3



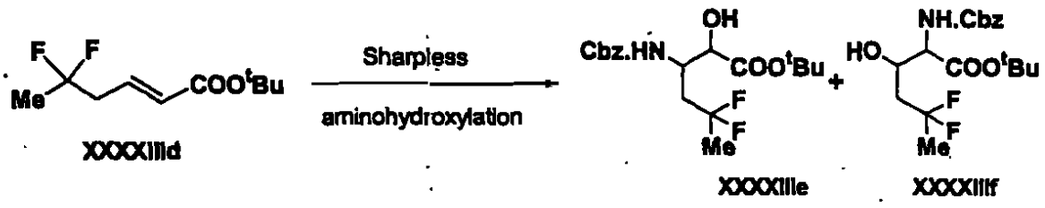
XXXXIIIc XXXXIIId

To a solution of **XXXXIIIc** the product from step 2 (4 g) in dry diethyl ether (150 ml) was added with cooling (ice bath) EtMgCl (28 ml). The reaction mixture was stirred in the cooling bath for ~6 hrs after which it was poured into saturated aqueous NH_4Cl with ice cooling. The organic layer was separated, washed with

brine, dried over anhydrous $MgSO_4$ and concentrated to dryness in vacuum. The residue was dissolved in CH_2Cl_2 (100 ml) and treated with Dess-Martin reagent (15.8 g). After stirring at room temperature for 1 hr $Ph_3P{=}CHCOO^tBu$ (10.54 g) was added. Stirring was continued for ~20 hrs. Ethyl acetate (~200 ml) was added followed by a mixture of saturated $Na_2S_2O_3$ and saturated $NaHCO_3$ (200 ml; 1/1) and stirred for ~ 10 min. The organic layer was separated and washed successively with saturated NaHCO3 and brine. The washed organic phase was dried over anhydrous $MgSO_4$ and evaporated to dryness under vacuum to provide the desired crude product.

The above reaction was repeated using the product from step 2 (10.6 g). The final crude products from the two reactions were combined and subjected to purification by chromatography on silica gel (10% CH_2Cl_2 in n-hexane) to provide **XXXXIIId** (7.93 g; 57%).

Step 4



XXXXIIId

XXXXIIIe

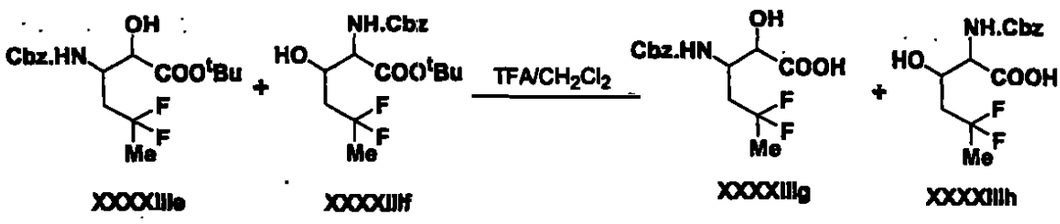
XXXXIIIf

Benzyl carbamate (8.92 g) was dissolved in n-propyl alcohol (79 ml). To the resulting solution was added with stirring a freshly prepared solution of NaOH (2.33 g) in water (145 ml), followed by tert-butylhypochlorite (6.57 ml). To the resulting mixture $(DHQ)_2PHAL$ (0.742 g) dissolved in n-propyl alcohol (66 ml) was added followed by **XXXXIIId** (19.05 mmol). The osmium catalyst, $K_2OsO_2(OH)_2$ was then added and the reaction mixture stirred at room temperature for 1 hr.

The above reaction was repeated using **XXXXIIId** (19. 36 mmol). The two reactions were combined followed by dilution with ethyl acetate (500 ml). The mixture was shaken with water (100 ml), the organic phase separated and

washed with water, brine and finally dried over anhydrous $MgSO_4$. Evaporation under vacuum provided the crude product which was chromatographed over silica gel (10%-20% ethyl acetate in n-hexane) to provide pure desired product (3 g) as a mixture of **XXXXIIIe** and **XXXXIIIf**

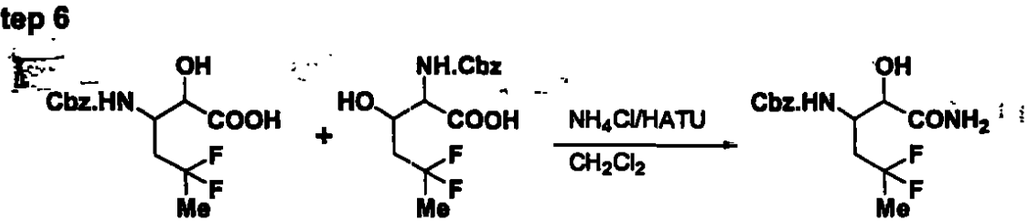
Step 5



XXXXIIIe **XXXXIIIf** **XXXXIIIg** **XXXXIIIh**

A stirred solution of **XXXXIIIf** and **XXXXIIIe** the product from step 4 in CH_2Cl_2 (50 ml) was treated with trifluoroacetic acid (50 ml). After 4 hrs the reaction mixture was concentrated to dryness under vacuum. The residue was dissolved in 10% aqueous Na_2CO_3 the solution washed with diethyl ether and the aqueous phase acidified with 2M H_2SO_4 to pH ~1.5. Extraction of the acidic solution with ethyl acetate followed by drying over anhydrous MgSO4 and evaporation under vacuum provided the desired product as a mixture of **XXXXIIIg** and **XXXXIIIh** (2.6 g).

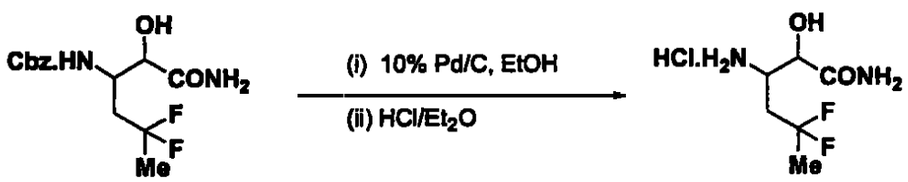
Step 6



XXXXIIIg **XXXXIIIh** **XXXXIIII**

To a solution of the product from step 5 (1 g) in CH_2Cl_2 (50 ml) was added HATU (1.43 g), NH_4Cl (0.842 g) and DMSO (5.59 ml). The reaction mixture was stirred at room temperature for ~20 hrs, diluted with ethyl acetate and washed with saturated $NaHCO_3$ and brine. The organic phase was then dried over anhydrous $MgSO_4$ and concentrated to dryness under vacuum to provide the crude product. Chromatography on silica gel (10% n-hexane in ethyl acetate) provided in one of the fractions the pure desired product **XXXXIIII** (0.205 g).

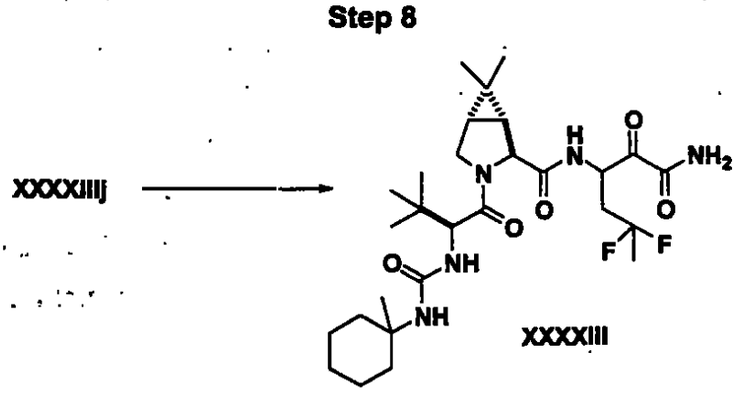
Step 7



XXXXIIIi XXXXIIIj

To a solution of **XXXXIIII** the product from step 6 (0.205 g) in ethanol (15 ml) was added 10% Pd/C catalyst. The resulting suspension was hydrogenated until thin layer chromatography indicated complete consumption of the starting material (~3 hrs). The catalyst was removed by filtration and washed with ethanol. The combined filtrate and washings were evaporated under vacuum to dryness to provide the desired product **XXXXIIIj** (0.164 g).

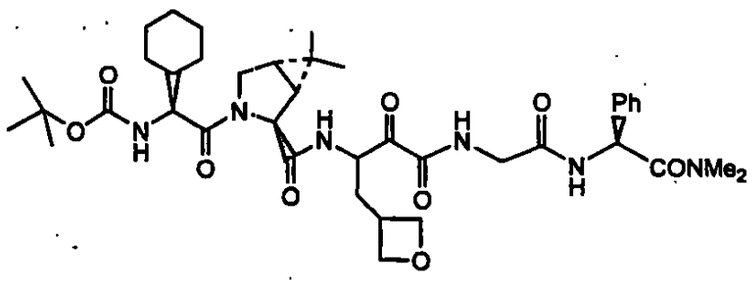
Step 8



XXXXIII

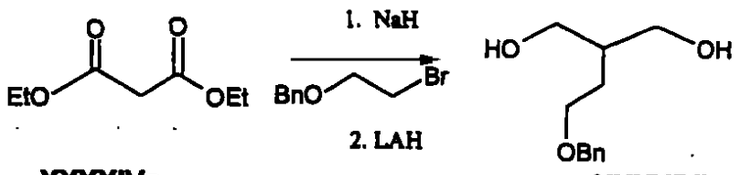
XXXXIIIJ was converted to XXXIII following the procedure similar to exmple XXVIII and XXXIII

Example XXXXIV Preparation of Compound of Formula XXXXIV



XXXXIV

Step 1

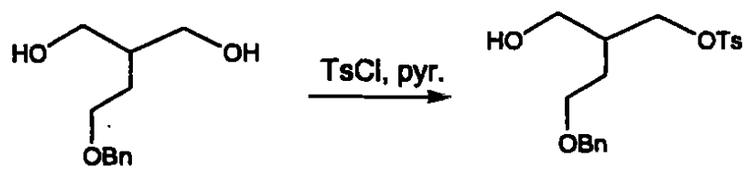


XXXXIVa XXXXIVb

Ethyl malonate **XXXXIVa** (5.4ml; 36mmol) was added to a suspension of NaH (1.44g of a 60% dispersion in mineral oil; 0.9eq.) in anhydrous tetrahydrofuran (THF; 60ml) at 0C, under an atmosphere of nitrogen and the mixture was stirred at room temperature for 30 min. Benzyl 2-bromoethylether (8.5ml; 40mmol) was added before refluxing the reaction for a period of 24h. After cooling, the reaction was partitioned between EtOAc and dilute HCl (approx. 1M). The organic layer was separated, dried ($MgSO_4$) and concentrated to yield a residue.

The aforementioned residue was dissolved in anhydrous THF (100ml) and a solution of lithium aluminum hydride (LAH; 66ml of a 1.0M solution) was added under an atmosphere of nitrogen and the resulting mixture was stirred at room temp. for a period of 4h. and EtOAc followed by dilute HCl was added. The organic layer was separated, washed with brine, dried (MgSO4) and concentrated. The crude reaction product was purified by silica gel column chromatography using EtOAc:Hexane (70:30) as eluent to provide the desired diol **XXXXIVb** (3.59g) as a colourless oil.

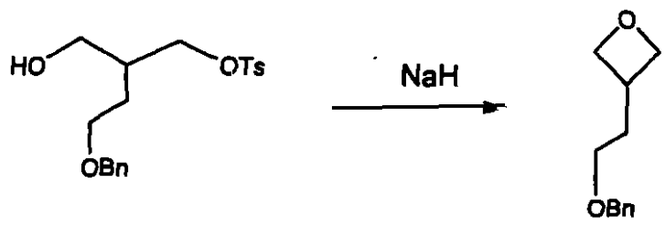
Step 2



XXXXIVb **XXXXIVc**

p-Toluene sulfonylchloride (1.12g; 5.9mmol) was added to the diol **XXXXIVb** (1.00g; 4.9mmol) in a mixture of dichloromethane (15ml) and pyridine (1.18ml; 14.6mmol) and the resulting mixture was stirred at room temperature overnight (approx 16h.). The reaction mixture was partitioned between EtOAc and dilute aqueous HCl. The organic phase was separated, washed with sat. aq. Sodium bicarbonate, dried (MgSO4) and concentrated under reduced preesure. The residue was purified by silica gel column chromatography using EtOAc: hexane (30:70) as eluent to provide I) the ditosylate (0.291g), followed by ii) the desired mono-tosylate **XXXXIVc** (1.02g) and iii) recovered diol (0:27g).

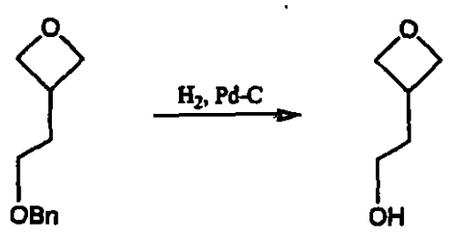
Step 3



XXXXIVc **XXXXIVd**

The mono-tosylate **XXXXIVc** (1.0g; 2.8mmol) in anhydrous dimethylformamide (DMF; 3ml) was added to a suspension of NaH (0.333g of a 60 % dispersion in mineral oil; 8.3mmol) in DMF (13ml) and the resulting mixture was stirred at room temperature for a period of 3h. The reaction mixture was partitioned between EtOAc and water. The organic phase was separated, washed with brine, dried ($MgSO_4$) and concentrated to provide a residue which was purified by silica gel column chromatography using EtOAc: hexane (1:5) as eluent to provide the desired oxetane **XXXXIVd** (0.37g) as a colourless oil.

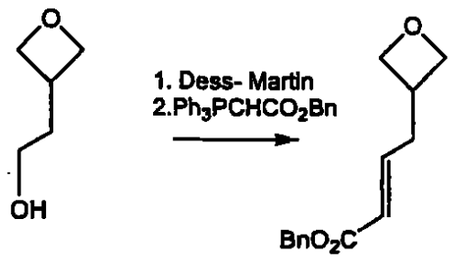
Step 4



XXXXIVd **XXXXIVe**

A suspension of 10% Pd-C (0.10g) and the benzylether **XXXXIVd** (0.33g) in methanol (10ml) was placed under an atmosphere of hydrogen (balloon) for a period of 1h. The reaction mixture was filtered through a pad of celite and the solid was washed thoroughly with methanol. The combined filtrate was concentrated under reduced pressure to provide the alcohol **XXXXIVe** (0.17g) as a colourless oil used in subsequent procedures without purification.

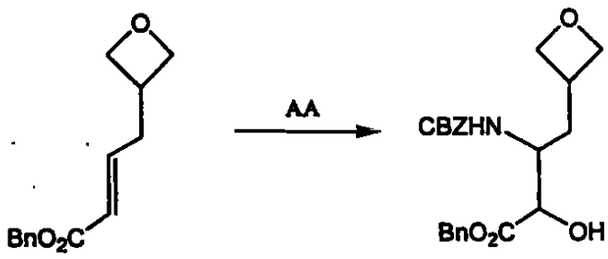
Step 5



XXXXIVe **XXXXIVf**

The Dess-Martin periodinane (0.658g; 0.16mmol) was added to a solution of the alcohol **XXXXIVe** (0.144g; 1.4mmol) in dichloromethane (5ml) and stirred at room temperature for a period of 1h., before adding the phosphorane (0.637g; 0.16mmol). The resulting reaction mixture was stirred for a period of approx. 16h., then partitioned between EtOAc and water. The organic phase was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:hexane; 1:5 to provide the ester **XXXXIVf** (0.131g) as a colourless oil.

Step 6

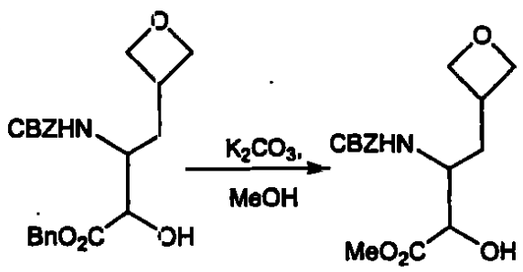


XXXXIVf **XXXXIVg**

Benzyl carbamate (0.657g; 4.3mmol) was dissolved in n-propanol (6ml). Aqueous sodium hydroxide (0.171g; 4.3mmol, in 11ml of water) was added followed by tert-butyl hypochlorite (0.49ml; approx 4.3mmol) and a solution of $(DHQ)_2PHAL$ (0.056g) in n-propanol (5ml). The resulting mixture was placed in a

water bath and and stirred for 5 min. before adding the olefin **XXXXIVf** (0.326g; 1.4mmol) followed by potassium osmate dihydrate (0.021g). The resulting reaction mixture was sirred for 3h., and added to EtOAc. The aqueous layer was separated and washed with EtOAc. The combined organic phases were wahed with brine, dried (MgSO4) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc; hexane (7:3) as eluent to give the alpha-hydroxy ester **XXXXIVg** (0.367g), containing approx. 20% of the undesired beta-hydroxy ester.

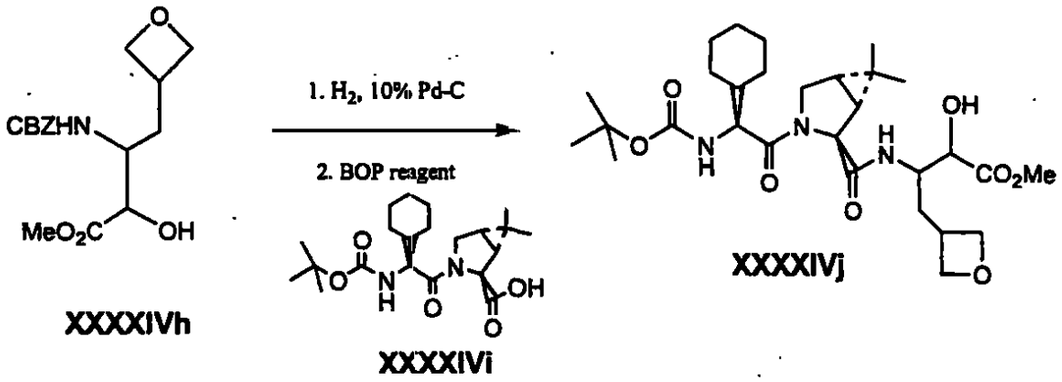
Step 7



XXXXIVg **XXXXIVh**

Potassium carbonate (0.100g) was added to a methanol (30ml) solution of approx. 2g of the benzyl ester **XXXXIVg** (contaminated with a small quantity of benzyl carbamate). The resulting mixture was stirred at room temperature for 2h., then partitioned between EtOAc and water. The organic phase was separated, washed with brine, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:hexanes (7:3) to provide the ester **XXXXIVh** (1.02g).

Step 8



XXXXIVh

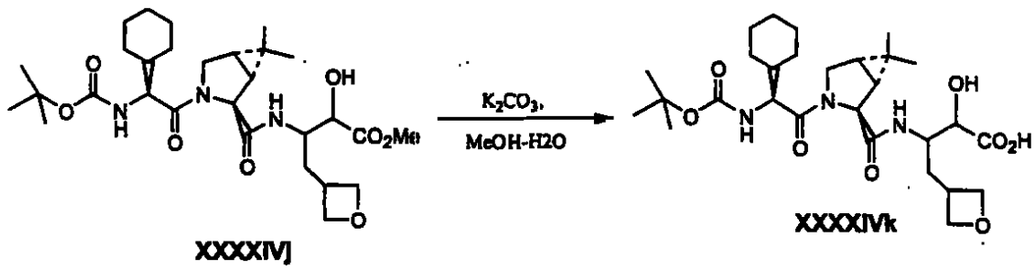
XXXXIVi

XXXXIVj

A suspension of 10% Pd-C (0.030g) and the benzyl carbamate **XXXXIVh** (0.090g) in methanol (5ml) was placed under an atmosphere of hydrogen (balloon) for a period of 1h. The reaction was filtered through a pad of celite and the solid was washed thoroughly with methanol. The combined filtrate was concentrated under reduced pressure to yield the intermediate amine (0.050g) which was used immediately.

BOP reagent (0.131g; 0.31mmol) followed by triethylamine (0.130ml;0.93mmol) were added to amixture of the amine (0.050g; 0.28mmol) and the carboxylic acid **XXXXIVI** (0.121g; 0.31mmol) in dichloromethane (3ml) and the resulting mixture was stirred for a period of 4h. and partitioned between dil. aq. HCl (approx. 1M) and EtOAc. The organic phase was separated, washed with sat. aq. Sodium bicarbonate, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc as eluent to provide the methyl ester **XXXXIVJ** (0.107g) as a white solid.

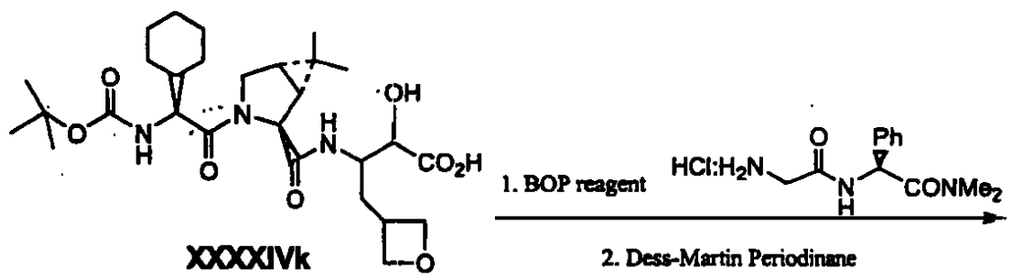
Step 9



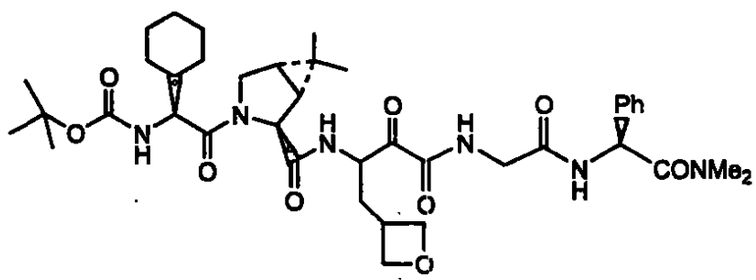
XXXXIVj XXXXIVk

Potassium carbonate (0.054g; 0.39mmol) was added to the ester **XXXXIVj** (0.107g; 0.19mmol) in a mixture of methanol (3ml) and water (1ml) and the resulting reaction was stirred for a period of 16h. and partitioned between EtOAc and water. The organic phase was separated, washed with brine, dried and concentrated to yield the acid **XXXXIVk** (0.099g).

Step 10



XXXXIVk

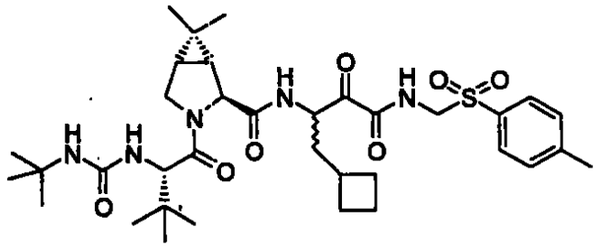


XXXXIV

Triethylamine (0.035ml; 0.25mmol) was added to a mixture of the carboxylic acid **XXXXIVk** (0.041g; 0.08mmol), the hydrochloride salt (0.023g; 0.08mmol) and BOP reagent (0.037g; 0.08mmol) in dichloromethane (3ml) and the resulting mixture was stirred at room temperature for a period of 4h. The reaction was partitioned between EtOAc and dilute aq. HCl (1M). The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried and concentrated under reduced pressure.

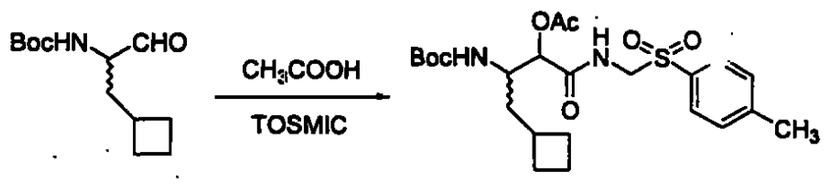
The residue from the aforegoing procedure was dissloved in dichloromethane (3ml) and Dess-Martin periodinane (0.065g; 0.15mmol) was added and the mixture stirred at room temperature for 2h. The reaction was partioned between 5% aq. sodium sulfite, sat. aq. sodium bicarbonate, water, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using CH_2Cl_2;MeOH; 20:1 as eluent to provide the alpha-keto amide **XXXXIV** (0.021g). FABMS: MH^+, 767.4.

Example XXXXVI Preparation of Compound of Formula XXXXVI



XXXXVI

Step 1

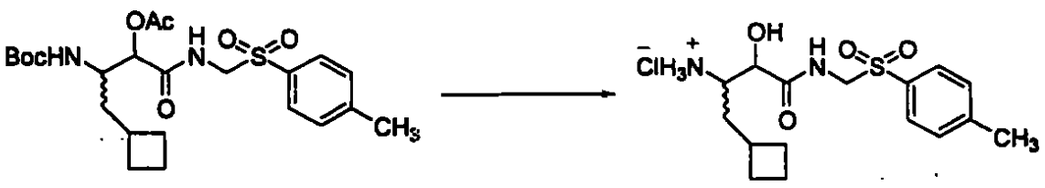


XXIIIe **XXXXVIa**

A solution of aldehyde **XXIIIe** (0.626 g, 2.75 mmol), TOSMIC (1.63 g, 8.27 mmol) and CH_3COOH (0.48 mL, 8.27 mmol) in dry CH_2Cl_2 (15 mL) was stirred at rt. for 36 h. The reaction mixture was concentrated in *vacuo* and purified by chromatography (SiO_2, EtOAc/Hex 2:3) to yield 0.90 g (68%) of **XXXXVIa** as a colorless solid

MS (ES) *m/z*, relative intensity 965 [$(2M+1)^+$, 30], 483 [$(M+1)^+$, 53], 427 (60), 383 (100), 365 (71), 272 (64).

Step 2

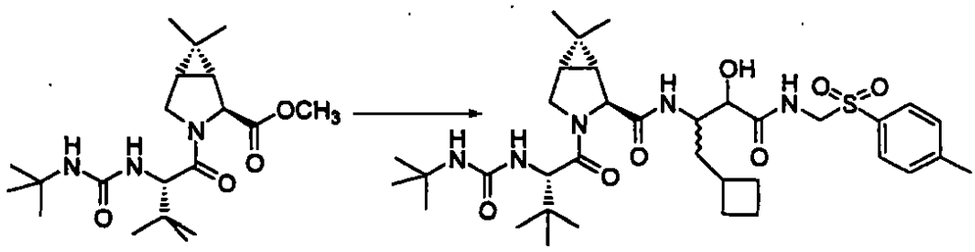


XXXXVIa **XXXXVIb**

A solution of **XXXXVIa** (0.9 g, 1.86 mmol) in HCl (30 mL, 6 M in CH_3OH, prepared by addition of acetyl chloride to CH_3OH at 0 °C) was stirred at rt. overnight. The reaction mixture was concentrated in *vacuo* and used as it is in the following step

MS (ES) *m/z*, relative intensity 681 [$(2M+1)^+$, 26], 341 [$(M+1)^+$, 100], 180 (40)

Step 3

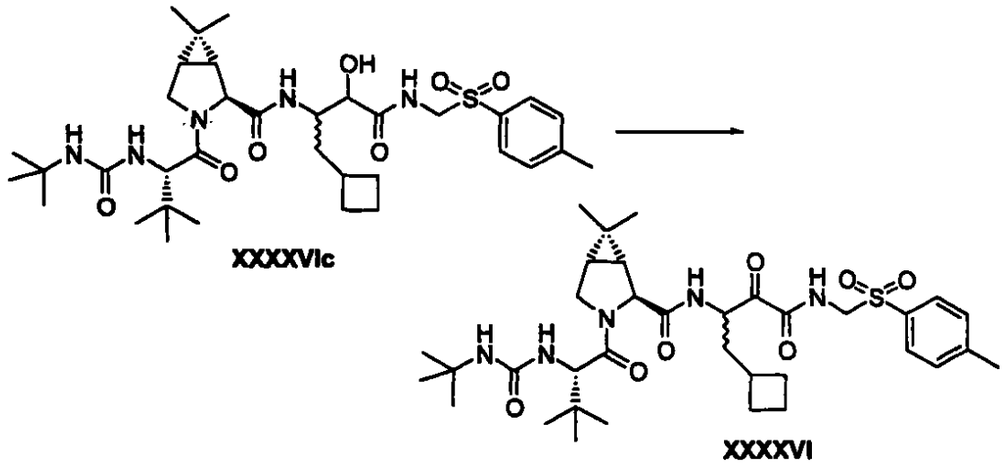


XXIVc XXXXVIc

The synthesis of **XXXXVIc** was accomplished using **XXIVc** (134 mg, 0.36 mmol), and amine **XXXXVIb** (120 mg, 0.32 mmol) following the procedure reported for example **XXIV** from **step 3** to yield product **XXXXVIc** which was used for further oxidation without purification

MS (ES) *m/z*, relative intensity 690 [$(M+1)^+$, 100], 591 (27), 537 (18), 513 (27), 478 (63), 438 (18), 414 (60), 268 (27)

Step 4



XXXXVIc XXXXVI

The synthesis of **XXXXVI** was accomplished by the oxidation of using alcohol **XXXXVIc** (219 mg, 0.32 mmol), EDCI (609 mg, 3.2 mmol), and $Cl_2CHCOOH$ (131 □L, 1.59 mmol) following the procedure reported in example **XXIV, step 4** which

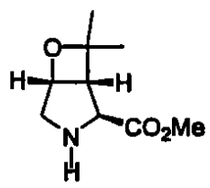
purified by chromatography (SiO_2, Acetone/Hexanes 3:7) to yield product **XXXXVI** (117 mg, 53% over 2 steps) as a colorless solid.

MS (ES) *m/z*, relative intensity 688 [$(M+1)^+$, 32], 589 (81), 476 (100)

5

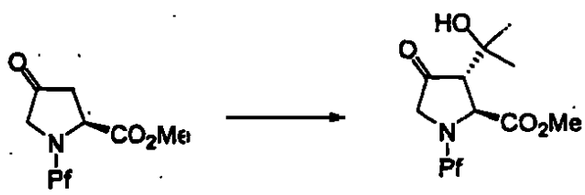
Synthesis of Intermediates

Example XXXXVII Preparation of intermediate of Formula XXXXVII



XXXXVII

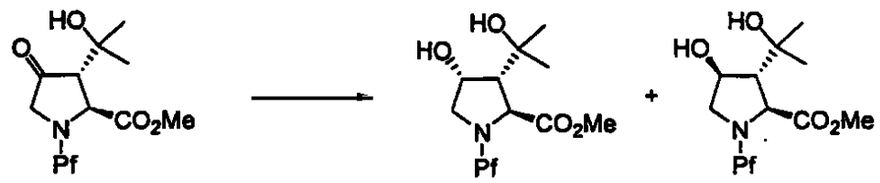
Step 1



XXXXVIIa XXXXVIIb

To the solution of ketone **XXXXVIIa** (4.93 g, 12.8 mmol) in anhydrous THF (100 mL) at -78°C was added a solution of lithium hexamethyldisilylazide (LiHMDS) (17.0 mL, 17.0 mmol). The resulting solution was stirred at that temperature for 1 h before a solution of acetone (1.51 mL, 20.5 mmol) and $BF_3{\cdot}Et_2O$ (2.60 mL, 20.5 mmol) in THF (15 mL) was added. After stirred for another 4 h, 5% H_3PO_4 (20 mL) was added followed by saturated ammonium chloride solution (200 mL) and diethyl ether (200 mL). The layers were separated and aqueous layer was extracted with diethyl ether (2 X 200 mL). The combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography with 20-50% EtOAc/hexane to give 1.84 g of **XXXXVIIb** (33%) and 3.26 g starting material **XXXXVIIa**

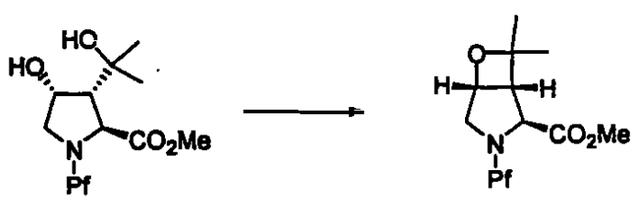
Step 2



XXXXVIIb **XXXXVIIc** **XXXXVIId**

To the solution of the ketone **XXXXVIIb** (0.94 g, 2.13 mmol) in anhydrous THF (20 mL) at -78°C was added a solution of $LiAlH_4$ in THF (2.6 mL, 2.6 mmol) and the reaction mixture was stirred for 40 min before $KHSO_4$ solution (1.0 M, 16 mL) was added. The mixture was allowed to warm to rt and to it was added EtOAc (100 mL) and water (50 mL). After the layers were separated and aqueous layer was extracted with EtOAc (2 X 50 mL). The combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography with 30-100% EtOAc/hexane to give 0.49 g of **XXXXVIIc** (52%) and 0.18 g (19%) **XXXXVIId**.

Step 3

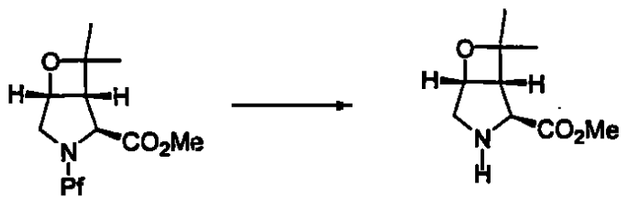


XXXXVIIc **XXXXVIIe**

The solution of **XXXXVIIc** (103 mg, 0.232 mmol), triphenylphosphine (120 mg, 0.456 mmol) and diethyl azodicarboxylate (0.055 mL, 0.349 mmol) in anhydrous CH_2Cl_2 (5 mL) was stirred at rt for 18 h. After concentrated in vacuo, the mixture

was purified by flash column chromatography using 10-30% EtOAc/hexane to give 24 mg (24 %) of **XXXXVIIe**.

Step 4

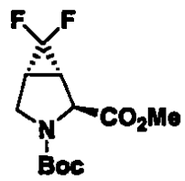


XXXXVIIe **XXXXVII**

The solution of **XXXXVIIe** in EtOH was hydrogenated at rt in the 10% Pd-C catalyst to **XXXXVII**.

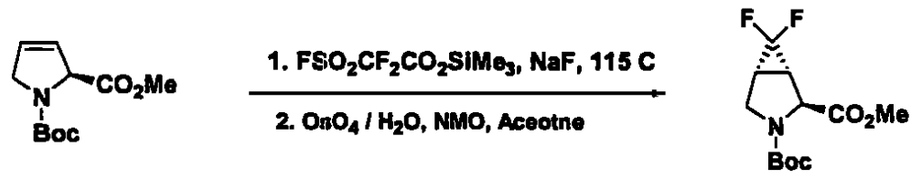
A number of inhibitors described in **table-6** using the intermediates **XXXXVII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example XXXXVIII Preparation of intermediate of Formula XXXXVIII



XXXXVIII

Step 1

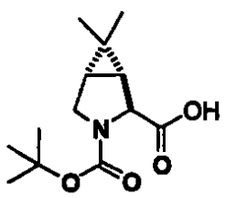


XXXXVIIIa XXXXVIII

To 5g (22 mmol) of N-Boc-dehydroprolinemethylester **XXXXVIIIa** was added 25 mg of NaF and 2g of Toluene. At 110C, was added via syringe –pump 1.6equiv (35 mmol, 8.75g) of TMSfluorosulfonyldifluoroacetate (TFDA) in 1h. After 2h, reaction is cooled down to RT. To the mixture is added NMO(6.8g, 50 mmol), Acetone (50 mL), H2O (25 mL) and OsO4 (0.015 M in H2O, 1 mol%, 0.44 mmol, 28 mL). Reaction is stirred overnight at RT then diluted with EtOAc and washed with H2O and Brine. Organic layer was dried over MgSO4, filtered and concentrated to dryness. Purification by flash column chromatography (10 EtOAc, Hexane, silica) furnished Product **XXXXVIII** (0.76g).

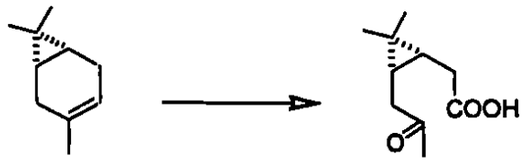
A number of inhibitors described in **table-6** using the intermediate **XXXXVIII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX** .

Example IL Preparation of Intermediate of Formula IL



IL

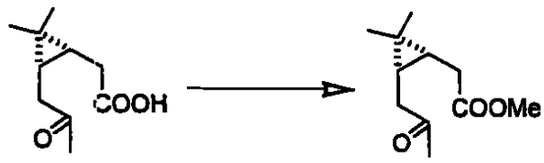
Step 1.(1R,3S)- 2,2-DIMETHYL-3-(2-OXOPROPYL)CYCLOPROPANEACETIC ACID .



3-carene
ILa **ILb**

A mixture of 0.55 L *tert*-butanol, 1.1 L water, 100 mL 3-carene **ILa** (Aldrich Chemical Co.), and 490 g $NaIO_4$, was treated with 2.2 g ruthenium chloride hydrate. The vigorously stirred mixture was alternately heated and cooled for 2 hr. to maintain a temperature of 35-40°C. The vigorously stirred mixture was alternately heated and cooled for another 1 hr. to maintain a temperature of 40-50°C. The vigorously stirred mixture was then heated for another 1/2 hr. to maintain a temperature of 50-55°C. The mixture was then cooled to 30°C, filtered on a Buchner funnel, and the precipitates were washed with 700 mL of *iso*-propyl ether. The aqueous portion of the filtrate was extracted with 900 mL of EtOAc-hexane (2:1), and the extract was combined with the ethereal portion of the filtrate. The combined organics were washed with 300 mL of 20% aqueous NaCl, then extracted with a solution of 36 g NaOH in 2.2 L water. The cooled aqueous extract was acidified with 100 mL of 12 N HCl and extracted with Et_2O (3 x 800 mL). The extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated *in vacuo* to leave the title compound **ILb** 98 g (88%) as a gum. H^1NMR ($CDCl_3$) δ 2.39 (m, 2), 2.28 (m,2), 2.19 (s, 3), 1.1.12 (s, 3), 0.90 (m, 2), 0.63 (s, 3).

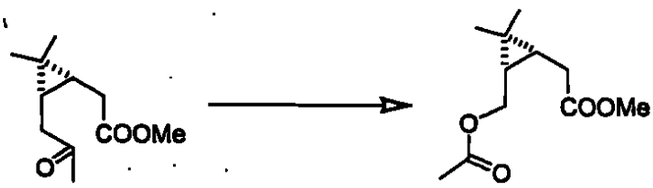
Step 2. (1R,3S)-METHYL 2,2-DIMETHYL-3-(2-OXOPROPYL)CYCLOPROPANEACETATE.



ILb ILc

A solution of 98 g of **ILb**, the product of the preceding step and 0.55 L DMF was treated with 98 g Cs_2CO_3. The mixture was stirred for 10 minutes, 41.5 mL MeI was added, and the mixture was stirred at 40°C for 1 hr. The mixture was cooled and filtered on a Buchner funnel. The filtrate was quenched with 2.5 L of 18% aqueous NaCl, the organic layer was separated, and the aqueous solution was extracted with Et_2O-hexane (1:1; 2 x 1 L). The combined organic layer and extracts were washed with water, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo* to leave the title compound **ILc** as 91 g (86%) thick oil. H^1NMR ($CDCl_3$) δ 3.67 (s, 3), 2.3 (m, 4), 2.17 (s, 3), 1.12 (s, 3), 0.97 (m, 2), 0.91 (s, 3).

Step 3. (1R,3S)-METHYL 3-(ACETOXYMETHYL)-2,2-DIMETHYLCYCLOPROPANEACETATE.

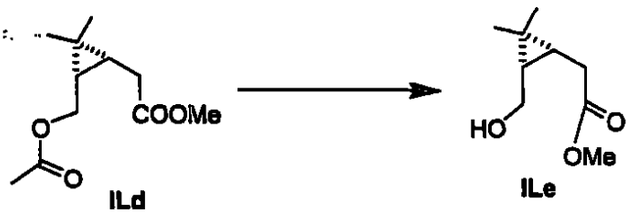


ILc ILd

A solution of **ILc** 91 g of the product of the preceding step and 0.7 L 1,1,2-trichloroethane was treated with 165 g of 70% *m*-chloroperbenzoic acid. The

mixture was stirred at ambient temperature for 1 hr, then heated with an oil bath to maintain a reaction temperature of 65-70°C for 1 hr., and then heated at 75°C for 1 hr. more. The mixture was cooled, filtered on a Buchner funnel, and the filter cake was washed with fresh trichloroethane. The combined filtrate and washings were concentrated *in vacuo* to 0.5 L, and the residue was diluted with 2.5 L of hexane-Et_2O (3:1). The organic solution was washed repeatedly with a solution of 3.5% aqueous K_2CO_3-brine (3:1; 8 x 0.9 L), then with brine, then dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo* to leave the title compound **ILd** as 98 g (100%) thick oil. H^1NMR ($CDCl_3$) δ 4.1-3.9 (m, 2), 3.68 (s, 3), 2.34 (d, 2), 2.04 (s, 3), 1.12 (s, 3), 1.04 (m, 2), 1.00 (s, 3).

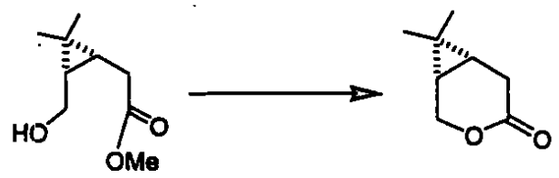
Step 4. (1R,3S)-METHYL 3-(HYDROXYMETHYL)-2,2-DIMETHYLCYCLOPROPANEACETATE



ILd **ILe**

A solution of 98 g **ILd** of the product of the preceding step and 1 L methanol was treated with 19 g K_2CO_3, and the mixture was stirred at 30°C for 1 hr. The mixture was concentrated *in vacuo* to remove 0.6 L methanol, the residue was quenched with cold 10 % aqueous KH_2PO_4, and the mixture was extracted with EtOAc. The extract was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo* to leave 70 g (89%) of the title compound **ILe** as a gum. H^1NMR ($CDCl_3$) δ 3.80 (q, 1), 3.73 (s, 3), 3.52 (m, 1), 2.68 (d of d, 1), 2.23 (d of d, 1), 1.09 (s, 3), 1.1-0.9 (m, 2), 0.98 (s,3).

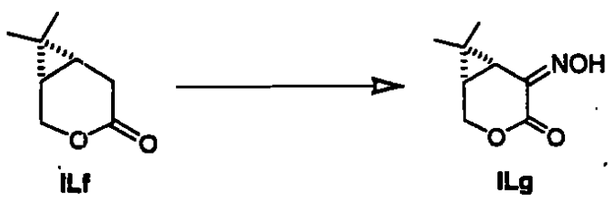
Step 5. (1S,6R)-7,7-DIMETHYL-3-OXABICYCLO[4.1.0]HEPTAN-4-ONE.



ILe ILf

A solution of **ILe** 70 g of the product of the preceding step and 1.1 L xylenes was treated with 30.8 g DBU. The solution was heated to a gentle reflux for 18 hr. as methanol was removed from the distillate. The solution was cooled, washed with cold 1 N HCl, then with brine; dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The residue was chromatographed on 600 g silica gel using a gradient of CH_2Cl_2 to 1:10 EtOAc-CH_2Cl_2 to obtain the title compound **ILf** as 54 g (94%) oil. H^1NMR ($CDCl_3$) δ 4.71 (d of d, 1), 4.04 (d of d, 1), 2.75 (d of d, 1), 2.16 (d of d, 1), 1.16 (s, 3), 1.25 (m, 1), 1.12 (s, 3).

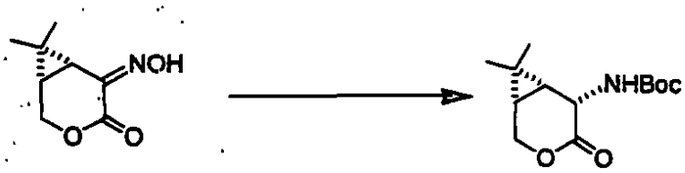
Step 6. (1S,6R,5E)-7,7-DIMETHYL-3-OXABICYCLO[4.1.0]HEPTANE-4,5-DIONE, 5-OXIME.



ILf ILg

A solution of 42 g of the product of the preceding step **ILf** and 300 mL anhydrous toluene was treated with 102 mL of 90% *tert*-butylnitrite. The stirred mixture was alternately heated and cooled as needed as 45 g potassium *tert*-butoxide was added in 6 portions over 20 minutes at 30-35°C. Then 180 mL of anhydrous methanol was added, the temperature raised to 40°C, and stirring continued at 40°C for 2.5 hr. The mixture was cooled, quenched with a cold solution of 1.1 L of 10% aqueous and 20 mL 12N HCl, then extracted with EtOAc-toluene (3:1). The extracts were washed with 5% aqueous $NaHCO_3$, then brine; dried over anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The residue (25 g) was chromatographed on 150 g silica gel using a gradient of CH_2Cl_2 to 35:65 EtOAc-CH_2Cl_2 to obtain 15 g (29%)of the title compound **ILg** as an oil. H^1NMR ($CDCl_3$) δ 4.82 (d of d, 1), 4.55 (d of d, 1), 2.40 (d, 1), 1.49 (m, 1), 1.27 (s, 3), 1.18 (s, 3).

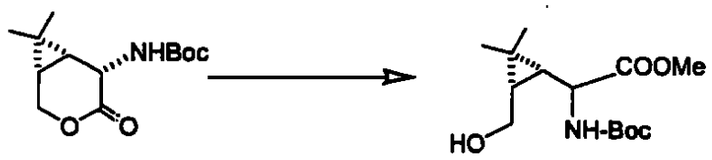
Step 7.



ILg **ILh**

A solution of 18 g of the product of the preceding step **ILg** and 400 mL EtOAc was treated with 32 g di-*tert*-butyldicarbonate (Boc_2O), and 2.0 g of 10% Pd on carbon. The mixture was hydrogenated at 2.5 atm for 18 hr, filtered, and the filtrate evaporated to leave 36 g of the title compound mixed with Boc_2O, which was taken directly to the next step. A portion was chromatographed to obtain **ILh** as pure title compound: H^1NMR (DMSO-d_6) δ 7.28 (d, NH), 4.76-4.64 (m, 2), 4.44 (d, 1), 1.40 (s, 9), 1.24 (m, 1), 1.11 (m, 2), 1.07 (s, 3), 0.99 (s, 3).

Step 8. (1R,3S)-METHYL ALPHA(S)-[[(1,1-DIMETHYLETHOXY)CARBONYL]AMINO]-3-(HYDROXYMETHYL)-2,2-DIMETHYLCYCLOPROPANEACETATE



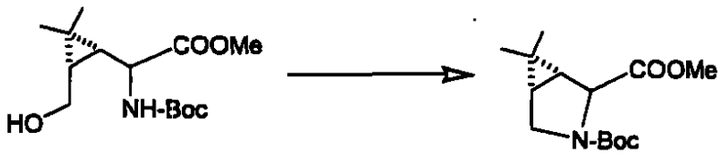
ILh **ILi**

A solution of 35 g of **ILh** the product mixture of the preceding step and 350 mL anhydrous methanol was treated with 12 g of finely ground anhydrous K_2CO_3. The mixture was vigorously stirred for 2 hr., concentrated *in vacuo* with a 25°C bath, and then quenched with 0.6 L of 10% aqueous KH_2PO_4. The solution was extracted with EtOAc-hexane (95:5; 2 x 200 mL), the extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered, and the filtrate was evaporated *in vacuo* to leave **ILi** 22 g (70%) of the title compound as a gum mixture of the two epimers in an α-*S*/α-*R* ratio of 8:2, which did not have to be separated for the present purpose. A portion was chromatographed with Et_2O-hexane (60:40) to obtain pure α-*S* -epimer of the title compound: H^1NMR ($CDCl_3$) δ 5.2 (br s, 1), 4.05 (br s, 1), 3.81 (m, 1), 3.76 (s, 3), 3.65 (m, 1), 1.43 (s, 9), 1.14 (s, 3), 1.06 (s, 3), 1.05 (m, 1), 0.86 (m, 1). Optical rotation: $[\alpha]_D^{25}$ – 62.9° (c=1, MeOH). Elemental analysis: theory C 58.52, H 8.77, N 4.87; found C 58.48, H 8.75, N 5.10...

Further elution provided the α-*R*-epimer of the title compound: H^1NMR ($CDCl_3$) δ 4.95 (br d, 1), 4.03 (m, 1), 3.82 (m, 1), 3.78 (s, 3), 3.71 (m, 1), 1.44 (s, 9), 1.13 (m, 1), 1.10 (s, 3), 1.08 (s, 3), 0.86 (m, 1). Optical rotation: $[\alpha]_D^{25}$ –

32.8° (c=1, MeOH). Elemental analysis: theory C 58.52, H 8.77, N 4.87; found C 58.46, H 8.69, N 4.74.

Step 9. (1R,5S)-6,6-DIMETHYL-,3-AZABICYCLO[3.1.0]HEXANE-2(S),3-DICARBOXYLIC ACID 3-(1,1-DIMETHYLETHYL) 2-METHYL ESTER



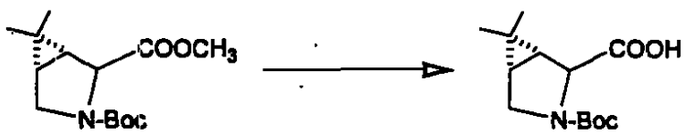
ILI ILj

A solution of 21.6 g triphenylphosphine and 250 mL anhydrous THF was cooled to –10 °C and treated dropwise with 16.2 g diisopropylazodicarboxylate as the temperature of the reaction rose to +5 °C. After 5 minutes additional stirring, the mixture was treated a solution of 19.7 g of **ILi** the product mixture of the preceding step in 35 mL THF. After 10 minutes additional stirring, the mixture was heated at reflux for 3 hr., cooled, and evaporated *in vacuo*. The residue was transferred to a separatory funnel with a total of 450 mL of methanol-water (1:1), and he 2 phase mixture was extracted with hexane (7 x 225 mL). The combined extracts were washed with 20 mL of methanol-water (1:1), then brine; dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated *in vacuo*. The residue was taken up in 400 mL hexane, suction-filtered through a pad of 30 g silica gel, and the silica pad was eluted with an additional 210 mL of EtOAc-hexane (1:9). The combined filtrates were evaporated *in vacuo* to leave 12.8 g (69%) of the title compound **ILj** as a gum mixture of 2 epimers, contaminated with a small amount of diisopropylhydrazinedicarboxylate, but suitable for the subsequent reactions.

The pure *S*-epimer of the preceding step was treated in the same fashion to afford the pure *S*-epimer of the title compound: H^1NMR ($CDCl_3$) δ 4.21 and 4.09 (s+s, 1), 3.75 (s, 3), 3.65 (m, 1), 3.41 (m, 1), 1.44 and 1.39 (s+s, 9), 1.38 (m, 2), 1.03 (s, 3), 0.98 and 0.97 (s+s, 3). Elemental analysis: theory C 62.43, H .8.61, N 5.20; found C 61.82, H 8.67, N 5.15.

The *R*-epimer of the preceding step was treated in the same fashion to afford the *R*-epimer of the title compound: H^1NMR ($CDCl_3$) δ 4.49 and 4.30 (d+d, 1), 3.62 (s, 3), 3.59 (m, 1), 3.42 (m, 1), 1.65 (m, 1), 1.45 and 1.39 (s+s, 9), 1.36 (m, 1), 1.10 (s, 3), 0.99 (s, 3).

Step 10.



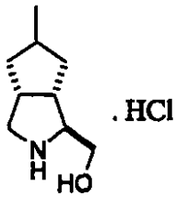
ILJ IL

A solution of 14.5 g of the product mixture **ILJ** of the preceding step and 270 mL 1,4-dioxane was treated with 135 mL of 1M aqueous LiOH, and the mixture was heated at 80°C for 4 hr. The mixture was cooled, concentrated *in vacuo* to half volume, diluted with 200 mL water, and extracted with hexane. The aqueous layer was chilled and treated with a solution of 9 ml of 12N HCl in 50 mL of 10% aqueous KH_2PO_4, and then extracted with EtOAc. The extract was washed with brine, dried over anhydrous Na_2SO_4, filtered, and the filtrate evaporated *in vacuo* to leave the title compound **IL** as 10.8 g (78%) gum, > 90% chemically and diasteriomerically pure by PMR, and suitable for subsequent synthesis: H^1NMR ($CDCl_3$) δ 4.20 and 4.11 (s+s, 1), 3.62 (m, 1), 3.44 (m, 1), 1.68 and 1.45 (d+unk,

1), 1.46 and 1.40 (s+s, 9), 1.45 (m buried under 1.46, 1), 1.07 (s+s, □□= 2 Hz, 3), 0.99 and 0.95 (s+s, 3).

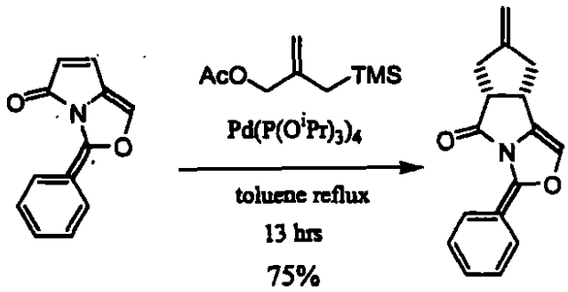
A number of inhibitors described in **table-6** using the intermediates **IL** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example L Preparation of intermediate of Formula L



L

Step 1

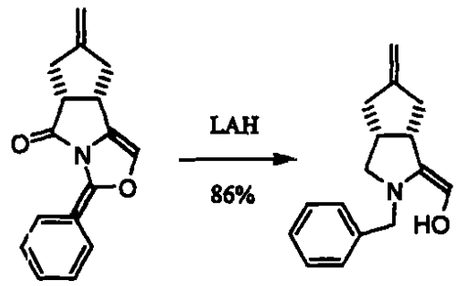


La **Lb**

To a mixture of **La** (10.0 g, 50.0 mmole), 2-[(trimethylsilyl) methyl]-2-propanen-1-yl acetate (22.0 g, 118 mmole) and triisopropyl phosphite (18.6 g, 89.2 mmole) in toluene (50 ml) was added palladium (II) acetate (2.5 g, 11 mmole)

with stirring at room temperature under an Ar atmosphere. It was heated to 120 °C (oil bath) for thirteen hours. Cooling down to room temperature followed by flash chromatography (CH_2Cl_2: Hexane = 4:1) provided 9.55 gram of **Lb** (75%). $[\square]^{25}$ = +132 ° ($CHCl_3$). HRMS (FAB) Calcd for $C_{16}H_{18}NO_2$ (MH+): 256.1338; found: 256.1340.

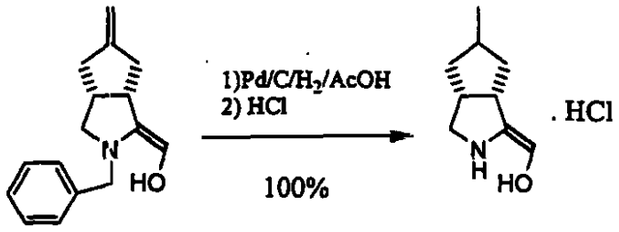
Step 2



Lb **Lc**

To a solution of **Lb** (2 g, 7.8 mmol) in anhydrous THF (50 ml) was added LAH (1.13g, 28.9 mmol) in small portions at 0 °C. The mixture then refluxed for six hours before cooled to 0 °C. To the reaction were carefully added 2ml of H_2O, 2ml of 15% NaOH and 6 ml of H_2O. The solid was removed by filtration and the concentrated filtrate was chromatographed (2% MeOH in CH_2Cl_2) to give 1.33 gram of **Lc** (70%). HRMS (FAB) Calcd for $C_{16}H_{22}NO$ (MH+): 244.1701; found: 244.1697.

Step 3

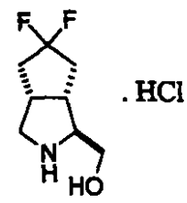


Lc **L**

A mixture of compound **Lc** (1.33 g, 5.46 mmol) and 10% Pd on carbon (1.3 gram) in acetic acid (20 ml) was hydrogenated under 60 psi for three days. The catalyst was filtered off and the filtrate was concentrated in vacuum. The residue was dissolved in 20 ml of 4N HCl in dioxane and the solution was evaporated to dryness. Compound L was obtained in 1.04 gram (100%) as a 1: 1 mixture of two epimers. HRMS (FAB) Calcd for $C_9H_{18}NO$ (MH+): 156.1388; found: 156.1390.

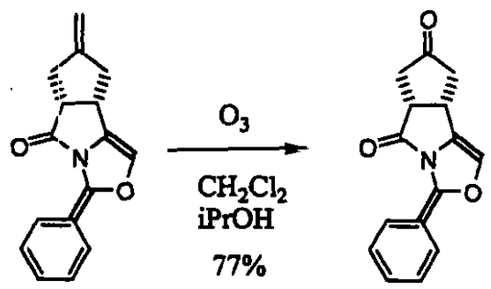
A number of inhibitors described in **table-6** using the intermediates **L** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX, and XXXX**

Example LI Preparation of intermediate of Formula LI



LI

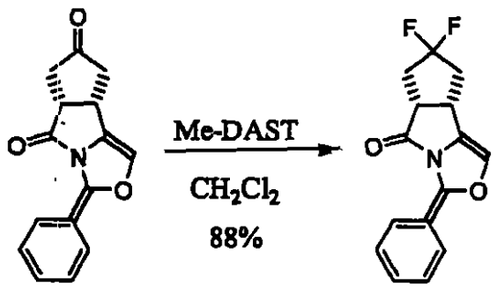
Step 1



Lb LIa

Compound **Lb** (2.6 g, 10.2 mmol) in a mixture of CH_2Cl_2 (30 ml) and ^iPrOH (10 ml) was ozonized at –78 °C until a bluish color persisted (Ca. 40 minutes). Dimethyl sulfide (10 ml) was added and the solution was stirred at room temperature over night. The solvent was removed in vacuum and the residue was partitioned between water and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and concentrated. Flash chromatography (2% MeOH in CH_2Cl_2) provided 2.32 gram of **LIa** (77%). MS (MH+, FAB) = 257.

Step 2

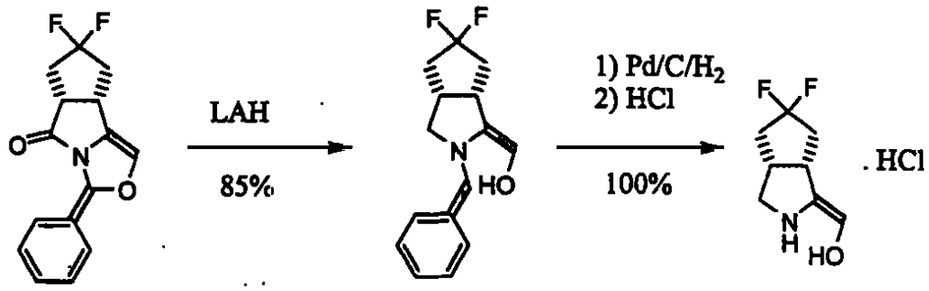


LIa LIb

To a solution of **LIa** (0.86 g, 3.35 mmol) in dry CH_2Cl_2 (30 ml) was added dimethylaminosulfur trifluoride (methyl DAST, 2.23 g, 16.8 mmol) at room temperature. The solution was stirred at room temperature for two days. It was

carefully added to a mixture of ice and saturated $NaHCO_3$ and extracted with EtOAc. The EtOAc solution was washed with brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed (0.8 % of MeOH in CH_2Cl_2) to give **LIb** (0.82 g, 88%). HRMS (FAB) Calcd for $C_{15}H_{16}NO_2F_2$ (MH+): 280.1149; found: 280.1152.

Step 3

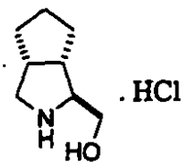


LIb **LIc** **LI**

By following the same procedures as described for the preparation of **L** from **Lb** through **L** 0.44 gram of **LIb** provided 0.31 gram of **LI** (92% in two steps). HRMS (FAB) Calcd for $C_8H_{14}NOF_2$ (MH+): 178.1043; found: 178.1042.

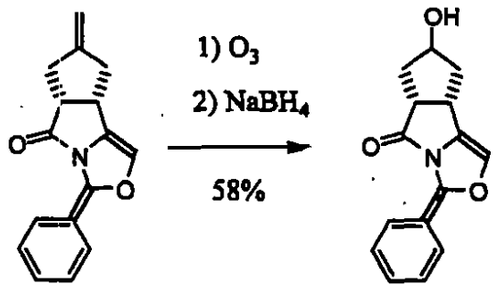
A number of inhibitors described in **table-6** using the intermediates **LI** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX, and XXXX**

Example LII Preparation of intermediate of Formula LII



LII

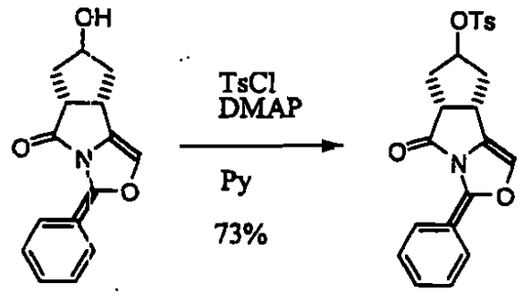
Step 1



Lb LIIa

Compound **Lb** (3.74 g, 14.7 mmol) in CH_2Cl_2 (30 ml) was ozonized at –78 °C until a bluish color persisted (Ca. 60 minutes). It was purged with N_2 for 5 min, and was added to a cold solution of $NaBH_4$ (4.44g, 117 mmol) in 50 ml of EtOH/H2O (1: 1).. It was stirred for 12 hrs at RT then extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was chromatographed (2% MeOH in CH_2Cl_2) to give **LIIa** (2.19 g, 58%). HRMS (FAB) Calcd for $C_{15}H_{18}NO_3$ (MH+): 260.1287; found: 260.1283.

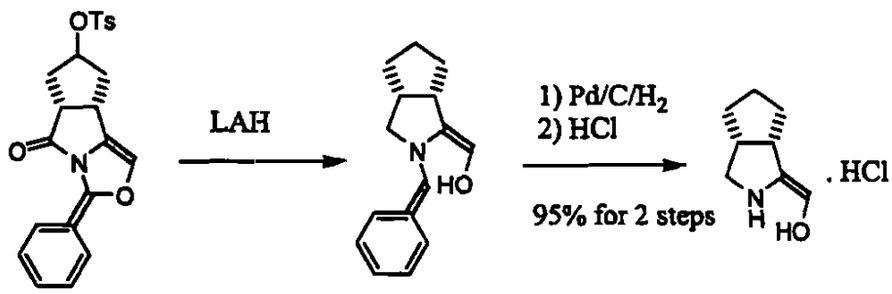
Step 2



LIIa **LIIb**

To a solution of **LIIa** (2.18 g, 8.40 mmol) in dry pyridine (50 ml) were added toluenesulfonyl chloride (3.2 g, 16.8 mmol) and N, N-dimethylaminopyridine (1.03 g, 8.40 mmol). It was stirred at RT for 3 days and concentrated in vacuum. The residue was partitioned between 3% citric acid and EtOAc. The organic layer was washed with 3% citric acid again, followed by brine. After removing the solvent the residue was chromatographed to provide **LIIb** (2.54 g, 73%). HRMS (FAB) Calcd for $C_{22}H_{24}SNO_5$ (MH+): 414.1375; found: 414.1378.

Step 3

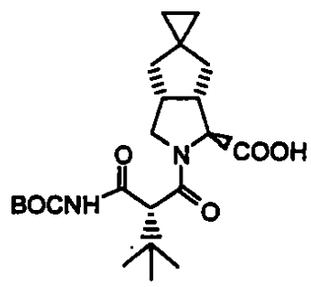


LIIb **LIIc** **LII**

By following the same procedures as described for the preparation of **L** from **Lb** through **L**, 2.53 gram of **LIIb** provided 1.03 gram of **LII** (95% in two steps). HRMS (FAB) Calcd for $C_8H_{16}NO$ (MH+): 142.1232; found: 142.1233.

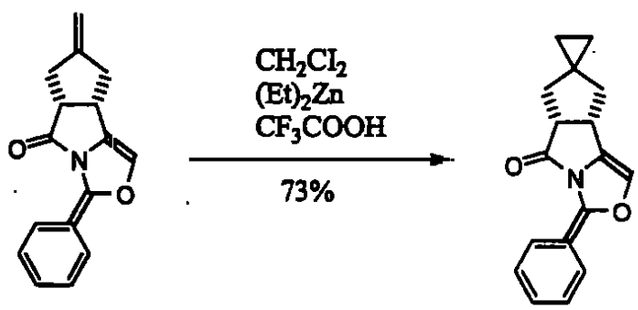
A number of inhibitors described in **table-6** using the intermediates **LII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LIII Preparation of intermediate of Formula LIII



LIII

Step 1

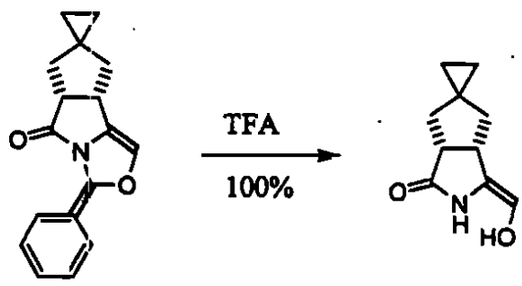


Lb **LIIIa**

To 7.84 mmol of diethyl zinc (I N in hexane) in dry CH_2Cl_2 (30 ml) was added trifluoroacetic acid (0.893 g, 7.84 mmol) dropwise at 0 °C. Upon stirring for an additional 20 min diiodomethane (2.10 g, 7.84 mmol) was added, followed by **Lb** (1 g, 3.92 mmol) in 5 ml of CH_2Cl_2 in 20 min. The ice bath was removed and the mixture was stirred at RT for 14 hours. The reaction was quenched by saturated NH4Cl and extracted with EtOAc. The EtOAc solution was washed with

saturated Na_2SO_4, followed by brine and concentrated in vacuum. The residue was chromatographed to provide **LIIIa** (4.61 g, 73%). HRMS (FAB) Calcd for $C_{17}H_{20}NO_2$ (MH+): 270.1494; found: 270.1497.

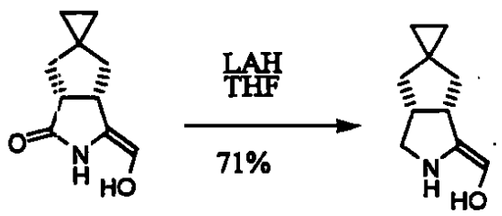
Step 2



LIIIa **LIIIb**

Trifluoroacetic acid (TFA, 10 ml) was added to a solution of **LIIIa** (4.6 g, 17.1 mmol) in THF (20 ml) and H_2O (20 ml) at RT. After stirring overnight the solvents were removed in vacuum. The residue was partitioned between saturated $NaHCO_3$ and EtOAc. The aqueous phase was back extracted with EtOAc five times. The combined organic phase was dried over Na_2SO4 and concentrated. The residue was chromatographed to give **LIIIb** (3.1 g, 100%). HRMS (FAB) Calcd for $C_{10}H_{16}NO_2$ (MH+): 182.1181; found: 180.1182.

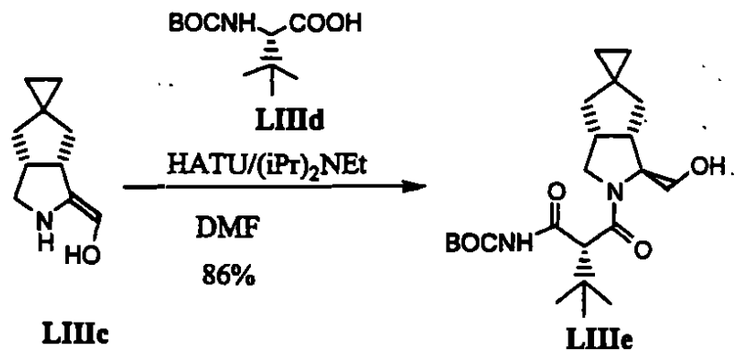
Step 3



LIIIb **LIIIc**

LAH (1.76 g, 46.3 mmol) was added to **LIIIb** in dry THF (50 ml) in small portions at 0 °C. The mixture then refluxed for six hours before cooled to 0 °C. To the reaction were carefully added 2ml of H_2O, 2ml of 15% NaOH and 6 ml of H_2O. The solid was removed by filtration and the concentrated filtrate was chromatographed (30% MeOH in CH_2Cl_2 with 1% NH_4OH) to give 0.39 gram of **LIIIc** (71%). HRMS (FAB) Calcd for $C_{10}H_{18}NO$ (MH+): 168.1388; found: 168.1389.

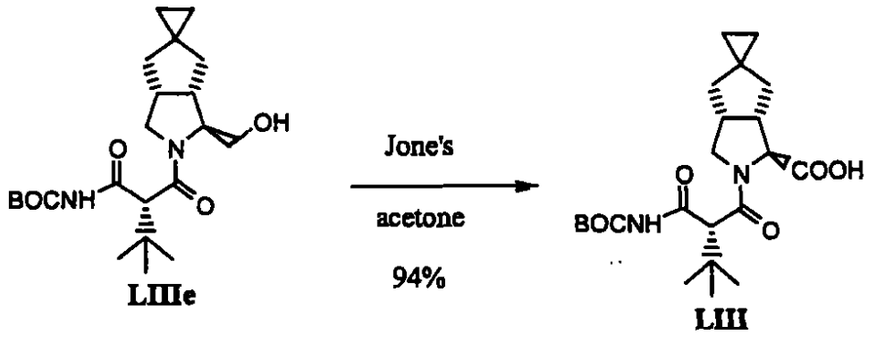
Step 4



LIIIc **LIIIe**

To a mixture of **LIIIc** (0.5 g, 2.99 mmol), **LIIId** (0.69 g, 2.99 mmol) and HATU (1.14 g, 3 mmol) in dry DMF (20 ml) was added N, N-diisopropylethylamine (1 ml, 5.89 mmol)) at 0 °C. It was stirred at RT for 3 hrs. The reaction mixture was partitioned between H_2O and EtOAc. The organic layer was successively washed with 3% citric acid, saturated $NaHSO_4$ and brine, dried over Na_2SO4 and concentrated. The product **LIIIe** (0.978g, 86%) thus obtained was sufficiently pure for the next step. HRMS (FAB) Calcd for $C_{21}H_{37}N_2O_4$ (MH+): 381.2910; found: 381.2749.

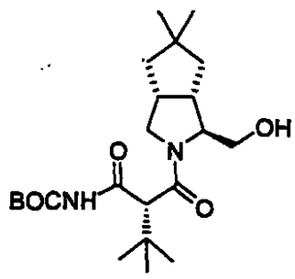
Step 5



To a solution of **LIIIe** (0.49 g, 1.29 mmol) in acetone (20 ml) was added Jone's reagent (2 ml of 2.5 M solution, 5 mmol) at 0 °C. It was stirred at 0 °C for 20 min, then at RT for 30 hrs. To this mixture were successively added EtOAc (50 ml), anhydrous Na_2SO_4 (3 g), celite (2g) and ^iPrOH (1 ml). It was stirred vigorously for 20 min. The solid was filtered off. The filtrate was washed with 3% citric acid, dried over Na_2SO_4 and concentrated in vacuum. The residue was chromatographed (3% MeOH in CH_2Cl_2, 0.5% acetic acid) to provide **LIII** (0.48 g, 94%). HRMS (FAB) Calcd for $C_{21}H_{35}N_2O_5$ (MH+): 395.2546; found: 395.2543.

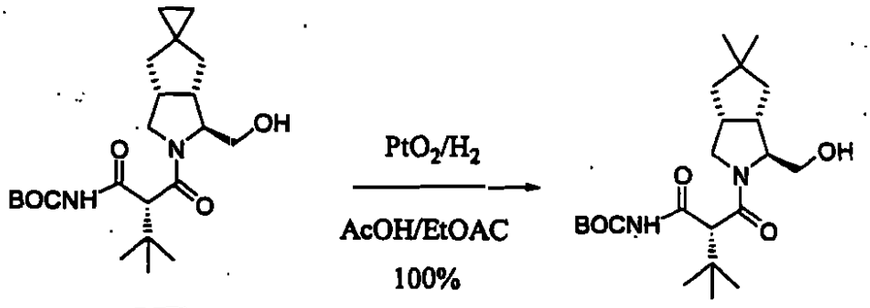
A number of inhibitors described in **table-6** using the intermediates **LIII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LIV Preparation of Intermediate of Formula LIV



LIV

Step 1

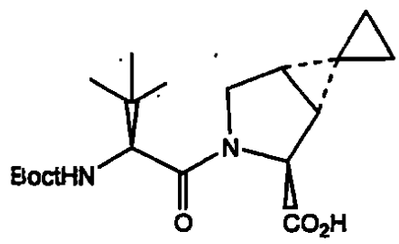


LIIIe **LIV**

Compound **LIIIe** (0.41 g, 1.08 mmol) in a mixture of solvent of AcOH (10 ml) and EtOAc (20 ml) containing PtO_2 (1 g) was hydrogenated under 1 atm of H_2 for 3 hrs. The catalyst was removed by filtration and the filtrate was concentrated in vacuum to provide **LIV** (0.41g, 100%). HRMS (FAB) Calcd for $C_{21}H_{39}N_2O_5$ (MH+): 383.2910; found: 383.2906.

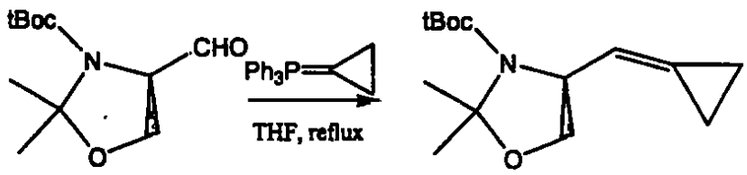
A number of inhibitors described in **table-6** using the intermediates **LIV** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LV Preparation of Intermediate of Formula LV



LV

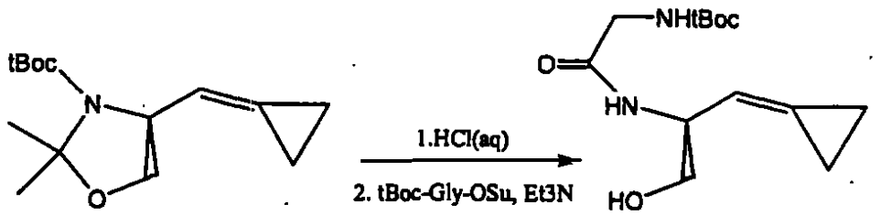
Step 1



LVa **LVb**

Potassium bis(trimethylsilyl)amide (158ml of a 0.5M solution in toluene; 79mmol) was added to a stirred suspension of cyclopropyltriphenylphosphonium bromide (33.12g; 86.4mmol) in anhydrous tetrahydrofuran (130ml) and the resulting orange mixture was stirred under an atmosphere of nitrogen at room temperature for a period of 1h., before the addition of the aldehyde **LVa** (9.68g; 42.2mmol) in THF (8ml). The reaction was then refluxed under an atmosphere of nitrogen for a period of 2h. After cooling, methanol, diethyl ether and Rochelles salt were added. The organic phase was separated, washed with brine, dried and concentrated under reduced pressure. The crude reaction product was purified by silica gel column chromatography using EtOAc-hexane (1:99) to EtOAc-hexane (5:95) to provide the alkene **LVb** (8.47g) as a yellow oil.

Step 2



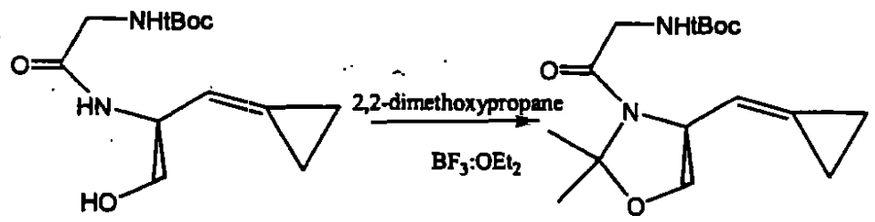
LVb **LVc**

A solution of 1M HCl in MeOH/MeOAc was prepared by adding14.2ml of acetylchloride dropwise into cold methanol and diluting the resulting solution to 200ml at room temperature.

The carbamate **LVb** (9.49g; 37.5mmol) was dissolved in methanol (12ml) and added to 1M HCl in MeOH/MeOAc (150ml) while cooled in an ice bath. The resulting mixture was maintained at this temperature for 1h., then the ice bath was removed and stirring continued overnight at room temperature. The volatiles were removed under reduced preesure to yield a yellow oil which was used in the next step without purification.

The yellow oil is dissolved in a mixture of THF (30ml) and MeOH (20ml) and treated with triethylamine (15ml; 108mmol) until the solution was pH=9-10. After placing in an ice bath, the mixture was treated with N-Boc-Gly-OSu (11.22g; 41mmol). The icebath was withdrawn and the reaction stirred at room temp. for 1h. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using methanol (1-3%) in dichloromethane providing the desired amide **LVc** (9.09g).

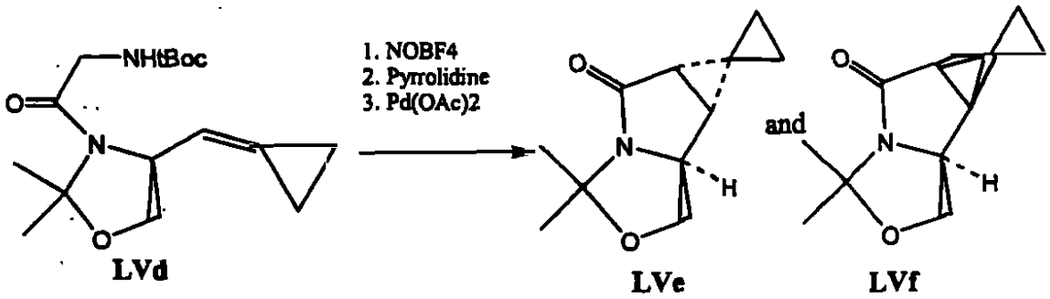
Step 3



LVc LVd

The alcohol **LVc** (9.09g; 33.6mmol) was dissolved in acetone (118.5ml) and treated with 2,2-dimethoxypropane (37.4ml;304mmol) and BF_3:Et2O (0.32ml; 2.6mmol) and the resulting mixture was stirred at room temperature for a period of 5.5h The reaction solution was treated with a few drops of triethylamine and the volatiles were removed under reduced pressure.The residue was purified by silica gel column chromatography using 5-25% EtOAc in hexanes to provide the N,O-acetal **LVd** (8.85g).

Step 4



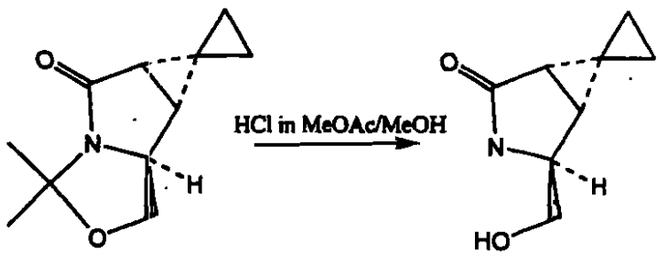
LVd LVe LVf

The carbamate **LVd** (8.81g; 28.4mmol) was dissloved in acetonitrile (45ml) and the solution was cooled to –40C under an atmosphere of nitrogen. Pyridine (6.9ml; 85.3mmol) followed by nitrosium tetrafluoroborate (6.63g; 56.8mmol) were added and the resulting reaction mixture maintained below 0C until TLC indicated

that no starting material remained (approx. 2.25h.). Pyrrolidine (20ml; 240mmol) was added and the cooling bath was withdrawn and stirring was continued at room temperature for 1h. and then the volatiles were removed under reduced pressure. The residue was quickly passed through a pad of silica gel to provide a yellow oil.

.The yellow oil was dissolved in anhydrous benzene (220ml) and palladium acetate (0.317g; 1.41mmol) was added before heating the resulting mixture to reflux, under an atmosphere of nitrogen for a period of 1.5h. After cooling, the volatiles were removed under reduced pressure and the dark residue was purified by silica gel column chromatography using EtOAc-hexane (1:4) to provide the i) the trans- pyrrolidinone **LVe** (1.94g) followed by ii) the cis-pyrolidinone **LVf** (1.97g).

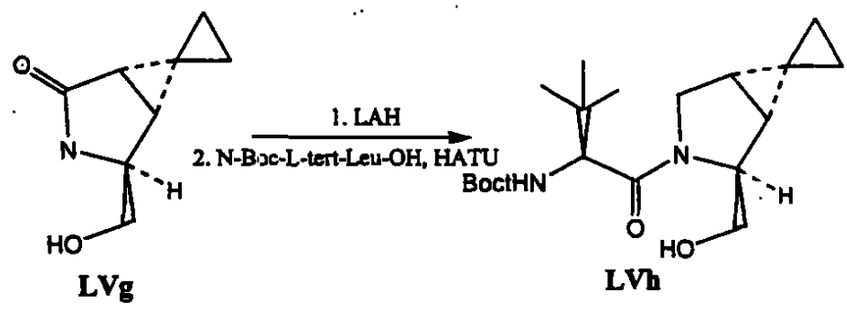
Step 5



LVe **LVg**

Freshly prepared 1M HCl in MeOAc/MeOH (10ml; as described above) was added to the N,O-acetal **LVe** and stirred at room temperature for 1h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using 0-4%MeOH in dichloromethane as eluent to provide the desired alcohol **LVg** (1.42g), a yellow oil.

Step 6

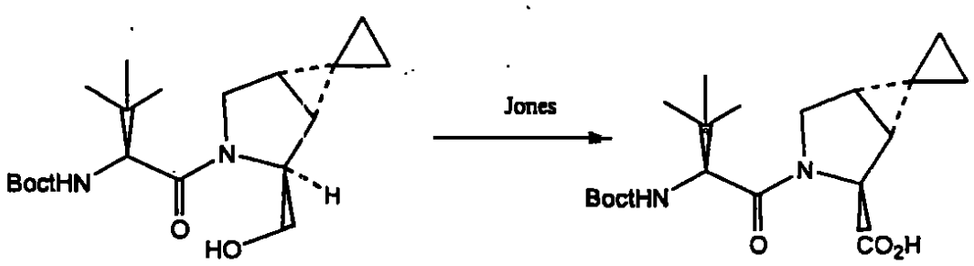


LVg LVh

To a solution of the lactam **LVg** (1.29g; 8.44mmol) in anhydrous tetrahydrofuran (55ml) was added lithium aluminum hydride (2.40g; 63.2mmol) and the resulting mixture was refluxed for 8h. After cooling, water, followed by 15% aq. NaOH were added and the resulting mixture was filtered through celite and the solid was washed thoroughly with THF and MeOH. The solvent was removed under reduced pressure and the residue redisolved in dichloromethane, dried and concentrated under reduced pressure to provide the pyrrolidine, used without purification.

Hunigs base (4.5ml; 25.8mmol) was added to a mixture of N-Boc-L-tert-Leu-OH (1.76g; 7.6mmol), The crude pyrrolidine and HATU (2.89g; 7.6mmol) in anhydrous dichloromethane (50ml) at –60C, under an atmosphere of nitrogen. The resulting reaction was allowed to come to room temperature slowly, overnight. EtOAc was added and the yellow solution was washed with dil.aq. HCl, sat. aq. sodium bicarbonate, water, brine. The organic layer was dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using EtOAc:hexanes (1:3) to give the desired amide **LVh** (2.00g).

Step 7

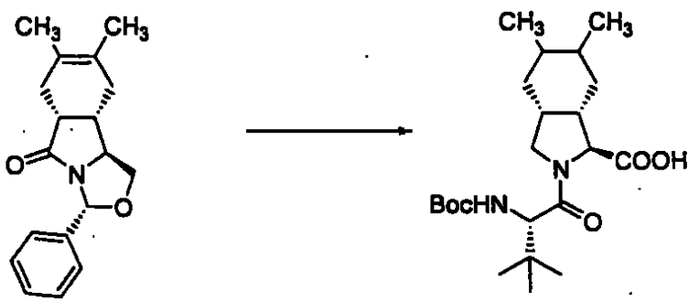


LVh **LV**

The alcohol **LVh** (2.00g; 5.67mmol) was dissolved in acetone (116ml) and cooled in an ice bath for 10min. This solution was then added to a cooled Jones reagent (14.2ml; approx 2mmol/ml) and the resulting mixture was stirred at 5C for 0.5h and the cooling bath was removed. The reaction was stirred for a further 2h. at room temp., before adding to sodium sulfate (28.54g), celite (15g) in EtOAc (100ml). Isopropanol (15ml) was added after 1min and then stirred for a further 10min. and filtered. The filtrate was concentrated under reduced pressure, providing a brown oil which was dissolved in EtOAc. This solution was washed with water, 3% aq. citric acid, brine, dried and concentrated to provide the desired carboxylic acid **LV** (1.64g) as a white solid.

NOTE: Alternatively XXIVc- acid, XXVIg-acid, XXVIIc, could be synthesized following the procedure mentioned above in good yields. A number of inhibitors described in **table-6** using the intermediates **LV** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LVI Preparation of intermediate of Formula LVI

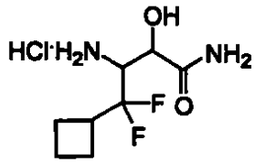


LVIa LVI

The synthesis of **LVIa** was accomplished following the procedure reported in Bailey, J, H.; Cherry, D, T.; Crapnell, K, M.; Moloney, M. G.; Shim, S. B.; Bamford, M. J.; Lamont, R. B. Tetrahedron (1997), 53, 11731. This was converted to **LVI** similar to the procedure for **LIII** (Step2 to Step 5)

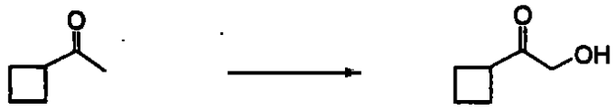
A number of inhibitors described in **table-6** using the intermediates **LVI** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LVII Preparation of intermediate of Formula LVII



LVII

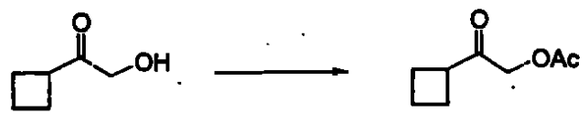
Step 1



LVIIa **LVIIb**

To the stirred solution of TFA (22.6 mL, 305 mmol), water (120 mL) and [bis(trifluoroacetoxy)iodo]benzene (131 g, 305 mmol) in acetonitrile (600 mL) was added cyclobutyl methyl ketone **LVIIa** (15.0 g, 153 mmol). The resulting solution was heated to reflux and stirred for 4 h. Acetonitrile was removed in vacuo. Water (120 mL) was added and the mixture was extracted with diethyl ether (2 X 500 mL). The combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography with 30% Et_2O/hexane to give 8.82 g of **LVIIb** (51%).

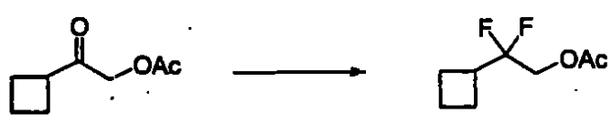
Step 2



LVIIb **LVIIc**

To the solution of **LVIIb** (1.4 g, 12.3 mmol), acetic anhydride (1.3 mL, 13.5 mmol) and triethyl amine (3.4 mL, 24.5 mmol) in CH_2Cl_2 (50 mL) was added DMAP (0.67 g, 5.5 mmol). The reaction mixture was stirred at rt for 4 h before 5% H_3PO_4 (50 mL) was added. After layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 X 50 mL). Combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo to 2.0 g crude product **LVIIc**.

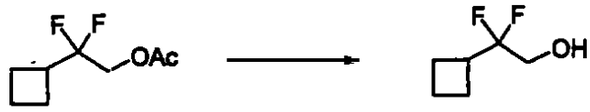
Step 3



LVIIc **LVIId**

The mixture of **LVIIc** (1.9 g, 12.2 mmol) and DAST (Diethyl amino sulfur trifluoride, 3.0 mL, 22.3 mmol) was heated to 50°C and stirred for 2 h. The mixturte was then slowly poured into ice water (50 mL), and extracted with diethyl ether (3 X 50 mL). The combined organic solution was dried ($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography with 10-40% Et_2O/hexane to give 0.62 g of **LVIId** (29%) and 0.68 g starting material **LVIIc**.

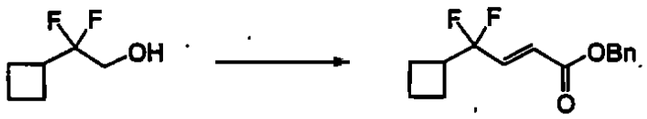
Step 4



LVIId **LVIIe**

The mixture of **LVIId** (3.10 g, 17.4 mmol) and lithium hydroxide (0.84 g, 34.8 mmol) in water (10 mL) was vigorously stirred at rt for 6 h before it was diluted with water (50 mL) and extracted with diethyl ether (3 X 60 mL). The combined organic solution was dried ($MgSO_4$), filtered and carefully concentrated in vacuo to give **LVIIe** 2.68 g crude product.

Step 5

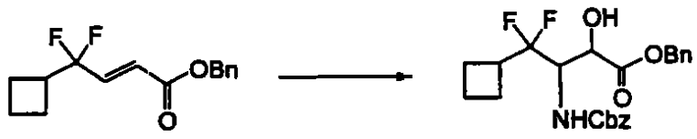


LVIIe **LVIIf**

The solution of compound **LVIIe** and Dess-Martin reagent in CH_2Cl_2 was stirred at rt for 1 h before $Ph_3P{=}CHCO_2Bn$ was added and stirring was continued for another 20 h. Diethyl ether was added followed by saturated NaS2O3 and saturated NaHCO3 solutions. After stirred for 15 min, the layers were separated. The organic solution was washed with saturated NaHCO3 and brine, dried

($MgSO_4$), filtered and concentrated in vacuo. The crude product was purified by flash chromatography to give the desired product **LVIIf**.

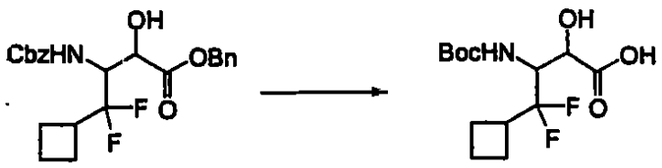
Step 6



LVIIf **LVIIg**

Compound **LVIIg** was prepared as described above (Step 4, Example **XXXXIII**) with appropriate amounts of reagents.

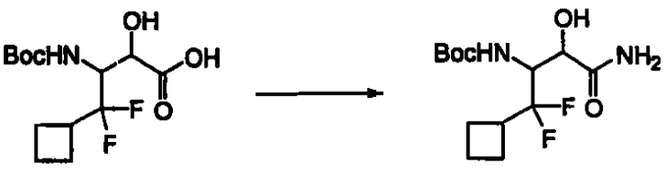
Step 7



LVIIg **LVIIh**

Catalytic hydrogenation of **LVIIg** over 10%Pd/C in MeOH followed by treatment with Boc_2O in $NaHCO_3$/THF/water will afford **LVIIh**.

Step 8



LVIIh **LVIIi**

Conversion of **LVIIh** to compound **LVIIi** will follow previously described procedures (Step 5, Example **XXVIII**).

Step 9

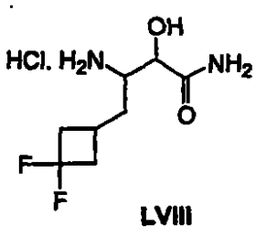


LVIII **LVII**

Conversion of **LVIII** to compound **LVII** follows previously described procedures (Step 9, Example **XXIII**).

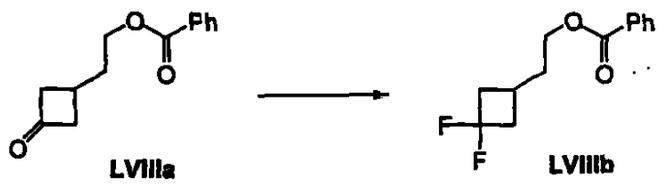
A number of inhibitors described in **table-6** using the intermediates **LVII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LVIII Preparation of intermediate of Formula LVIII



LVIII

Step 1

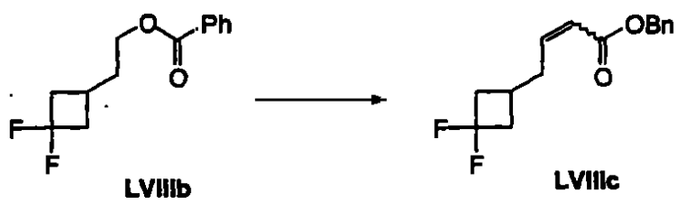


LVIIIa **LVIIIb**

To a solution of compound **LVIIIa** [for preparation of **LVIIIa** see J. Ramnauth and E. Lee-Ruff, *Can. J. Chem.*, **2001**, *79*, 114-120] (3g) in dichloromethane (75 mL)

was added DAST (Diethyl amino sulfur trifluoride, 9.1 mL) slowly and the reaction was stirred at room temperature overnight. The mixturte was slowly poured into ice/saturated sodium bicarbonate solution (100/200 mL) with stirring. Added 200 mL of dichloromethane and the organic layer was separated and washed with cold saturated sodium bicarbonate solution, brine, dried (Na_2SO_4) and concentrated. Purification by column chromatography (5/95 EtOAc/hexanes) afforded 2.59 g of **LVIIIb**.

Step 2



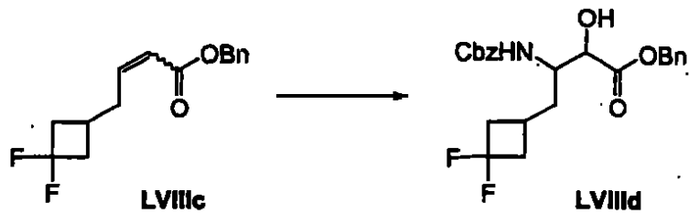
LVIIIb **LVIIIc**

Compound **LVIIIb** (3.42 g) was dissolved in THF/MeOH (1/1, 50 mL). To this was added a solution of potassium carbonate (1.97 g) in water (25 mL). The reaction mixture was stirred at room temperature for 4 hrs and then stored in the freezer (-10°C) overnight. The reaction mixture was warmed to room temperature over 3 hrs when TLC indicated complete consumption of **LVIIIb**. Brine (100 mL) was added to the reaction mixture and was extracted with ethyl ether (3 x 100 mL). The ether layers were combined, dried (Na_2SO_4) and concentrated to afford a residue (2.77g) which was processed further without purification.

The residue thus obtained was dissolved in CH_2Cl_2/DMSO (6/1, 140 mL). To this solution was added benzyl (triphenylphosphoranylidene)acetate (11.7 g) and then Dess-Martin's Periodinane (12.09 g, in three equal portions) carefully. The reaction mixture was stirred at room temperature for 4 hrs and quenched with cold sodium bicarbonate solution (200 mL) and diluted with CH_2Cl_2 (100 mL). The CH_2Cl_2 layer was separated and washed with 10% $Na_2S_2O_3$ solution (125 mL), $NaHCO_3$ solution (125 mL), water (125 mL), dried (Na_2SO_4) and concentrated.

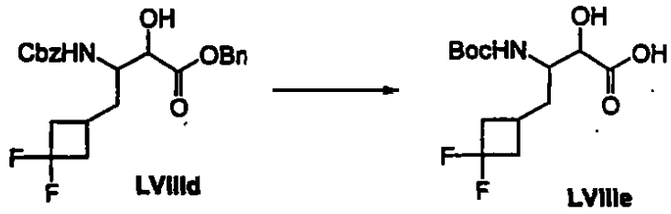
The residue was purified by column chromatography using 50/50 CH_2Cl_2/hexanes to afford the required compound, **LVIIIc** (2.25 g).

Step 3



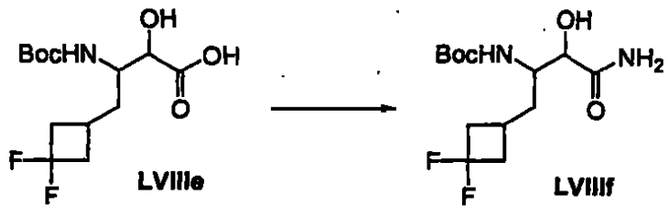
Compound **LVIIId** was prepared as described above (Step 4, Example **XXXXIII**) with appropriate amounts of reagents.

Step 4



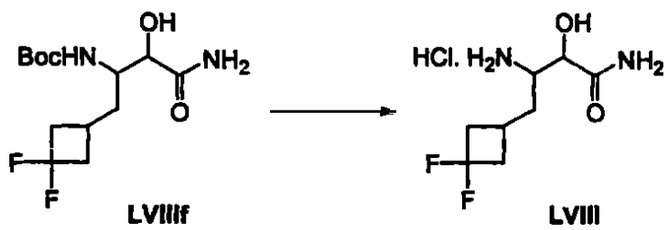
Catalytic hydrogenation of **LVIIId** over 10%Pd/C in MeOH followed by treatment with Boc_2O in $NaHCO_3$/THF/water will afford **LVIIIe**.

Step 5



Conversion of **LVIIIe** to compound **LVIIIf** will follow previously described procedures (Step 5, Example **XXVIII**).

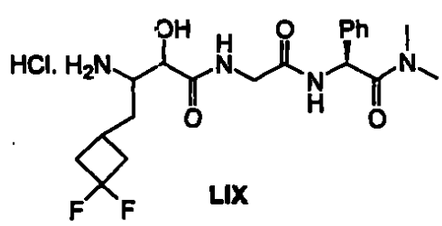
Step 6



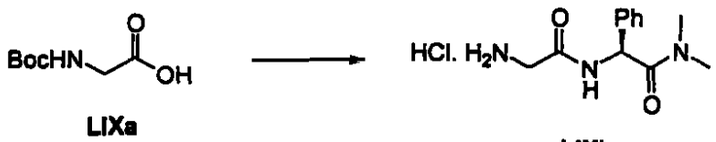
Conversion of **LVIIIF** to compound **LVIII** will follow previously described procedures (Step 9, Example **XXIII**).

A number of inhibitors described in **table-6** using the intermediates **LVIII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LIX Preparation of intermediate of Formula LIX



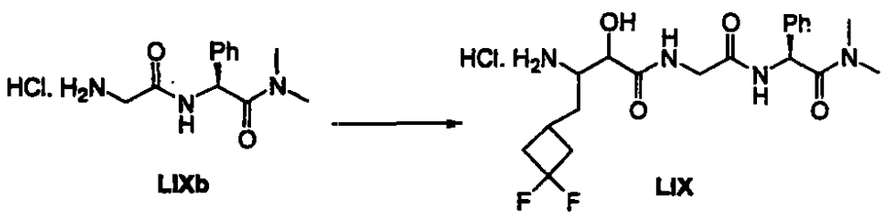
Step 1



LIXa **LIXb**

Commercially available N-Boc protected glycine **LIXa** was reacted with the amine **XV** from Example **XV** in the manner previously described in Example **XXI**, Step 4. The resulting intermediate was then treated with HCl in the manner previously described in Example **XXIII**, Step 9 to afford product **LIXb**.

Step 2

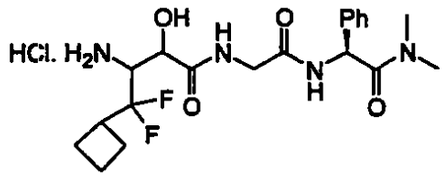


LIXb **LIX**

Acid **LVIIe** (from above) can be reacted with **LIXb** in the manner previously described in Example **XXI**, Step 4. The resulting intermediate can then be treated with HCl in the manner previously described in Example **XXIII**, Step 9 to afford product **LIX**.

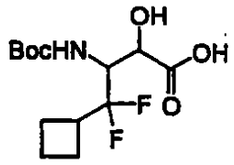
A number of inhibitors described in **table-6** using the intermediates **LIX** were synthesized following the procedures outlined for preparative **examples XXIX**, and **XXXX**

Example LX Preparation of intermediate of Formula LX



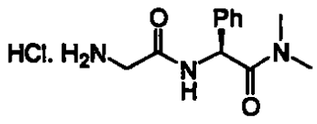
LX

Step 1

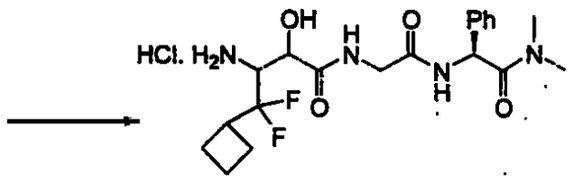


LVIIh

+



LIXb

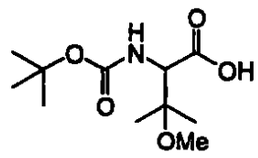


LX

Acid **LVIIh** (from above) was reacted with **LIXb** in the manner previously described in Example **XXI**, Step 4. The resulting intermediate was then treated with HCl in the manner previously described in Example **XXIII**, Step 9 to afford product **LX**.

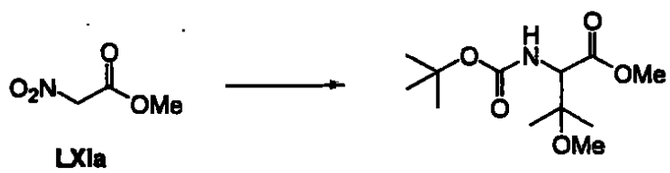
A number of inhibitors described in **table-6** using the intermediates **LIX** were synthesized following the procedures outlined for preparative **examples XXIX**, and **XXXX**

Example LXI Preparation of intermediate of Formula LXI



LXI

Step 1

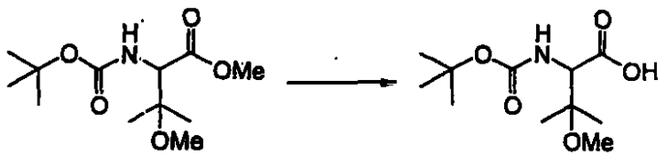


LXIa **LXIb**

To a solution of methyl nitroacetate **LXIa** (3 g) in benzene (15 mL) was added dimethoxy propane (6.2 mL) and acetic anhydride (4.87 mL). The mixture was refluxed overnight. The reaction mixture was concentrated. It was resubjected to the above conditions. The residue after concentration was taken in EtOAc (100 mL) and washed with cold saturated sodium bicarbonate solution (3 x 75 mL), brine (100 mL), dried (Na_2SO_4) and concentrated.

The residue from above was taken in MeOH (150 mL). Boc_2O (6 g) and 10% Pd/C (150 mg) were added and the mixture was hydrogenated using a balloon filled with hydrogen gas. After 24 hours, added some more 10% Pd/C and repeated the procedure. The reaction mixture was then filtered through celite, concentrated, and purified by column chromatography using 5/95 to 10/90 EtOAc/hexanes to afford 2.2 g of **LXIb**.

Step 2

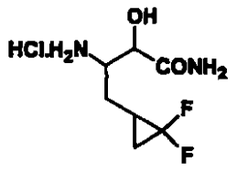


LXIb LXI

Compound **LXIb** was prepared from **LXI** in quantitative yield using procedures described above for the conversion of **XXVIg** to **XXVIh** (see Example **XXVI**).

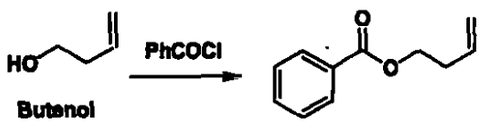
A number of inhibitors described in **table-6** using the intermediates **LVIII** were synthesized following the procedures outlined for preparative **examples XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LXII Preparation of intermediate of Formula LXII



LXII

Step1:

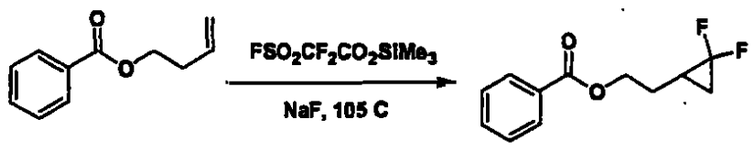


Butenol

LXIIa LXIIb

Butenol **LXIIa** was reacted in the manner previously described in preparative example XXXXIII step 1 to afford product **LXIIb**

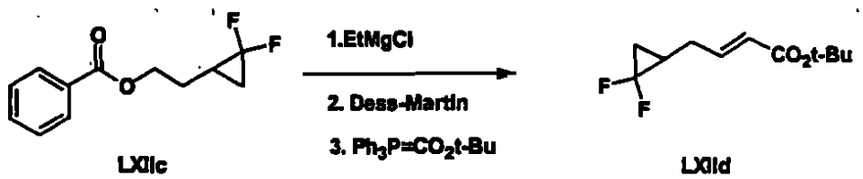
Step2:



LXIIb **LXIIc**

To 5.3g (30 mmol) of **LXIIb** product of step 1 was added 25 mg of NaF. At 110 °C, was added via syringe-pump 1.6equiv (48 mmol, 12g) of TMSfluorosulfonyldifluoroacetate (TFDA) in 2h. After 2h, reaction is cooled down to RT. Purification by flash column chromatography (3% EtOAc, Hexane, silica) furnished **LXIIc**, Product of step 2 (4.93g).

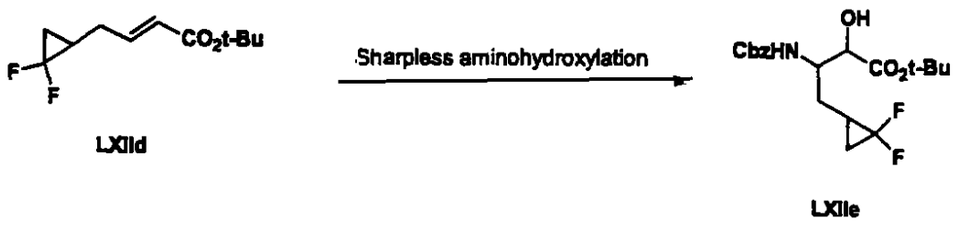
Step3:



LXIIc **LXIId**

Product of step 2, **LXIIc** (1g) was treated in the manner previously described in step3 of preparative **XXXXIII** to afford **LXIId**, Product of step 3 (0.89g)

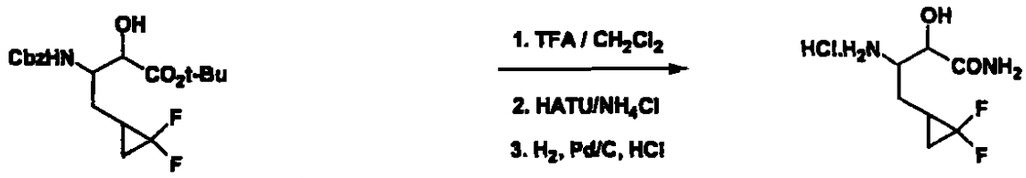
Step4:



LXIId LXIIe

Product of step 3, **LXIId** (3.2g) was treated in the manner previously described in step4 of preparative **XXXXIII** to afford Product **LXIIe** (1.4g).

Step5:

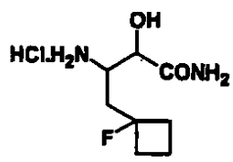


LXIIe LXIIf

Product of step 4, **LXIIe** (0.54g) was treated in the manner previously described in step5 then step6 and finally step7 of preparative example **XXXXIII** to afford Product **LXIIf** (0.24g).

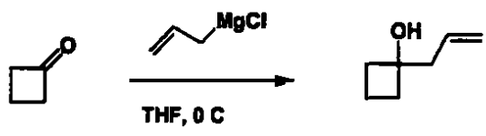
A number of inhibitors described in **table-6** using the intermediate **LXII** were synthesized following the procedures outlined for preparative examples **XXIII, XXIV, XXVIII, XXIX,** and **XXXX**

Example LXIII Preparation of intermediate of Formula LXIII



LXIII

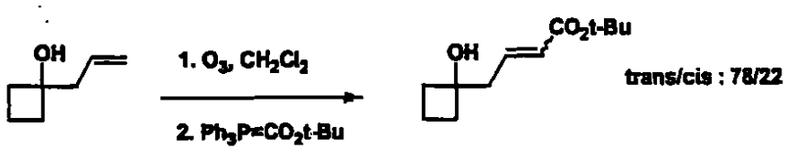
Step1:



LXIIIa LXIIIb

To a –78 °C solution of cyclobutanone (15g, 214 mmol) in THF (100 mL) is added dropwise Allylmagnesiumchloride (2.0 M in THF, 1.1 equiv, 118 mL). After 1 hour, reaction is stopped by the addition of ice and HCl 1.0 N (100 mL). The mixture was diluted with ethyl acetate (~200 ml) and the organic phase was separated; washed with brine and dried over anhydrous $MgSO_4$. Concentration in-vacuo and purification by chromatography over silica gel (10% ethyl acetate in n-hexane) provided product **LXIIIb** (21g).

Step2:

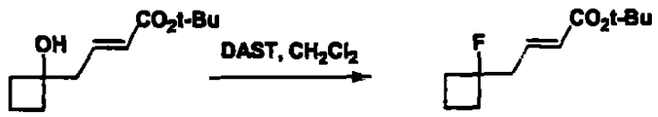


LXIIIb LXIIIc

To a –78 °C solution of product of step 1, **LXIIIb** (11.2g) in CH_2Cl_2 (200 mL) is bubbled Ozone until a persistent blue color was observed (after 1 hour). Ozone was stopped and N_2 was flushed into the reaction mixture for 10 minutes. Me_2S (10 equiv., 7.3 mL) was added and reation was gradually warmed-up to room temperature overnight.

After 18 hours, $Ph_3P{=}CHCOO^tBu$ (40 g) was added. Stirring was continued for ~24 hrs Evaporation under vacuum provided the crude product which was chromatographed over silica gel (10% ethyl acetate in n-hexane) to provide product **LXIIIc** as a mixture of isomers (6.65g of trans isomer) and (1.9g of cis olefin).

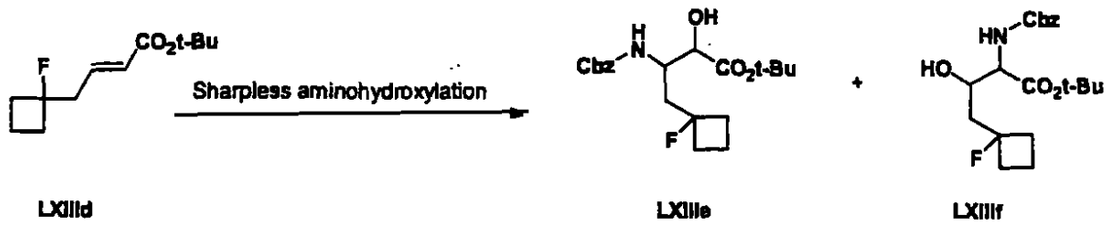
Step3:



LXIIIc LXIIId

To a 0 °C solution of product of step2, **LXIIIc** (0.21g) in CH_2Cl_2 (3 mL) is added DAST (1.1 equiv., 0.135 mL). After 15 minutes, reaction was stopped by the addition a cold saturated solution of Na_2CO_3 (150 ml). The mixture was diluted with ethyl acetate (~10 ml) and after stirring for ~30 min the organic phase was separated; washed with brine and dried over anhydrous $MgSO_4$. Concentration in-vacuum and purification by chromatography over silica gel (5% to 10% CH_2Cl_2 in n-hexane) provided **LXIIId** (0.1 g; 47%).

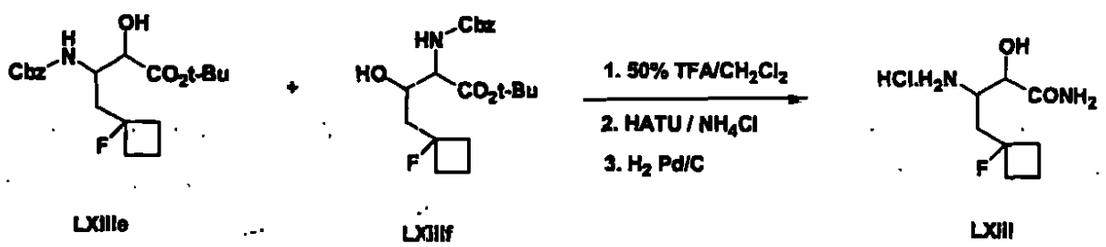
Step4:



LXIIId LXIIIe LXIIIf

Product of step 3, **LXIIId** (3.5g) was treated in the manner previously described in step4 of preparative **XXXXIII** to afford Products **LXIIIe and LXIIIf** as a mixture (3.25g).

Step5:

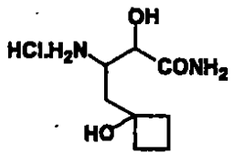


LXIIIe LXIIIf LXIII

Products of step 4 **(LXIIIe+LXIIIf)** (2.3g) was treated in the manner previously described in step5 then step6 and finally step7 of preparative example **XXXXIII** to afford Product **LXIII** (0.47g).

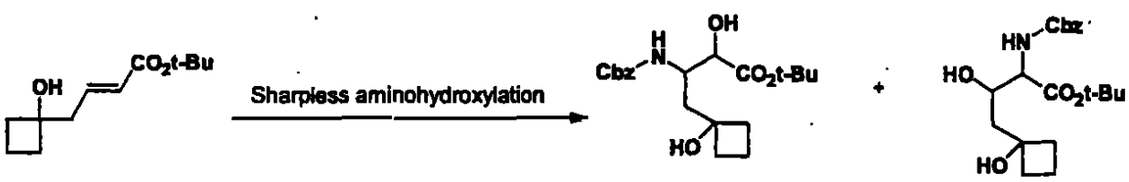
A number of inhibitors described in **table-6** using the intermediate LXII were synthesized following the procedures outlined for preparative examples **XXIII, XXIV, XXVIII, XXIX**, and **XXXX**

Example LXIV Preparation of intermediate f Formula LXIV



LXIV

Step1:



LXIIIc "trans isomer"

LXIVa

LXIVb

Product **LXIIIc** (1.36g) was treated in the manner previously described in step4 of preparative example **XXXXIII** to afford Products **LXIVa** and **LXIVb** as a mixture (1.3g).

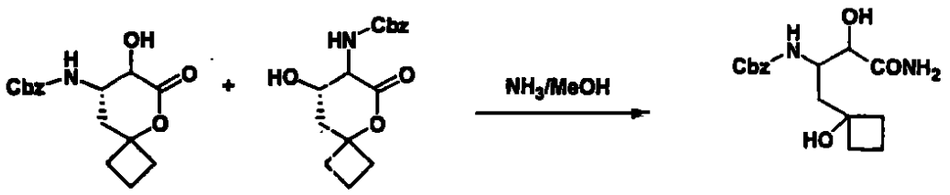
Step2:



LXIVa LXIVb LXIVc LXIVd

A stirred solution of Products of step 1 (**LXIVa+LXIVb**) (1.2g) in CH_2Cl_2 (40 ml) was treated with trifluoroacetic acid (40 ml). After 45 minutes the reaction mixture was concentrated to dryness under vacuum. The residue was chromatographed over silica gel (2% MeOH in CH_2Cl_2) to provide products **LXIVc** and **LXIVd** as a mixture (0.97g).

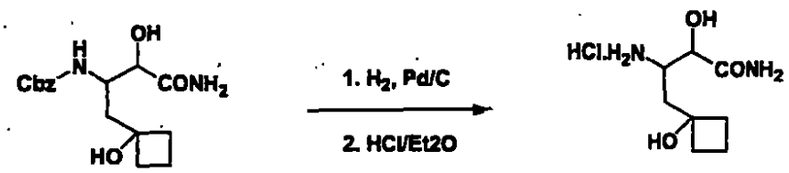
Step3:



LXIVc LXIVd LXIVe

To products of step 2 (**LXIVc+LXIVd**) (0.4g) was added 30 mL of NH_3 (2.0 M in MeOH). After 4 hours, the reaction mixture was concentrated to dryness under vacuum. The residue was preparative chromatography over silica gel (100% CH_3CN) to provide desired product **LXIVe** (0.3g).

Step4:

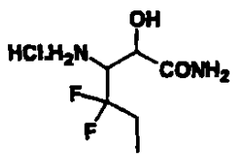


LXIVe LXIV

Product of step 3 **LXIVe** (0.054g) was treated in the manner previously described in step7 of preparative example XXXXIII to afford Product **LXIV** (0.032g)

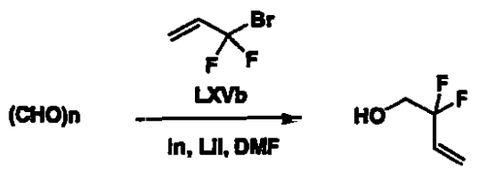
A number of inhibitors described in **table-6** using the intermediate **LXII** were synthesized following the procedures outlined for preparative examples **XXIII, XXIV, XXVIII, XXIX,** and **XXXC**

Example LXV Preparation of intermediate of Formula LXV



LXV

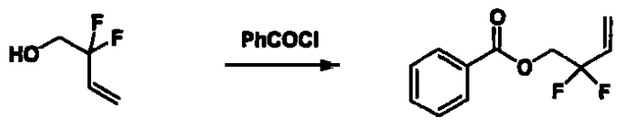
Step1:



LXVa LXVc

To a room temperature solution of paraformaldehyde **LXVa** (12g, 400 mmol) and 1-bromo-1,1-difluorop2-ene **LXVb** (6.3g, 40 mmol) in DMF (100 mL) was added In(0) (6.5g, 57 mmol) and LiI (0.4g, 3 mmol). The resulting slurry was stirred at RTfor 48 h . After 48 h, reaction was filtered trough a pad of celite. The filtrate was diluted with EtOAc (250 mL) and washed with H_2O (3 times) then brine. The organic phase separated and finally dried over anhydrous $MgSO_4$. Evaporation under vacuum provided product **LXVc**, which was used as it is directly in the next step.

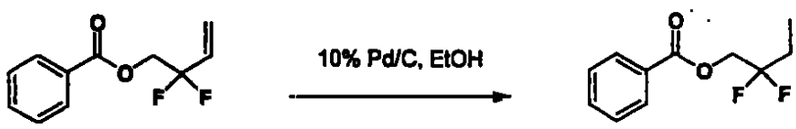
Step2:



LXVc **LXVd**

Product of step 1, **LXVc** (4g, 37 mmol) was reacted in the manner previously described in preparative example **XXXXIII step 1** to afford after purification by chromatography over silica gel (10% to 50% CH_2Cl_2 in n-hexane) product **LXVd** (4.3g).

Step3:

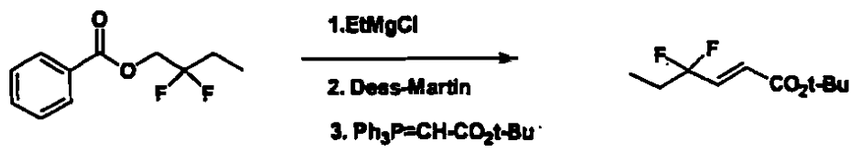


LXVd **LXVe**

To a solution of the product from step 2, **LXVd** (3.8 g) in ethanol (30 ml) was added 10% Pd/C catalyst (0.76g). The resulting suspension was hydrogenated until NMR experiment indicated complete consumption of the starting material (~4

hrs). The catalyst was removed by filtration trough a pad of celite and washed with ethanol. The combined filtrate and washings were evaporated under vacuum to dryness to provide the desired product, **LXVe** (3.8g).

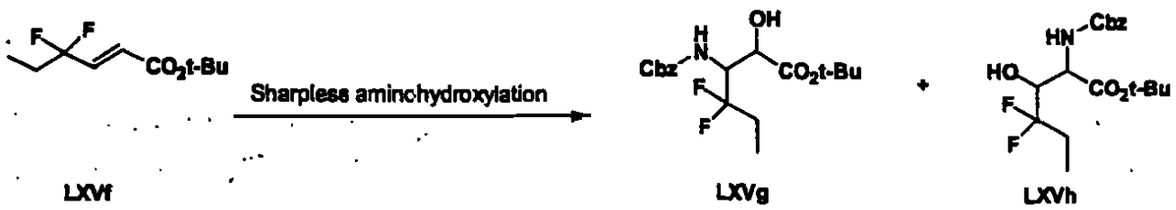
Step4:



LXVe LXVf

Product of step 3, **LXVe** (3.4g) was treated in the manner previously described in step3 of **XXXXIII** to afford Product **LXVf** (2.5g).

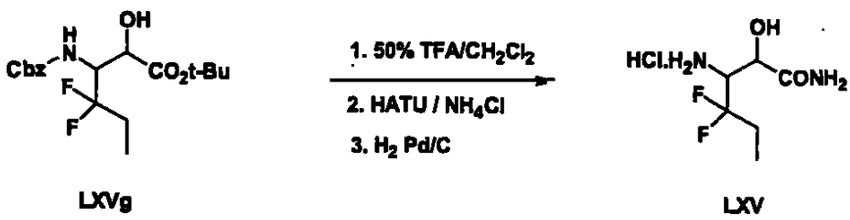
Step5:



LXVf LXVg LXVh

Product of step 4, **LXVf** (2g) was treated in the manner previously described in step4 of preparative example **XXXXIII** to afford after purification by chromatography over silica gel (30% EtOAc in n-hexane) to give **LXVg** (0.27g) and **LXVh** (0.26g).

Step6:



LXVg LXV

Product of step 5 **LXVg** (0.17g) was treated in the manner previously described in step5 then step6 and finally step7 of preparative example **XXXXIII** to afford Product **LXV** (0.025g).

A number of inhibitors described in **table-6** using the intermediate **LXV** were synthesized following the procedures outlined for preparative examples **XXIII, XXIV, XXVIII, XXIX**, and **XXXX**

Seperation of diastereomers: The diastereomers arising from the α-center of ketoamide were seperated using either chromatography (SiO_2) or HPLC (YMC diol column) with Hexane/CH_2Cl_2/Isopropanol/CH_3CN = 85/7.5/6.5/1 as the solvent, as is known to those skilled in the art.

Assay for HCV Protease Inhibitory Activity:

Spectrophotometric Assay: Spectrophotometric assay for the HCV serine protease was performed on the inventive compounds by following the procedure described by R. Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, the disclosure of which is incorporated herein by reference. The assay based on the proteolysis of chromogenic ester substrates is suitable for the continuous monitoring of HCV NS3 protease activity. The substrates were derived from the P side of the NS5A-NS5B junction sequence (Ac-DTEDVVX(Nva), where X = A or

P) whose C-terminal carboxyl groups were esterified with one of four different chromophoric alcohols (3- or 4-nitrophenol, 7-hydroxy-4-methyl-coumarin, or 4-phenylazophenol). Presented below are the synthesis, characterization and application of these novel spectrophotometric ester substrates to high throughput screening and detailed kinetic evaluation of HCV NS3 protease inhibitors.

Materials and Methods:

Materials: Chemical reagents for assay related buffers were obtained from Sigma Chemical Company (St. Louis, Missouri). Reagents for peptide synthesis were from Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) and Perseptive Biosystems (Framingham, Massachusetts). Peptides were synthesized manually or on an automated ABI model 431A synthesizer (from Applied Biosystems). UV/VIS Spectrometer model LAMBDA 12 was from Perkin Elmer (Norwalk, Connecticut) and 96-well UV plates were obtained from Corning (Corning, New York). The prewarming block was from USA Scientific (Ocala, Florida) and the 96-well plate vortexer was from Labline Instruments (Melrose Park, Illinois). A Spectramax Plus microtiter plate reader with monochrometer was obtained from Molecular Devices (Sunnyvale, California).

Enzyme Preparation: Recombinant heterodimeric HCV NS3/NS4A protease (strain 1a) was prepared by using the procedures published previously (D. L. Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401). Protein concentrations were determined by the Biorad dye method using recombinant HCV protease standards previously quantified by amino acid analysis. Prior to assay initiation, the enzyme storage buffer (50 mM sodium phosphate pH 8.0, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside and 10 mM DTT) was exchanged for the assay buffer (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) utilizing a Biorad Bio-Spin P-6 prepacked column.

Substrate Synthesis and Purification: The synthesis of the substrates was done as reported by R. Zhang *et al*, (*ibid.*) and was initiated by anchoring Fmoc-Nva-OH to 2-chlorotrityl chloride resin using a standard protocol (K. Barlos *et al, Int. J. Pept. Protein Res.*, 37 (1991), 513-520). The peptides were subsequently assembled, using Fmoc chemistry, either manually or on an automatic ABI model 431 peptide synthesizer. The N-acetylated and fully protected peptide fragments were cleaved from the resin either by 10% acetic acid (HOAc) and 10% trifluoroethanol (TFE) in dichloromethane (DCM) for 30 min, or by 2% trifluoroacetic acid (TFA) in DCM for 10 min. The combined filtrate and DCM wash was evaporated azeotropically (or repeatedly extracted by aqueous Na_2CO_3 solution) to remove the acid used in cleavage. The DCM phase was dried over Na_2SO_4 and evaporated.

The ester substrates were assembled using standard acid-alcohol coupling procedures (K. Holmber *et al, Acta Chem. Scand.*, B33 (1979) 410-412). Peptide fragments were dissolved in anhydrous pyridine (30-60 mg/ml) to which 10 molar equivalents of chromophore and a catalytic amount (0.1 eq.) of para-toluenesulfonic acid (pTSA) were added. Dicyclohexylcarbodiimide (DCC, 3 eq.) was added to initiate the coupling reactions. Product formation was monitored by HPLC and found to be complete following 12-72 hour reaction at room temperature. Pyridine solvent was evaporated under vacuum and further removed by azeotropic evaporation with toluene. The peptide ester was deprotected with 95% TFA in DCM for two hours and extracted three times with anhydrous ethyl ether to remove excess chromophore. The deprotected substrate was purified by reversed phase HPLC on a C3 or C8 column with a 30% to 60% acetonitrile gradient (using six column volumes). The overall yield following HPLC purification was approximately 20-30%. The molecular mass was confirmed by electrospray ionization mass spectroscopy. The substrates were stored in dry powder form under desiccation.

Spectra of Substrates and Products: Spectra of substrates and the corresponding chromophore products were obtained in the pH 6.5 assay buffer. Extinction

coefficients were determined at the optimal off-peak wavelength in 1-cm cuvettes (340 nm for 3-Np and HMC, 370 nm for PAP and 400 nm for 4-Np) using multiple dilutions. The optimal off-peak wavelength was defined as that wavelength yielding the maximum fractional difference in absorbance between substrate and product (product OD - substrate OD)/substrate OD).

Protease Assay: HCV protease assays were performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) were optimized for the NS3/NS4A heterodimer (D. L. Sali *et al*, *ibid.*)). Typically, 150 µl mixtures of buffer, substrate and inhibitor were placed in wells (final concentration of DMSO ≤4 % v/v) and allowed to preincubate at 30 °C for approximately 3 minutes. Fifty µls of prewarmed protease (12 nM, 30°C) in assay buffer, was then used to initiate the reaction (final volume 200 µl).The plates were monitored over the length of the assay (60 minutes) for change in absorbance at the appropriate wavelength (340 nm for 3-Np and HMC, 370 nm for PAP, and 400 nm for 4-Np) using a Spectromax Plus microtiter plate reader equipped with a monochrometer (acceptable results can be obtained with plate readers that utilize cutoff filters). Proteolytic cleavage of the ester linkage between the Nva and the chromophore was monitored at the appropriate wavelength against a no enzyme blank as a control for non-enzymatic hydrolysis. The evaluation of substrate kinetic parameters was performed over a 30-fold substrate concentration range (~6-200 µM). Initial velocities were determined using linear regression and kinetic constants were obtained by fitting the data to the Michaelis-Menten equation using non-linear regression analysis (Mac Curve Fit 1.1, K. Raner). Turnover numbers (k_{cat}) were calculated assuming the enzyme was fully active.

Evaluation of Inhibitors and Inactivators: The inhibition constants (Ki*) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH and Ac-DTEDVVP(Nva)-OH were determined experimentally at fixed

concentrations of enzyme and substrate by plotting v_o/v_i vs. inhibitor concentration ($[I]_o$) according to the rearranged Michaelis-Menten equation for competitive inhibition kinetics: $v_o/v_i = 1 + [I]_o/(Ki^* (1 + [S]_o/K_m))$, where v_o is the uninhibited initial velocity, v_i is the initial velocity in the presence of inhibitor at any given inhibitor concentration ($[I]_o$) and $[S]_o$ is the substrate concentration used. The resulting data were fitted using linear regression and the resulting slope, $1/(Ki^*(1+[S]_o/K_m)$, was used to calculate the Ki^* value.

The obtained Ki^* values for the various compounds of the present invention are given in the afore-mentioned Tables wherein the compounds have been arranged in the order of ranges of Ki^* values. From these test results, it would be apparent to the skilled artisan that the compounds of the invention have excellent utility as NS3-serine protease inhibitors.

While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

Table 2

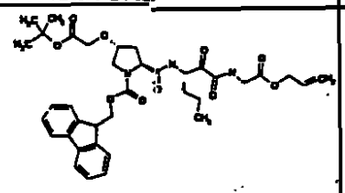
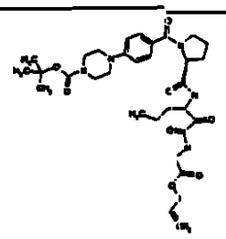
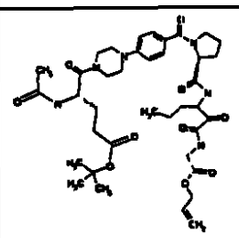
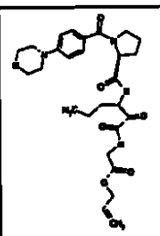
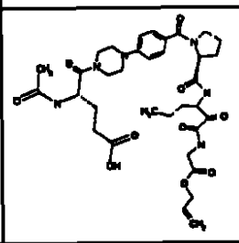
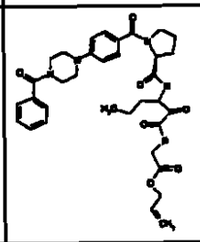
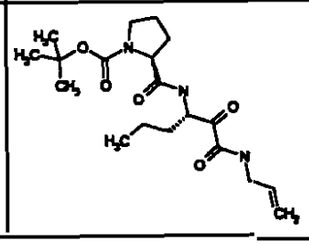
Ex. #	STRUCTURE	molecular weight
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3		754.8883
4		527.6259
5		698.7799
6		631.7352
7		381.476

Table 2

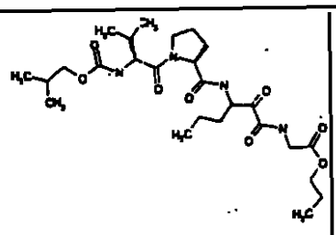
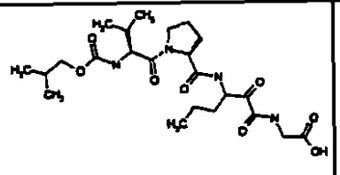
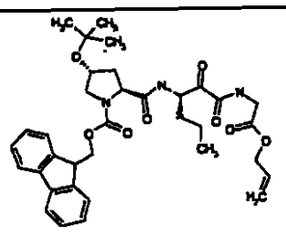
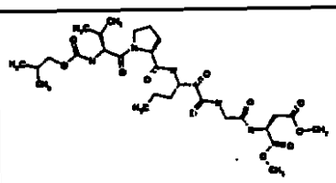
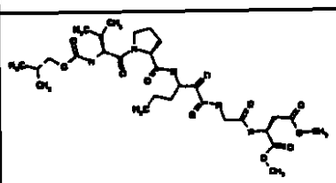
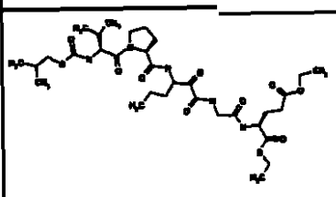
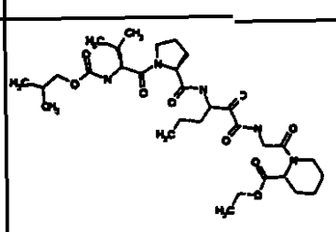
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9		498.5813
10		633.7482
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13		683.8061
14		637.7802

Table 2

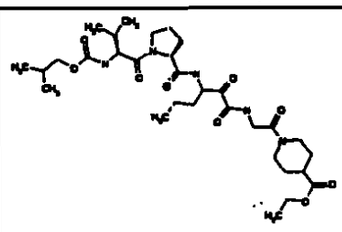
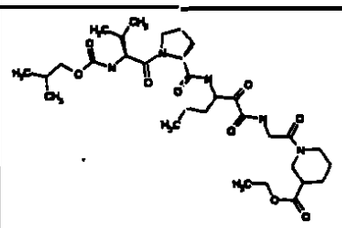
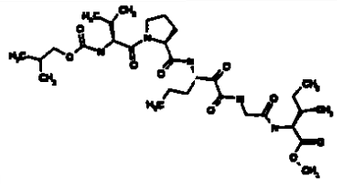
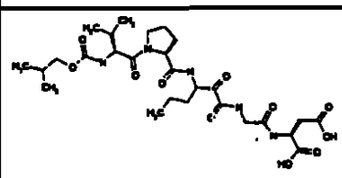
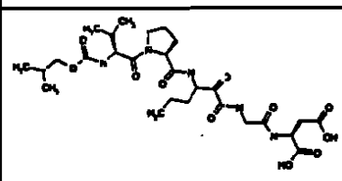
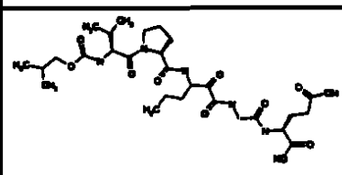
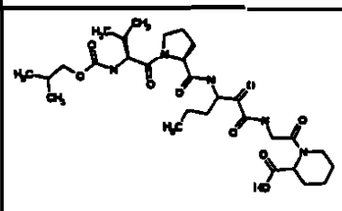
15		637.7802
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18		613.6707
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20		627.6978
21		609.726

Table 2

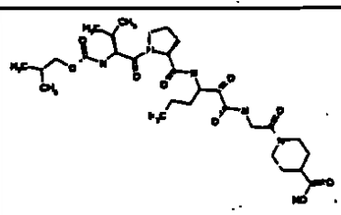
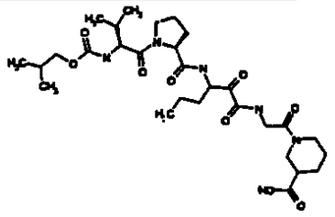
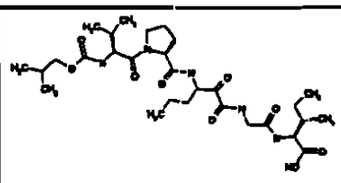
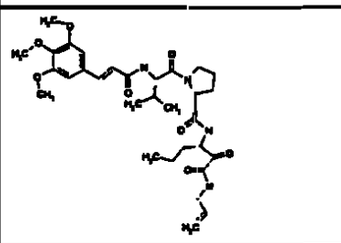
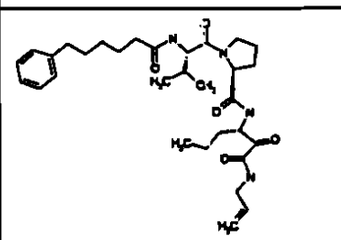
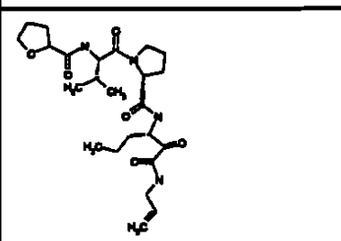
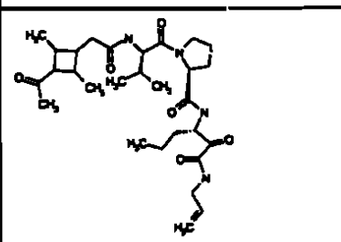
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23		609.726
24		611.742
25		600.7183
26		554.7361
27		478.5937
28		546.7132

Table 2

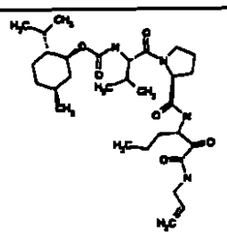
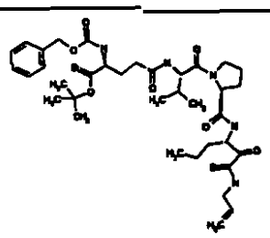
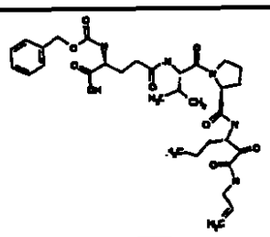
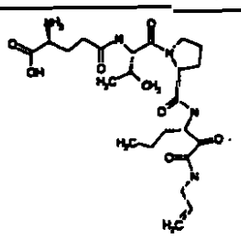
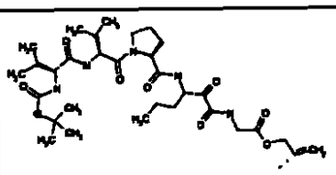
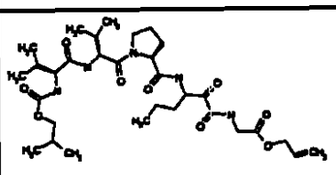
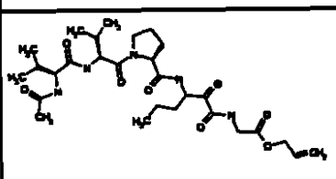
29		562.7562
30		699.8519
31		643.7435
32		509.6077
33		637.7802
34		637.7802
35		579.6995

Table 2

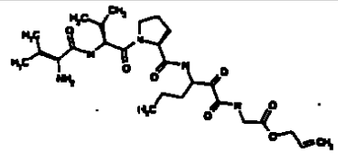
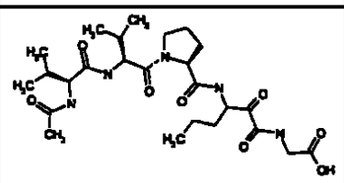
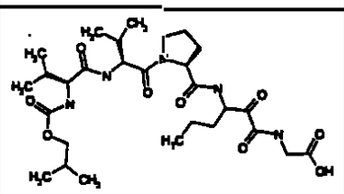
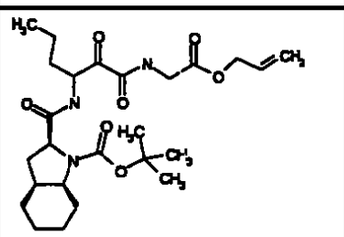
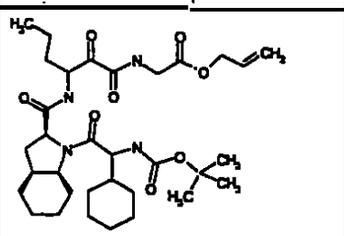
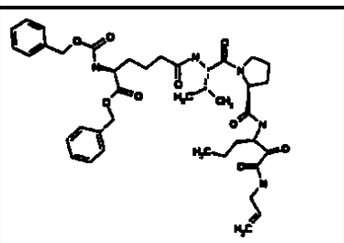
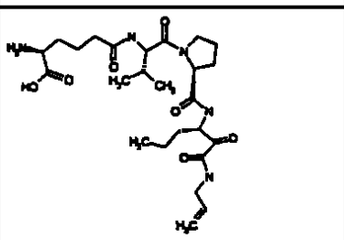
36		537.6619
37		539.6342
38		597.7149
39		493.6055
40		632.8044
41		747.8965
42		523.6348

Table 2

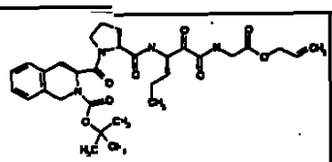
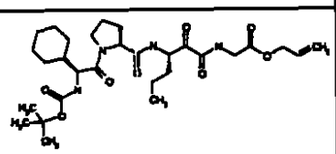
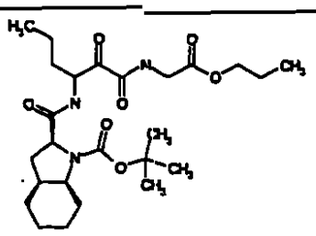
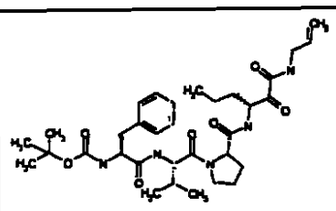
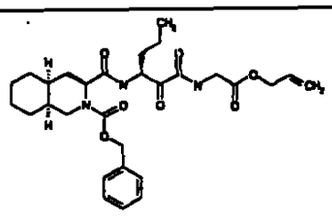
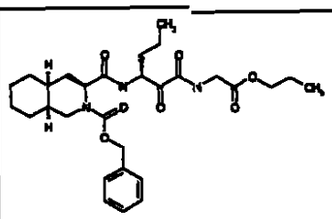
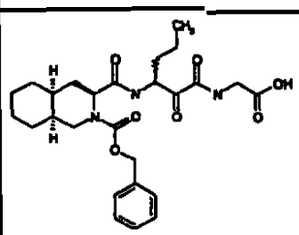
43		598.7024
44		578.712
45		495.6214
46		627.7878
47		541.6501
48		543.666
49		501.5847

Table 2

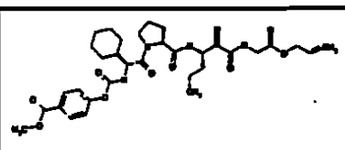
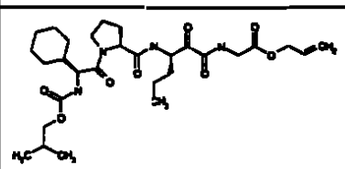
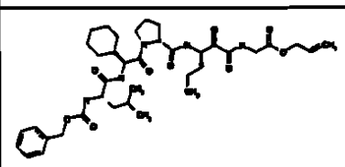
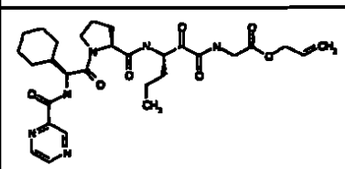
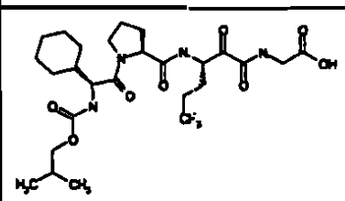
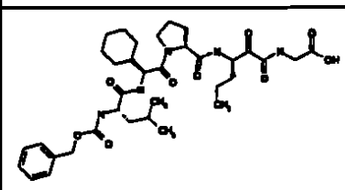
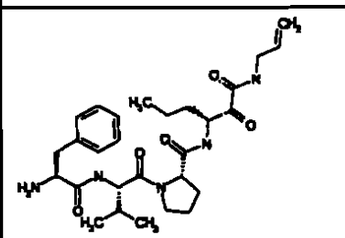
50		656.7394
51		578.712
52		725.8901
53		584.6782
54		538.6467
55		685.8248
56		527.6695

Table 2

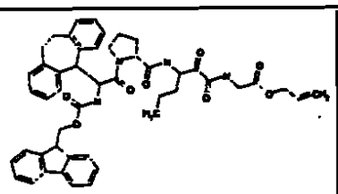
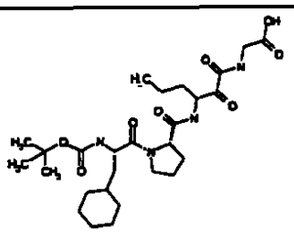
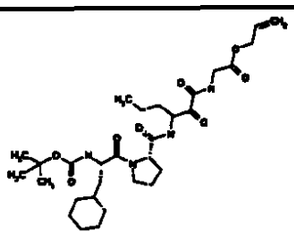
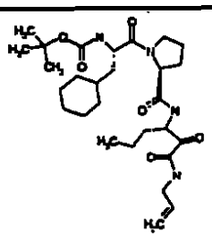
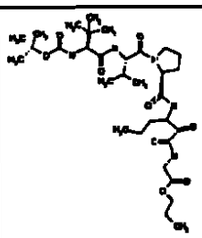
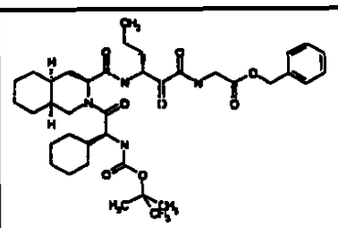
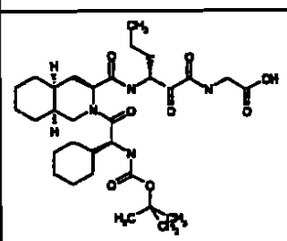
57		810.9557
58		552.6737
59		592.7391
60		534.702
61		653.8232
62		696.892
63		606.7662

Table 2

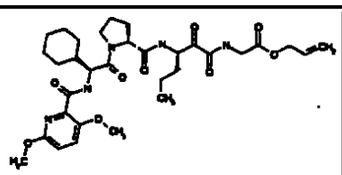
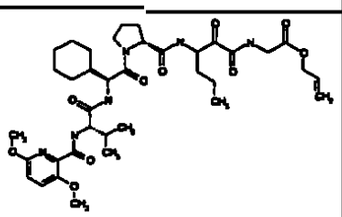
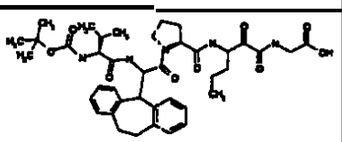
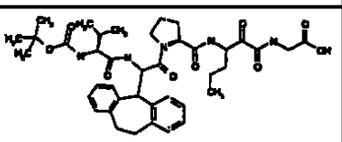
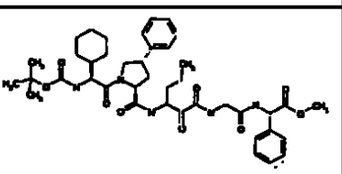
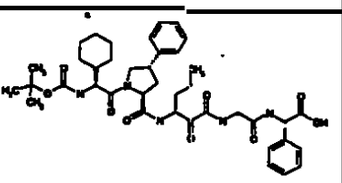
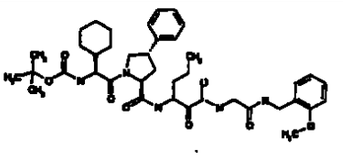
64		643.7435
65		742.8771
66		747.8965
67		747.8965
68		761.9236
69		747.8965
70		733.913

Table 2

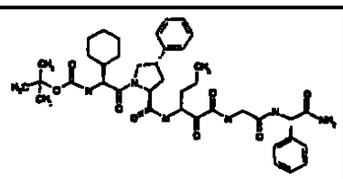
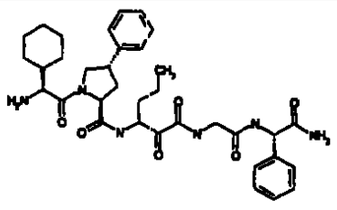
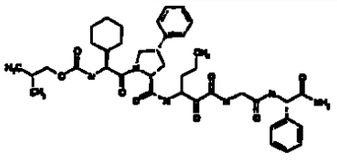
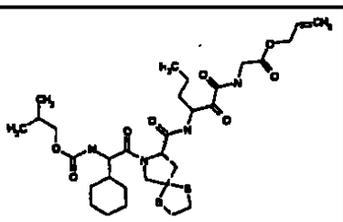
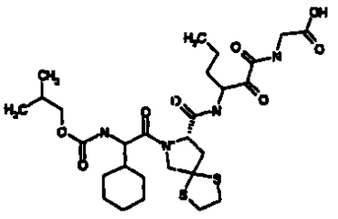
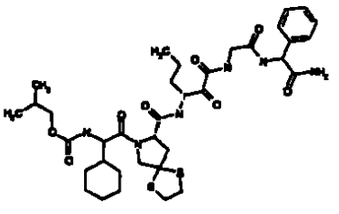
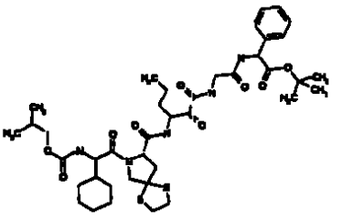
71		746.9118
72		646.7935
73		746.9118
74		668.8782
75		628.8129
76		760.9792
77		818.0723

Table 2

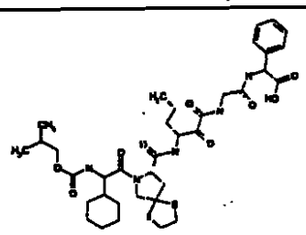
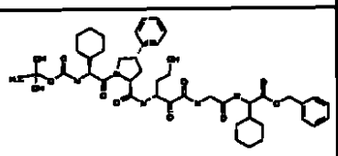
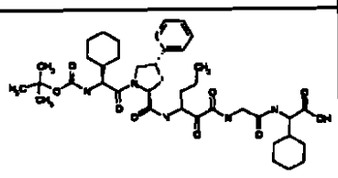
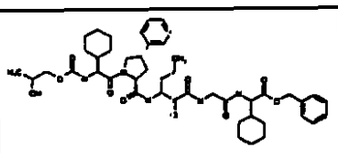
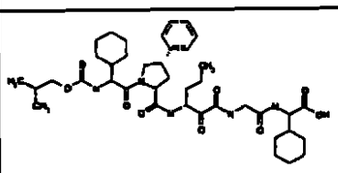
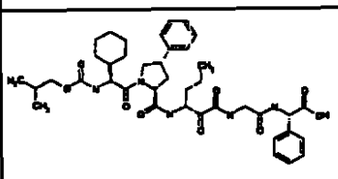
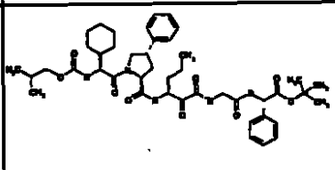
78		761.964
79		844.0702
80		753.9443
81		844.0702
82		753.9443
83		747.8965
84		804.0049

Table 2

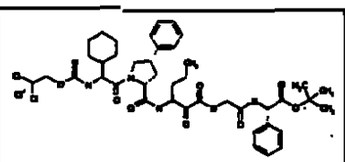
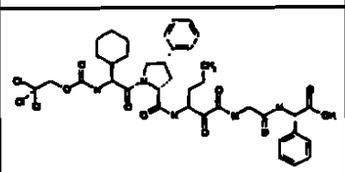
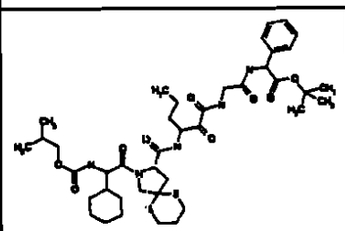
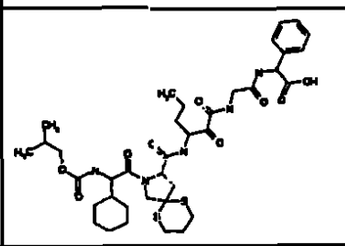
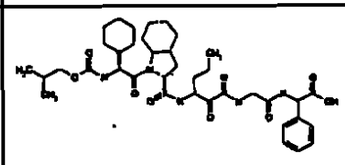
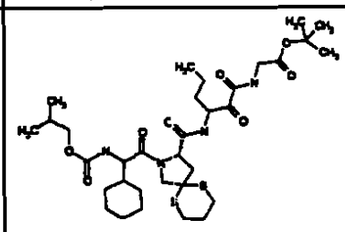
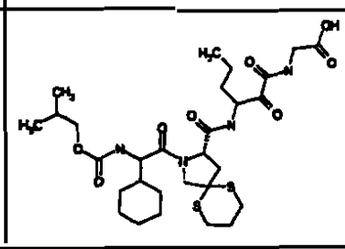
85		879.2858
86		823.1774
87		832.0994
88		775.9911
89		725.8901
90		698.9483
91		642.84

Table 2

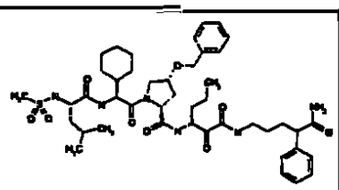
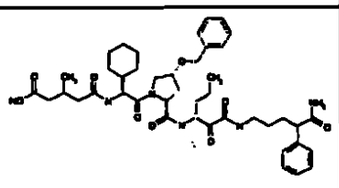
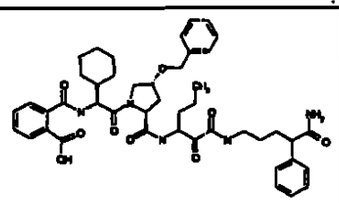
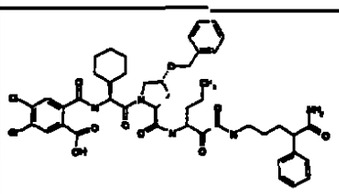
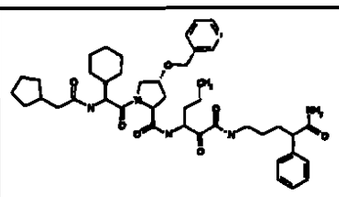
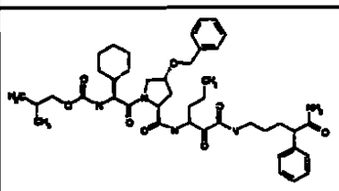
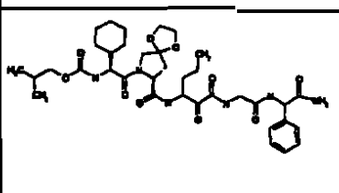
92		853.0995
93		789.9778
94		809.9682
95		878.8583
96		772.006
97		761.9672
98		728.85

Table 2

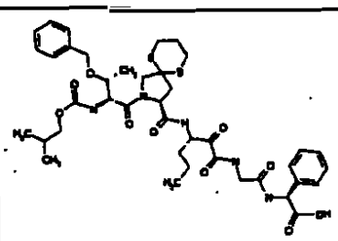
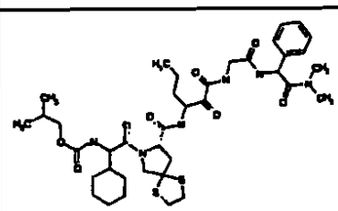
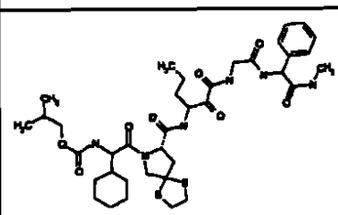
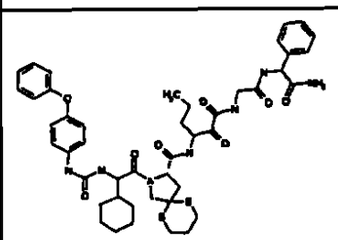
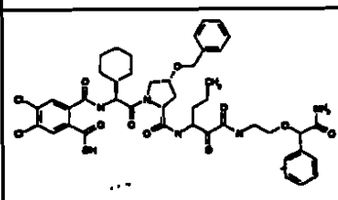
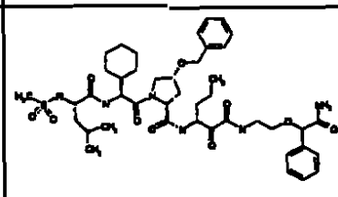
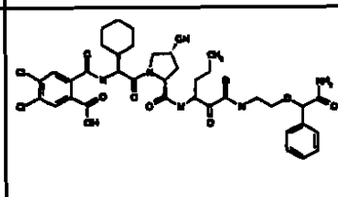
99		828.0239
100		789.0334
101		775.0063
102		886.1102
103		880.8306
104		855.0718
105		790.7047

Table 2

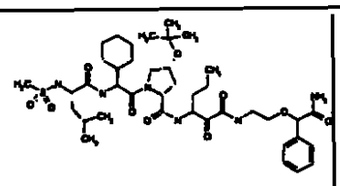
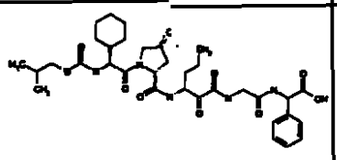
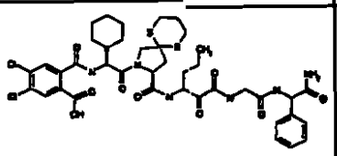
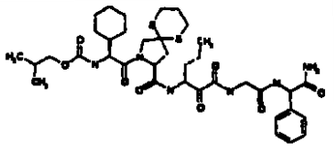
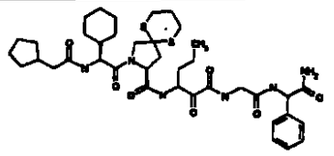
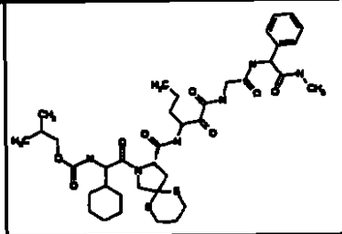
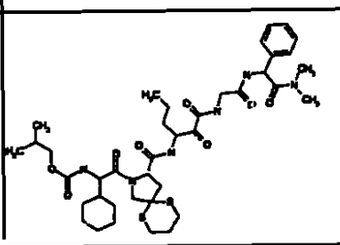
106		821.0543
107		685.7812
108		891.8973
109		775.0063
110		785.0452
111		789.0334
112		803.0605

Table 2

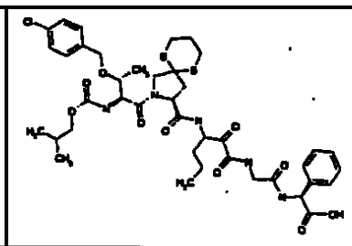
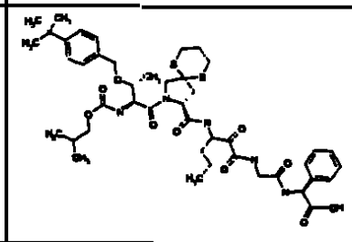
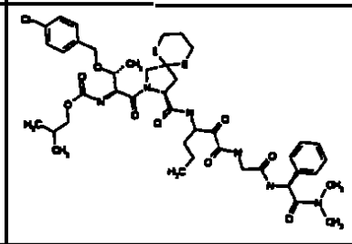
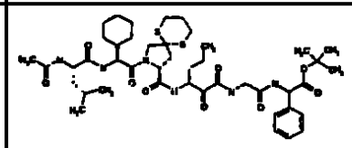
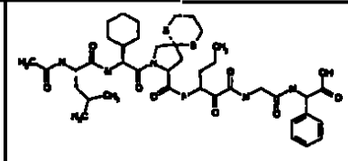
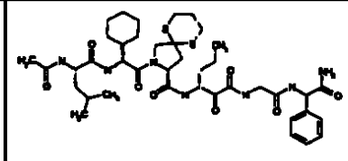
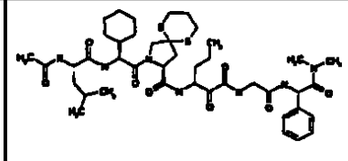
113		862.4689
114		884.1323
115		889.5384
116		887.1794
117		831.071
118		830.0863
119		858.1405

Table 2

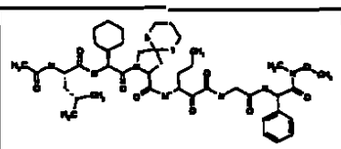
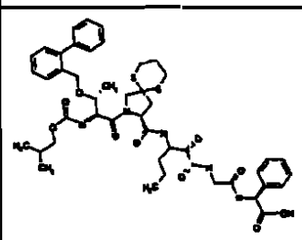
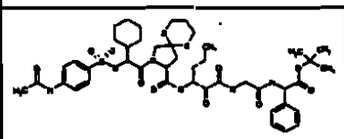
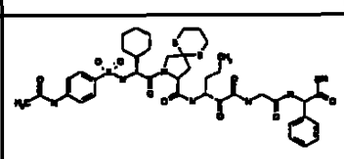
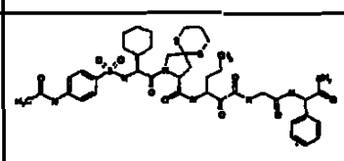
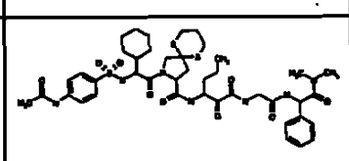
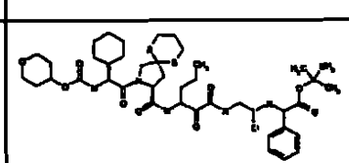
120		874.1399
121		904.1227
122		929.195
123		873.0867
124		872.1019
125		900.1561
126		860.11

Table 2

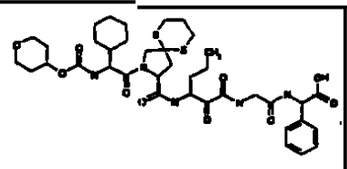
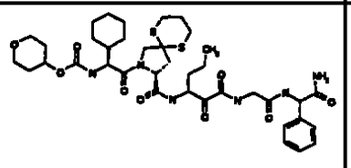
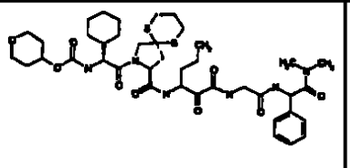
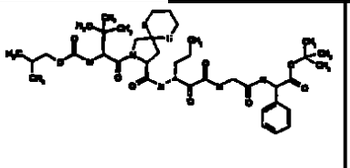
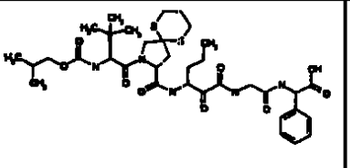
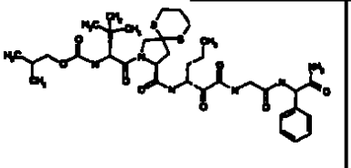
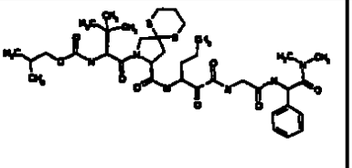
127		804.0016
128		803.0169
129		831.071
130		806.0612
131		749.9528
132		748.9681
133		777.0223

Table 2

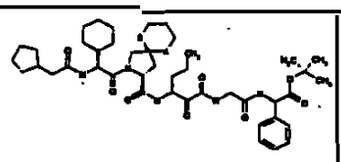
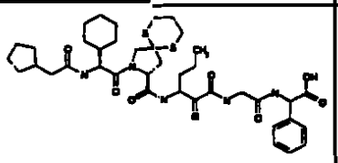
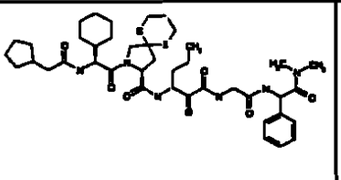
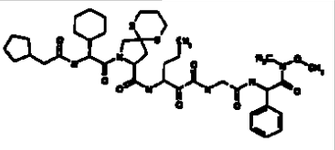
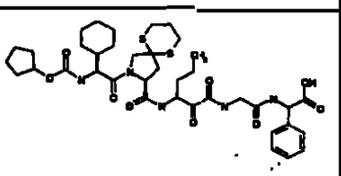
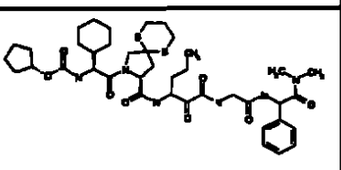
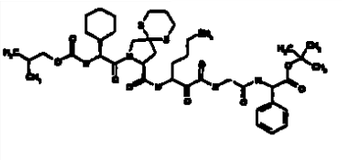
134		842.1382
135		786.0299
136		813.0994
137		829.0988
138		788.0022
139		815.0717
140		846.1265

Table 2

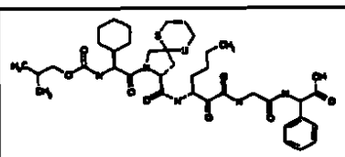
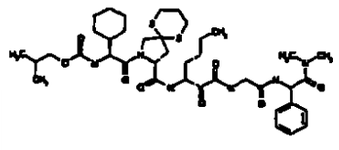
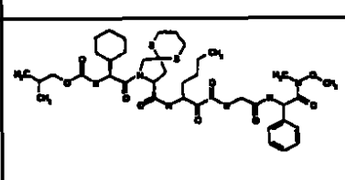
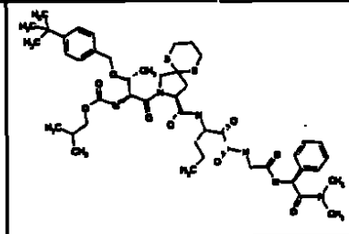
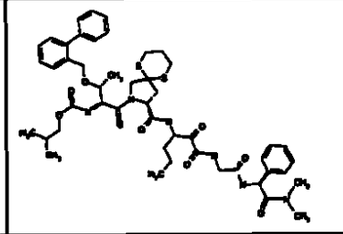
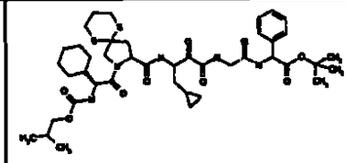
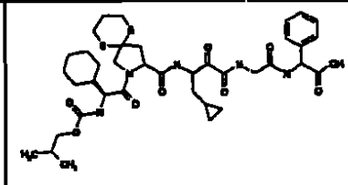
141		790.0181
142		817.0876
143		833.087
144		911.2017
145		931.1921
146		844.1106
147		788.0022

Table 2

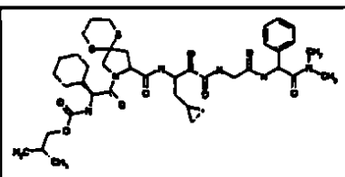
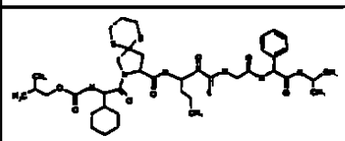
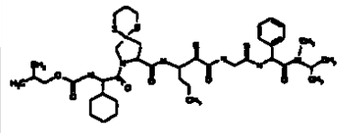
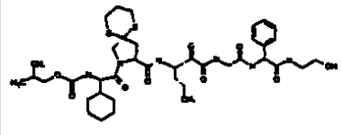
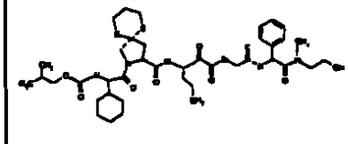
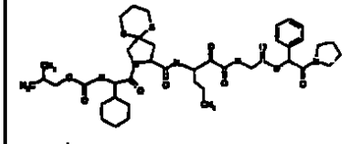
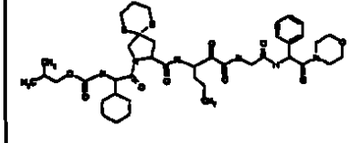
148		815.0717
149		817.0876
150		831.1147
151		819.0599
152		833.087
153		829.0988
154		845.0981

Table 2

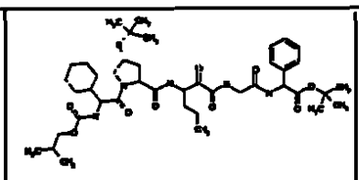
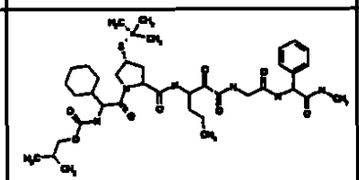
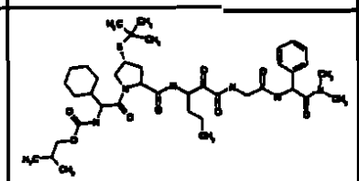
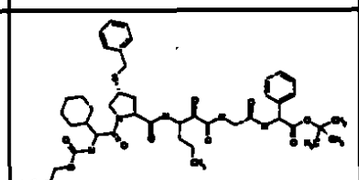
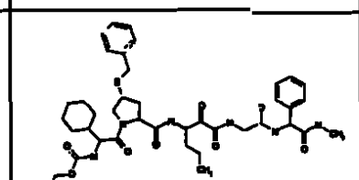
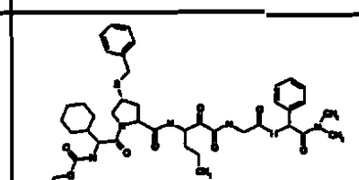
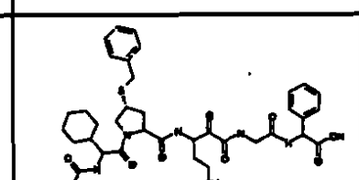
155		816.0784
156		773.0125
157		787.0396
158		850.0959
159		807.03
160		821.0571
161		793.9876

Table 2

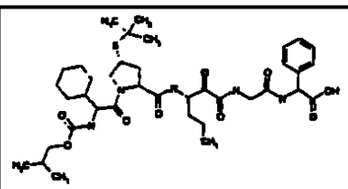
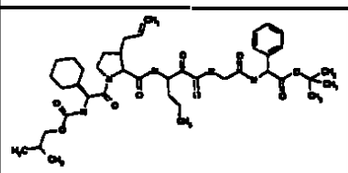
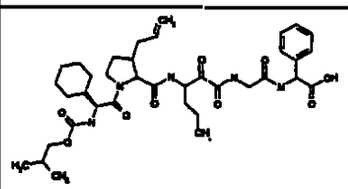
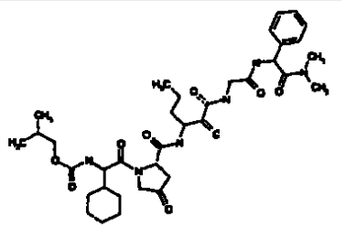
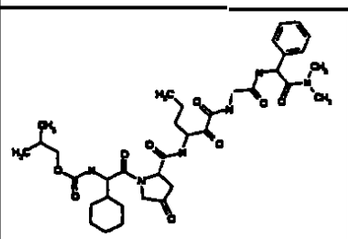
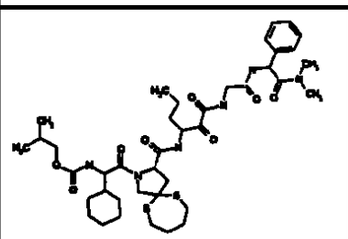
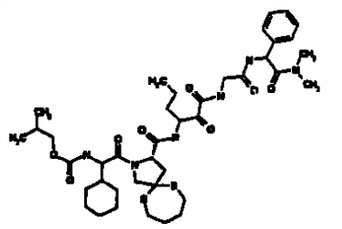
162		759.9701
163		767.9714
164		711.863
165		712.8506
166		712.8506
167		817.0876
168		817.0876

Table 2

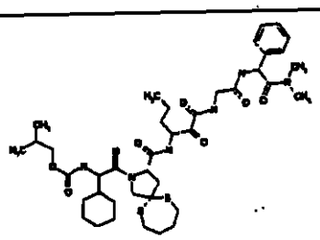
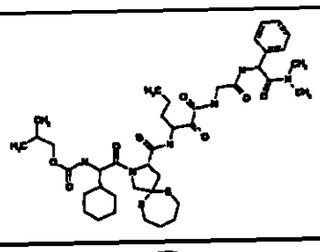
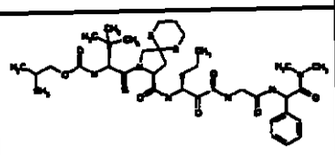
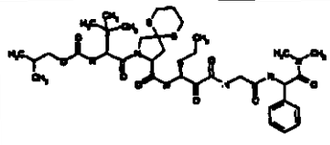
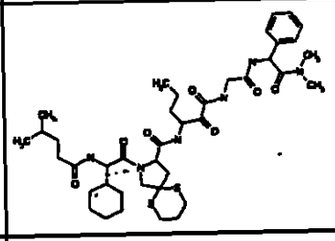
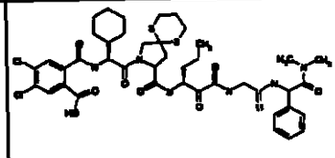
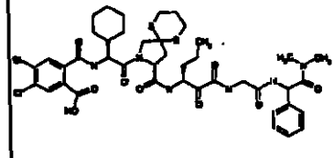
169		817.0876
170		817.0876
171		777.0223
172		777.0223
173		801.0882
174		919.9515
175		919.9515

Table 2

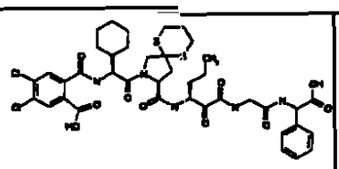
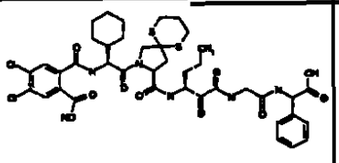
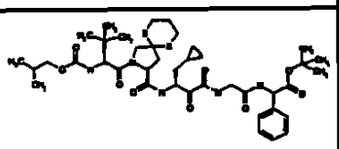
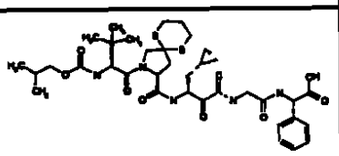
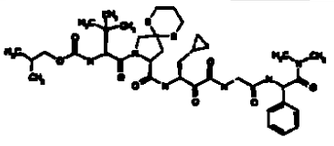
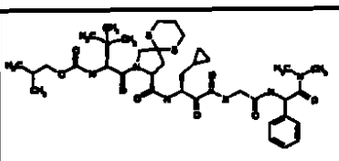
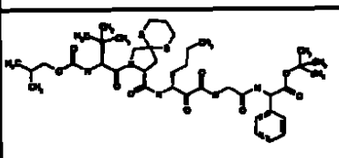
176		892.8821
177		892.8821
178		818.0723
179		761.964
180		789.0334
181		789.0334
182		820.0883

Table 2

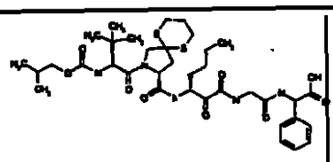
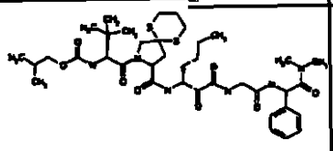
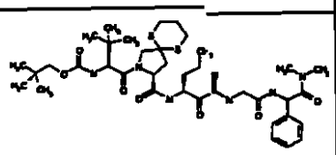
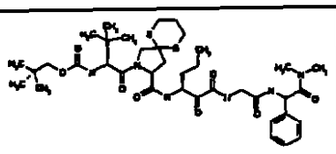
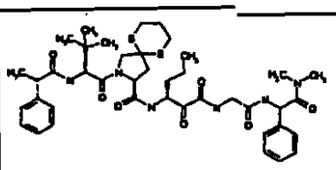
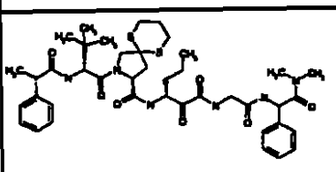
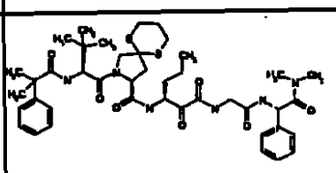
183		763.9799
184		791.0494
185		791.0494
186		791.0494
187		809.0674
188		809.0674
189		823.0945

Table 2

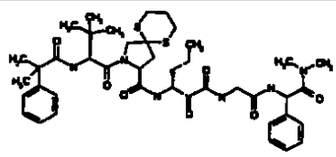
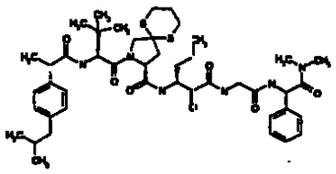
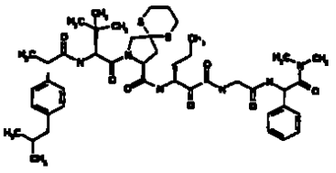
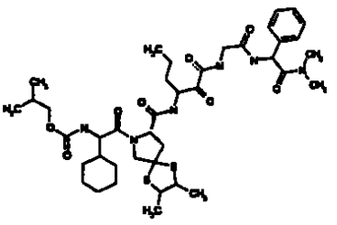
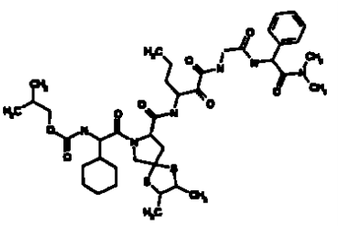
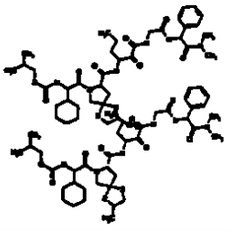
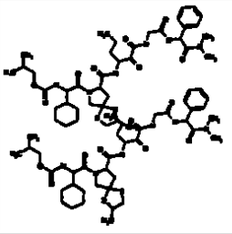
190		823.0945
191		865.1758
192		865.1758
193		817.0876
194		817.0876
195		1606.121
196		1606.121

Table 2

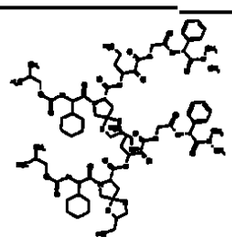
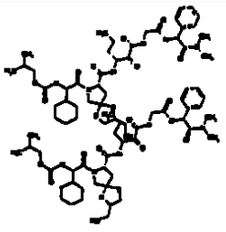
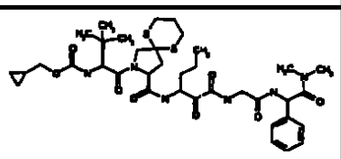
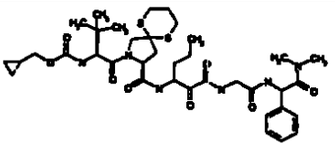
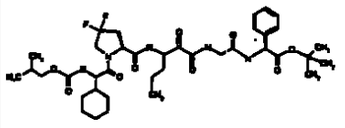
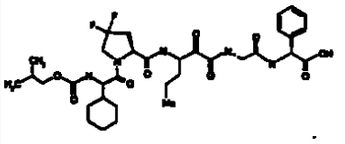
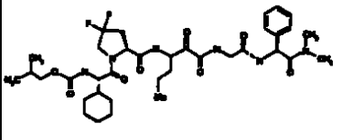
197		1638.12
198		1638.12
199		775.0063
200		775.0063
201		763.887
202		707.7786
203		734.848

Table 2

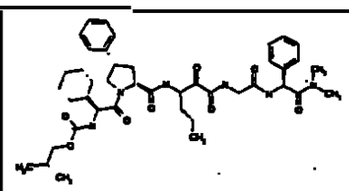
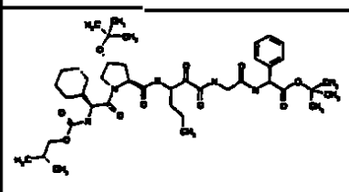
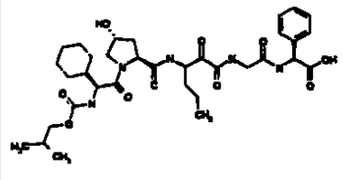
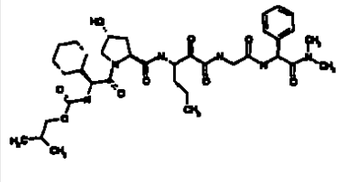
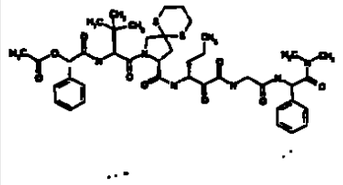
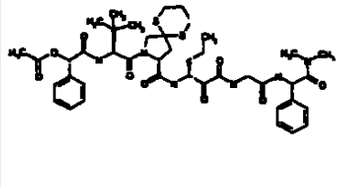
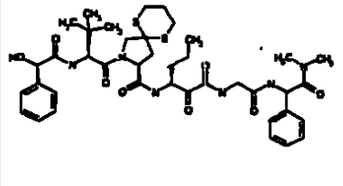
204		774.9659
205		800.0139
206		687.7971
207		714.8666
208		853.0774
209		853.0774
210		811.0398

Table 2

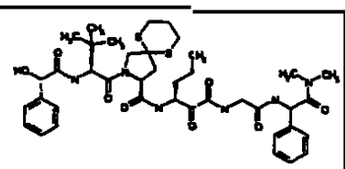
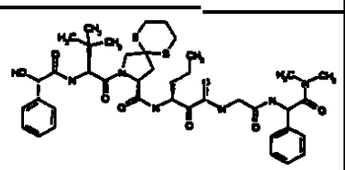
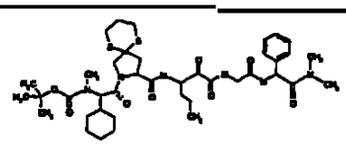
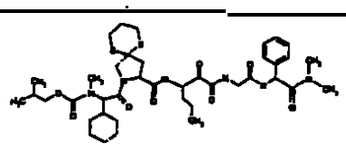
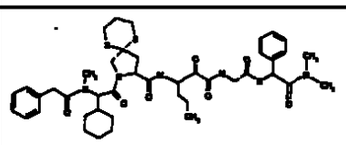
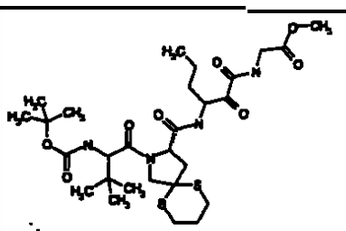
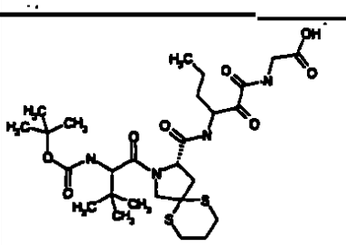
211		811.0398
212		811.0398
213		817.0876
214		817.0876
215		835.1057
216		630.8288
217		616.8018

Table 2

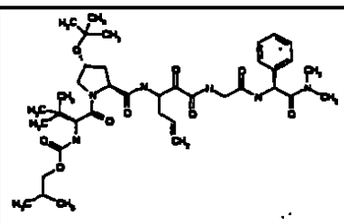
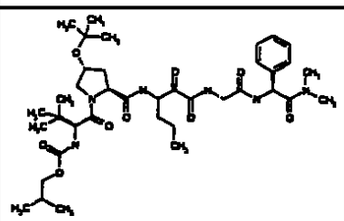
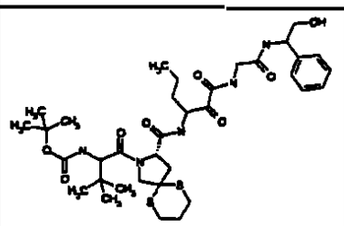
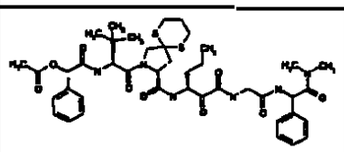
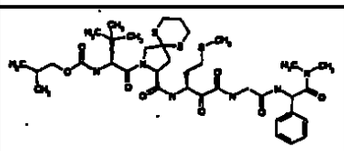
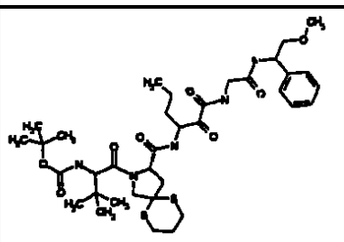
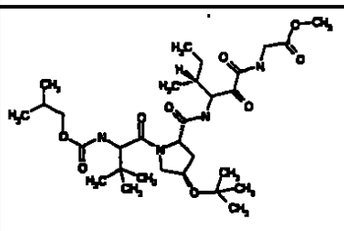
218		742.9208
219		744.9367
220		735.9694
221		853.0774
222		809.0862
223		749.9965
224		612.7703

Table 2

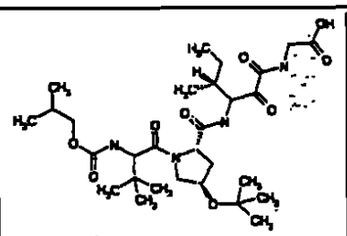
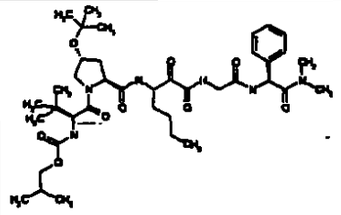
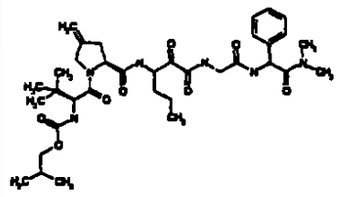
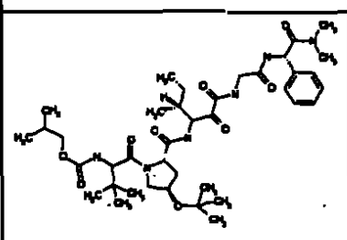
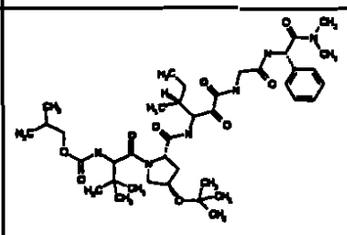
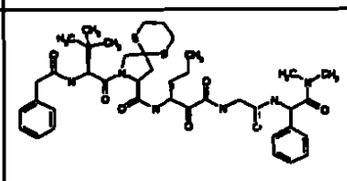
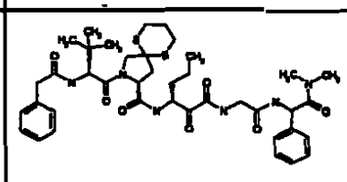
225		598.7432
226		758.9638
227		684.8401
228		758.9638
229		758.9638
230		795.0404
231		795.0404

Table 2

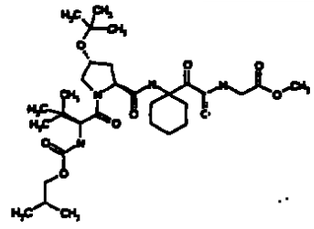
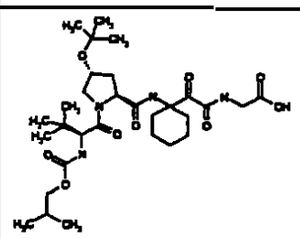
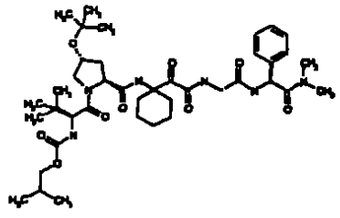
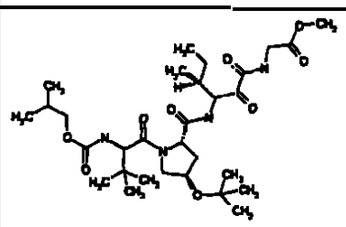
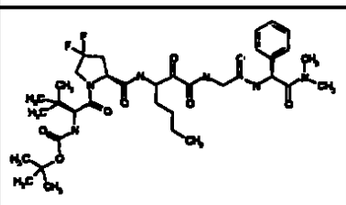
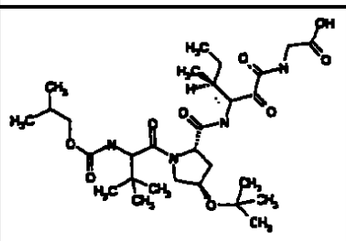
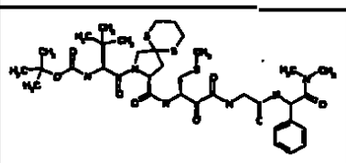
232		624.7815
233		610.7544
234		770.9749
235		612.7703
236		722.8369
237		598.7432
238		795.0592

Table 2

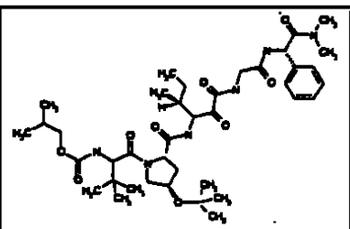
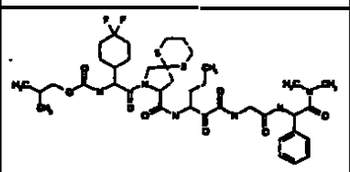
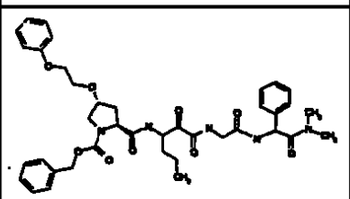
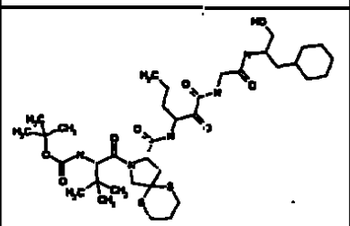
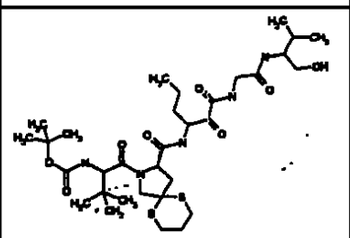
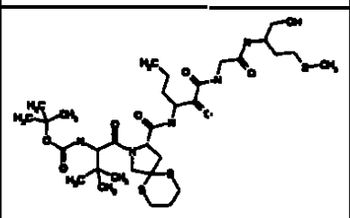
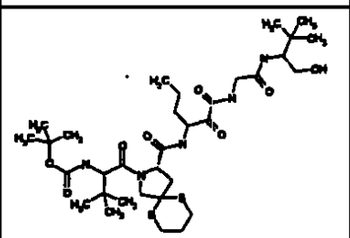
239		758.9638
240		839.0414
241		729.8375
242		756.0443
243		701.9518
244		734.0159
245		715.9789

Table 2

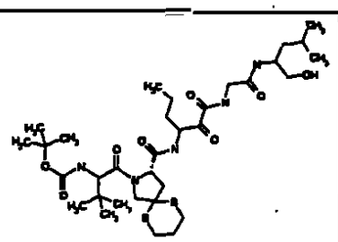
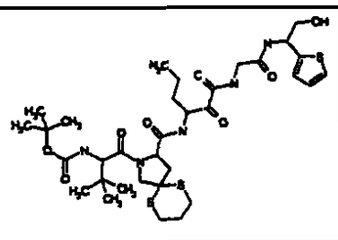
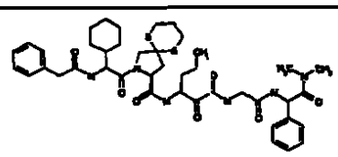
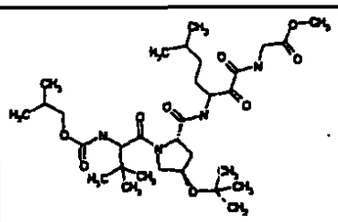
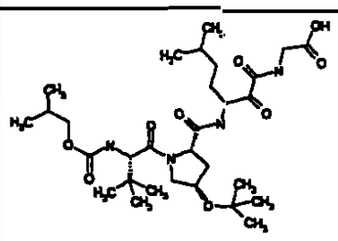
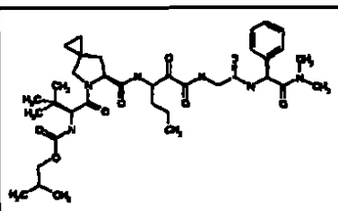
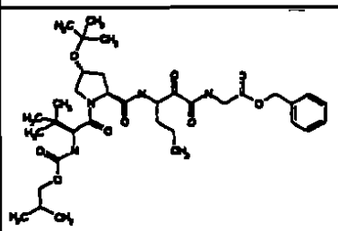
246		715.9789
247		741.9951
248		821.0786
249		626.7974
250		612.7703
251		698.8672
252		674.842

Table 2

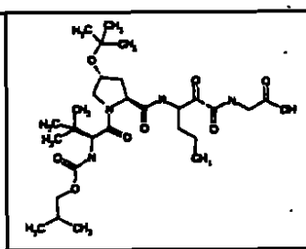
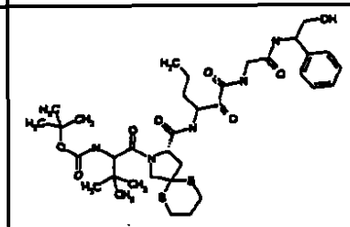
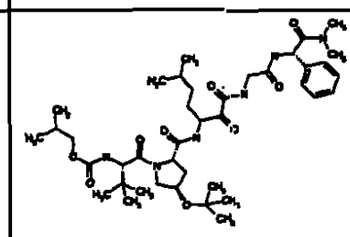
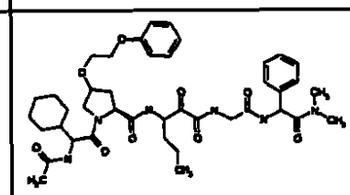
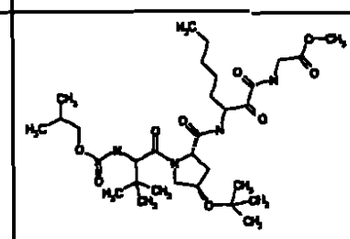
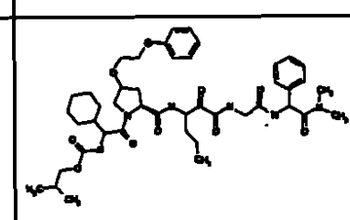
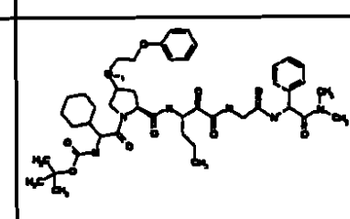
253		584.7162
254		735.9694
255		772.9909
256		776.9383
257		626.7974
258		835.0189
259		835.0189

Table 2

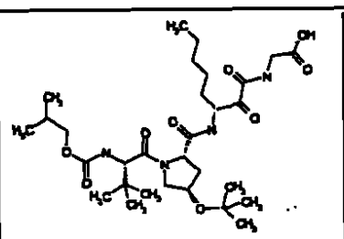
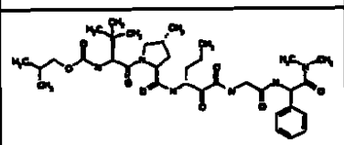
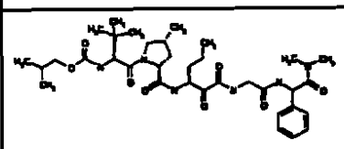
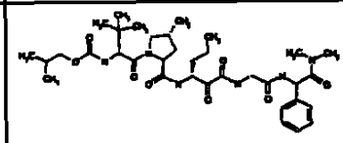
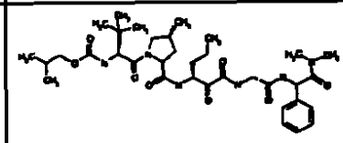
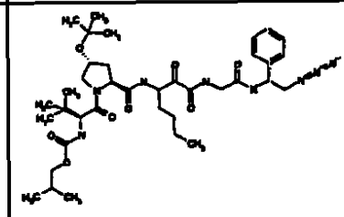
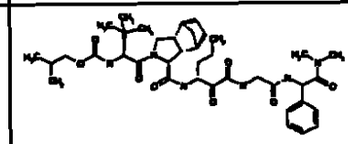
260		612.7703
261		686.856
262		686.856
263		686.856
264		686.856
265		742.9236
266		738.9325

Table 2

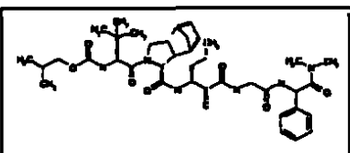
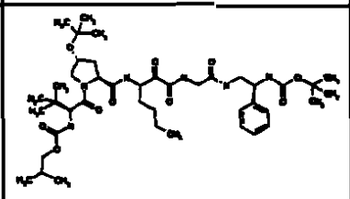
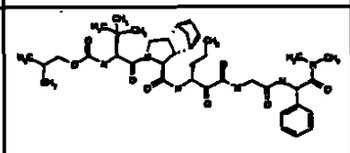
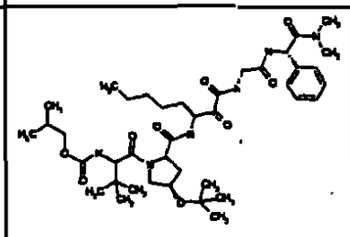
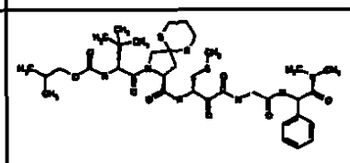
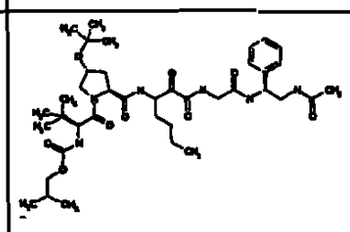
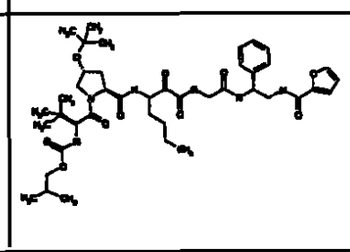
267		738.9325
268		817.0444
269		738.9325
270		772.9909
271		795.0592
272		758.9638
273		810.9966

Table 2

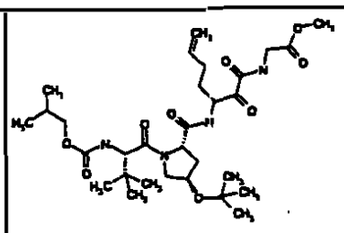
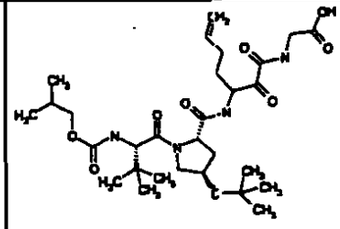
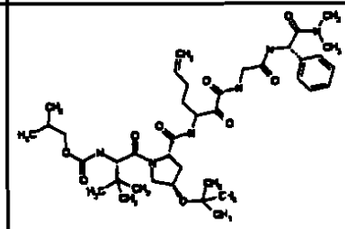
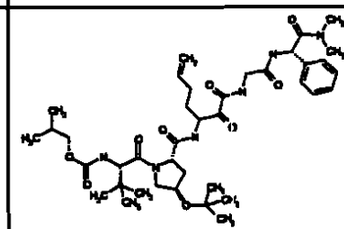
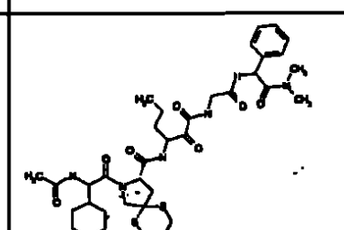
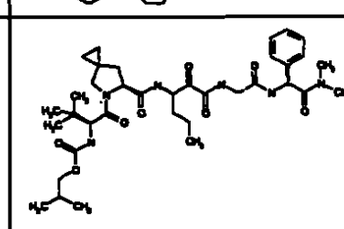
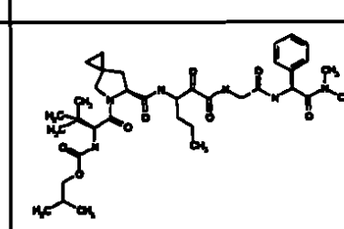
274		610.7544
275		596.7273
276		756.9479
277		756.9479
278		744.9799
279		698.8672
280		698.8672

Table 2

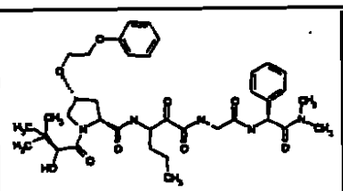
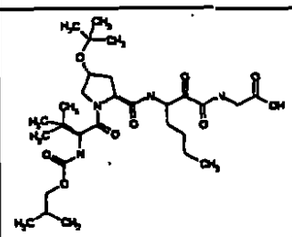
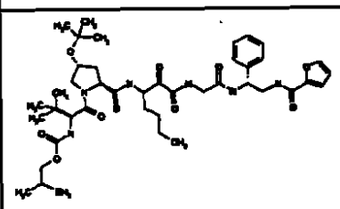
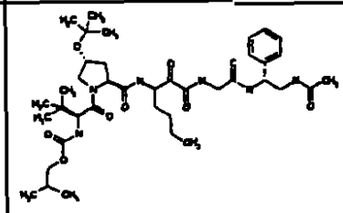
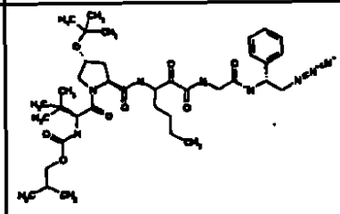
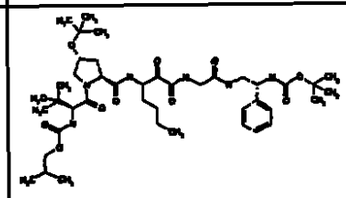
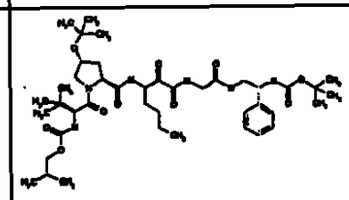
281		709.8471
282		598.7432
283		810.9966
284		758.9638
285		742.9236
286		817.0444
287		817.0444

Table 2

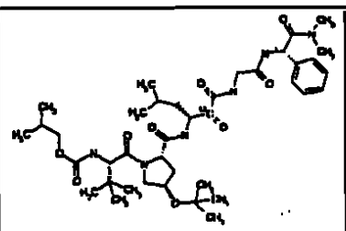
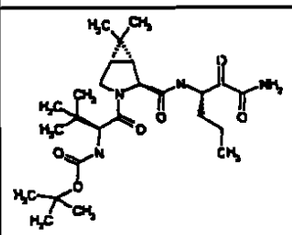
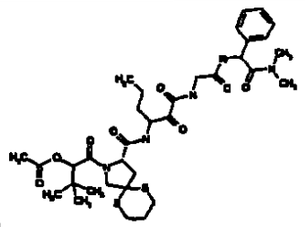
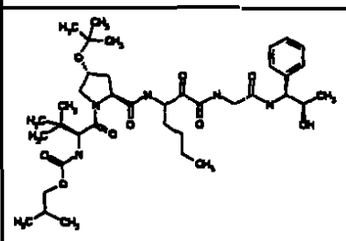
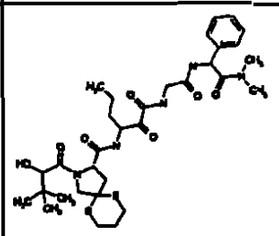
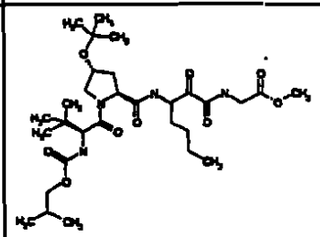
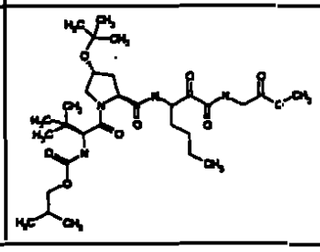
288		759.9526
289		494.6367
290		719.9263
291		731.938
292		677.8887
293		612.7703
294		612.7703

Table 2

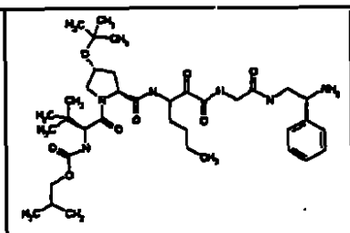
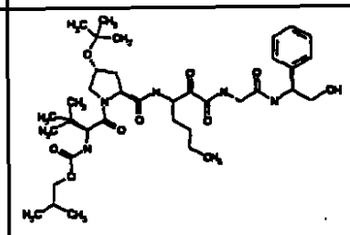
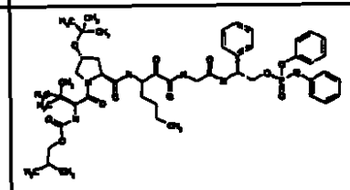
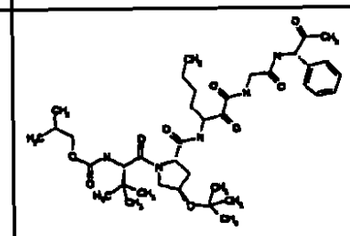
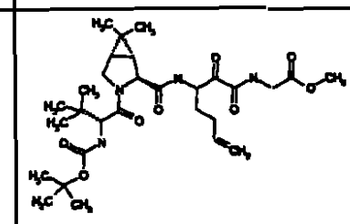
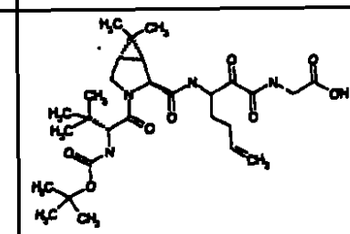
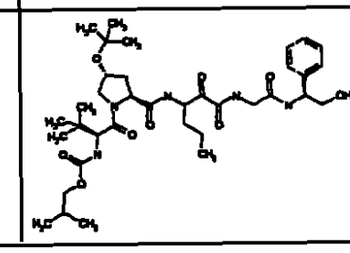
295		716.9261
296		717.9109
297		950.0884
298		729.9221
299		578.712
300		564.6849
301		703.8838

Table 2

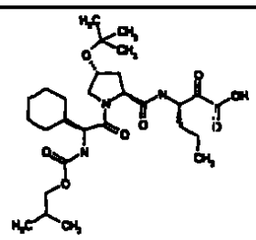
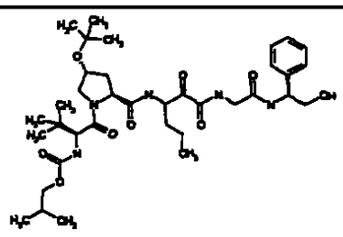
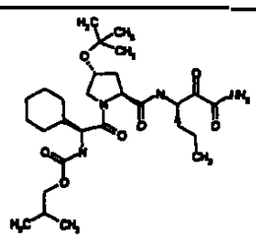
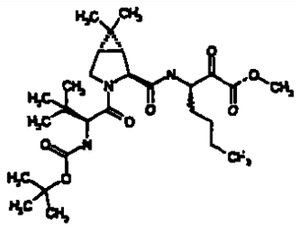
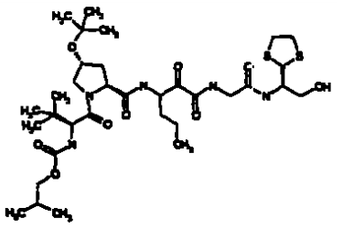
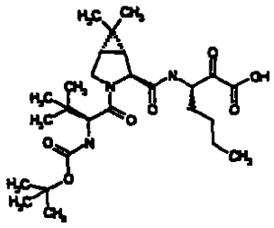
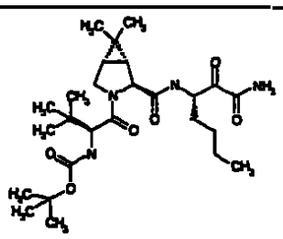
302		553.7021
303		703.8838
304		552.7173
305		523.6756
306		731.9783
307		509.6485
308		508.6638

Table 2

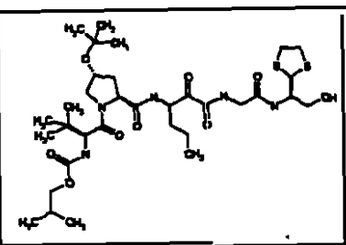
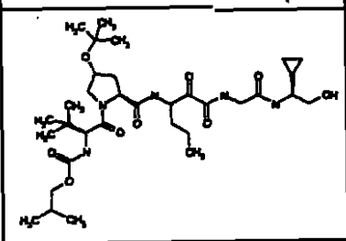
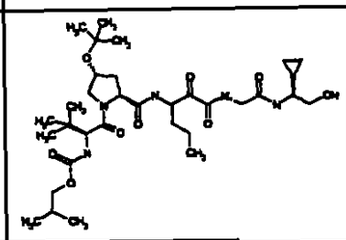
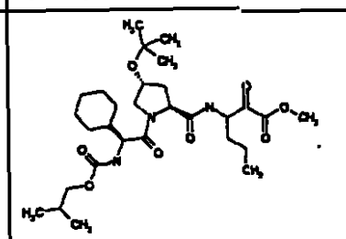
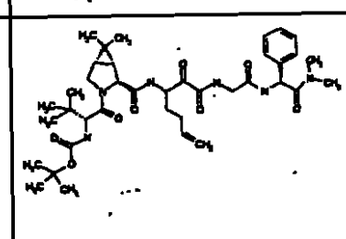
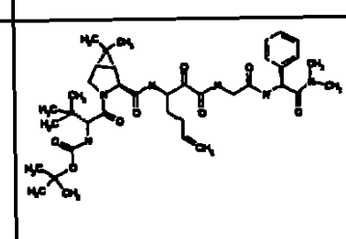
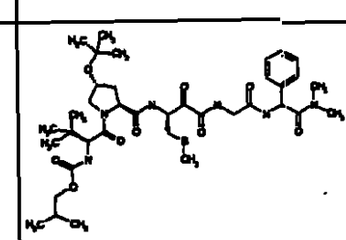
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310		667.8503
311		667.8503
312		567.7292
313		724.9054
314		724.9054
315		762.9736

Table 2

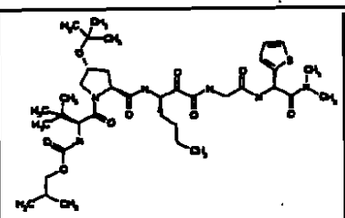
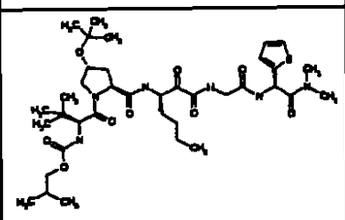
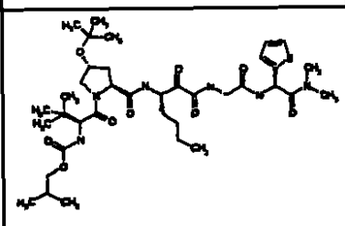
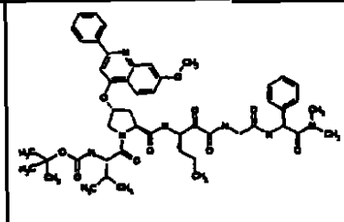
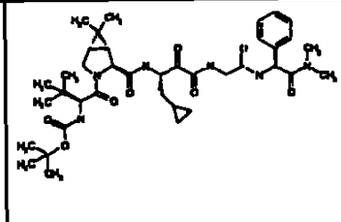
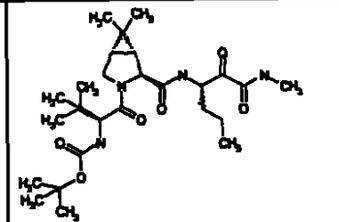
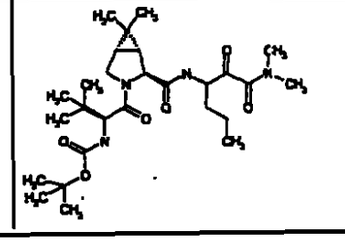
316		764.9896
317		764.9896
318		764.9896
319		908.0734
320		724.9054
321		508.6638
322		522.6909

Table 2

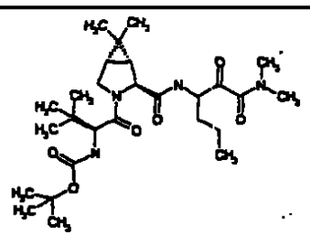
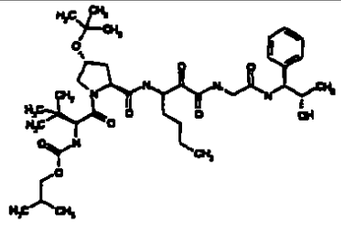
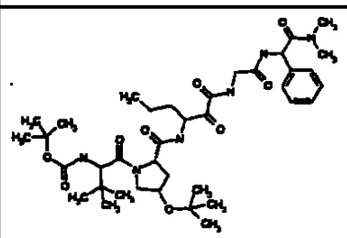
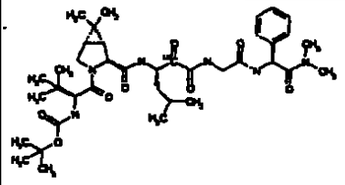
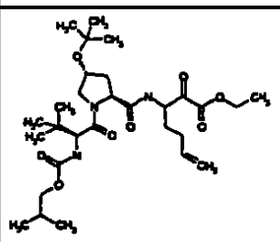
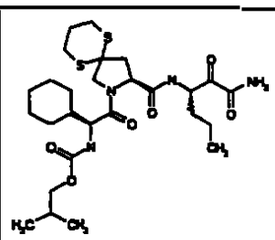
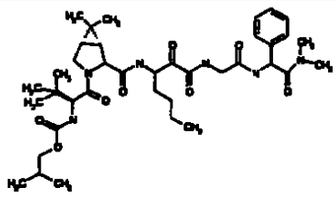
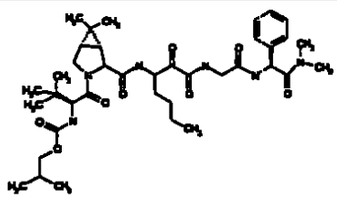
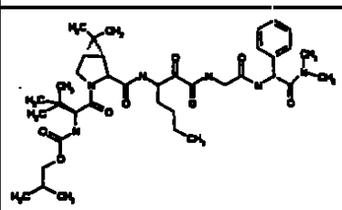
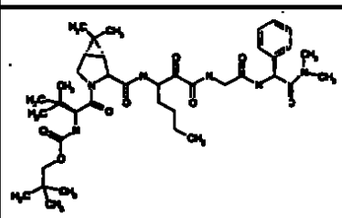
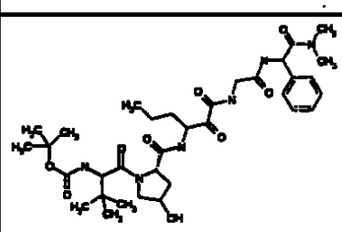
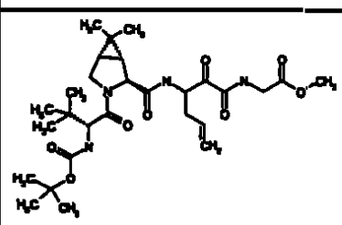
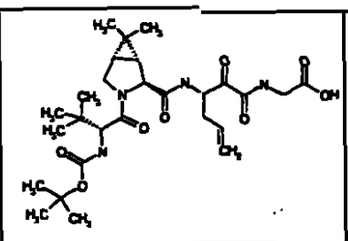
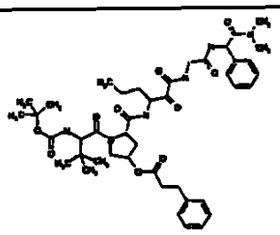
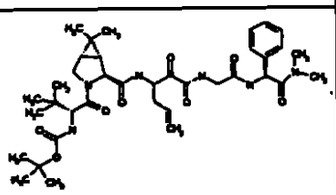
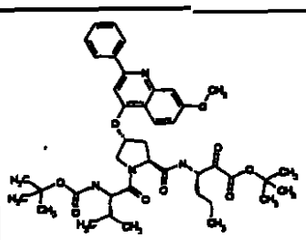
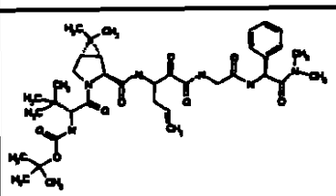
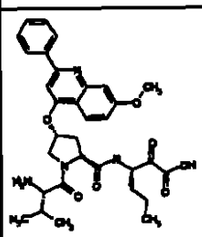
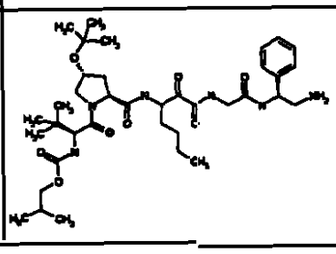
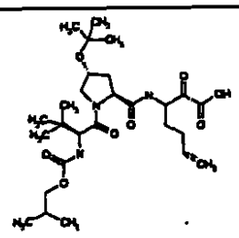
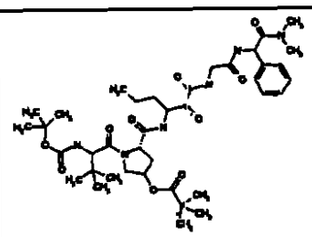
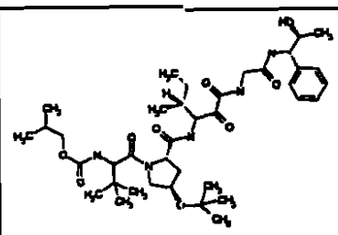
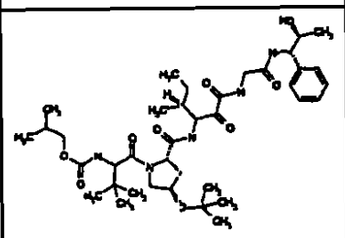
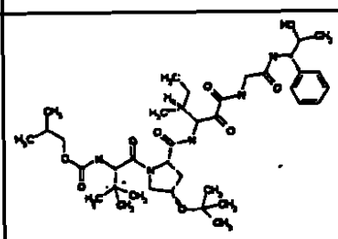
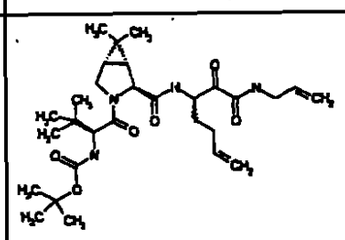
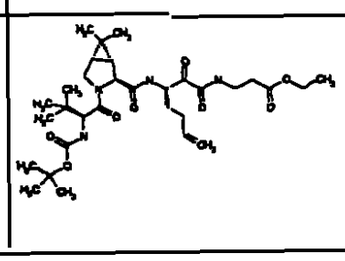
323		522.6909
324		731.938
325		744.9367
326		727.9102
327		567.7292

Table 2

328		584.8029
329		726.9214
330		726.9214
331		726.9214
332		740.9484
333		688.8284
334		564.6849

335		550.6578
336		820.9918
337		710.8784
338		746.9089
339		710.8784
340		590.6823
341		716.9261

342		539.675
343		772.9473
344		731.938
345		731.938
346		731.938
347		546.7132
348		606.7662

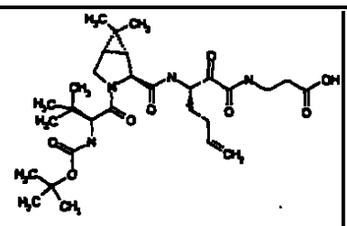
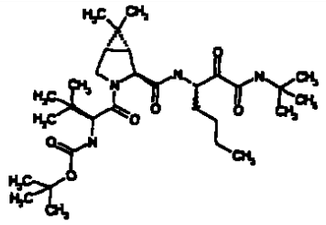
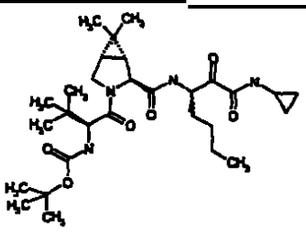
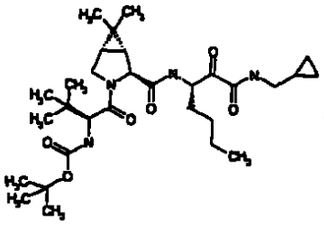
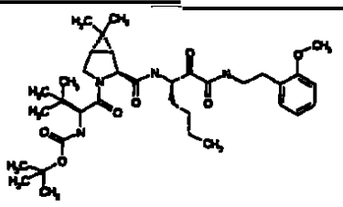
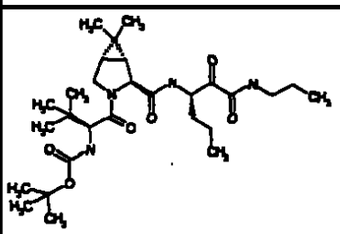
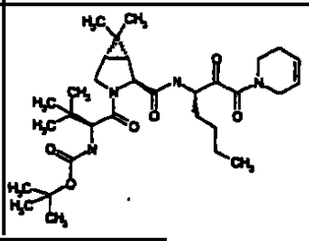
349		578.712
350		564.7722
351		548.7291
352		562.7562
353		642.8432
354		536.718
355		574.7673

Table 2

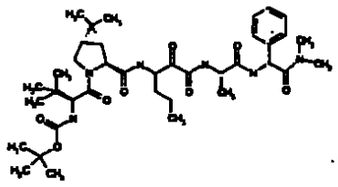
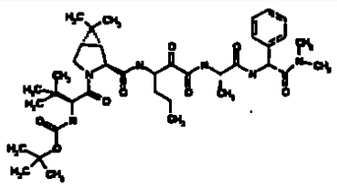
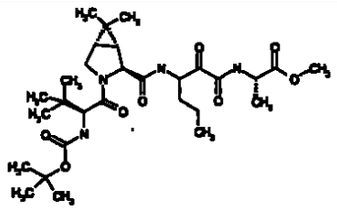
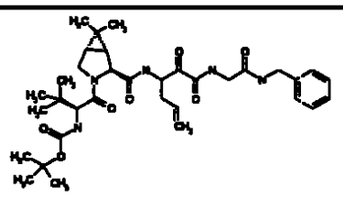
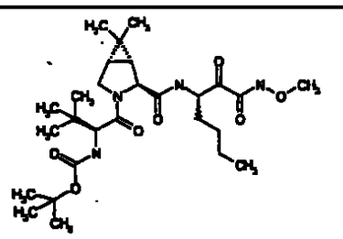
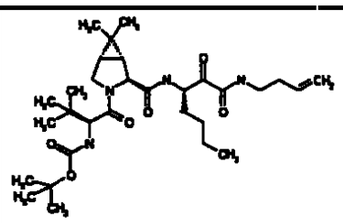
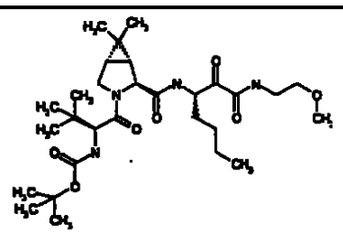
356		726.9214
357		726.9214
358		580.7279
359		639.799
360		538.6902
361		562.7562
362		566.7444

Table 4

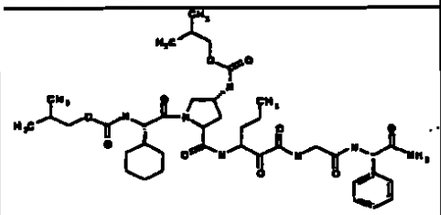
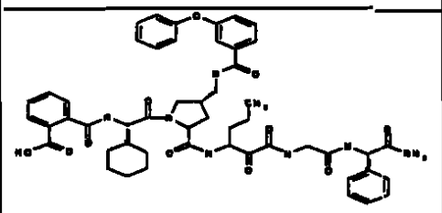
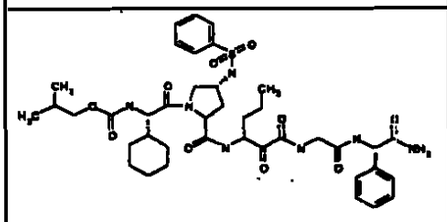
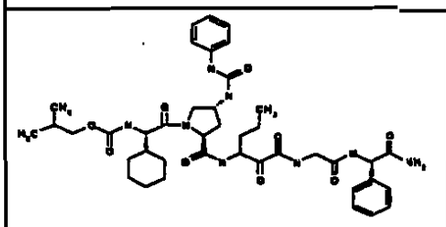
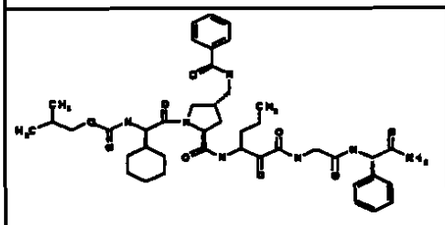
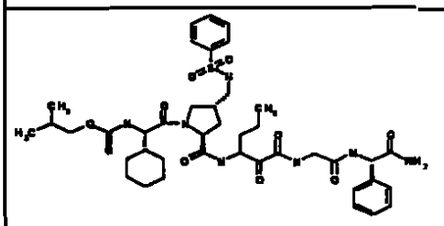
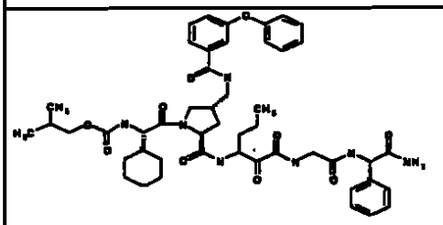
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4t-NHiBoc)-nV-(CO)-G-G(Ph)-Am	A
	(2-CO2)PhCO-G(Chx)-P(4t-MeNHCOPh(3-OPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-NHSO2Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-UreaPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHCOPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHSO2Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHCOPh(3-OPh))-nV-(CO)-G-G(Ph)-Am	B

Table 4

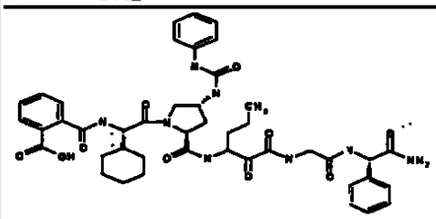
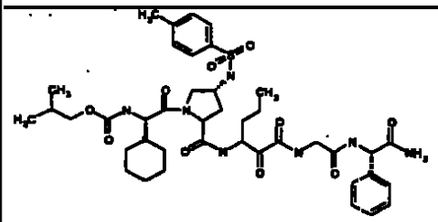
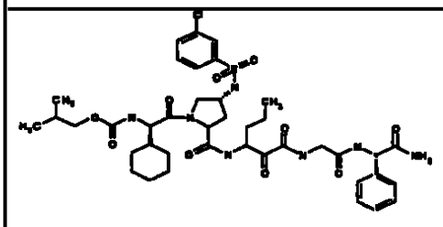
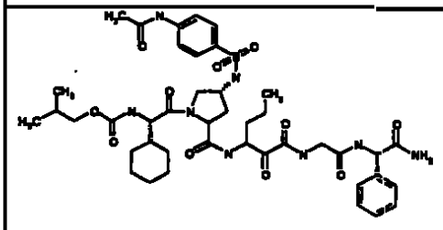
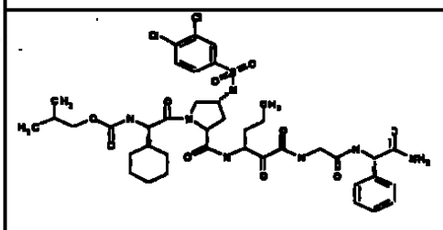
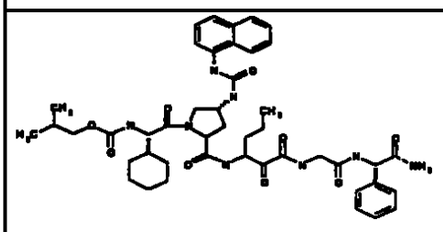
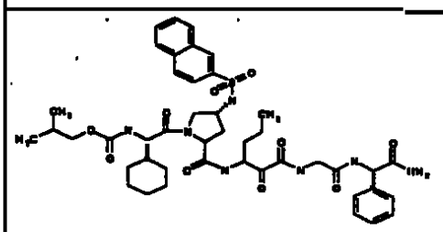
STRUCTURE	NAME	Ki* Range
	(2-CO2)PhCO-G(chx)-P(4t-UreaPh)-nV-(CO)-G-G(ph)-Am	C
	iBoc-G(Chx)-P(4t-NHSO2-(4Me)Ph)-nV(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-(3Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-(4-NHAc)Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-NHSO2-(3,4-diCl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-1-Np)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-2-Np)-nV-(CO)-G-G(Ph)-Am	B

Table 4

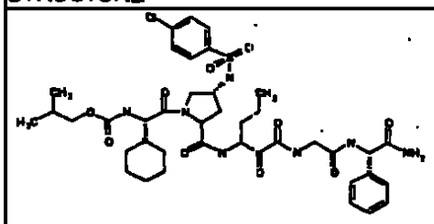
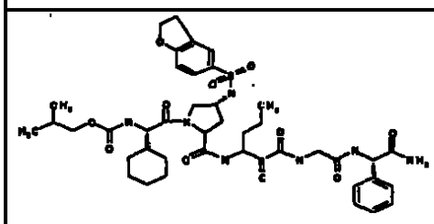
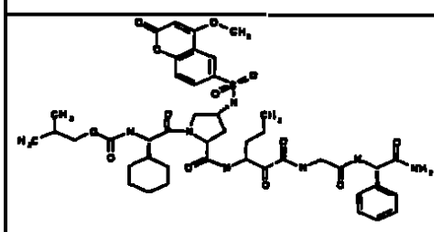
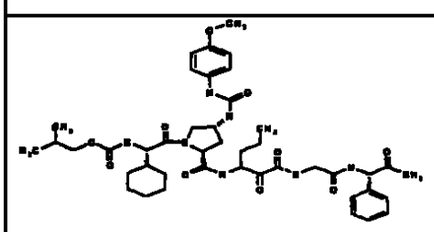
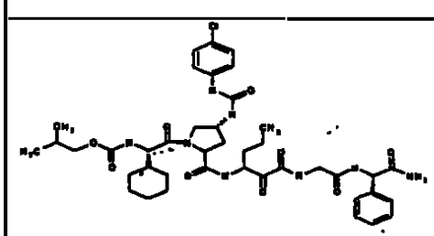
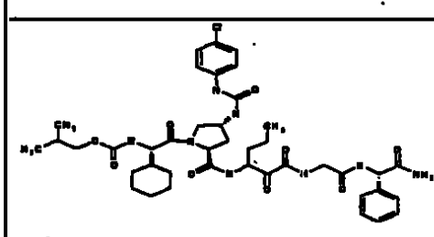
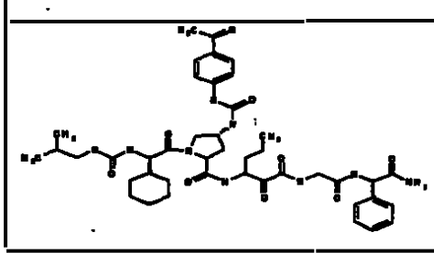
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4t-NHSO2-(4Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-5(2,3-dihydrobenzofuran))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-6(4-OMe)Courmarin)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-Ph(4-OMe))-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Cl))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Cl))-nV-(CO)-G-G(Ph)-Am	C
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Ac))-nV-(CO)-G-G(Ph)-Am	B

Table 4

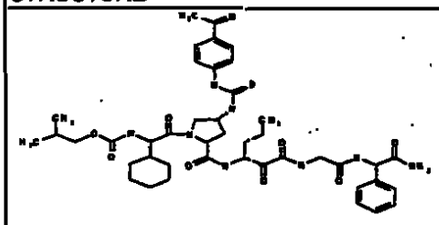
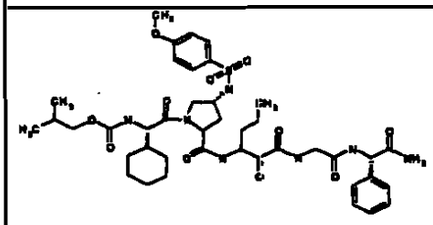
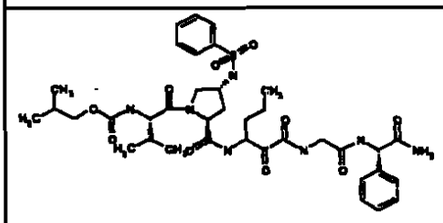
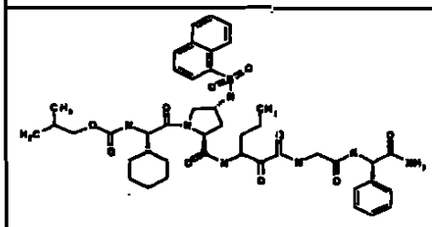
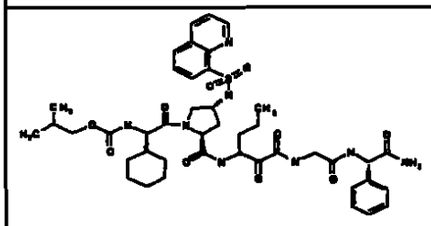
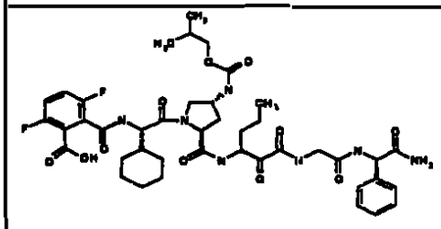
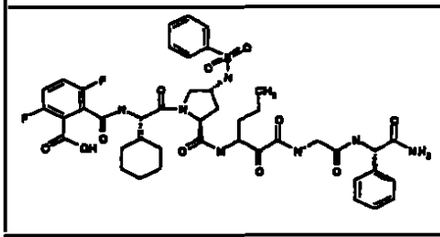
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Ac))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-Ph(4-OMe))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-V-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-1Np)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-8-Quinoline)-nV-(CO)-G-G(Ph)-Am	B
	(2,5-diF-6-CO2)PhCO-G(Chx)-P(4t-NH-iBoc)-nV-(CO)-G-G(Ph)-Am	A
	(2,5-diF-6-CO2)PhCO-G(Chx)-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	A

Table 4

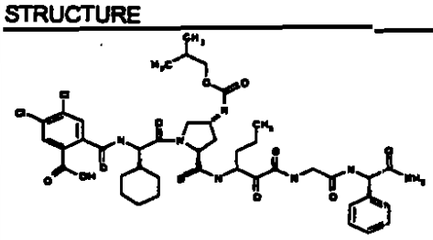
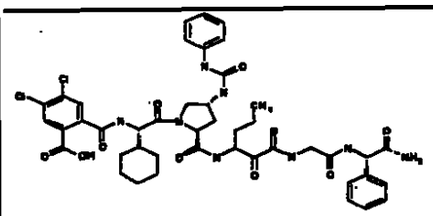
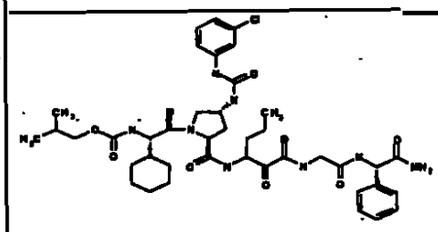
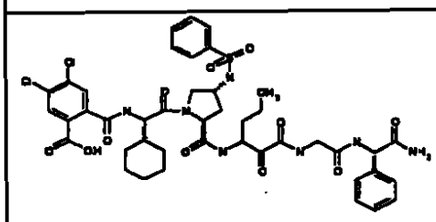
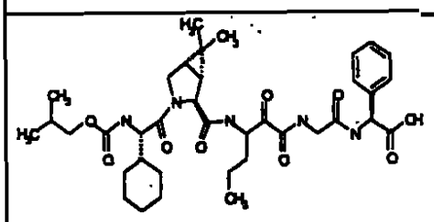
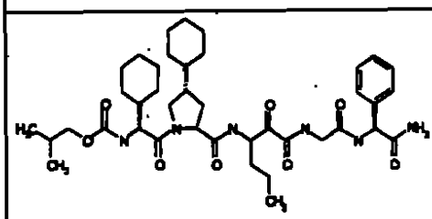
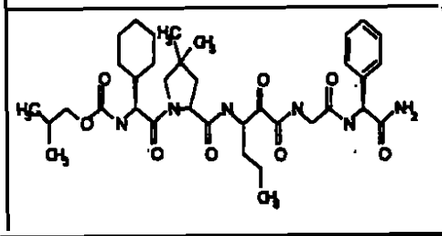
STRUCTURE	NAME	Kᵢ* Range
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-NH-iBoc)-nV-(CO)-G-G(Ph)-Am	A
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-UreaPh)-nV(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-Urea-(3-Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(3,4 iPr)-nV-(CO)-G-G(Ph)-OH	A
	iBoc-G(Chx)-P(4t-Chx)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4-diMe)-nV-(CO)-G-G(Ph)-Am	A

Table 4

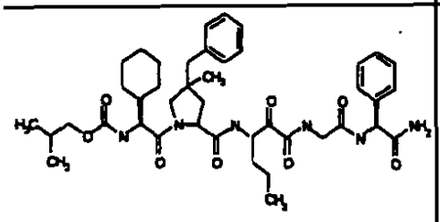
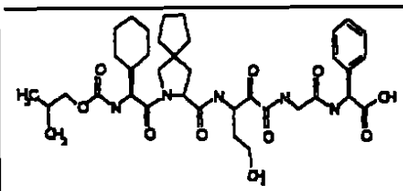
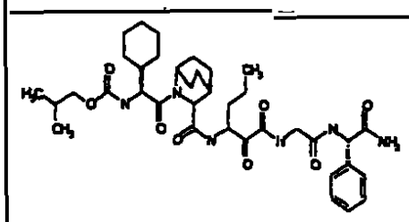
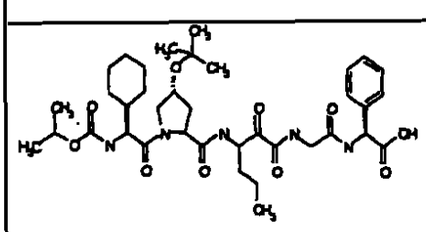
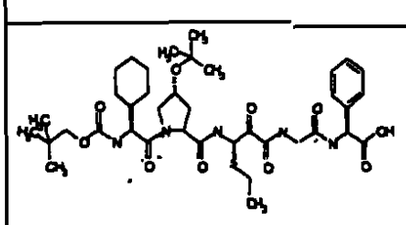
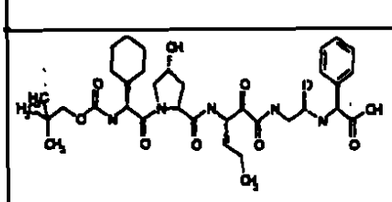
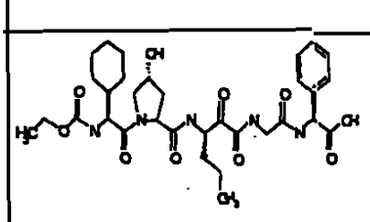
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4-Bn,4-Me)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4-spirocyclopentane)-nV-(CO)-G-G(Ph)-OH	A
	iBoc-G(Chx)-2-Azabicyclo[2.2.2]octane-3-CO-nV-(CO)-G-G(Ph)-Am	B
	iPrOCO-G(Chx)-P(4-OtBu)-nV-(CO)-G-G(Ph)-OH	A
	Neopentoxy(CO)-G(Chx)-P(4-OtBu)-nV- (CO)-G-G(Ph)-OH	B
	Neopentoxy(CO)-G(Chx)-P(OH)-nV-(CO)-G- G(Ph)-OH	B
	Ethoxy(CO)-G(Chx)-P(OH)-nV-(CO)-G- G(Ph)-OH	B

Table 4

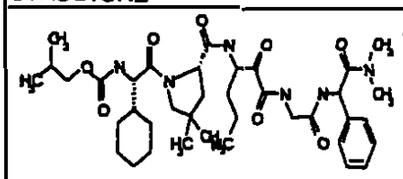
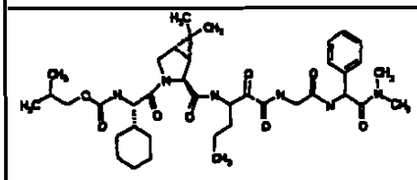
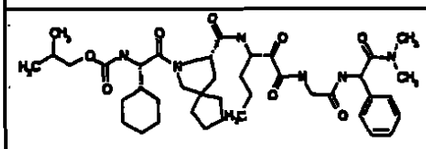
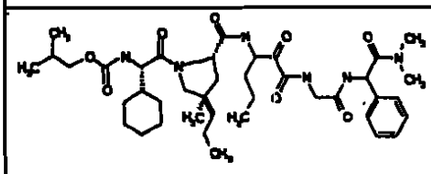
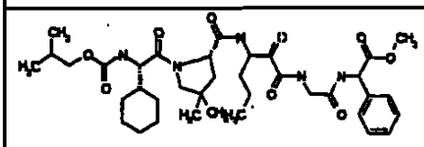
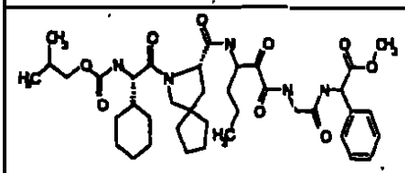
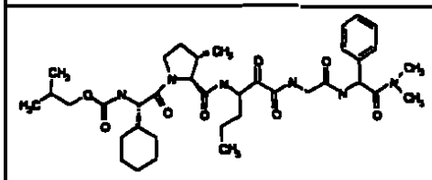
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4,4 diMe)-nV-(CO)- G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4 iPr)-nV-(CO)- G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4-spirocyclopentane)- nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4c-Me,4t-Pr)- nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4,4 diMe)-nV-(CO)- G-G(Ph)-OMe	A
	iBoc-G(Chx)-P(4-spirocyclopentane)- nV-(CO)-G-G(Ph)-OMe	A
	iBoc-G(Chx)-P(3t-Me)-nV-(CO)- G-G(Ph)-N(Me)2	A

Table 4

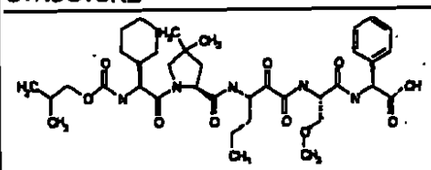
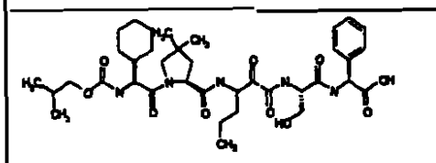
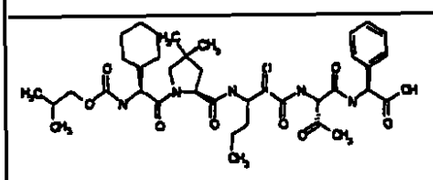
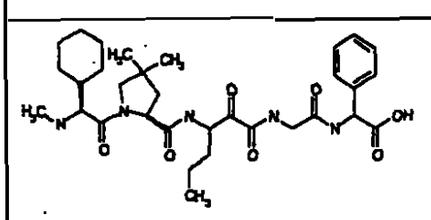
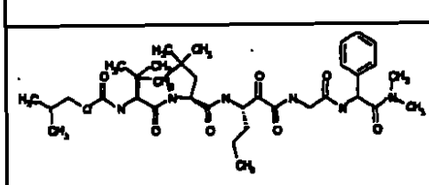
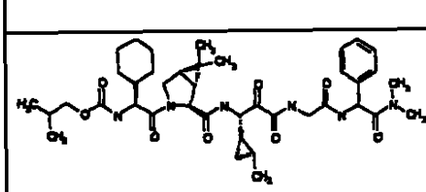
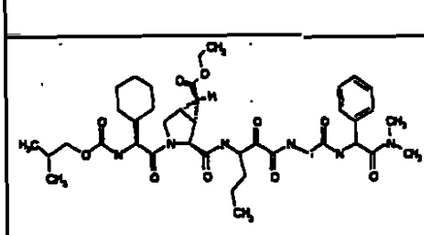
STRUCTURE	NAME	KI* Range
	iBoc-G(Chx)-P(4,4 diMe)-nV-(CO)-S(Me)-G(Ph)-OH	A
	iBoc-G(Chx)-P(4,4 diMe)-nV-(CO)-S-G(Ph)-OH	B
	iBoc-G(Chx)-P(4,4 diMe)-nV-(CO)-G(Ac)-G(Ph)-OH	C
	N-Me-G(Chx)-P(4,4-diMe)-nV-(CO)-G- G(Ph)-CO2H	C
	iBoc-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4 (diMe-cyclopropyl))-G((S,S)-Me-cyclopropyl)-(CO)-G-G(Ph)-N(Me)	A
	iBoc-G(Chx)-P(6S-CEM)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

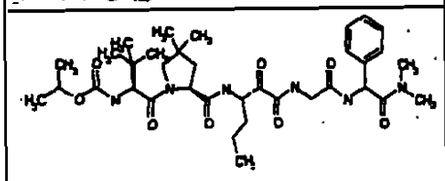
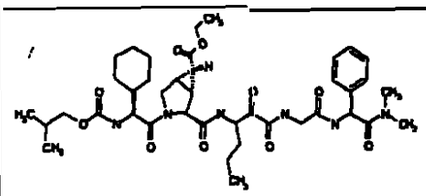
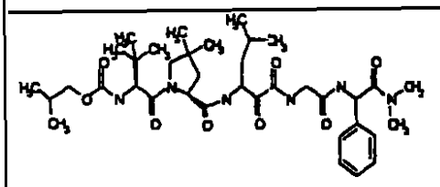
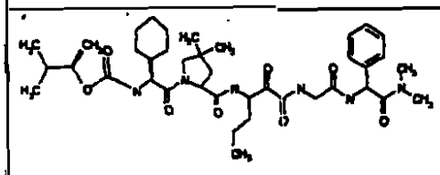
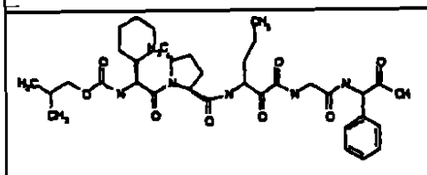
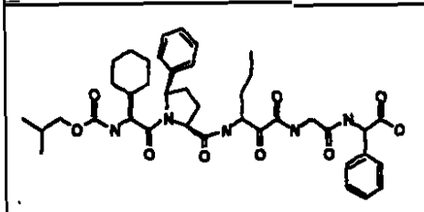
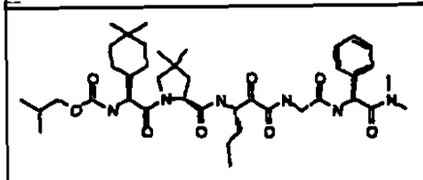
STRUCTURE	NAME	Ki* Range
	iPoc-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(6R-CEM)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(4,4-diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me-iBoc)-G(Chx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(5-c/t-Me)-nV-(CO)-G-G(Ph)-CO2H	A
	iBoc-G(Chx)-P(5-cis-Ph)-nV-(CO)-G-G(Ph)-CO2H	B
	iBoc-G(4,4-diMeChx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

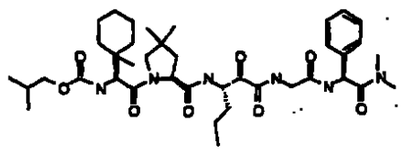
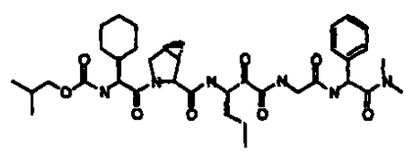
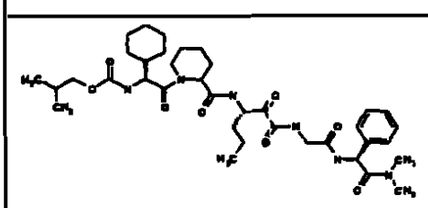
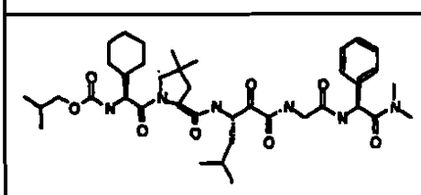
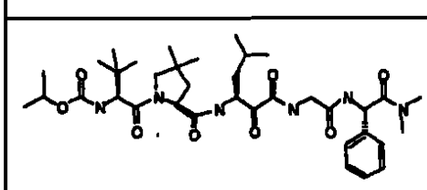
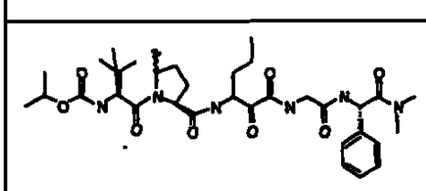
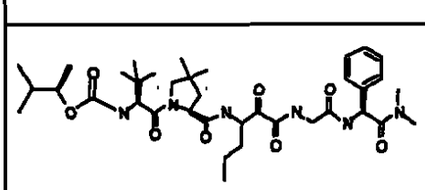
STRUCTURE	NAME	Ki* Range
	iBoc-G(1-MeChx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4 CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-Chg-Pip-nV-(CO)-G-G(Ph)-N(Me)2	C
	iBoc-G(Chx)-P(4,4 diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(4,4-diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(5-c/t-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me-iBoc)-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

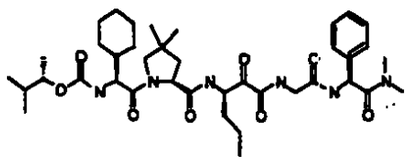
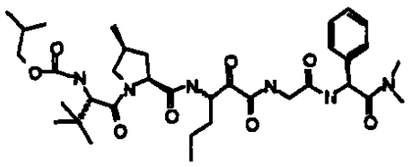
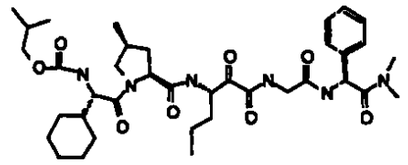
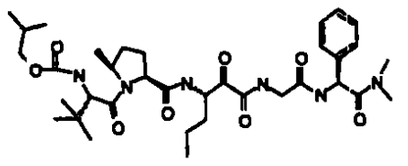
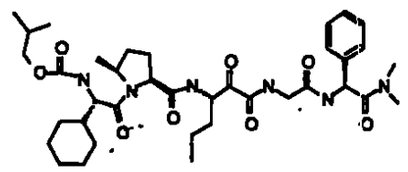
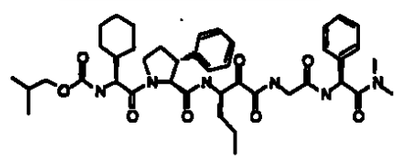
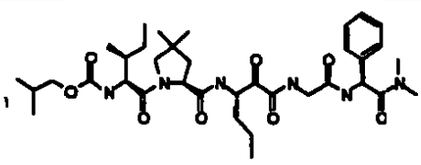
STRUCTURE	NAME	KI* Range
	(S)-1-MeiBoc-G(Chx)-P(4,4-dIMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(4-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(5-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(5-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(t-3Ph)-nV-(CO)-G-G(Ph)-N(Me)2	B
	iBoc-allo(Ile)-P(4,4-dIMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

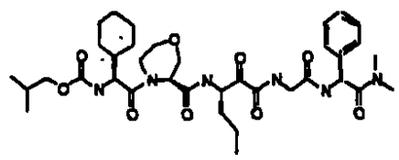
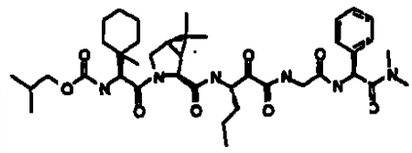
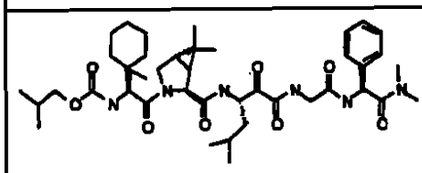
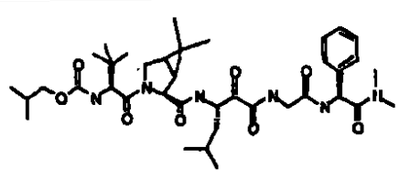
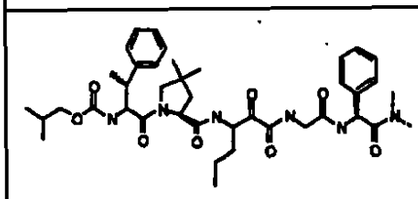
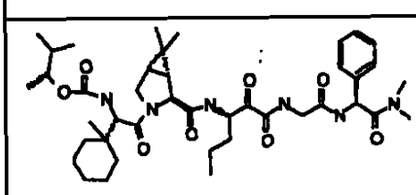
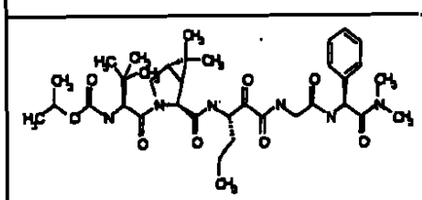
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-Pip(4-morpholino)-nV-(CO)-G-G(Ph)-N(Me)2	B
	iBoc-G(1-MeChx)-P[3,4-(diMe-cyclopropyl)]-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(1-MeChx)-P[3,4-(diMe-cyclopropyl)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P[3,4-(diMe-cyclopropyl)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-erythro-D,L-F(beta-Me)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(1-MeChx)-P[3,4-(diMe-cyclorpropyl)]-nV-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P[3,4-(diMe-cyclopropyl)]-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

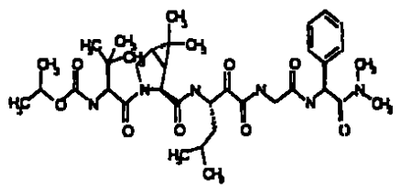
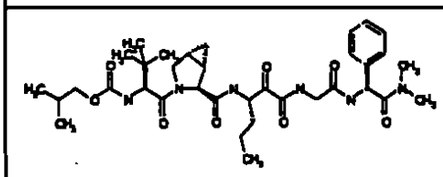
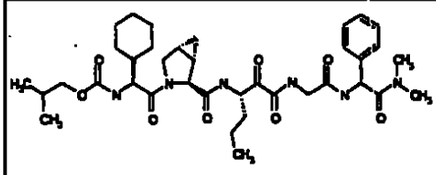
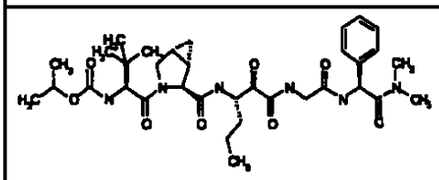
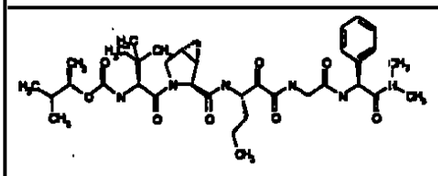
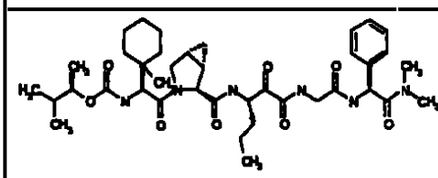
STRUCTURE	NAME	Ki* Range
	iPoc-G(tBu)-P[3,4-(diMe-cyclopropyl)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(1-MeChx)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 5

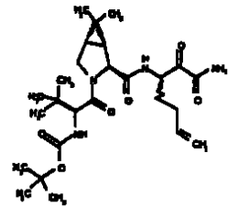
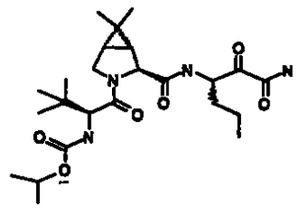
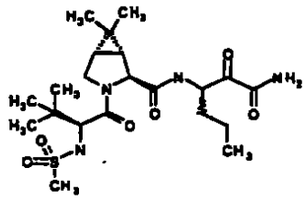
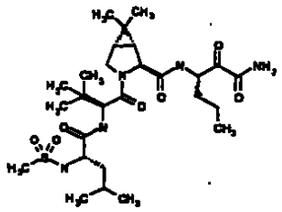
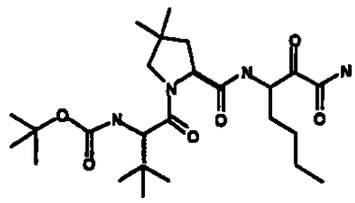
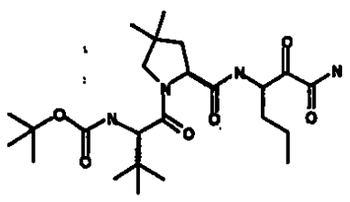
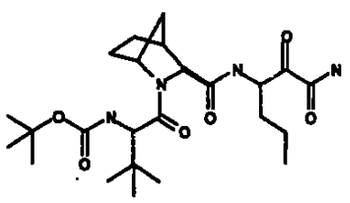
Structure	MW	KI* range
	507	B
	481	B
	473	C
	586	B
	497	C
	483	C
	481	C

Table 5

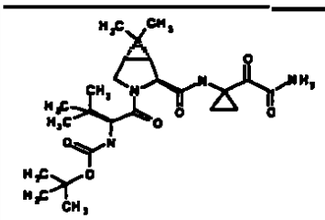
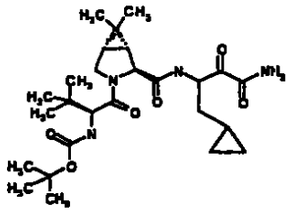
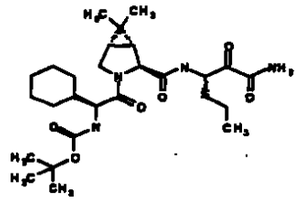
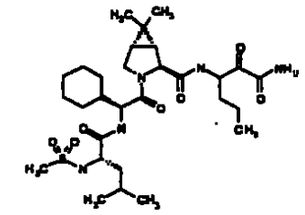
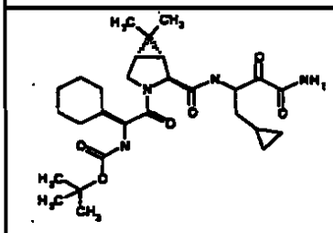
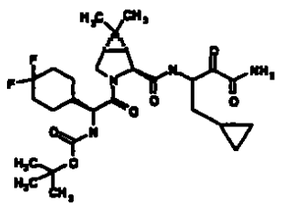
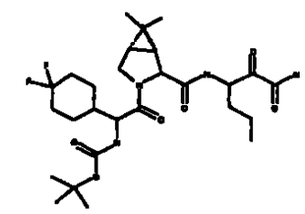
	479	B
	507	A
	521	A
	612	A
	533	A
	569	A
	557	B

Table 5

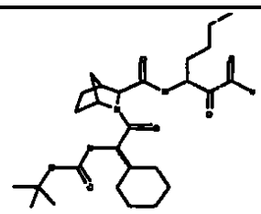
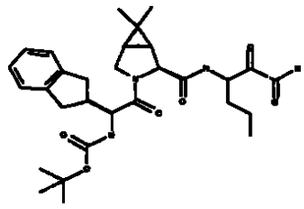
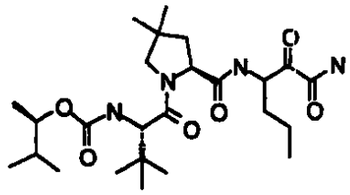
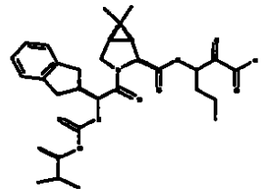
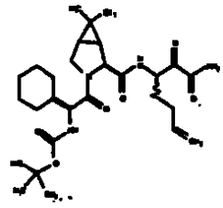
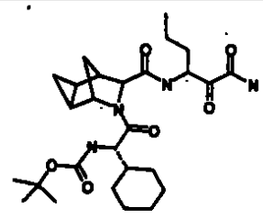
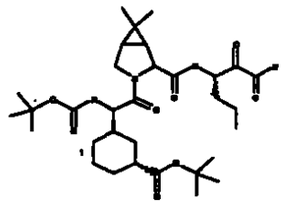
	521	C
	555	A
	497	C
	569	B
	533	B
	519	C
	621	B

Table 5

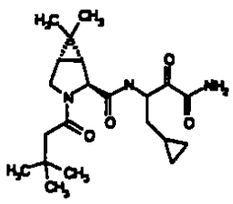
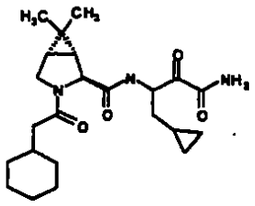
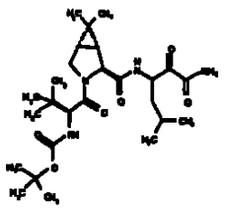
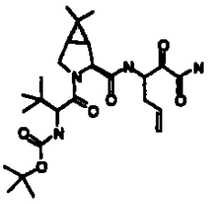
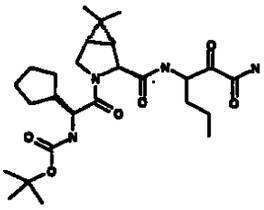
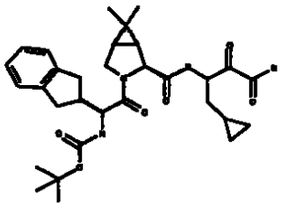
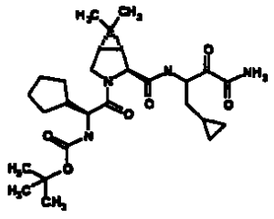
	392	C
	418	C
	509	B
	493	C
	507	B
	567	A
	519	A

Table 5

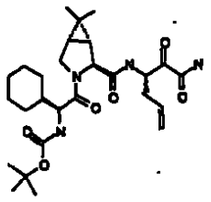
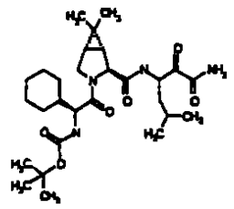
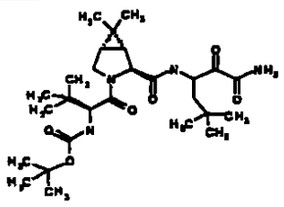
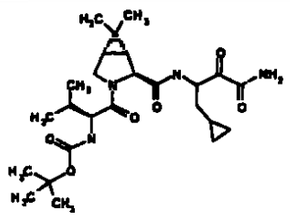
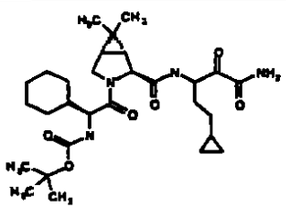
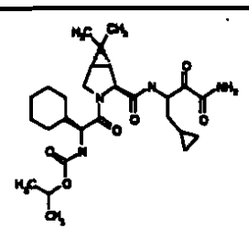
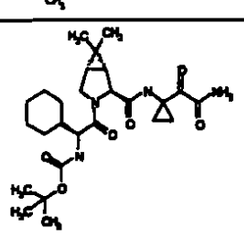
	519	B
	535	B
	523	C
	493	B
	547	B
	519	A
	505	C

Table 5

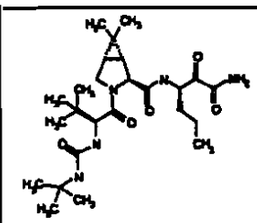
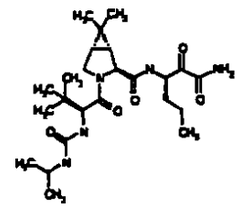
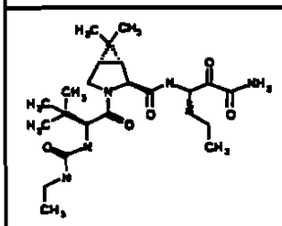
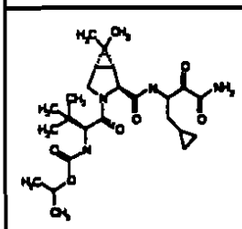
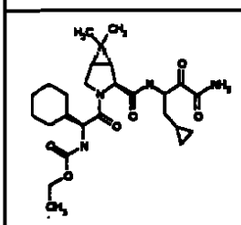
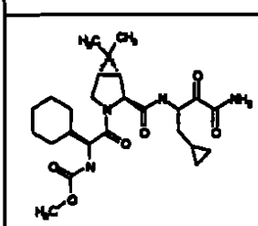
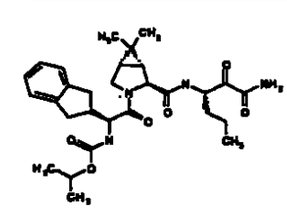
	494	B
	480	B
	466	C
	493	B
	505	B
	491	B
	541	B

Table 5

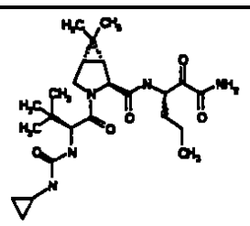
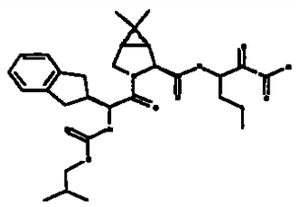
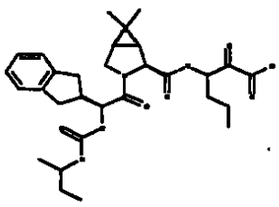
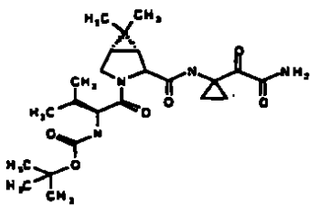
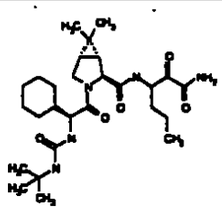
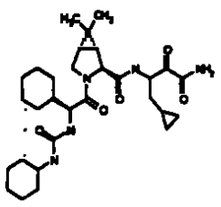
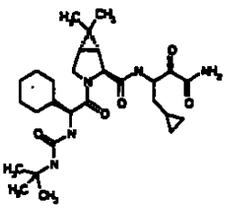
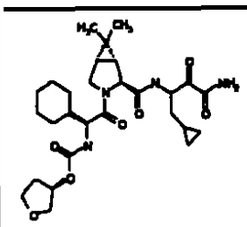
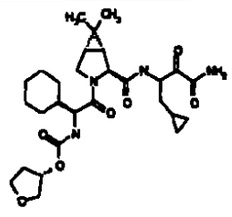
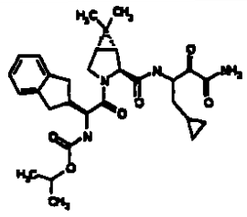
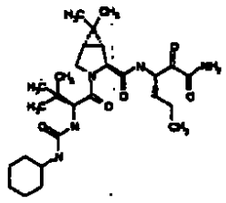
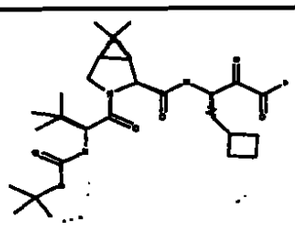
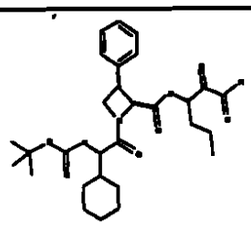
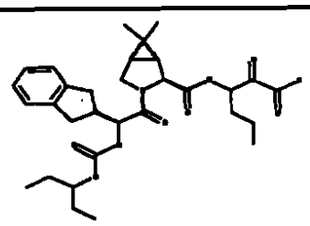
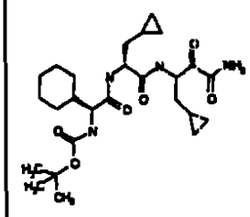
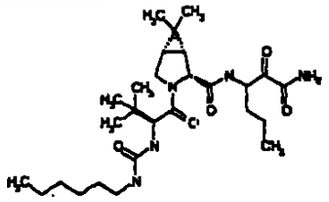
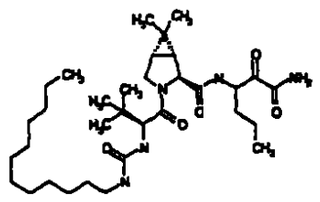
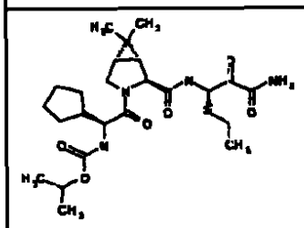
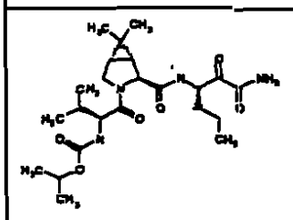
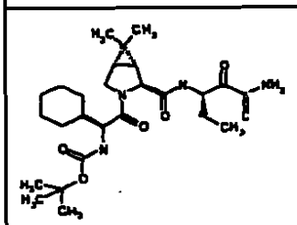
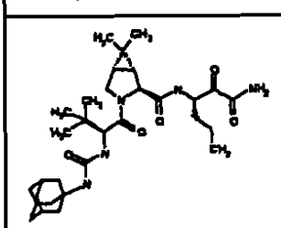
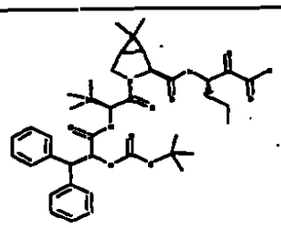
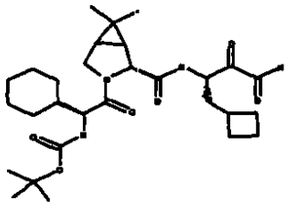
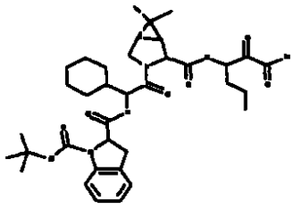
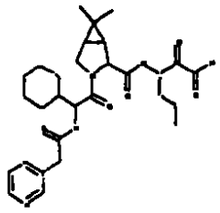
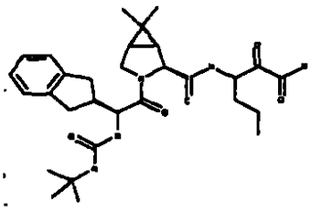
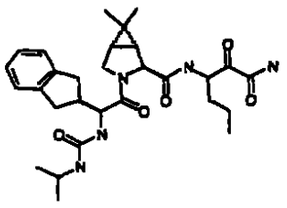
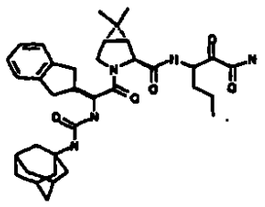
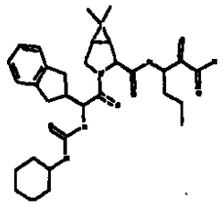
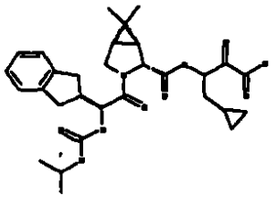
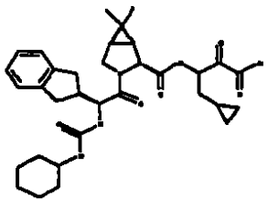
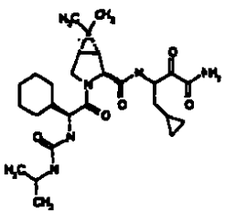
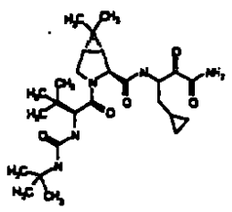
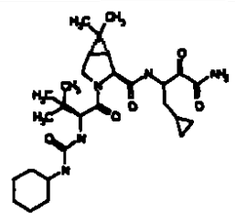
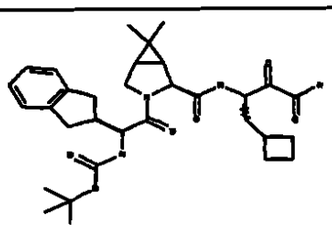
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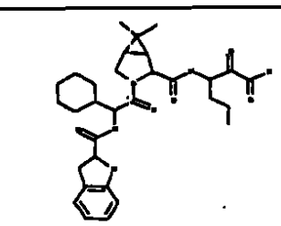
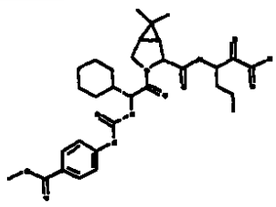
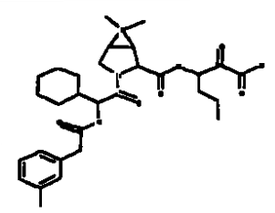
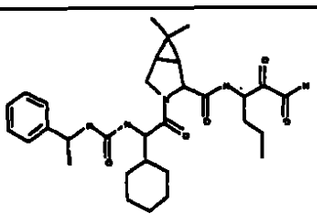
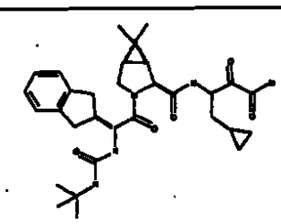
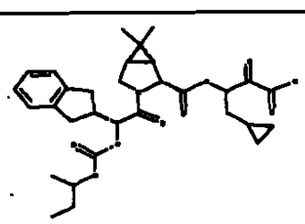
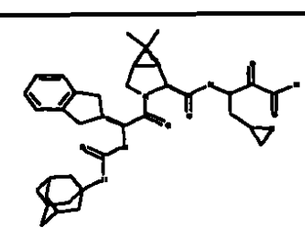
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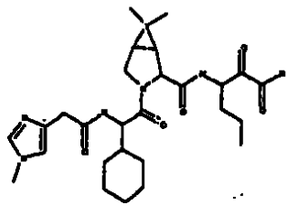
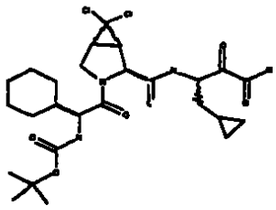
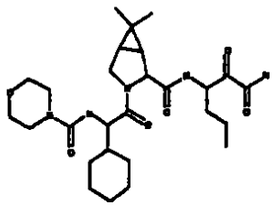
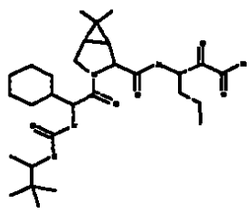
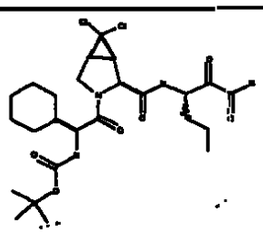
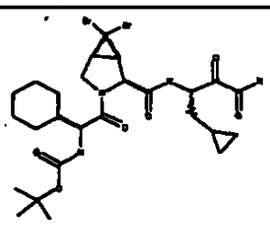
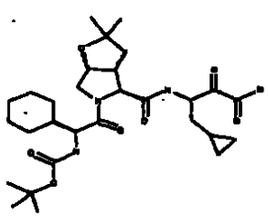
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	569	B

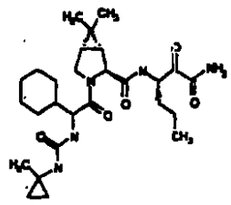
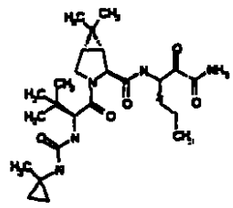
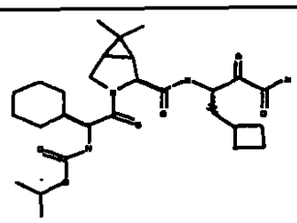
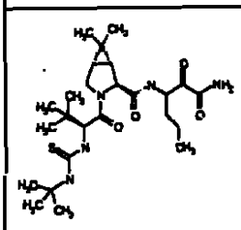
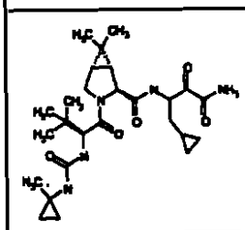
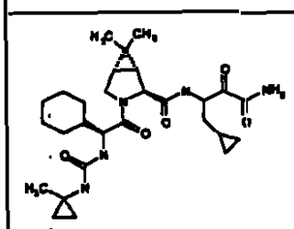
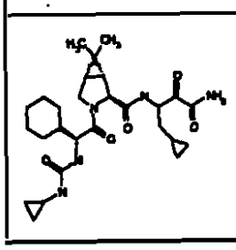
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	572	A

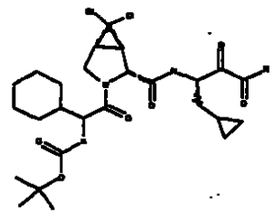
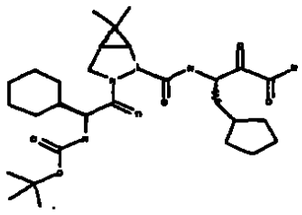
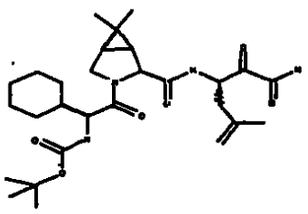
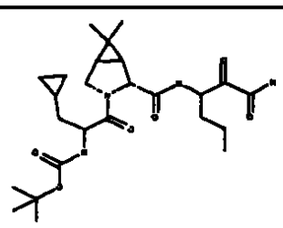
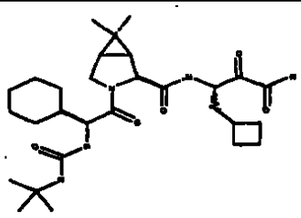
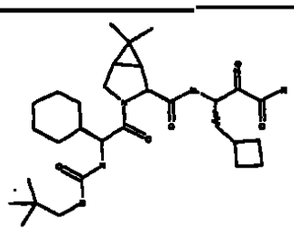
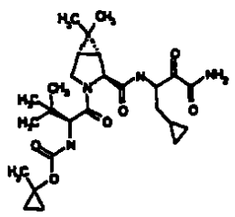
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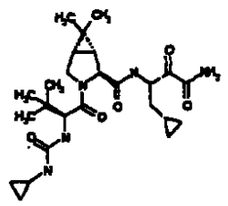
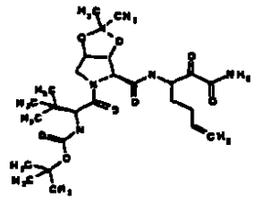
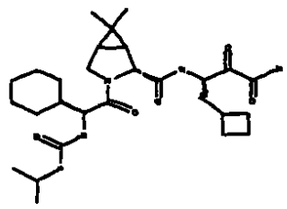
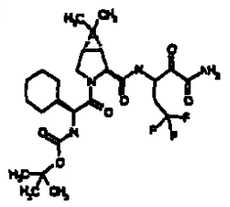
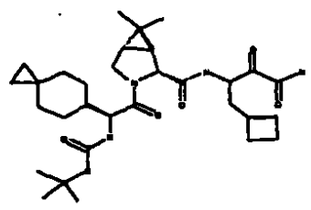
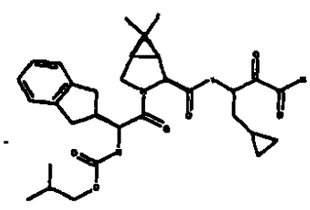
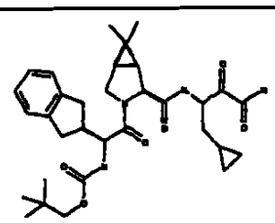
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	581	B

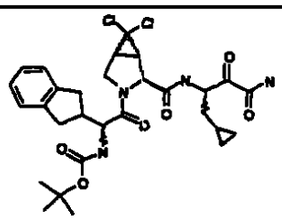
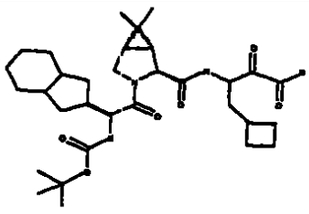
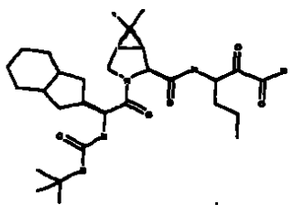
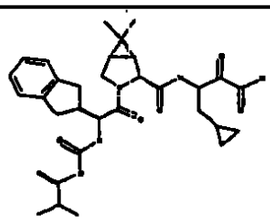
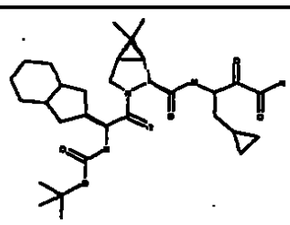
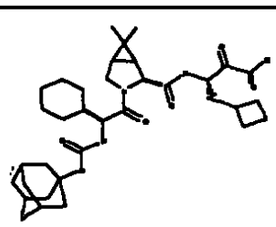
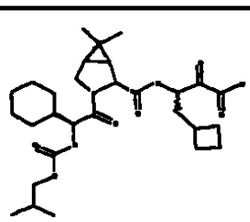
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	553	B
	568	B
	568	A
	566	A
	644	A

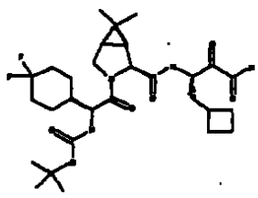
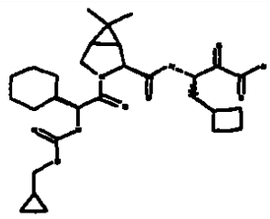
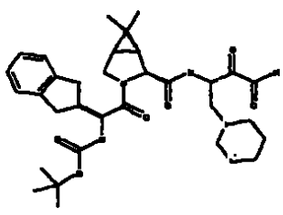
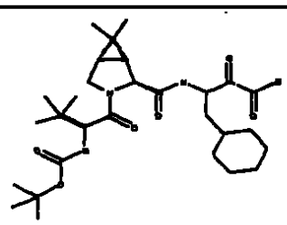
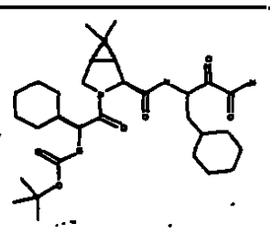
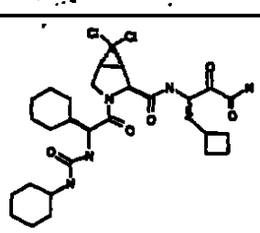
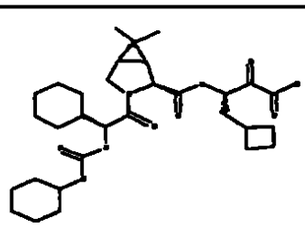
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	534	C
	549	B
	562	A
	682	A
	583	B

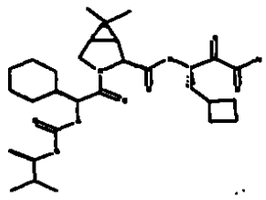
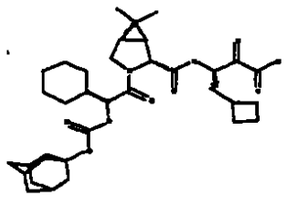
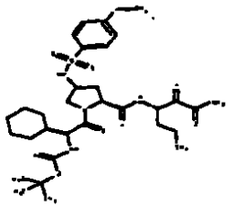
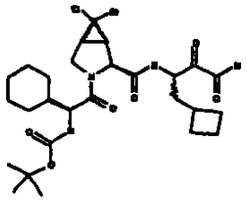
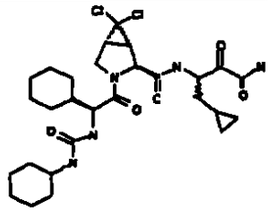
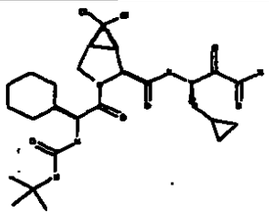
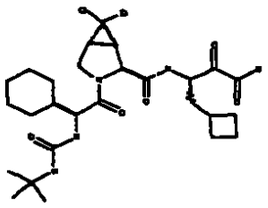
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	492	B
	533	A
	510	C
	504	A
	530	B
	516	B

	574	B
	561	B
	533	B
	493	C
	546	A
	561	A
	505	B

	490	B
	539	C
	532	A
	561	A
	573	A
	567	A
	581	A

	608	A
	587	B
	561	B
	581	A
	573	A
	624	A
	547	A

	583	A
	545	B
	609	C
	549	C
	575	C
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	573	A

	561	A
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	588	A
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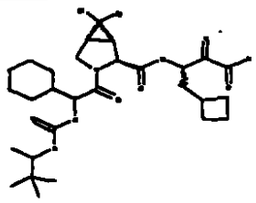
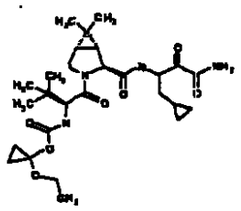
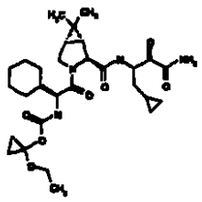
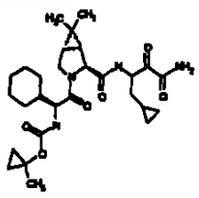
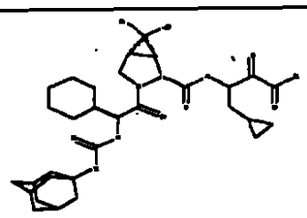
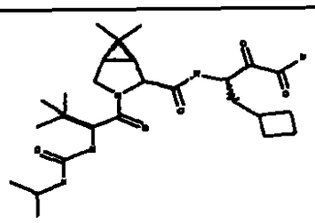
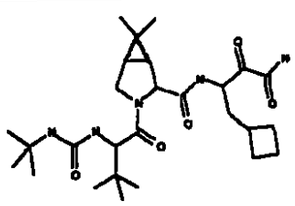
	615	A
	535	B
	561	A
	531	A
	651	A
	506	A
	520	A

Table 5

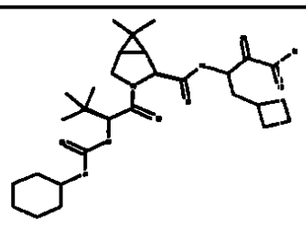
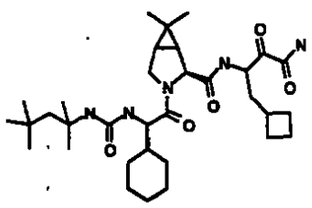
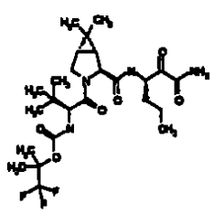
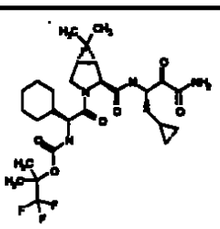
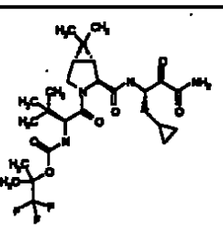
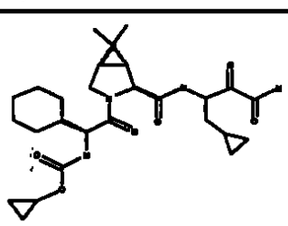
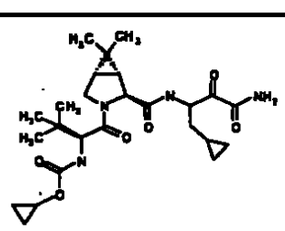
	546	A
	602	A
	549	B
	587	A
	561	A
	517	B
	491	B

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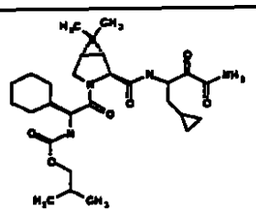
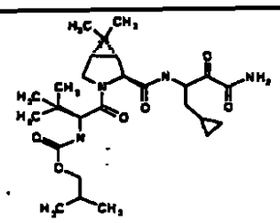
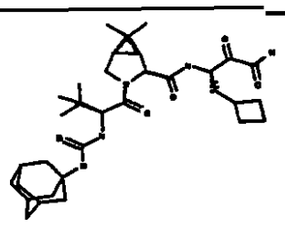
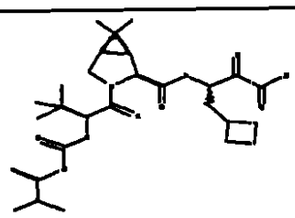
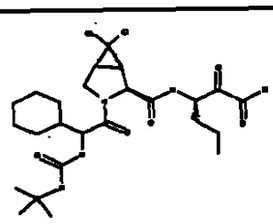
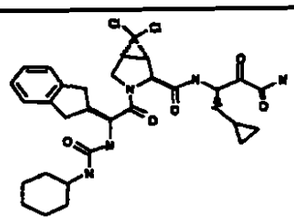
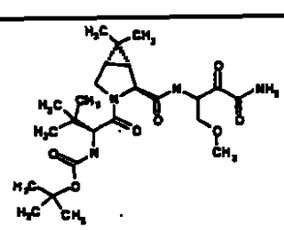
	533	B
	507	A
	598	A
	535	A
	561	A
	633	A
	497	C

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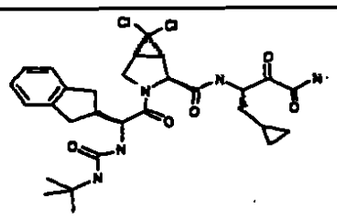
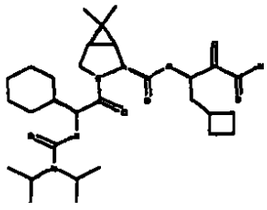
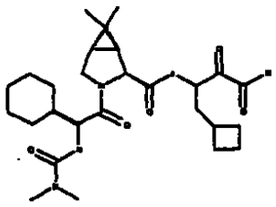
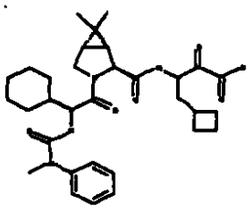
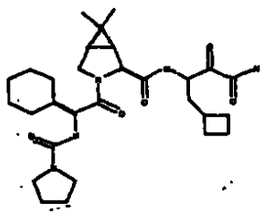
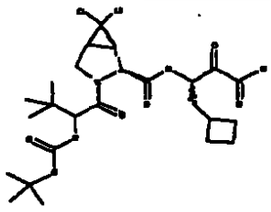
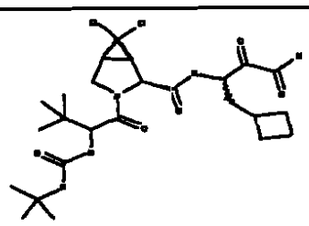
	607	A
	574	B
	518	B
	580	C
	544	B
	562	A
	561	A

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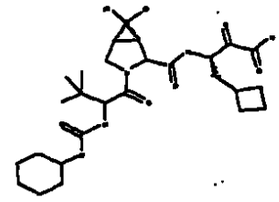
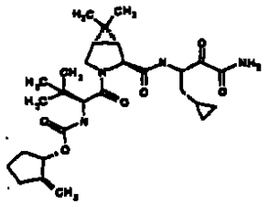
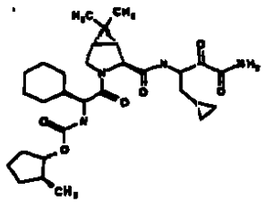
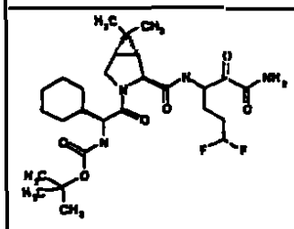
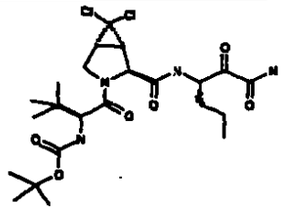
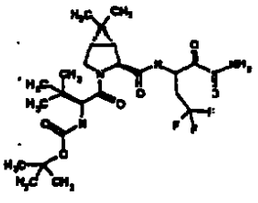
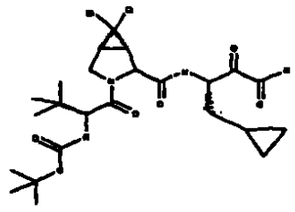
	587	A
	533	A
	559	A
	557	C
	535	A
	535	B
	547	A

Table 5

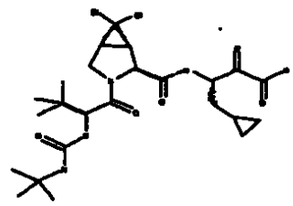
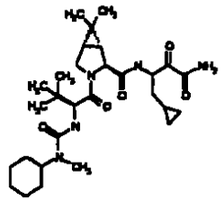
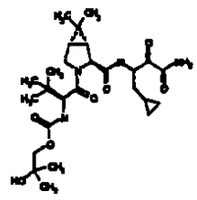
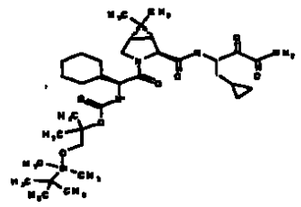
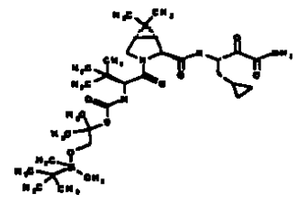
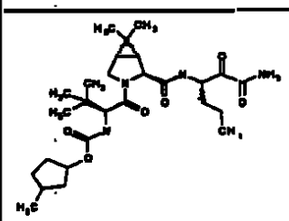
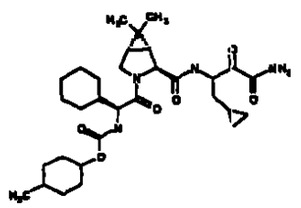
	546	A
	546	B
	523	B
	663	C
	637	C
	521	B
	573	B

Table 5

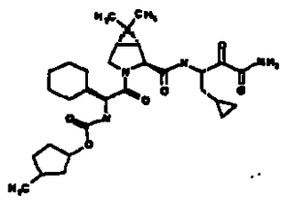
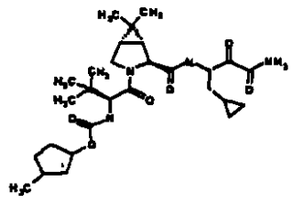
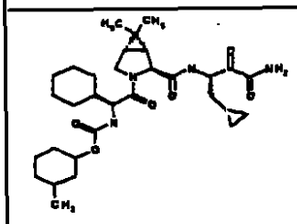
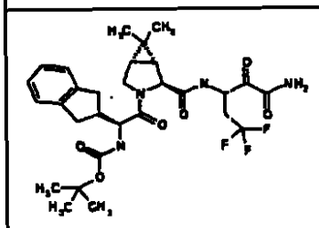
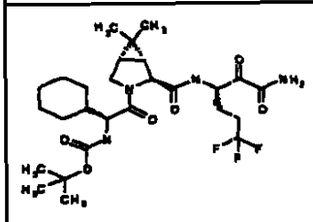
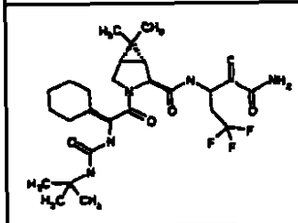
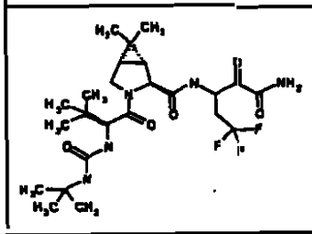
	559	A
	533	A
	573	B
	595	B
	575	A
	560	B
	534	C

Table 5

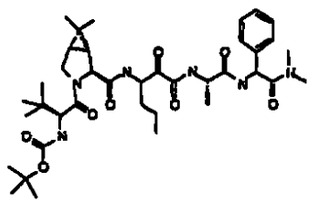
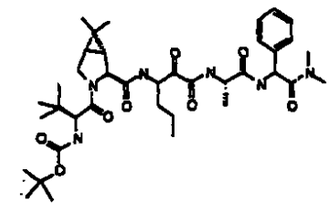
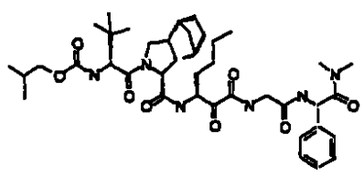
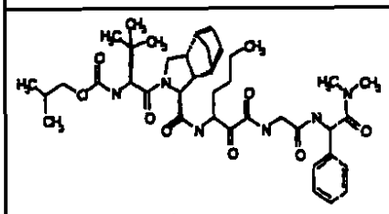
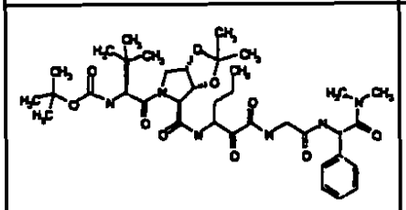
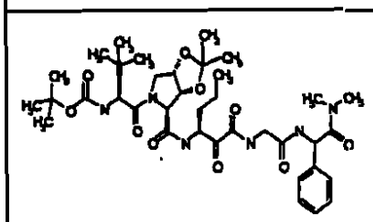
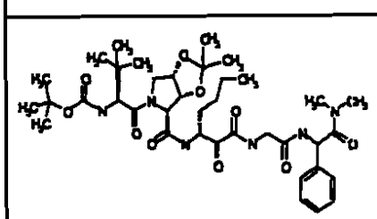
Structure	MW	Ki* Range
	727	A
	727	A
	753	C
	753	B
	745	A
	745	A
	759	C

Table 5

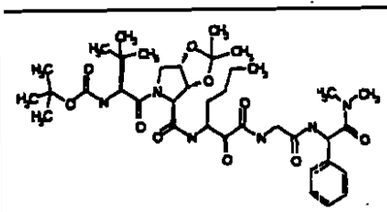
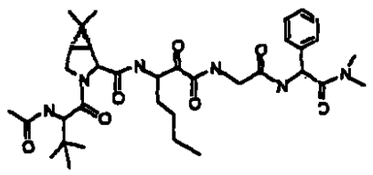
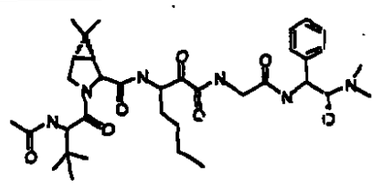
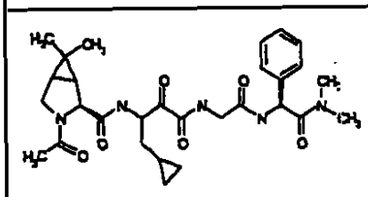
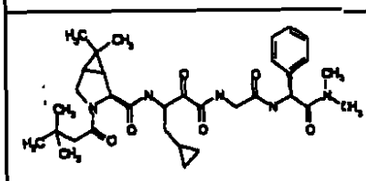
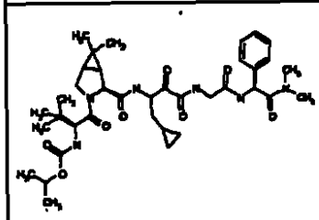
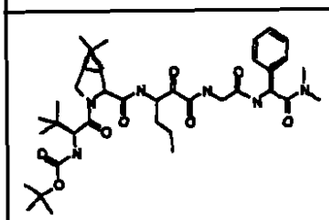
	759	B
	669	B
	669	A
	554	C
	610	B
	711	A
	713	A

Table 5

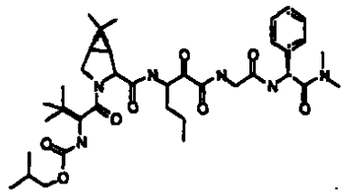
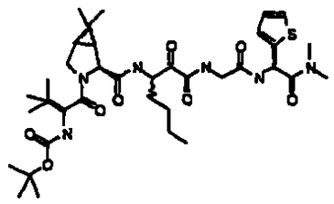
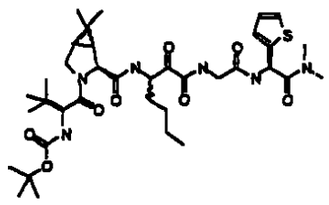
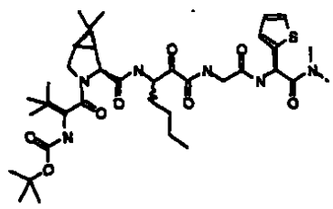
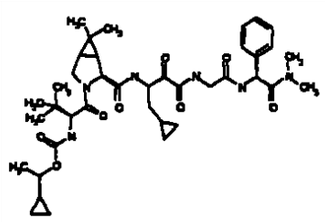
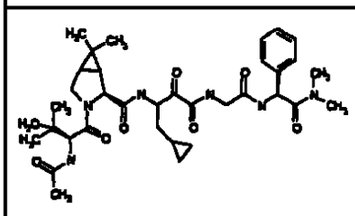
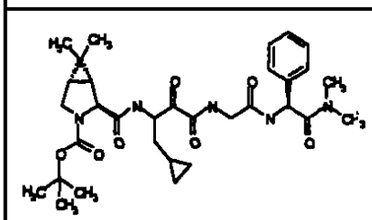
	713	A
	732	A
	733	A
	733	A
	737	A
	667	A
	612	C

Table 5

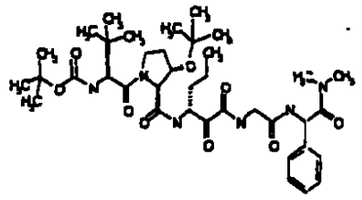
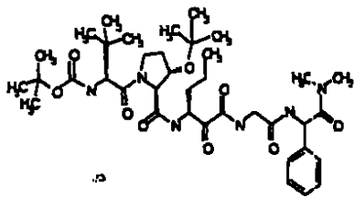
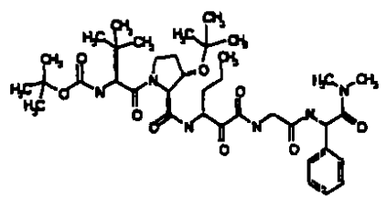
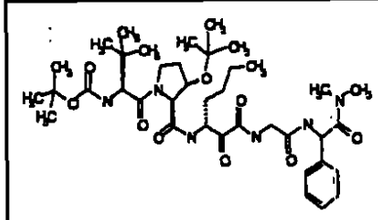
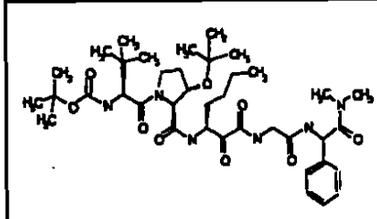
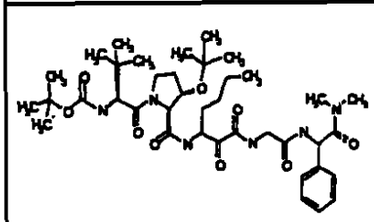
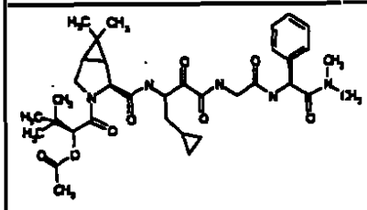
	745	C
	745	C
	745	C
	759	C
	759	C
	759	C
	668	C

Table 5

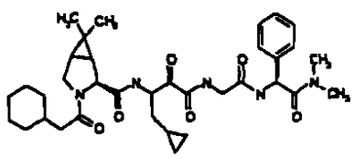
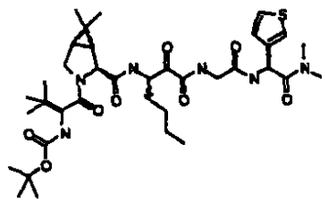
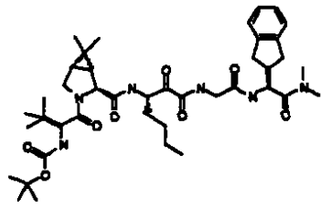
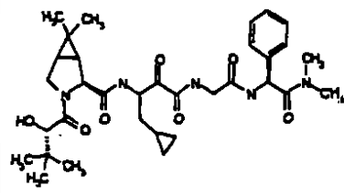
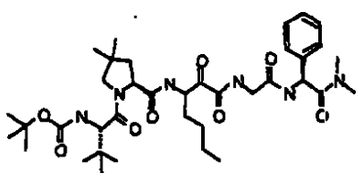
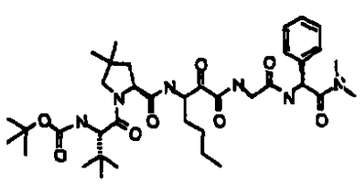
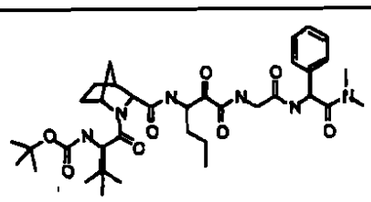
	636	B
	733	A
	767	B
	626	B
	715	C
	715	A
	699	B

Table 5

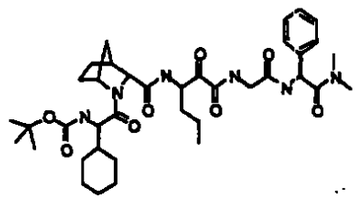
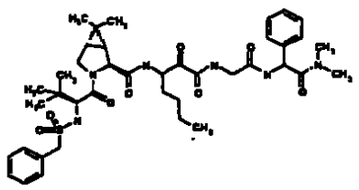
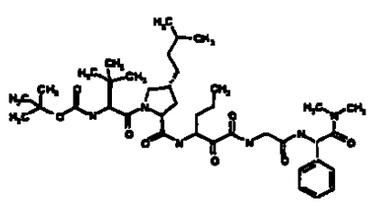
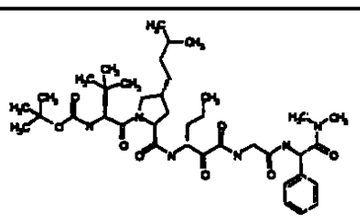
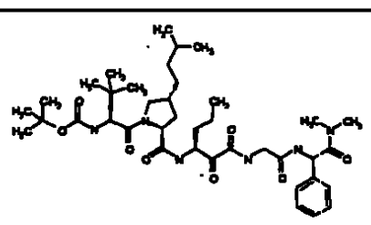
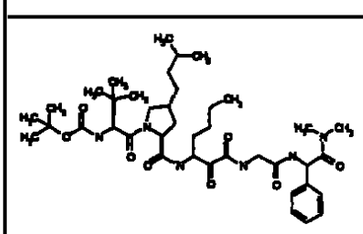
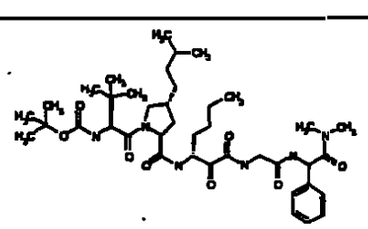
	725	A
	781	B
	743	B
	743	C
	743	A
	757	B
	757	C

Table 5

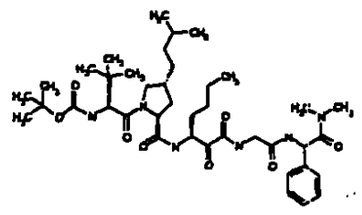
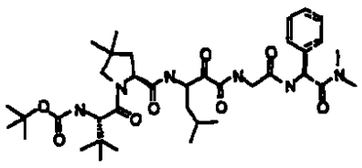
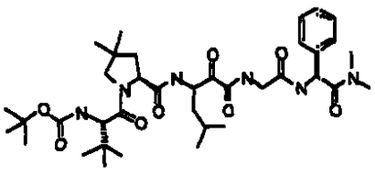
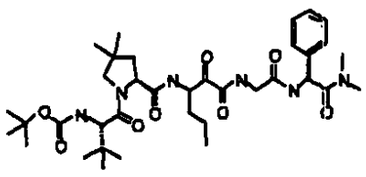
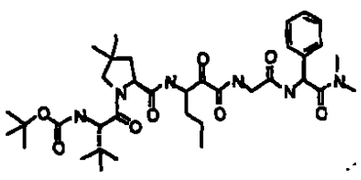
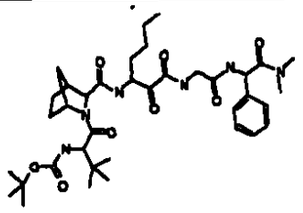
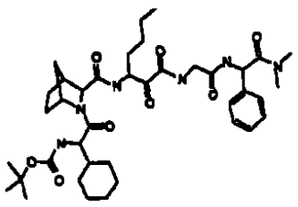
	757	B
	715	A
	715	A
	701	C
	701	A
	713	A
	739	A

Table 5

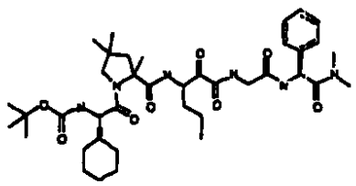
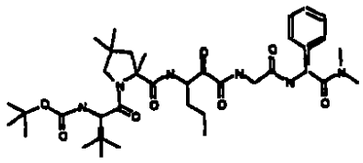
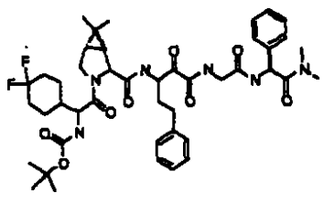
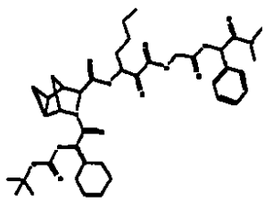
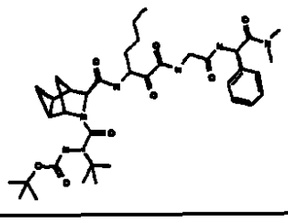
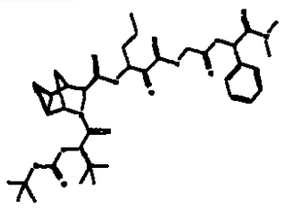
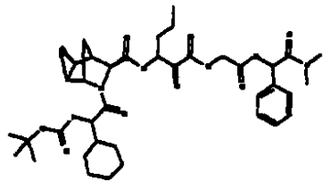
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	837	B
	751	A
	725	C
	711	C
	737	A

Table 5

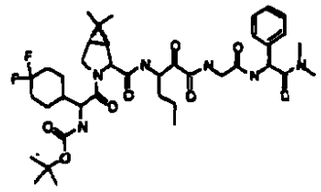
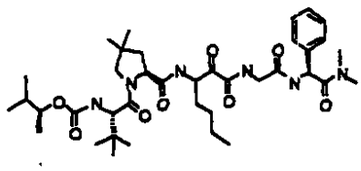
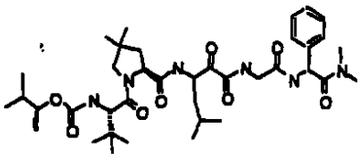
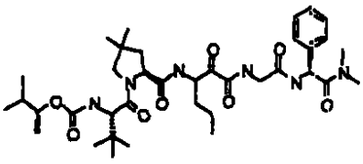
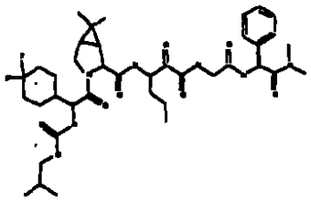
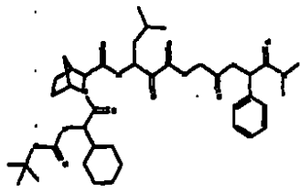
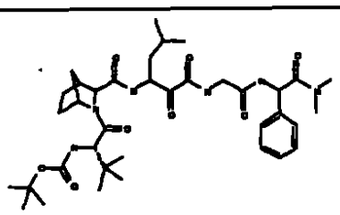
	775	A
	729	A
	729	A
	715	A
	775	A
	739	A
	713	A

Table 5

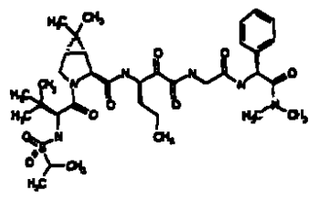
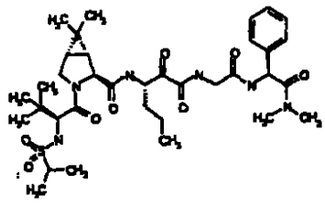
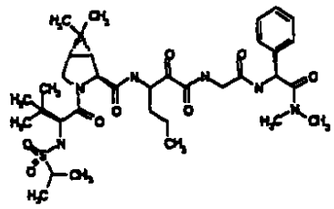
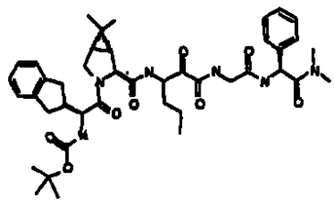
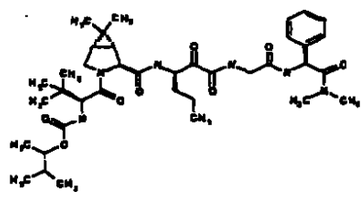
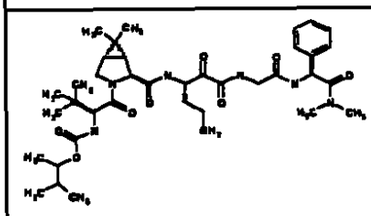
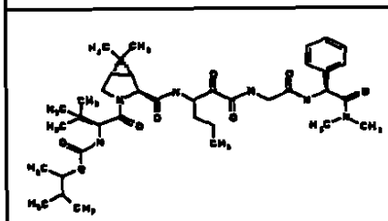
	719	A
	719	A
	719	A
	773	A
	727	A
	727	A
	727	A

Table 5

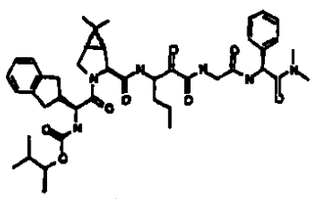
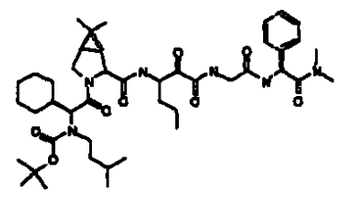
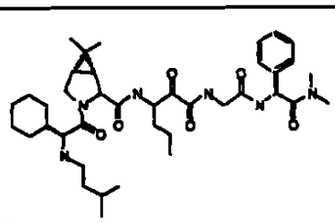
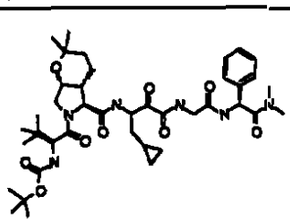
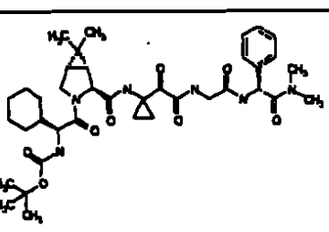
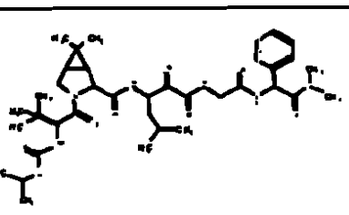
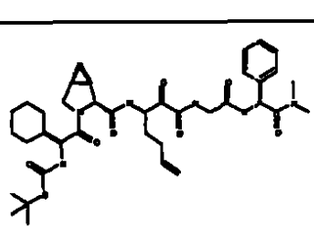
	787	A
	809	C
	709	A
	769	B
	723	C
	713	A
	723	A

Table 5

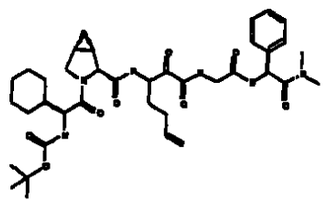
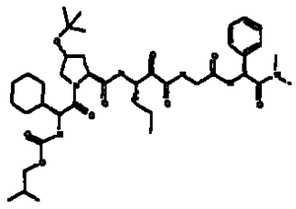
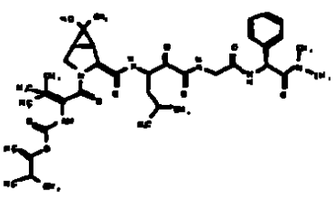
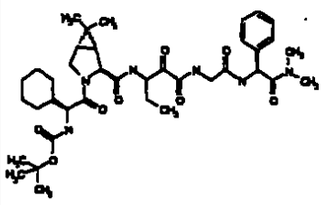
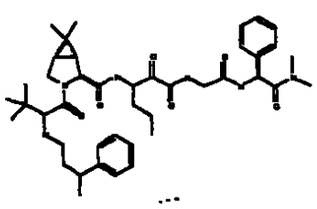
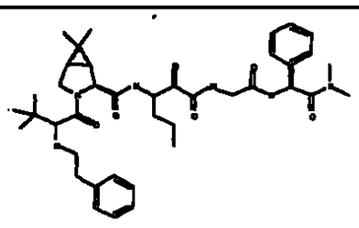
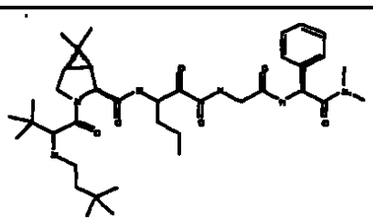
	723	B
	771	C
	741	A
	725	A
	745	A
	716	A
	733	A

Table 5

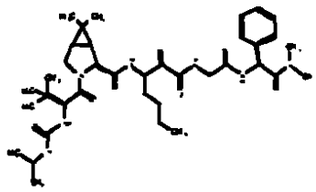
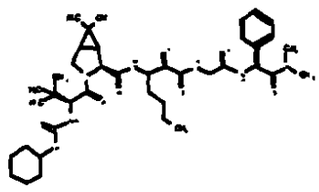
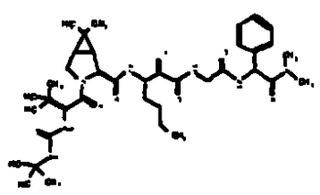
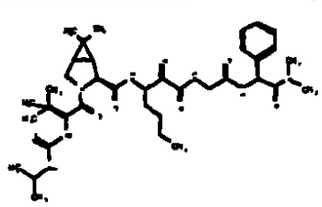
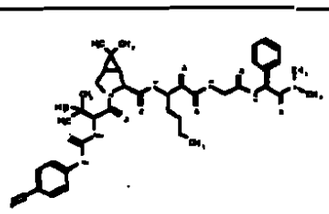
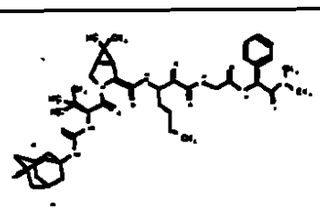
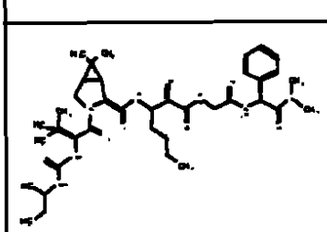
	713	A
	753	A
	726	A
	712	A
	771	B
	804	A
	726	A

Table 5

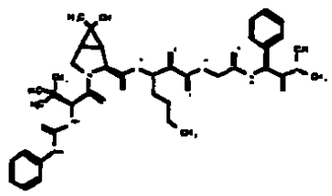
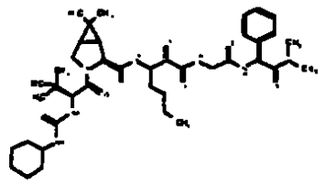
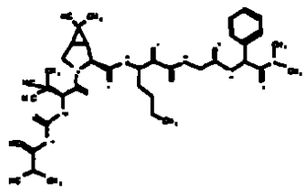
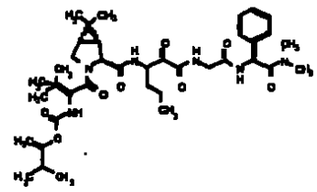
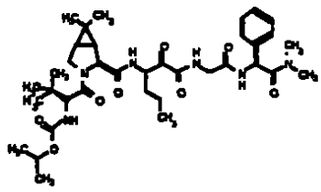
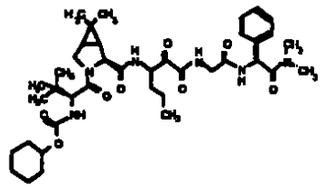
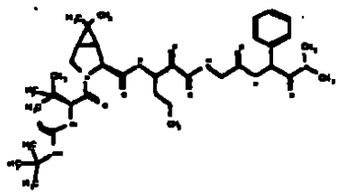
	746	A
	752	A
	741	A
	727	A
	699	A
	739	A
	712	A

Table 5

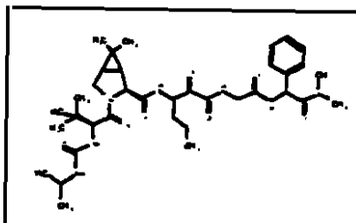
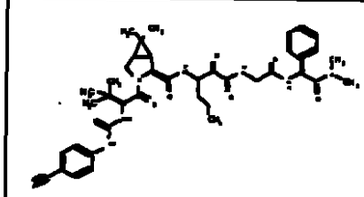
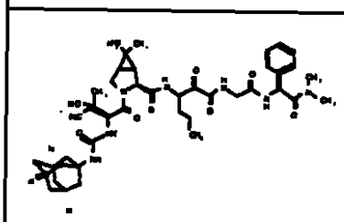
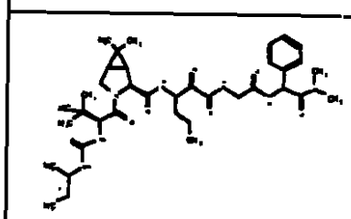
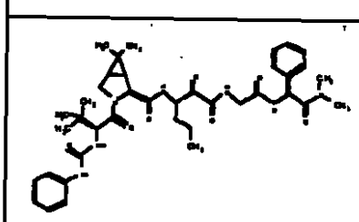
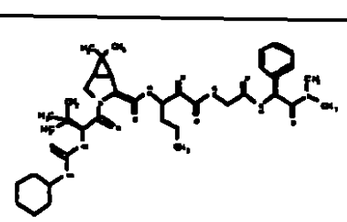
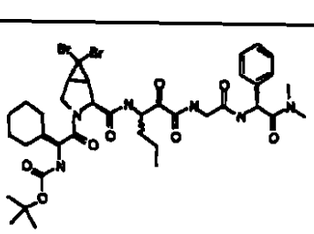
	698	A
	757	B
	790	A
	712	A
	732	A
	738	A
	869	A

Table 5

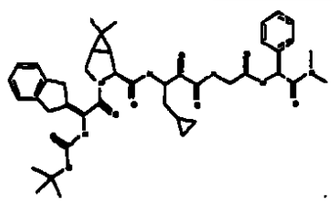
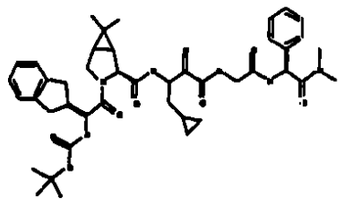
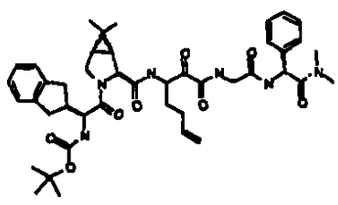
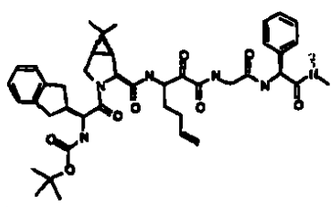
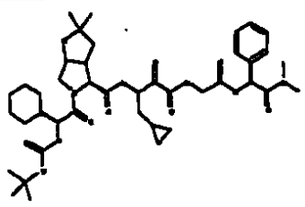
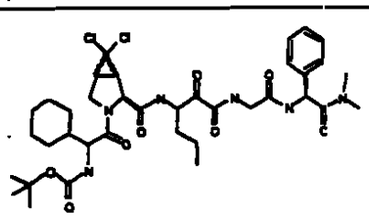
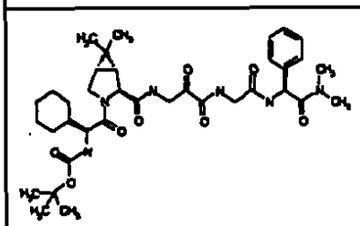
	785	A
	785	A
	785	A
	785	A
	781	A
	780	A
	697	C

Table 5

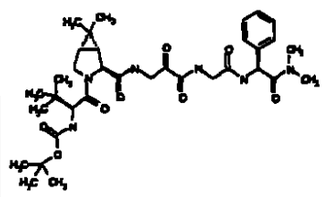
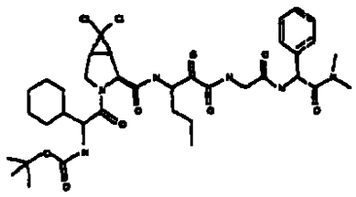
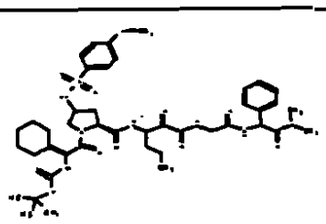
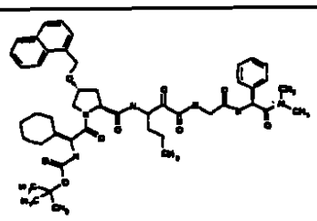
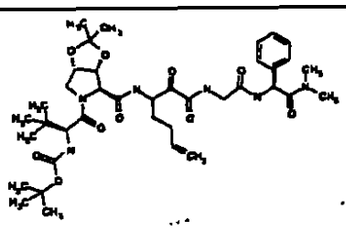
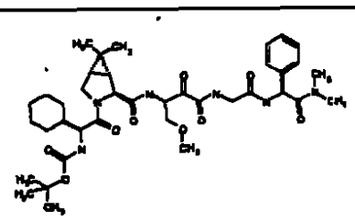
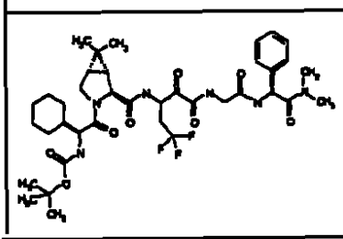
	671	C
	780	A
	884	A
	855	A
	757	B
	741	B
	779	B

Table 5

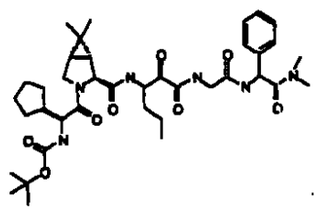
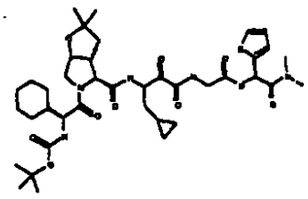
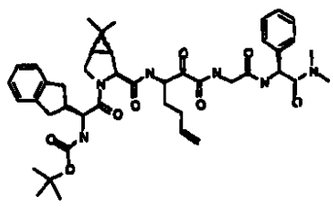
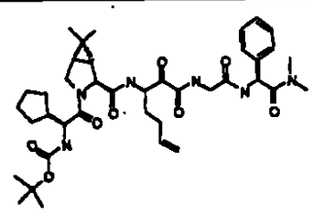
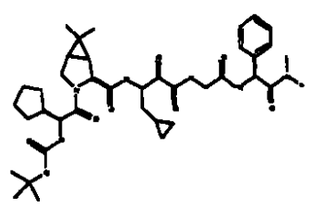
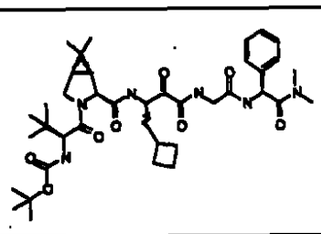
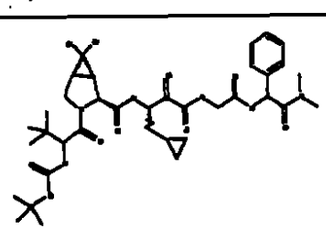
	725	A
	787	A
	785	A
	737	A
	737	A
	739	A
	855	A

Table 5

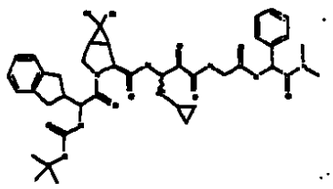
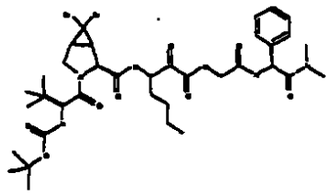
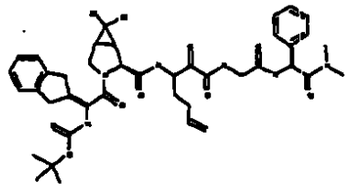
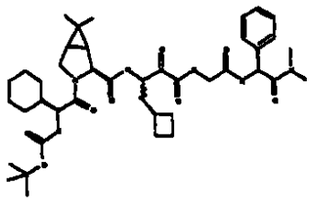
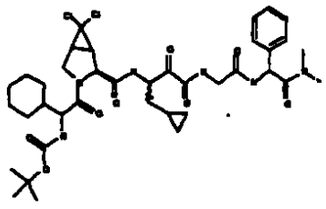
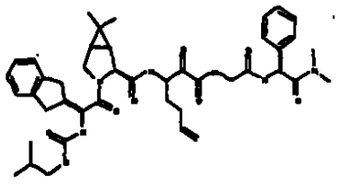
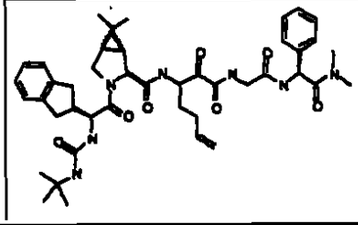
	826	A
	857	A
	826	A
	765	A
	792	A
	799	A
	784	A

Table 5

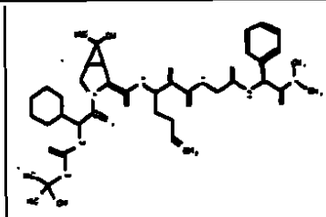
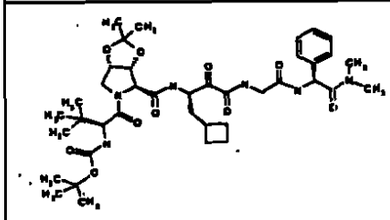
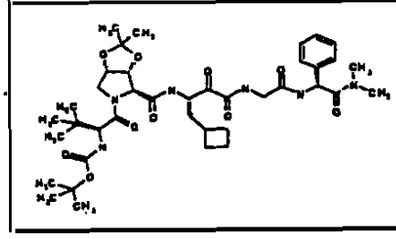
	750	A
	771	A
	771	A

Table 5

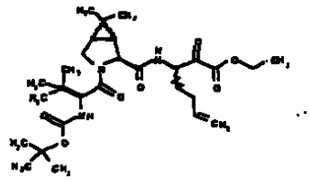
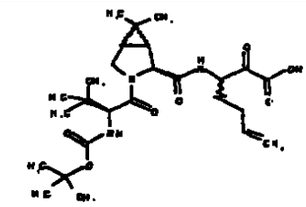
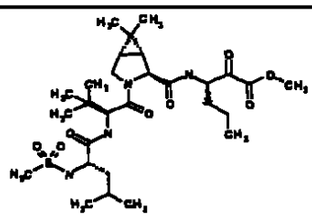
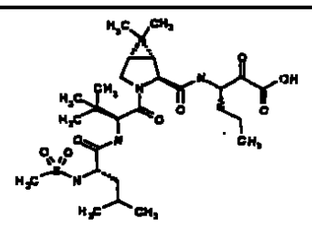
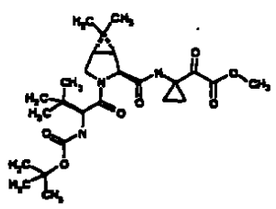
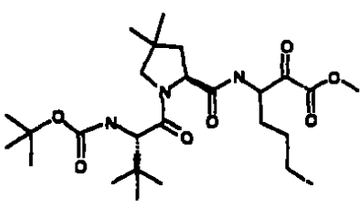
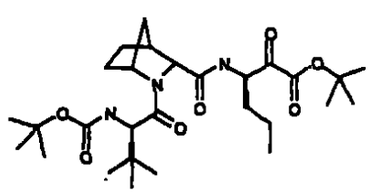
Structure	MW	Ki* range
	538	C
	508	B
	601	C
	587	B
	494	C
	512	C
	538	C

Table 5

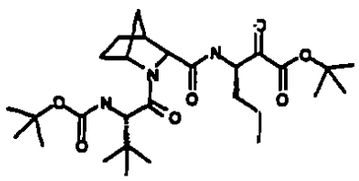
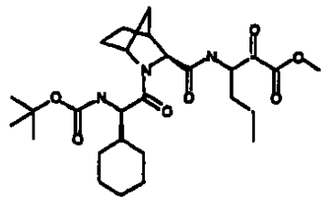
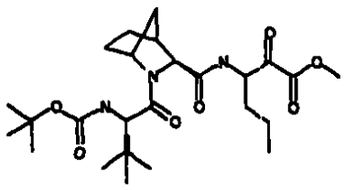
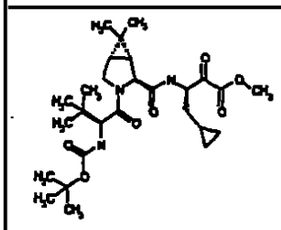
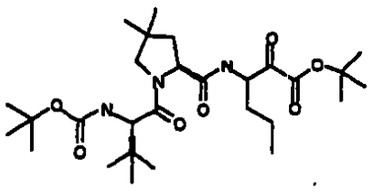
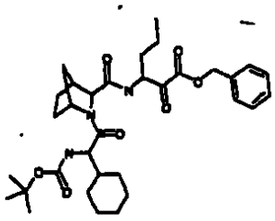
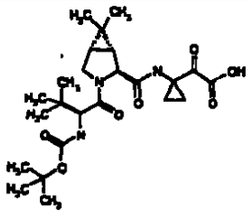
	538	C
	522	C
	496	C
	522	C
	540	C
	598	C
	480	C

Table 5

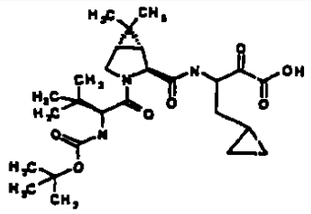
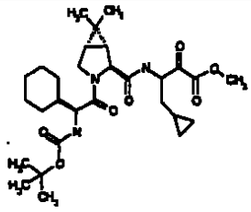
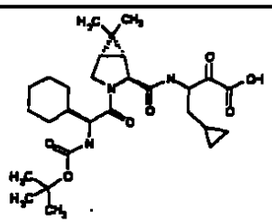
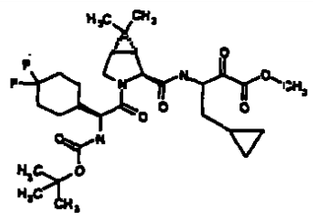
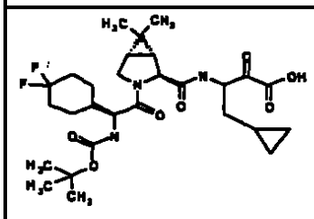
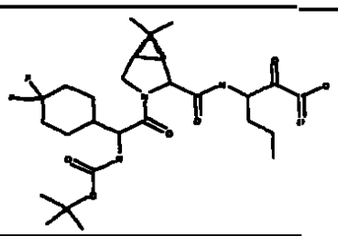
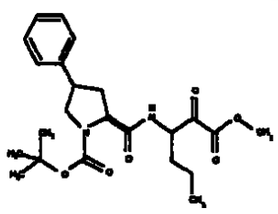
	508	B
	548	C
	534	B
	584	C
	570	B
	558	C
	433	C

Table 5

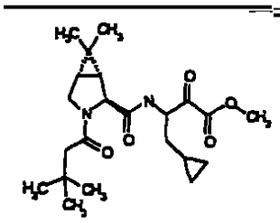
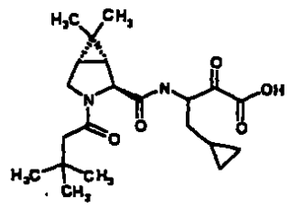
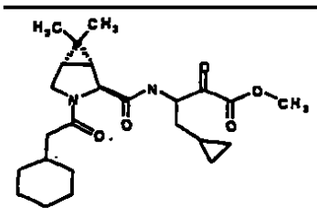
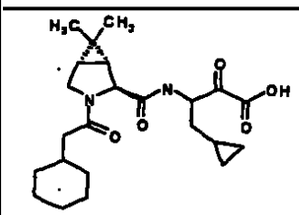
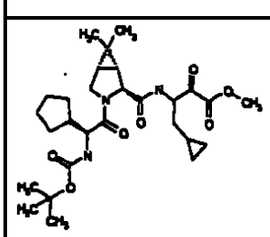
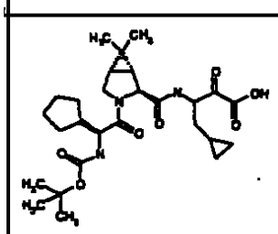
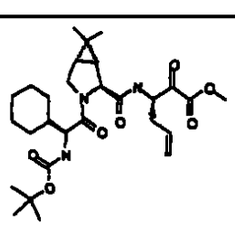
	407	C
	393	C
	433	C
	419	C
	534	C
	520	B
	534	C

Table 5

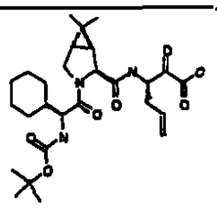
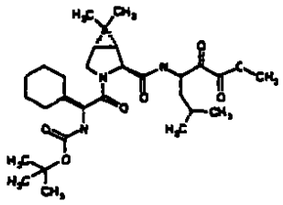
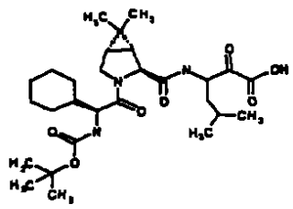
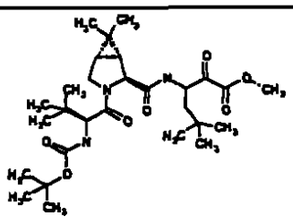
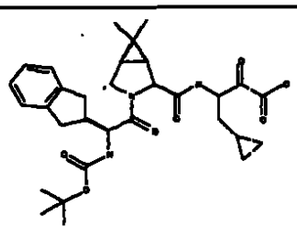
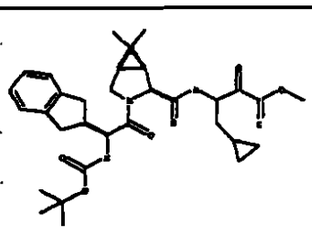
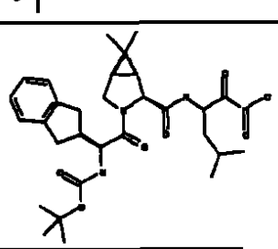
	520	B
	550	C
	536	C
	538	C
	568	B
	582	C
	570	C

Table 5

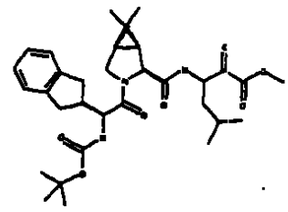
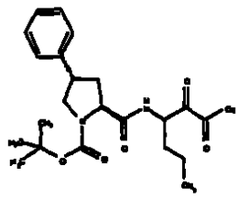
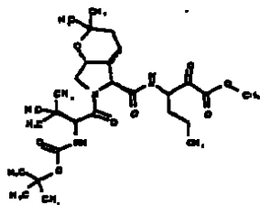
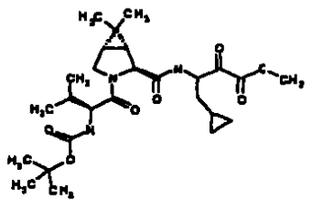
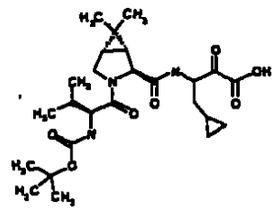
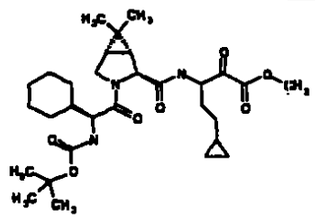
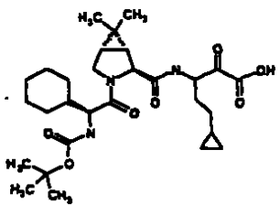
	584	C
	418	C
	554	C
	508	C
	494	B
	562	C
	548	A

Table 5

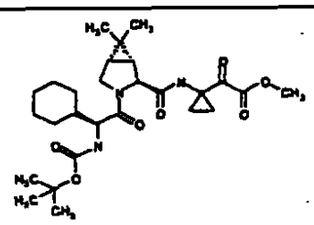
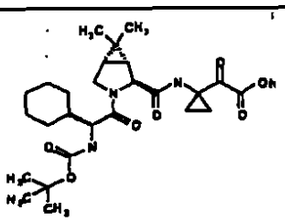
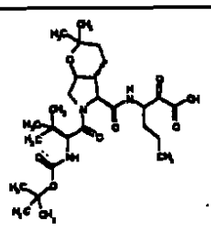
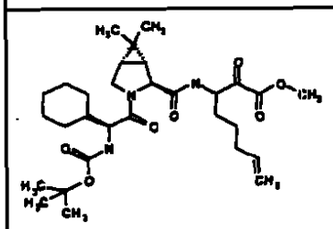
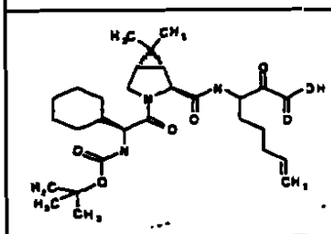
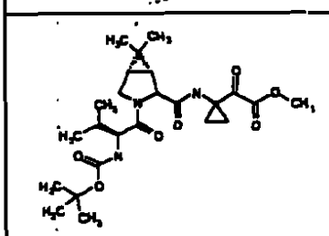
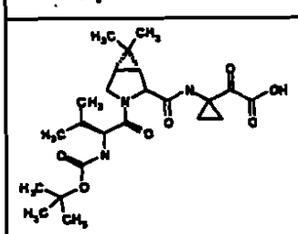
	520	C
	506	C
	540	C
	562	C
	548	B
	480	C
	466	C

Table 5

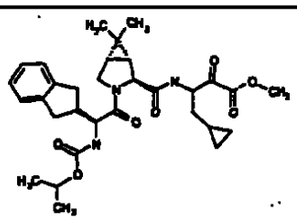
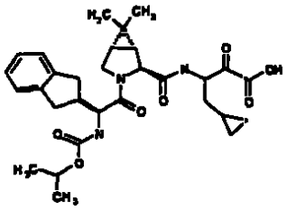
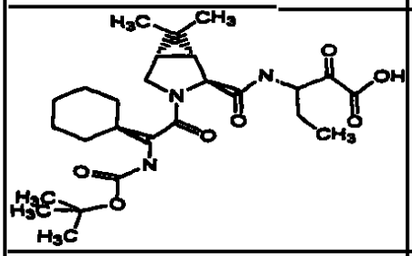
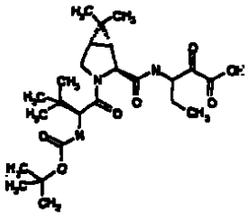
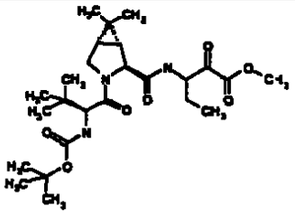
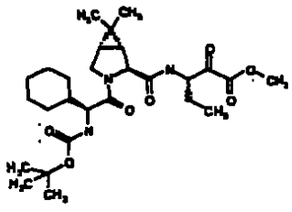
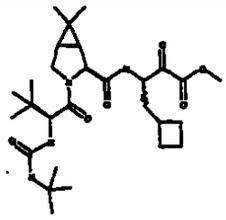
	568	C
	554	B
	508	B
	482	C
	496	C
	522	C
	535	C

Table 5

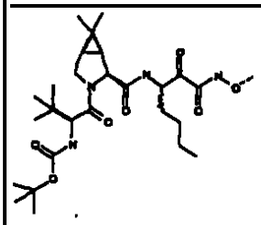
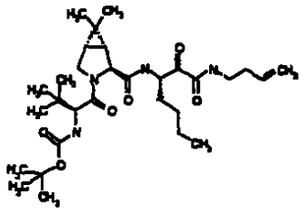
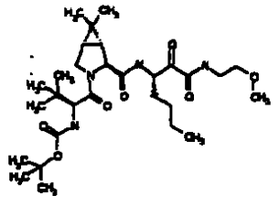
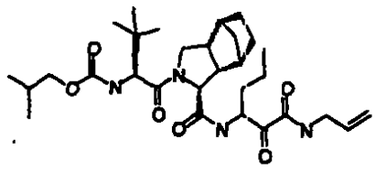
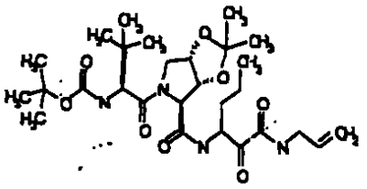
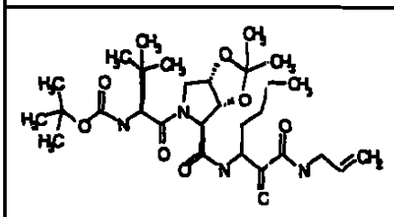
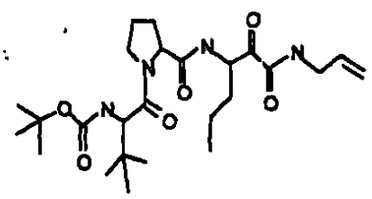
Structure	MW	Ki range
	539	B
	563	B
	567	C
	581	C
	567	C
	581	C
	495	C

Table 5

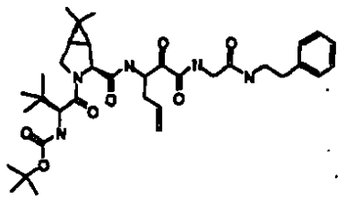
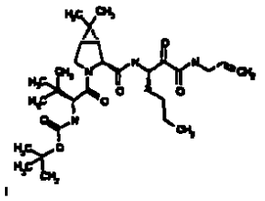
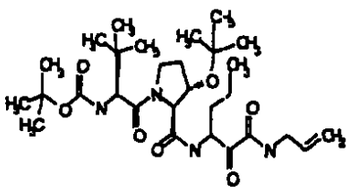
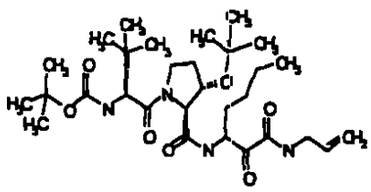
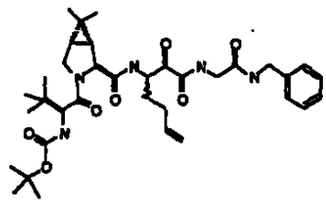
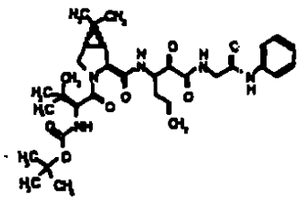
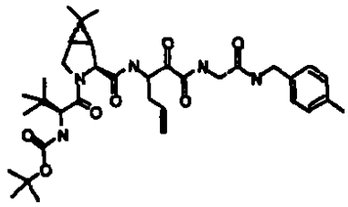
	654	B
	549	C
	567	C
	581	C
	654	C
	626	B
	654	A

Table 5

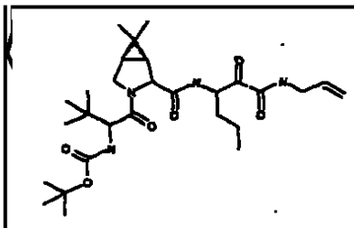
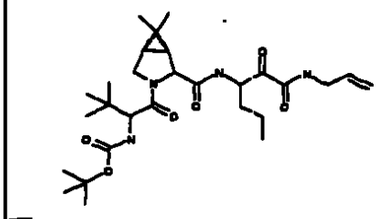
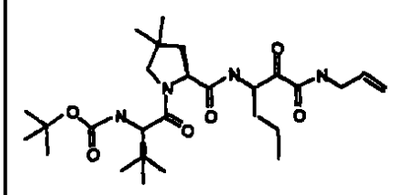
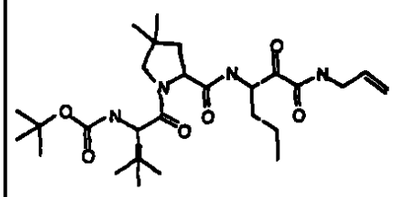
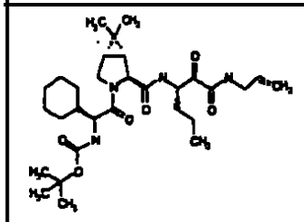
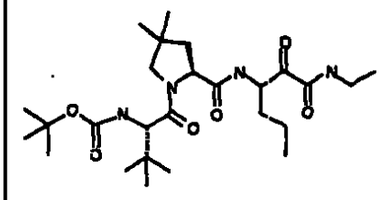
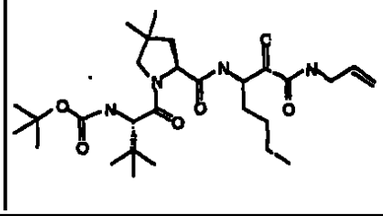
	535	C
	535	B
	523	C
	523	C
	561	B
	511	C
	537	C

Table 5

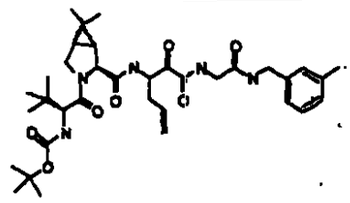
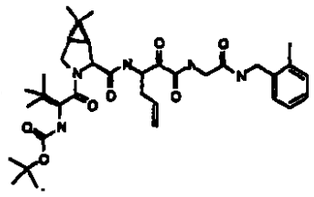
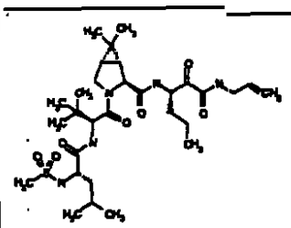
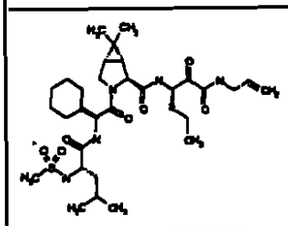
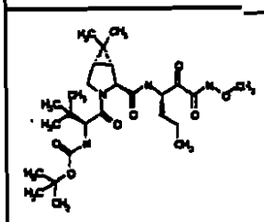
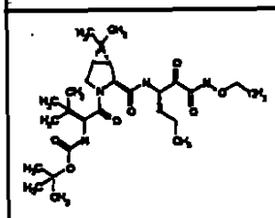
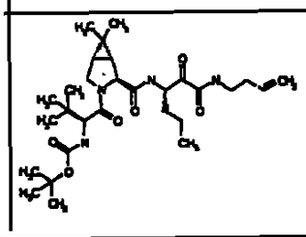
	654	B
	654	A
	626	B
	652	B
	525	C
	539	C
	549	C

Table 5

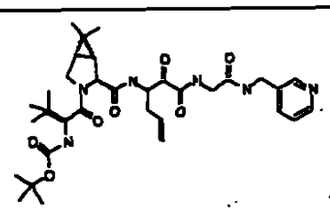
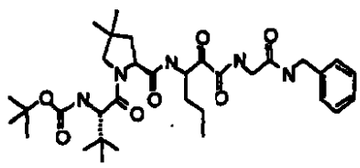
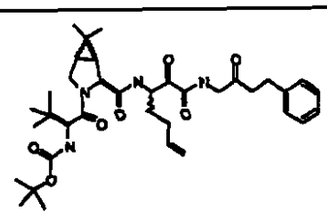
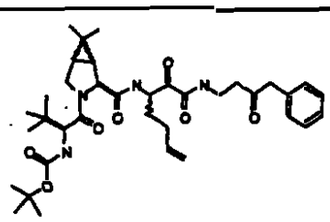
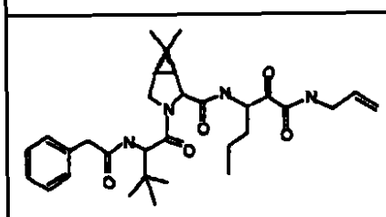
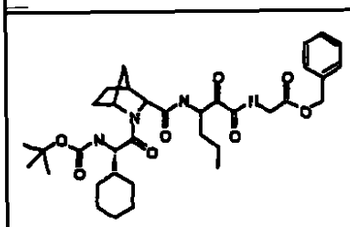
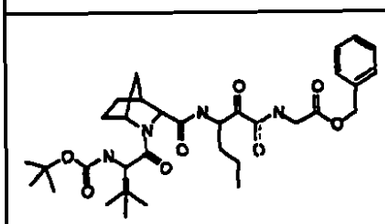
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	630	C
	653	B
	653	B
	553	C
	655	C
	629	C

Table 5

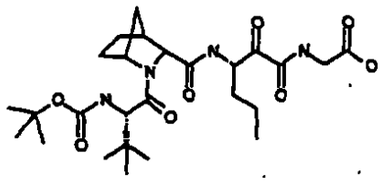
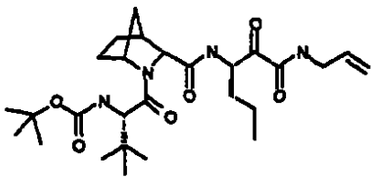
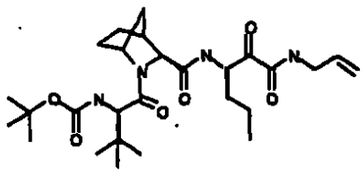
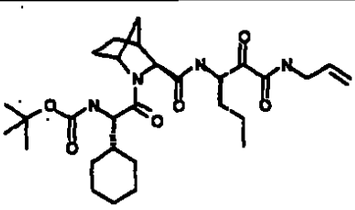
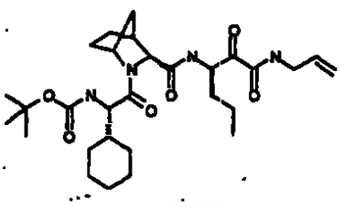
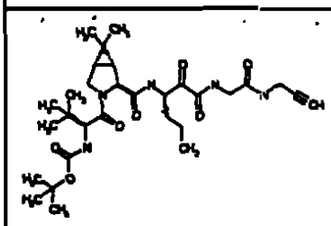
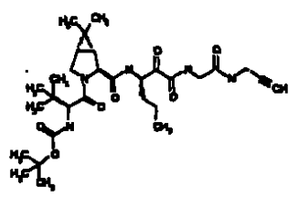
	539	C
	521	C
	521	C
	547	C
	547	C
	590	B
	590	B

Table 5

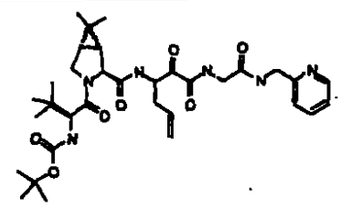
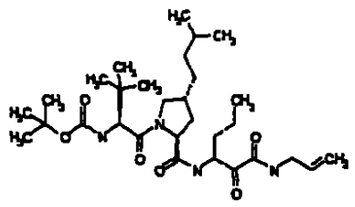
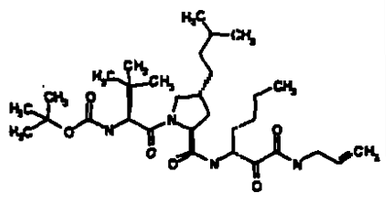
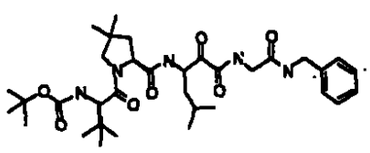
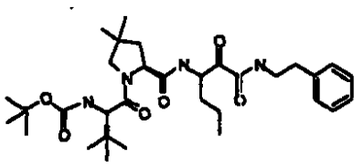
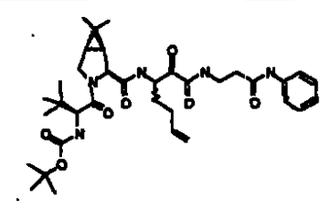
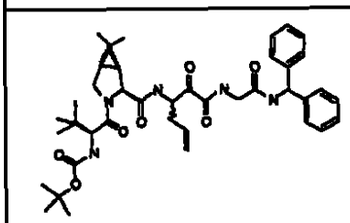
	641	B
	565	C
	579	C
	644	C
	587	C
	654	B
	716	B

Table 5

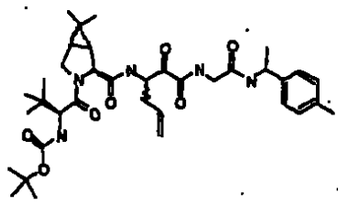
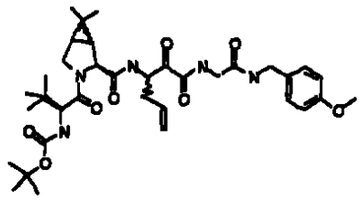
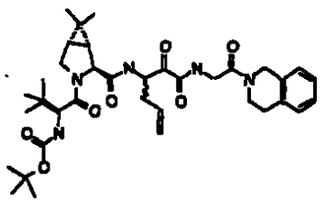
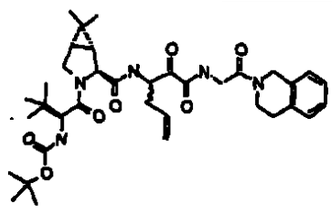
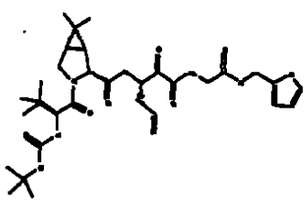
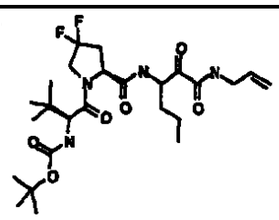
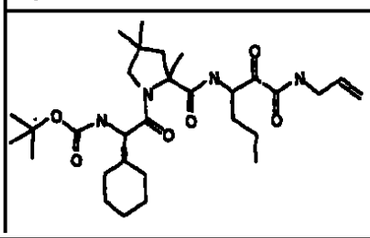
	668	B
	670	A
	666	C
	666	C
	630	B
	531	C
	563	C

Table 5

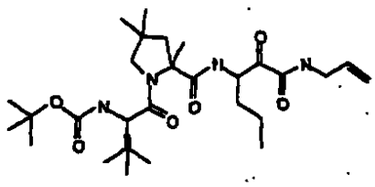
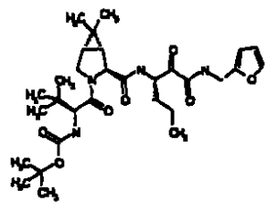
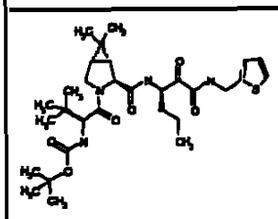
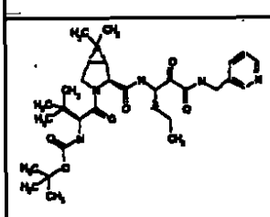
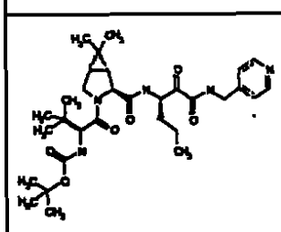
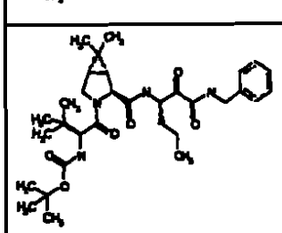
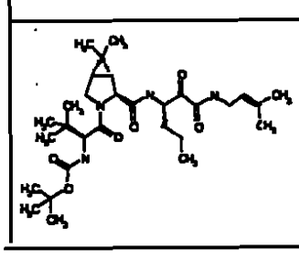
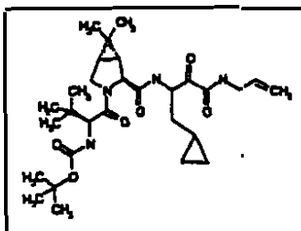
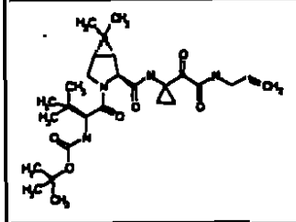
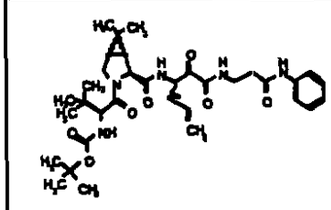
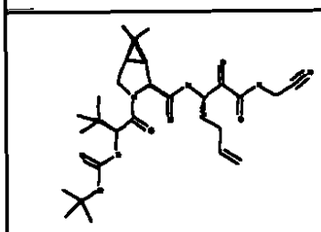
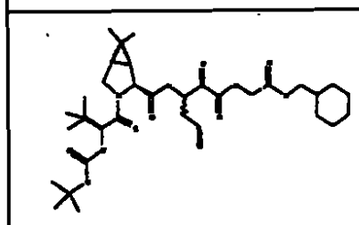
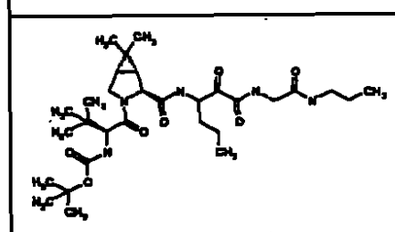
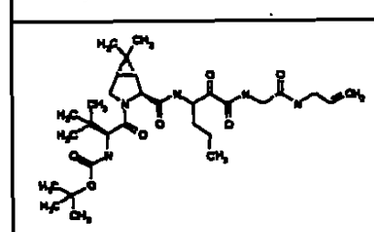
	537	C
	575	B
	591	B
	586	C
	586	C
	585	B
	563	B

Table 5

	547	B
	519	C
	640	B
	546	B
	646	B
	594	C
	592	B

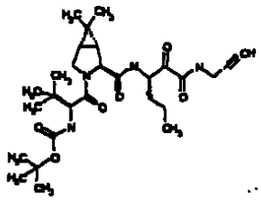
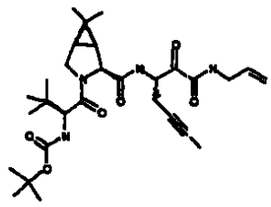
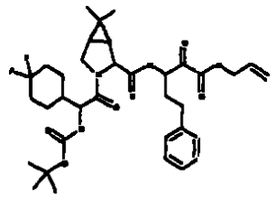
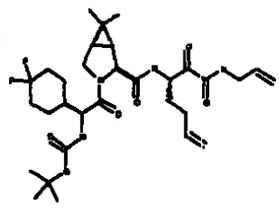
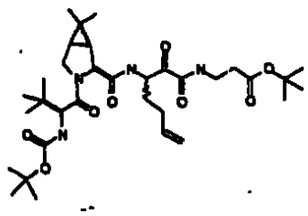
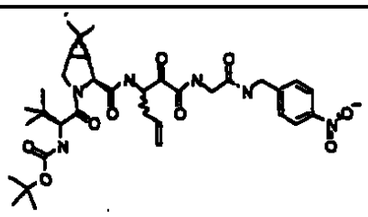
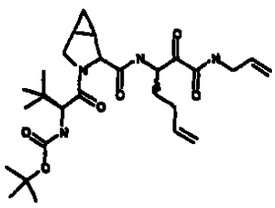
	533	C
	545	C
	659	B
	609	A
	635	B
	685	B
	519	C

Table 5

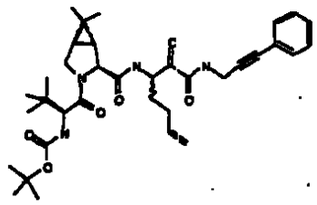
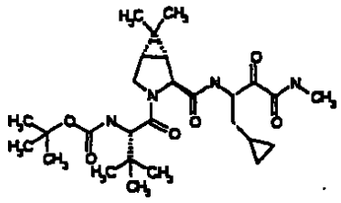
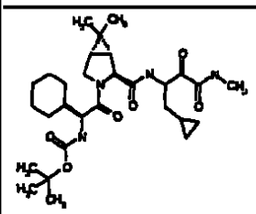
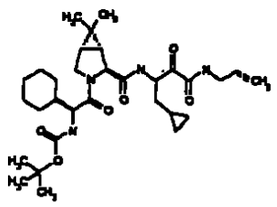
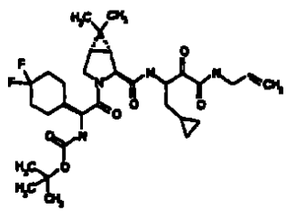
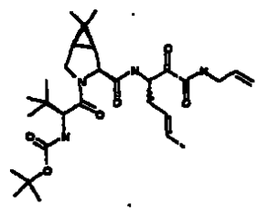
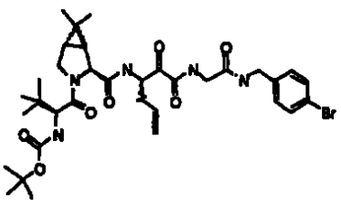
	621	B
	521	B
	547	B
	573	B
	609	B
	547	B
	719	B

Table 5

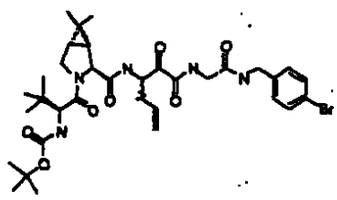
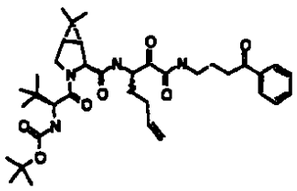
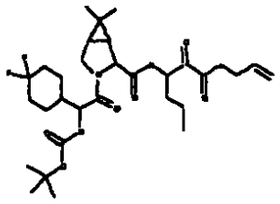
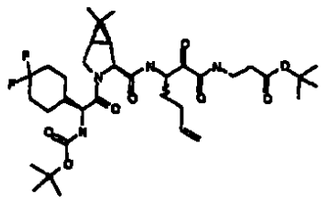
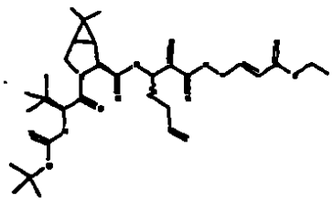
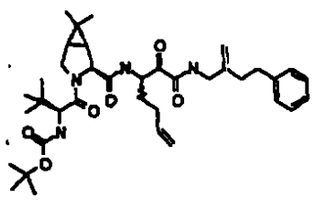
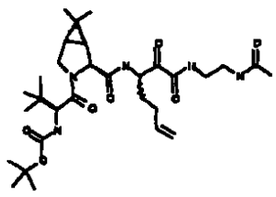
	719	C
	653	B
	597	B
	697	A
	619	B
	651	C
	592	B

Table 5

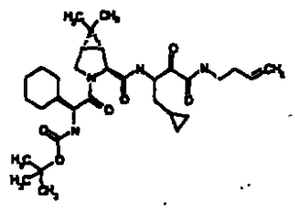
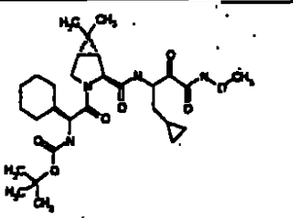
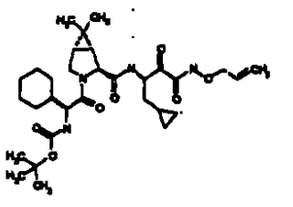
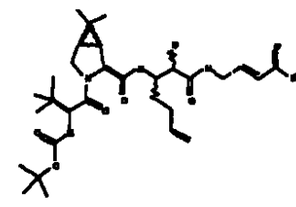
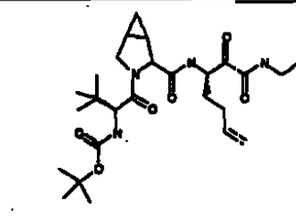
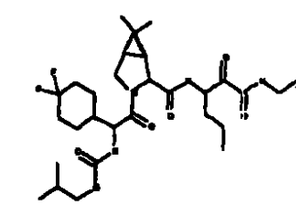
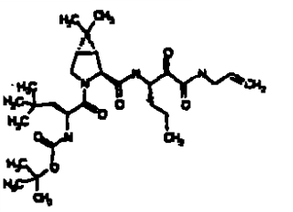
	587	C
	563	B
	589	C
	621	C
	519	C
	597	B
	549	C

Table 5

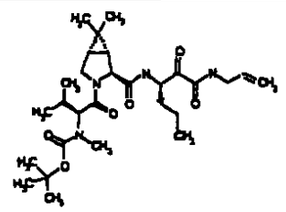
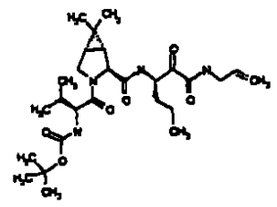
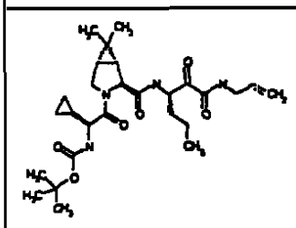
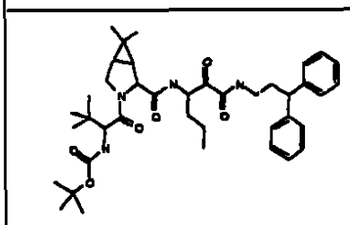
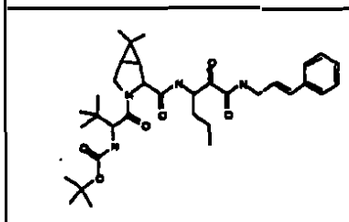
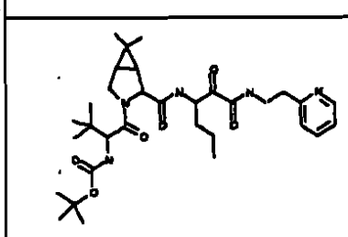
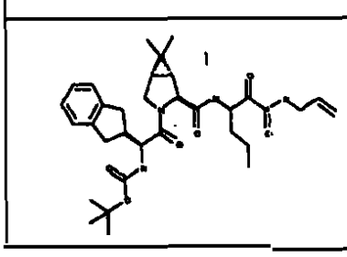
	535	C
	521	B
	519	C
	689	C
	611	C
	600	C
	595	B

Table 5

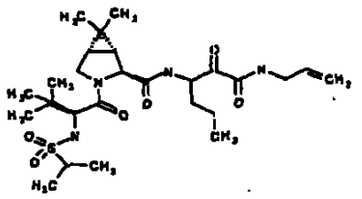
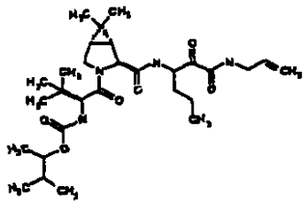
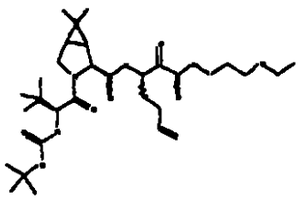
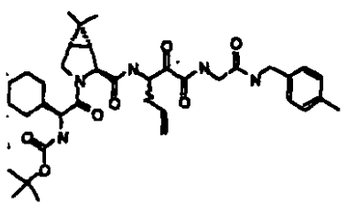
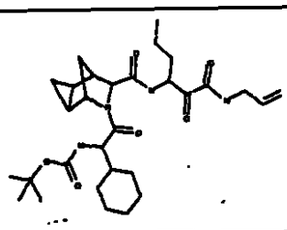
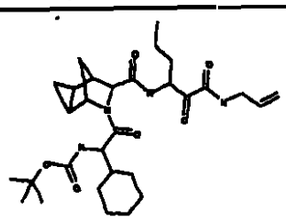
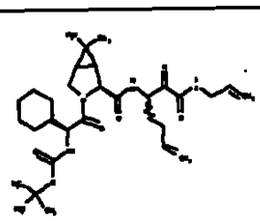
	541	C
	549	B
	593	C
	680	B
	559	C
	559	C
	573	B

Table 5

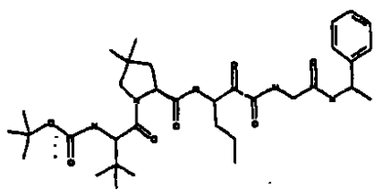
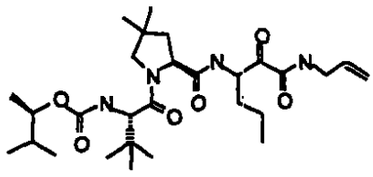
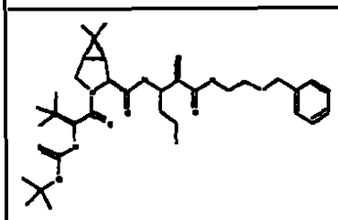
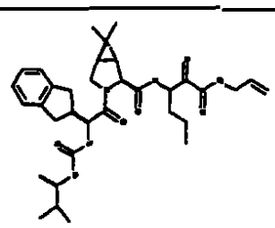
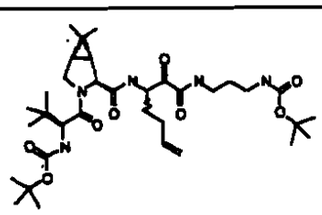
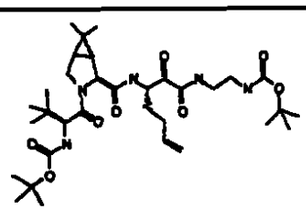
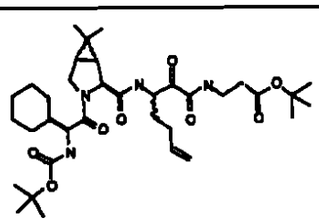
	644	C
	537	C
	627	C
	609	B
	664	B
	650	C
	661	B

Table 5

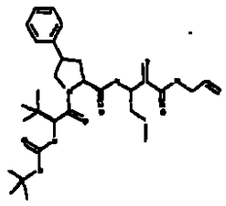
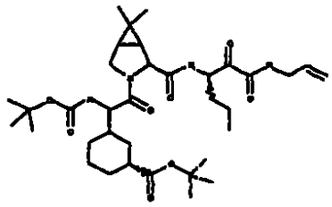
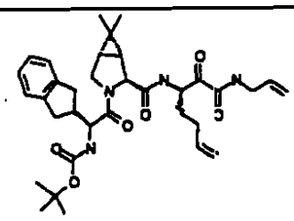
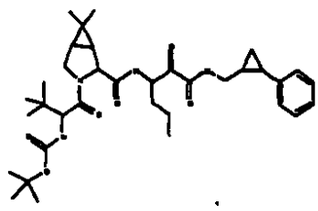
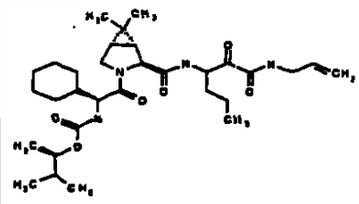
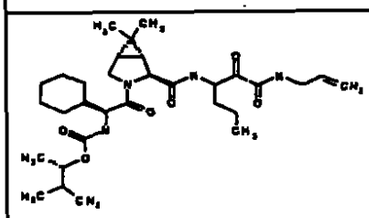
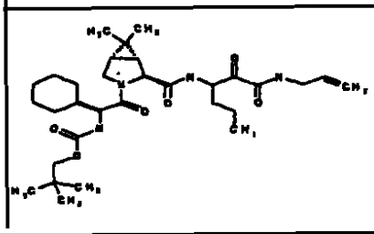
	571	C
	661	B
	607	B
	625	C
	575	B
	575	B
	575	B

Table 5

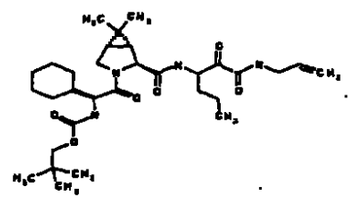
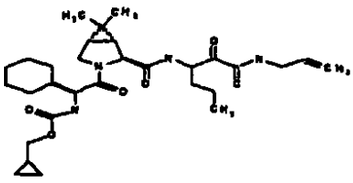
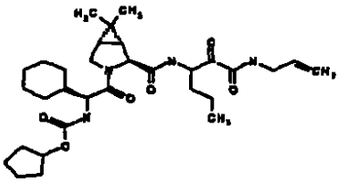
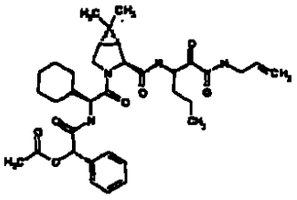
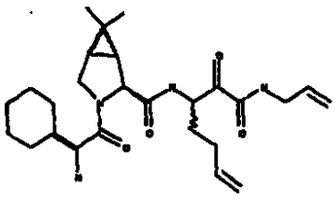
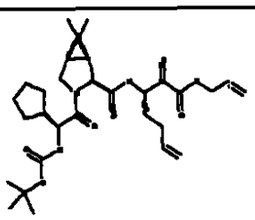
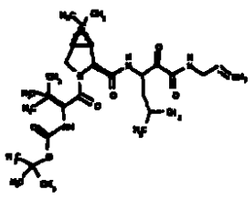
	575	B
	559	B
	573	B
	637	B
	473	C
	559	B
	549	C

Table 5

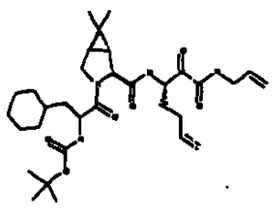
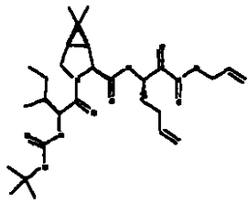
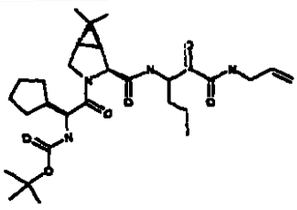
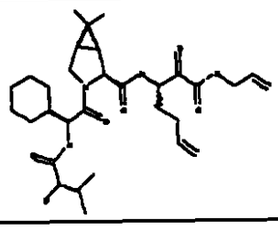
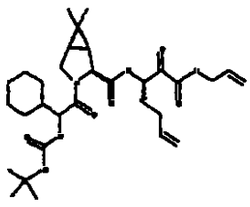
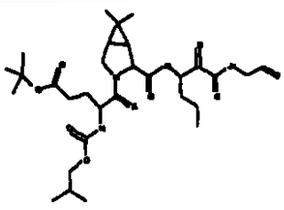
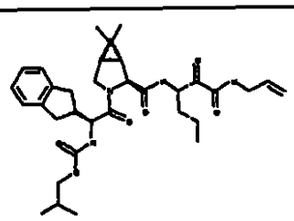
	587	C
	547	C
	547	B
	573	C
	573	C
	607	C
	595	B

Table 5

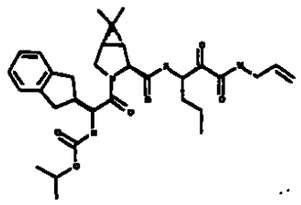
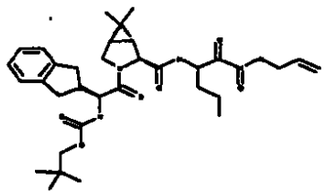
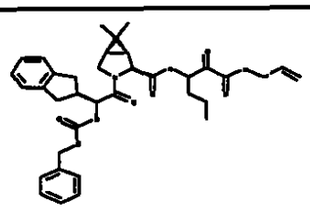
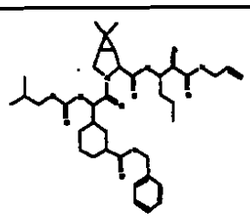
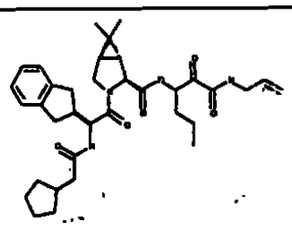
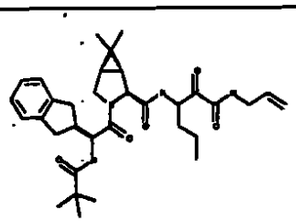
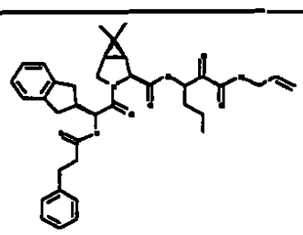
	581	B
	609	B
	629	C
	694	C
	605	C
	579	C
	627	C

Table 5

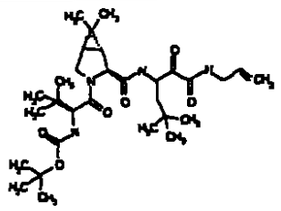
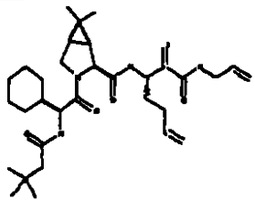
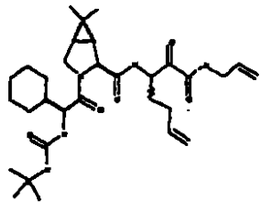
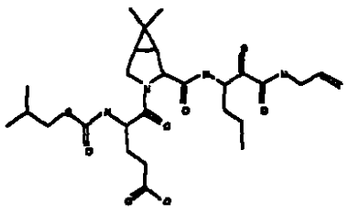
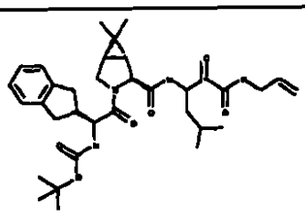
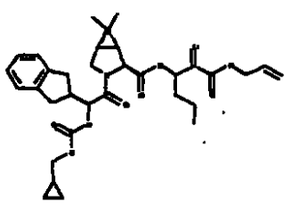
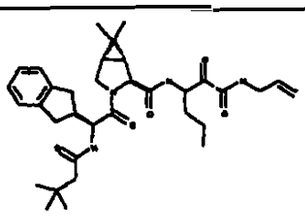
	563	C
	571	C
	572	B
	551	C
	609	C
	593	B
	593	C

Table 5

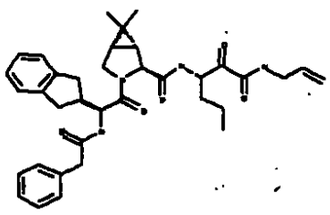
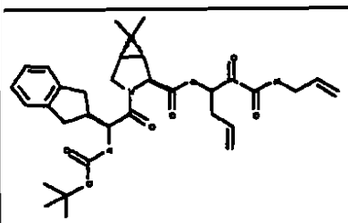
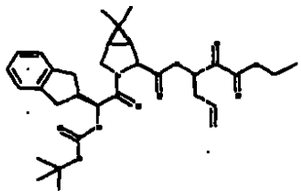
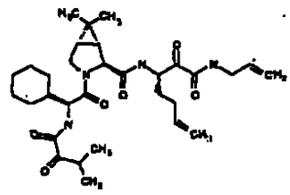
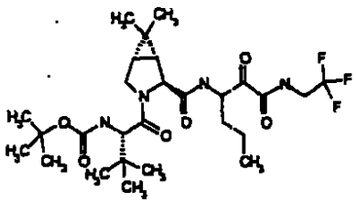
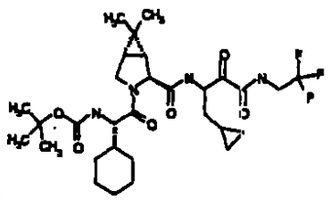
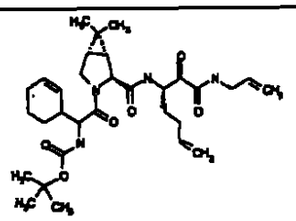
	613	C
	593	B
	581	C
	571	B
	577	C
	615	C
	571	C

Table 5

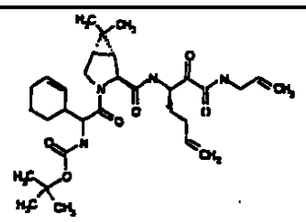
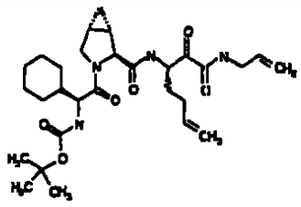
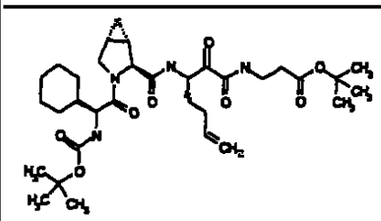
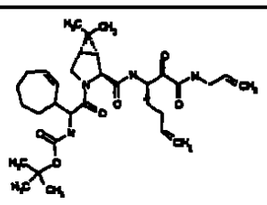
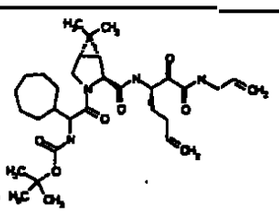
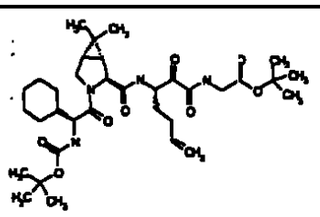
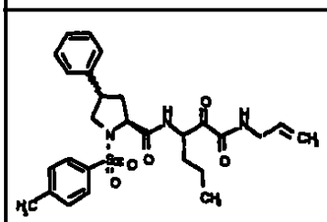
	571	C
	545	C
	633	C
	585	B
	587	B
	647	B
	512	C

Table 5

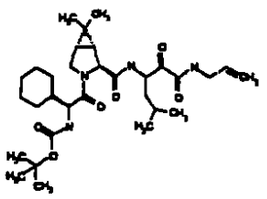
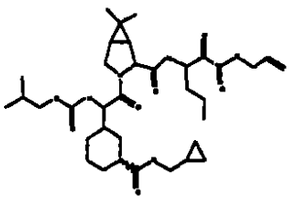
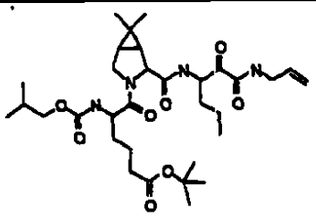
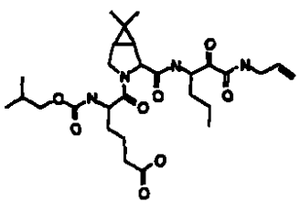
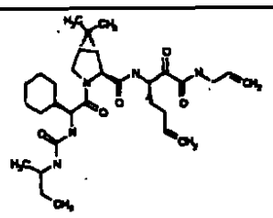
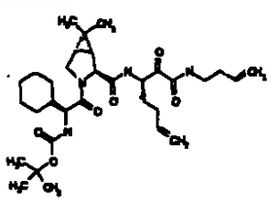
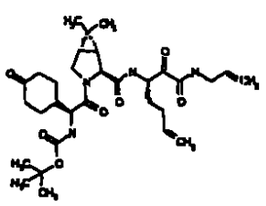
	575	C
	658	C
	621	C
	585	C
	572	A
	587	A
	587	B

Table 5

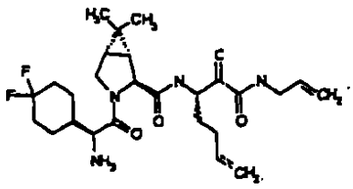
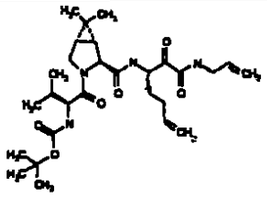
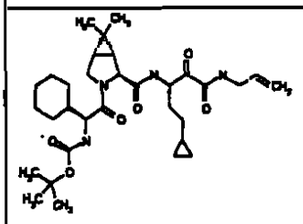
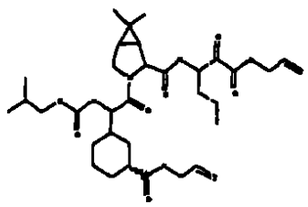
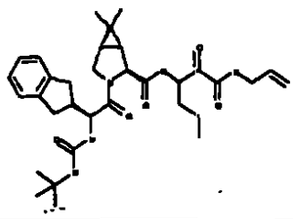
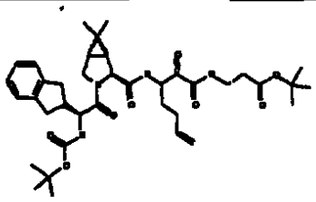
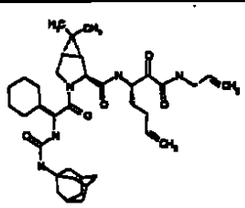
	509	C
	533	C
	587	B
	644	C
	594	B
	695	B
	650	B

Table 5

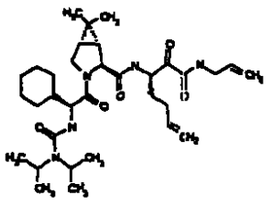
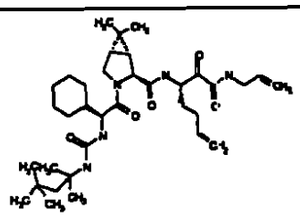
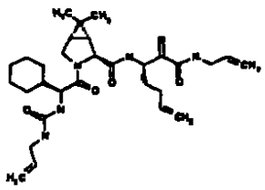
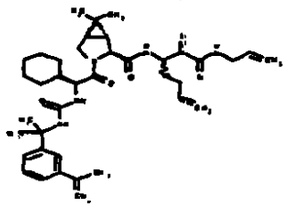
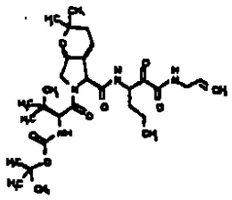
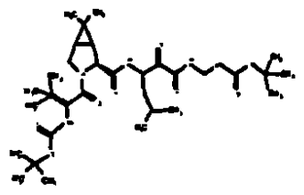
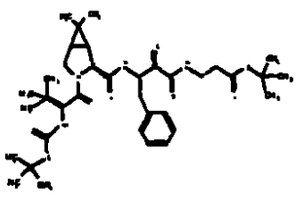
	600	B
	628	A
	556	B
	674	B
	579	C
	637	C
	671	C

Table 5

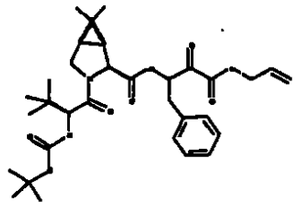
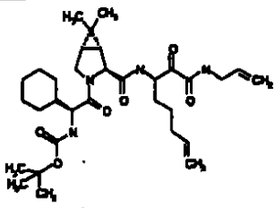
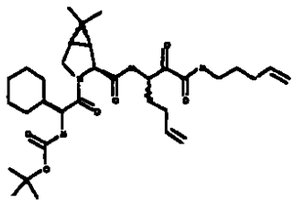
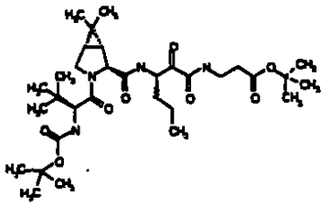
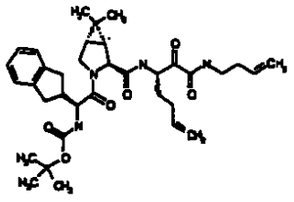
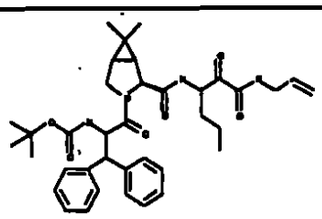
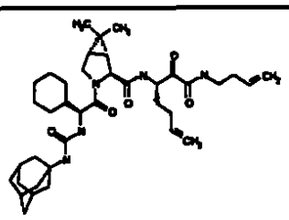
	583	C
	587	B
	601	B
	623	B
	621	A
	645	C
	664	B

Table 5

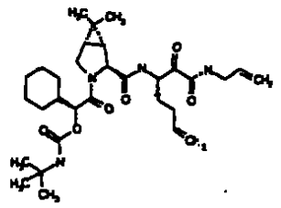
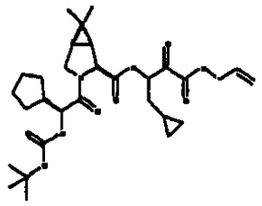
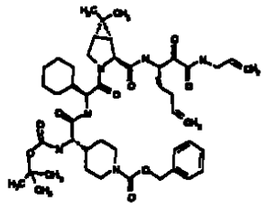
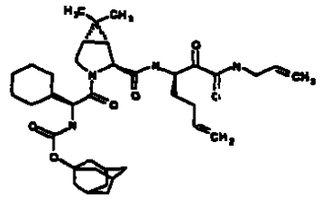
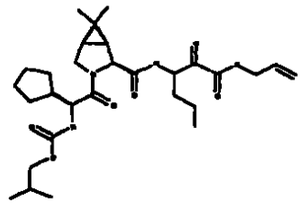
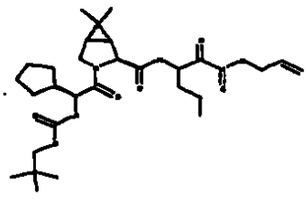
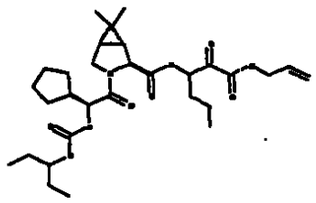
	573	C
	559	C
	847	B
	651	B
	547	C
	561	B
	561	B

Table 5

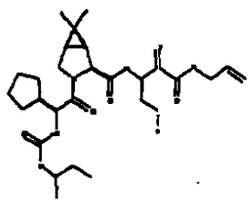
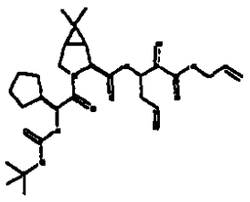
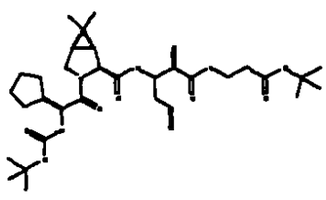
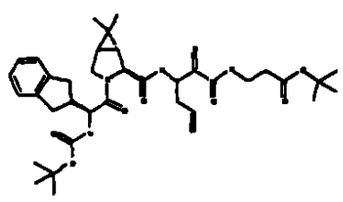
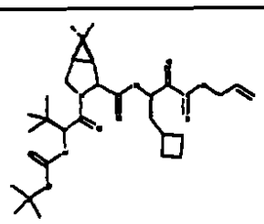
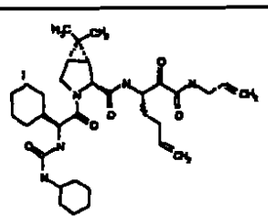
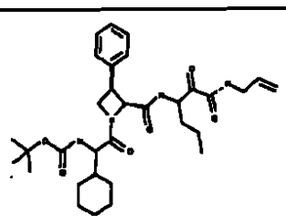
	546	C
	545	C
	633	B
	681	C
	561	C
	598	B
	583	C

Table 5

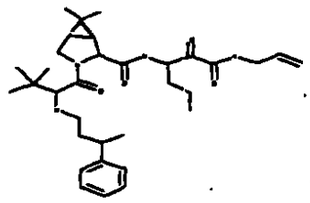
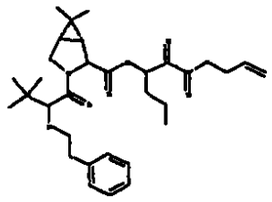
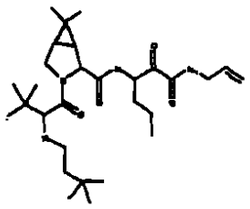
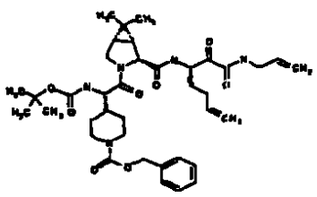
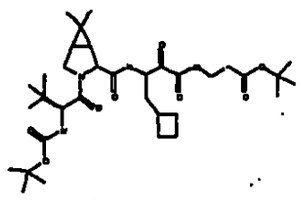
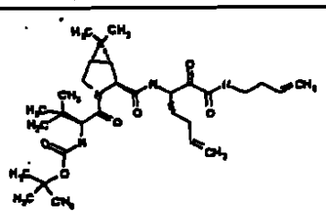
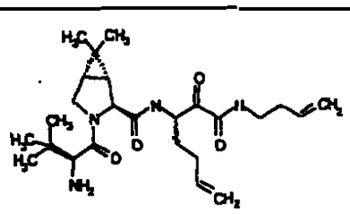
	567	C
	539	C
	519	C
	708	B
	649	C
	561	B
	461	C

Table 5

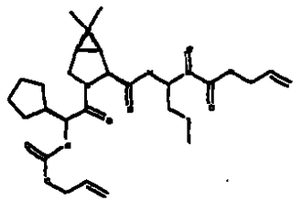
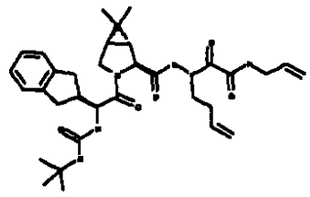
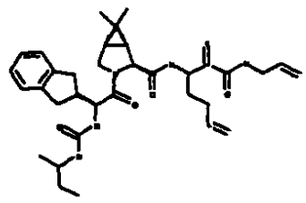
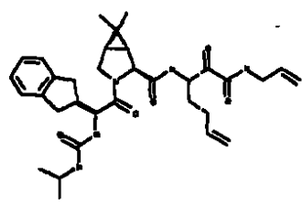
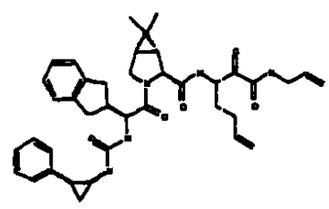
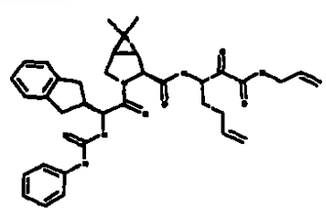
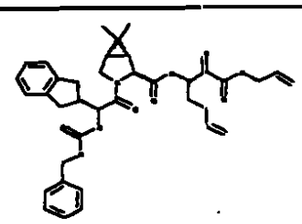
	531	C
	606	A
	606	A
	592	A
	666	C
	626	B
	640	B

Table 5

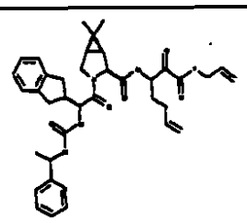
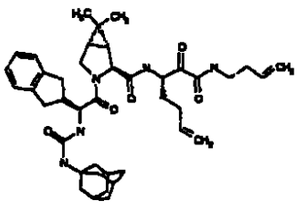
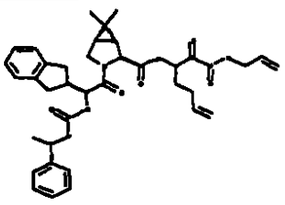
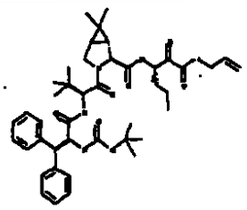
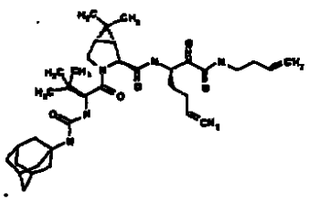
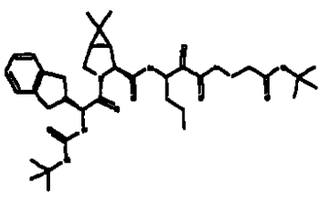
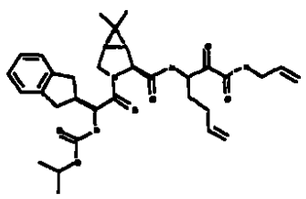
	654	B
	698	B
	654	B
	758	C
	638	A
	683	B
	593	A

Table 5

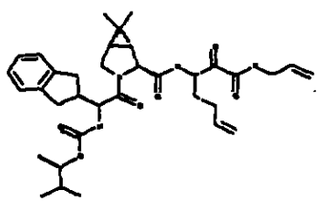
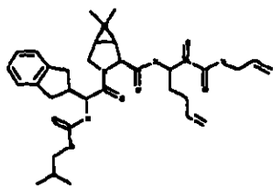
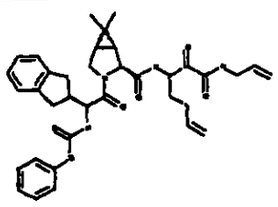
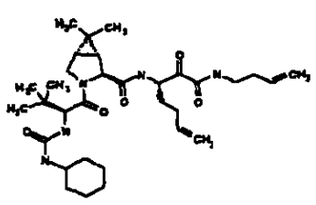
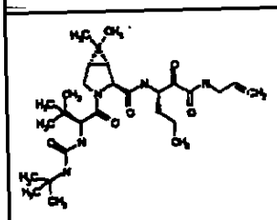
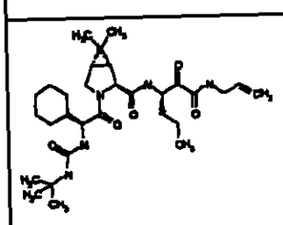
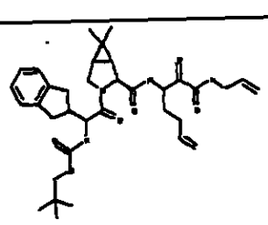
	621	A
	607	B
	627	B
	586	A
	534	B
	560	C
	621	A

Table 5

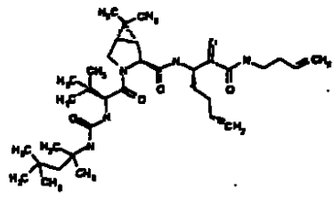
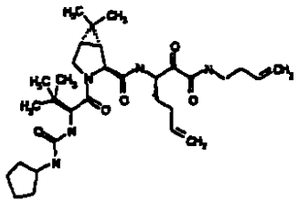
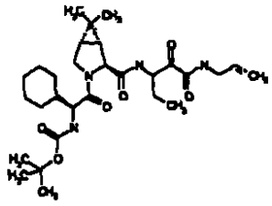
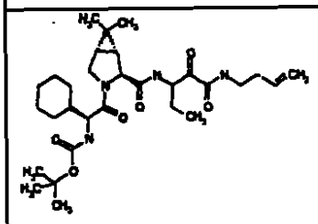
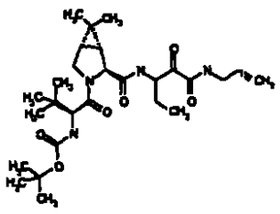
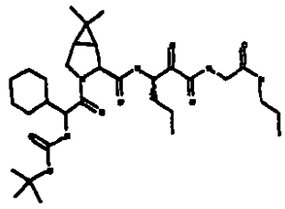
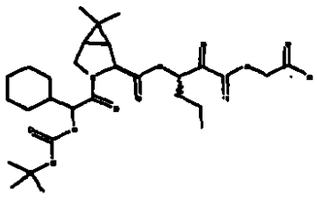
	616	B
	572	A
	547	C
	581	C
	521	C
	620	B
	578	B

Table 5

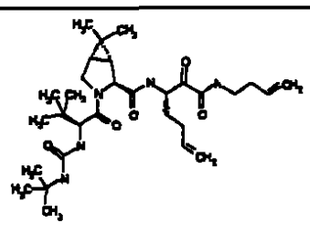
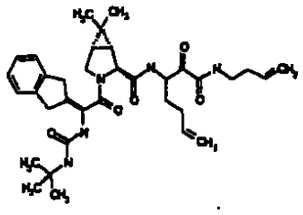
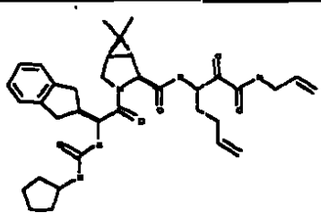
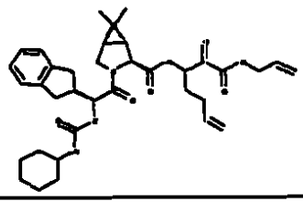
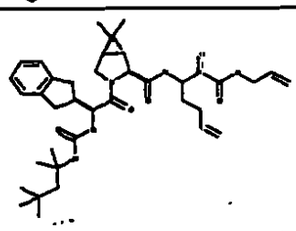
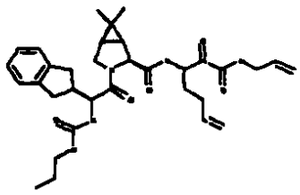
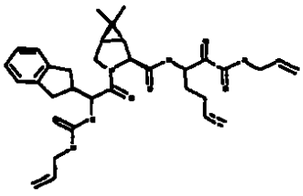
	560	A
	620	A
	618	B
	632	B
	662	B
	592	B
	590	B

Table 5

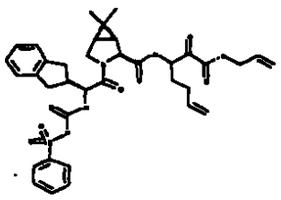
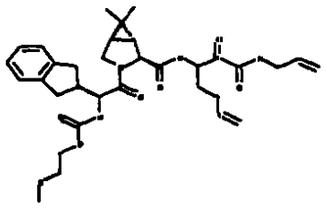
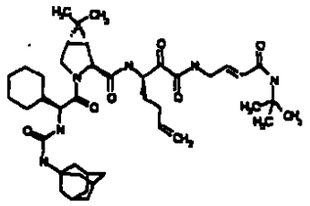
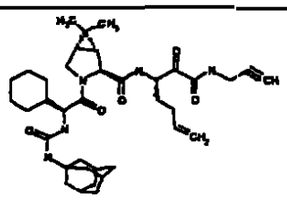
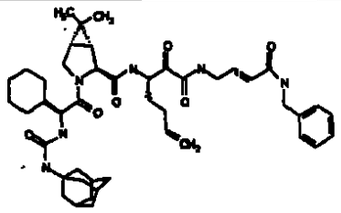
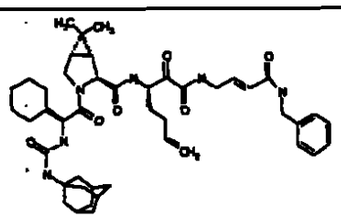
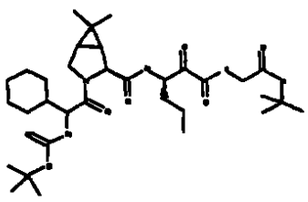
	690	B
	609	B
	749	B
	648	A
	783	B
	783	B
	634	C

Table 5

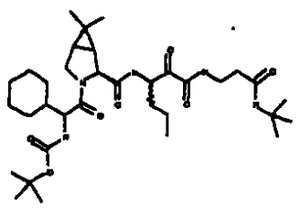
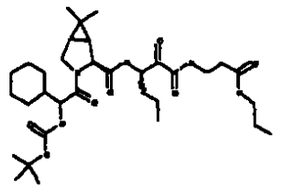
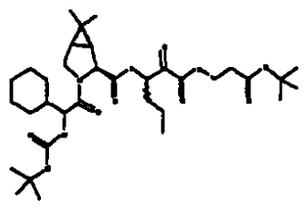
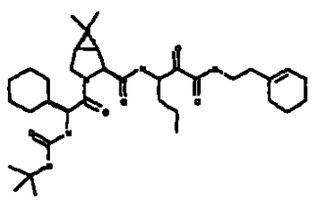
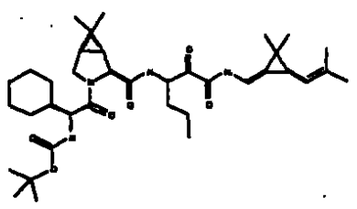
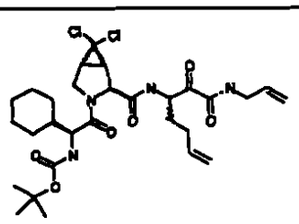
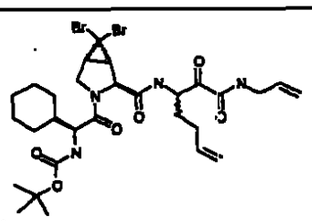
	648	C
	634	C
	649	C
	629	C
	657	C
	614	A
	702	B

Table 5

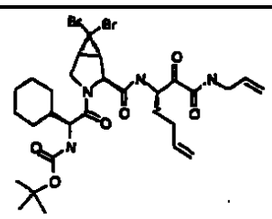
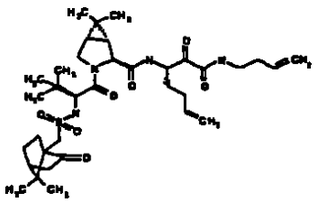
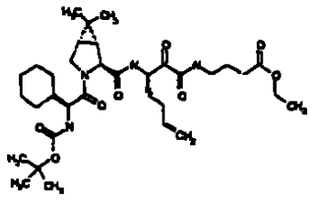
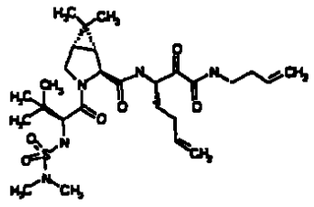
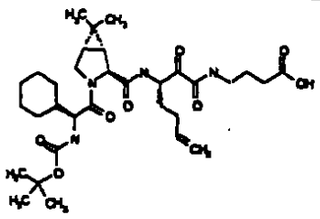
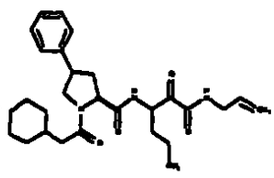
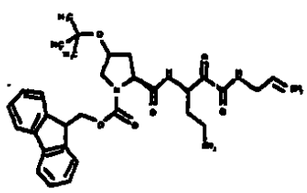
	702	A
	675	B
	647	B
	568	C
	619	C
	482	C
	576	C

Table 5

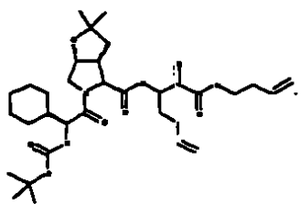
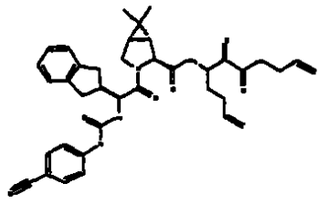
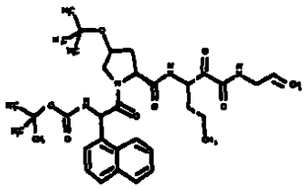
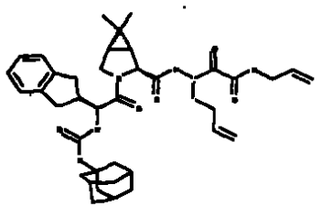
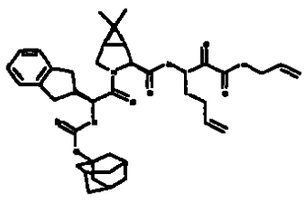
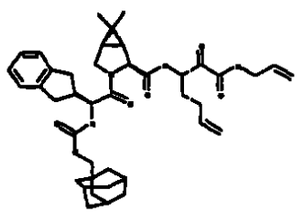
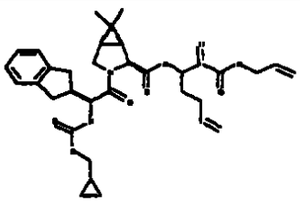
	617	B
	651	C
	637	C
	684	B
	685	B
	698	B
	605	B

Table 5

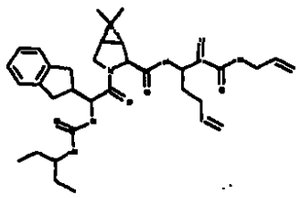
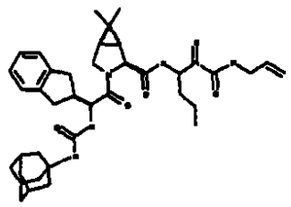
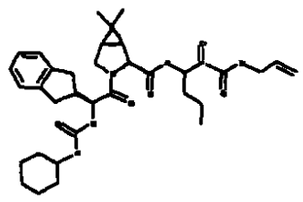
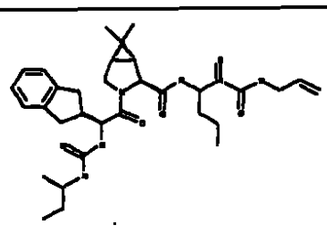
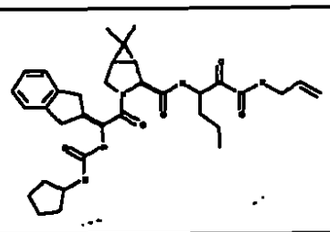
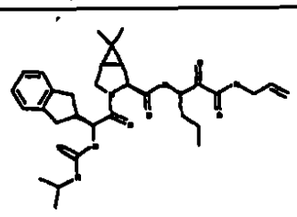
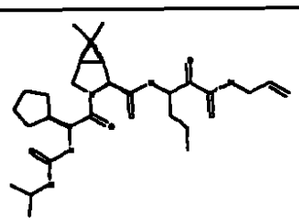
	620	B
	672	C
	620	B
	594	B
	606	B
	580	C
	532	B

Table 5

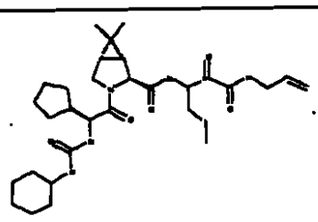
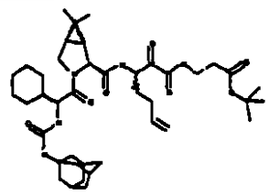
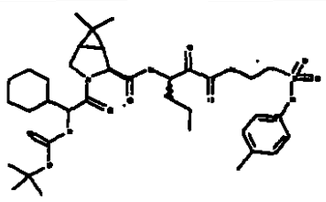
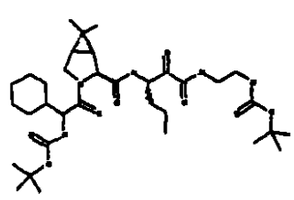
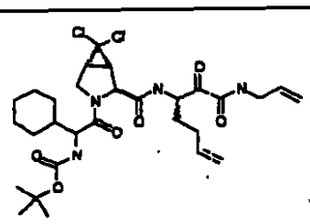
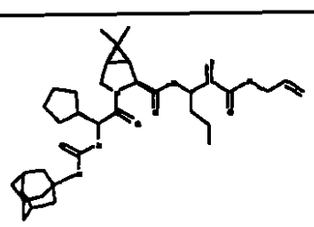
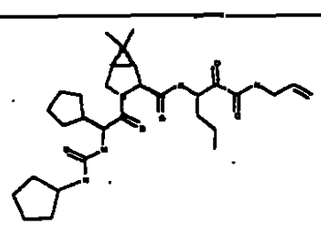
	572	B
	738	A
	718	B
	664	B
	614	B
	624	B
	558	B

Table 5

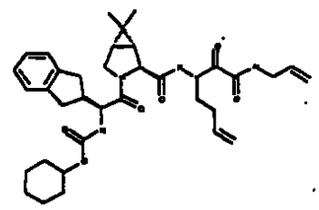
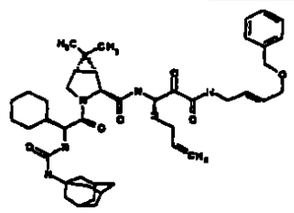
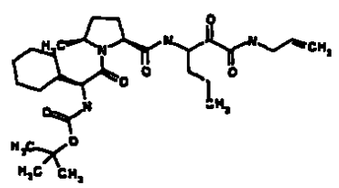
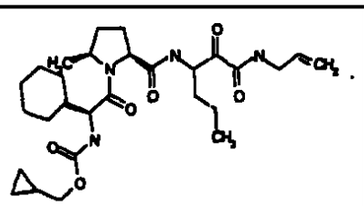
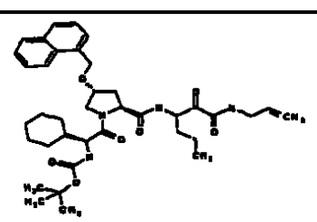
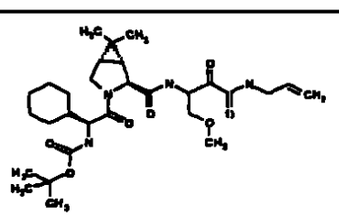
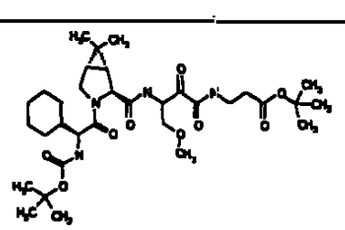
	633	B
	770	C
	535	C
	533	C
	677	C
	563	B
	651	A

Table 5

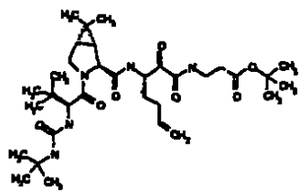
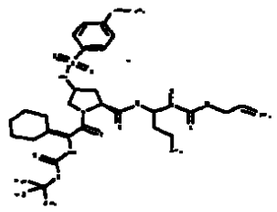
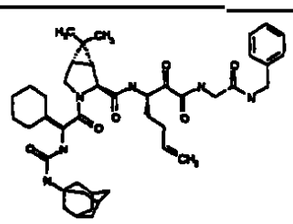
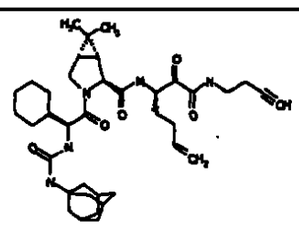
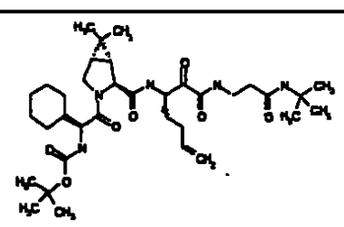
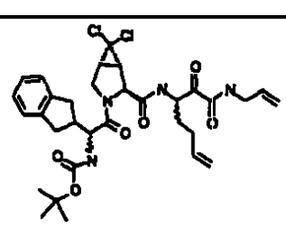
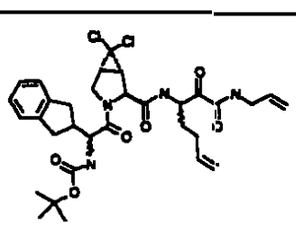
	634	A
	706	C
	757	A
	662	A
	660	A
	648	A
	648	C

Table 5

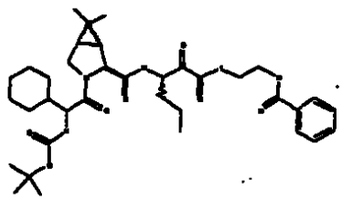
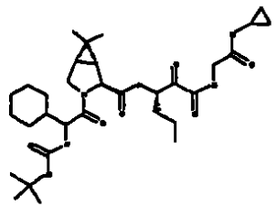
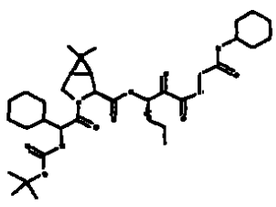
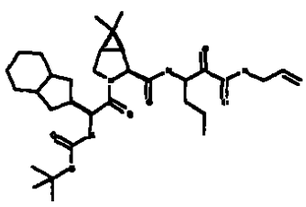
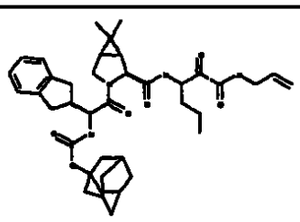
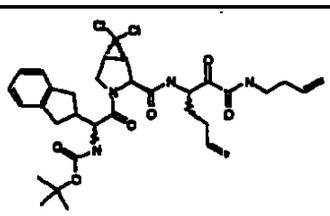
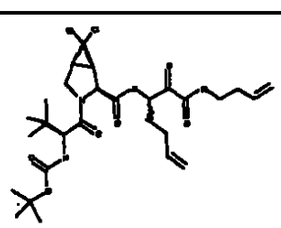
	668	B
	618	A
	660	B
	601	B
	673	B
	662	A
	602	A

Table 5

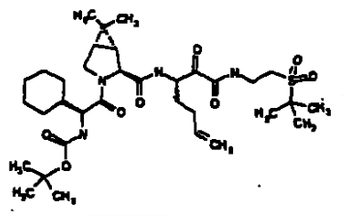
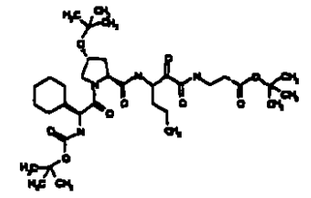
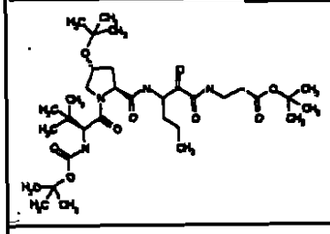
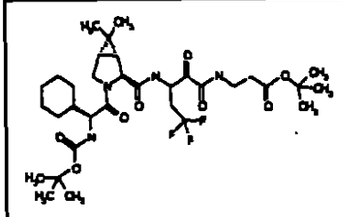
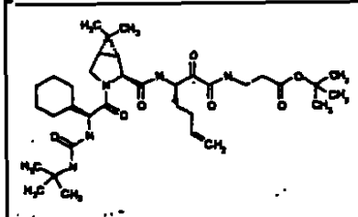
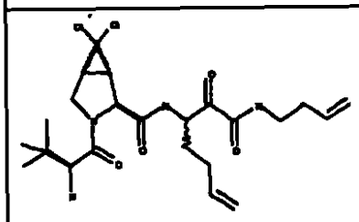
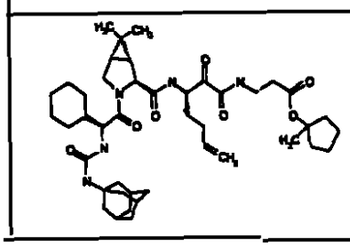
	681	A
	681	C
	655	C
	689	B
	660	A
	538	C
	764	A

Table 5

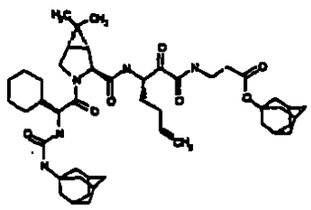
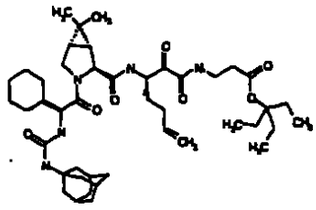
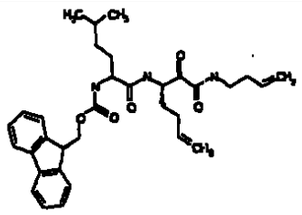
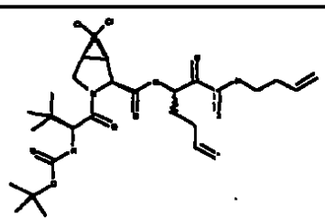
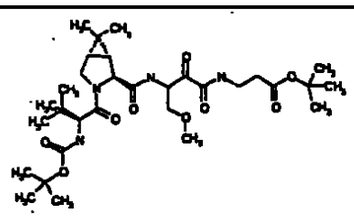
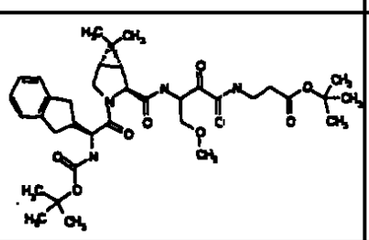
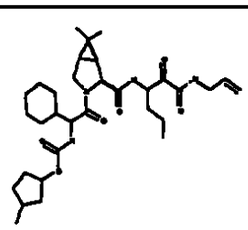
	816	C
	780	B
	560	C
	602	C
	625	B
	685	B
	587	A

Table 5

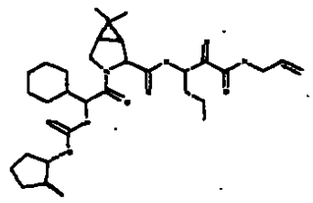
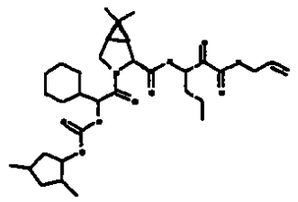
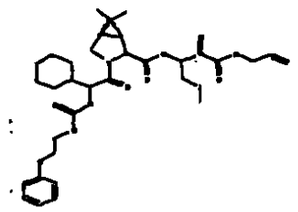
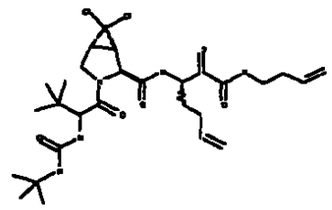
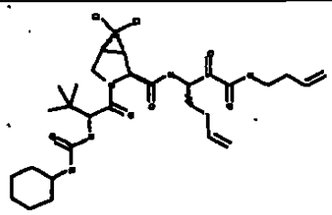
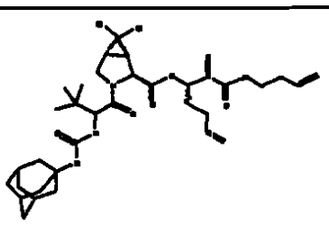
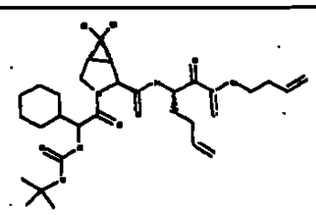
	587	A
	601	A
	625	B
	601	A
	627	B
	679	A
	628	A

Table 5

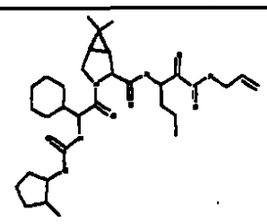
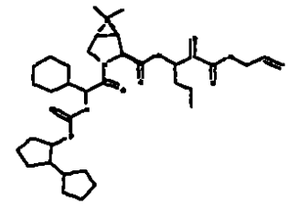
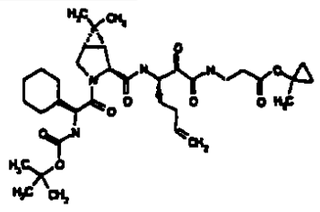
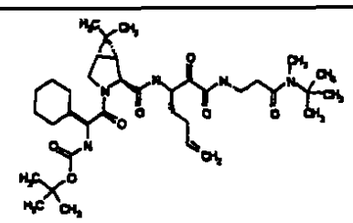
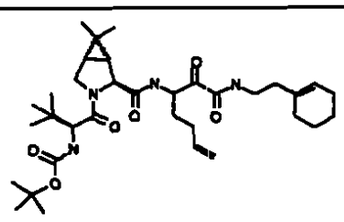
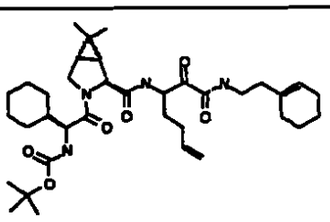
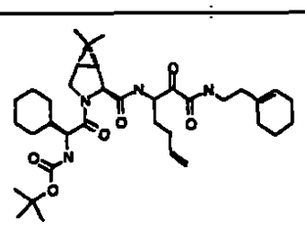
	587	A
	641	A
	659	A
	674	A
	615	B
	641	B
	641	B

Table 5

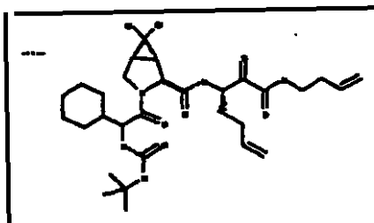
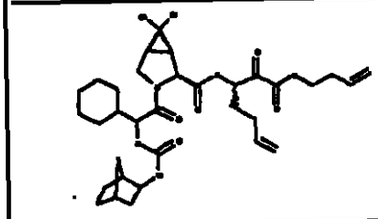
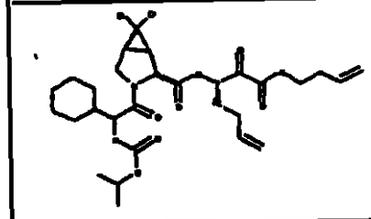
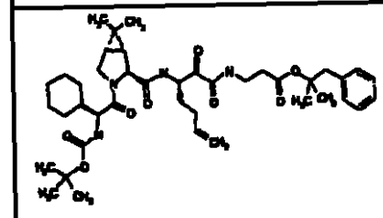
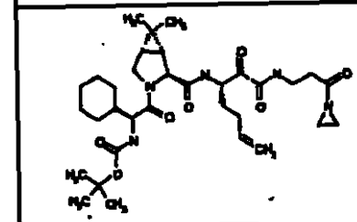
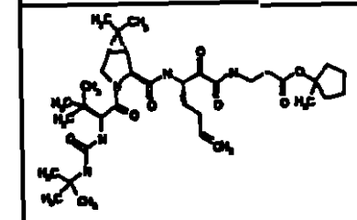
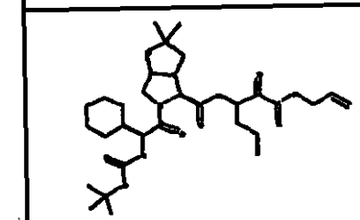
	627	A
	665	A
	614	A
	737	B
	666	A
	660	A
	591	C

Table 5

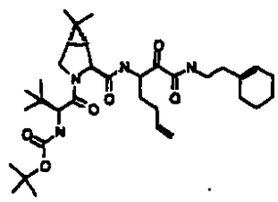
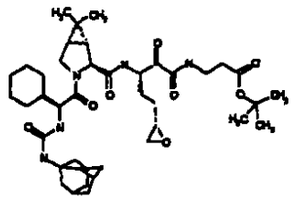
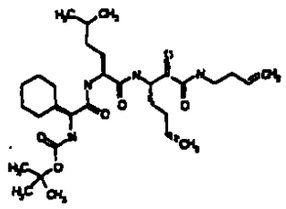
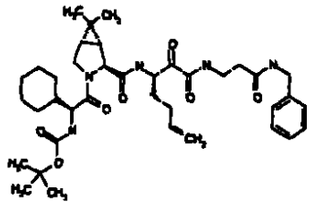
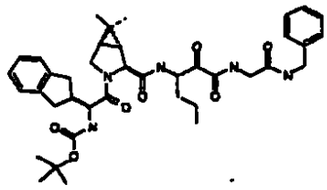
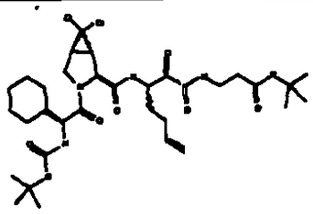
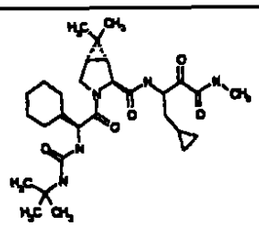
	615	C
	754	B
	577	C
	694	A
	702	A
	701	A
	546	B

Table 5

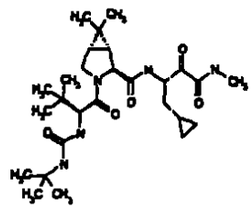
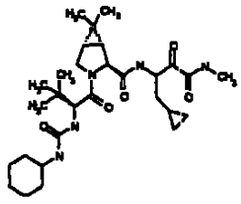
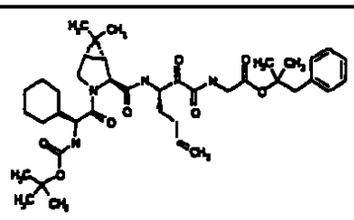
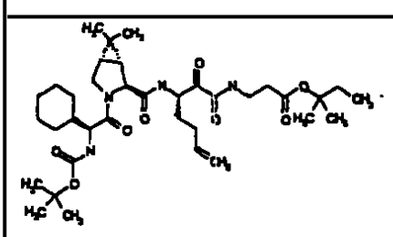
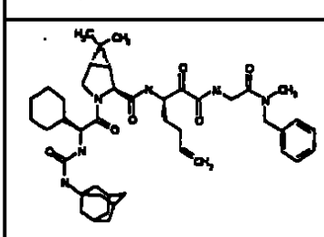
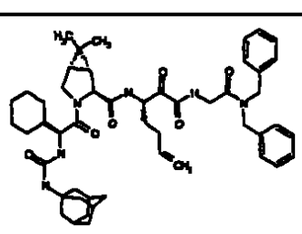
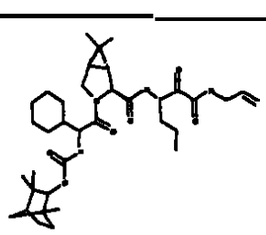
	520	B
	546	B
	723	B
	675	A
	771	B
	847	C
	641	A

Table 5

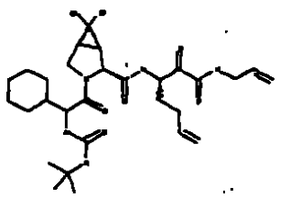
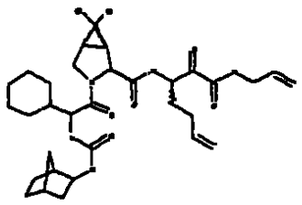
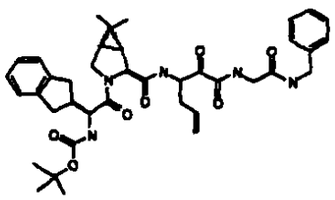
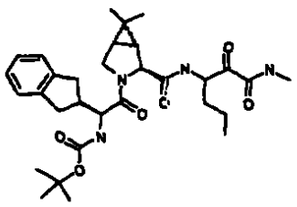
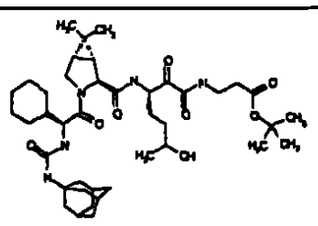
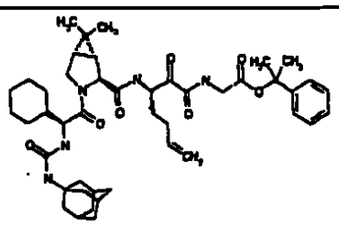
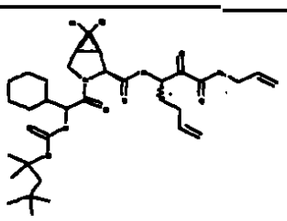
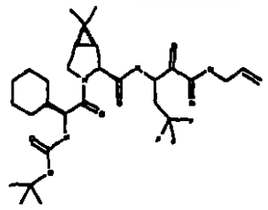
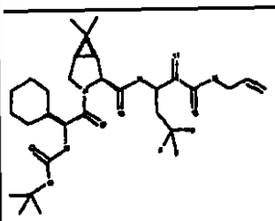
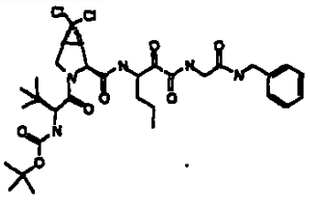
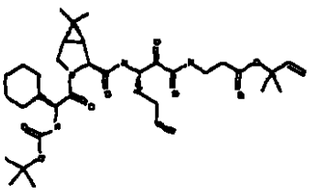
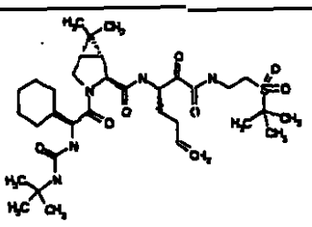
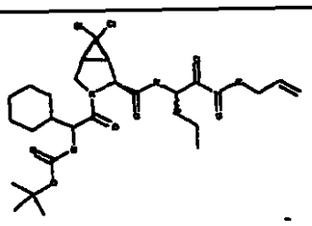
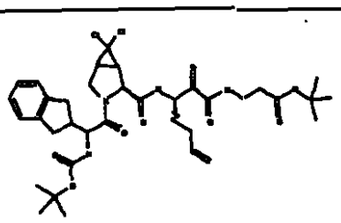
	613	A
	651	C
	700	A
	569	A
	756	B
	786	A
	669	B

Table 5

	601	A
	601	B
	683	A
	673	A
	680	A
	602	A
	735	A

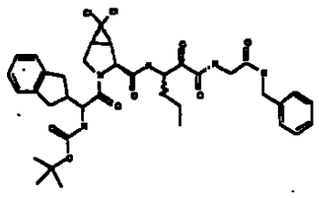
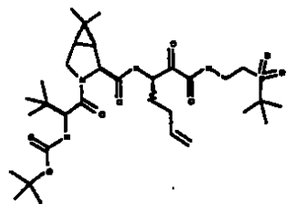
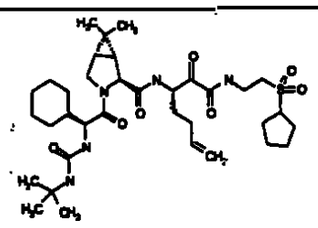
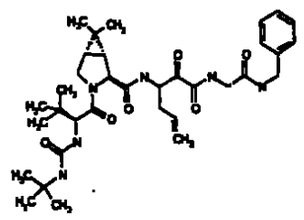
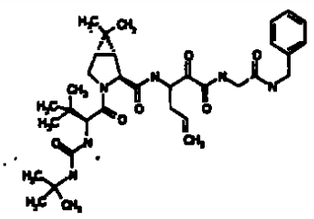
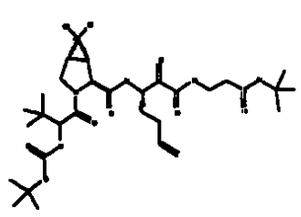
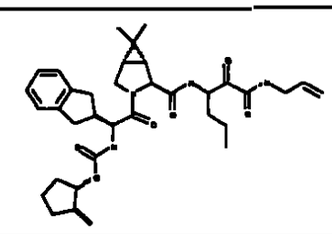
	743	A
	655	B
	692	A
	639	A
	639	A
	675	A
	621	A

Table 5

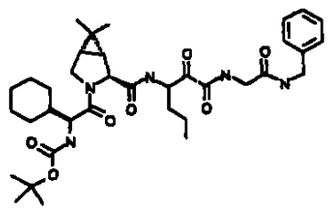
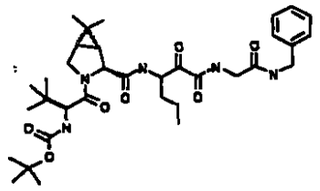
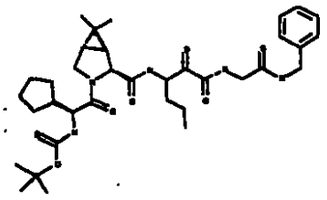
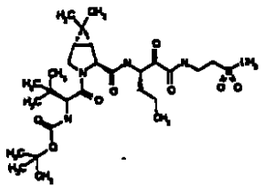
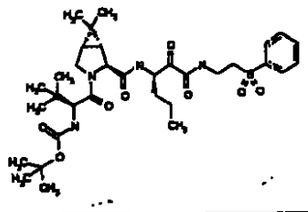
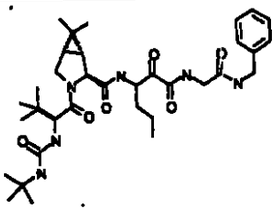
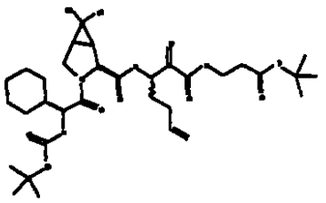
	668	A
	642	A
	654	A
	601	C
	663	B
	641	A
	702	A

Table 5

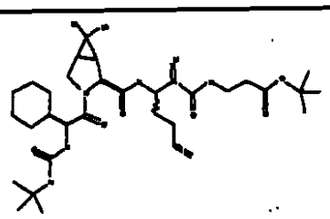
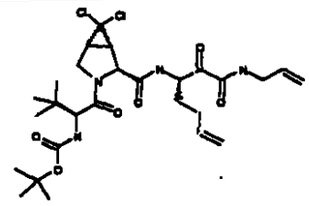
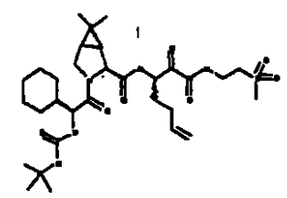
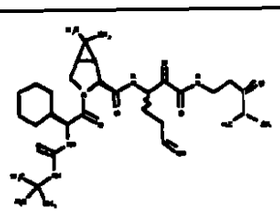
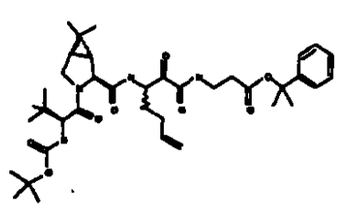
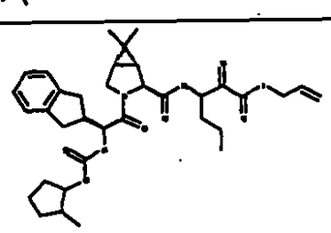
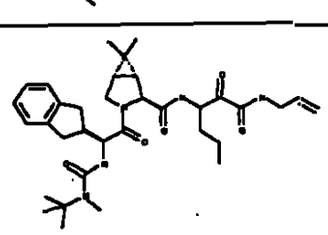
	701	A
	588	B
	638	A
	630	A
	697	A
	621	A
	608	B

Table 5

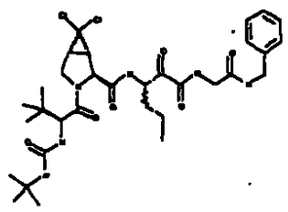
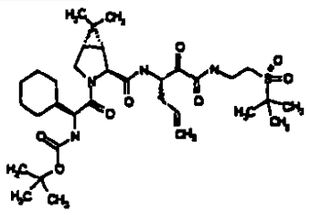
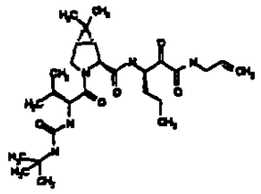
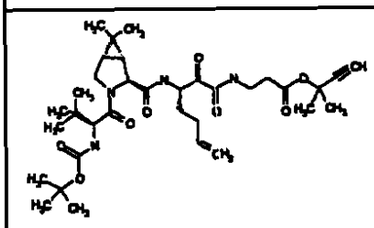
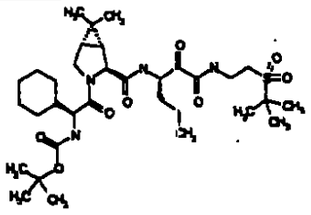
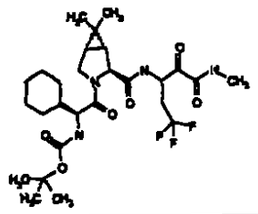
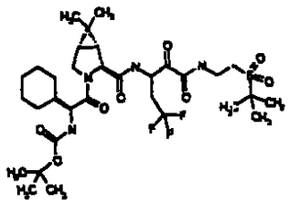
	682	A
	667	B
	520	B
	645	B
	669	C
	575	A
	709	B

Table 5

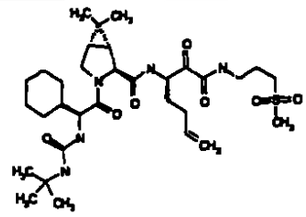
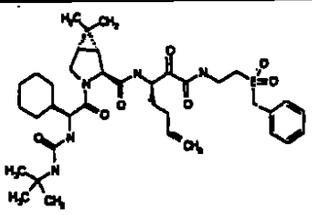
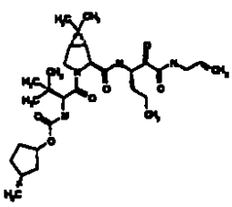
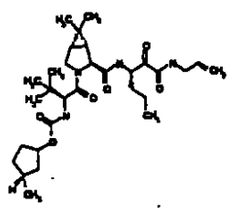
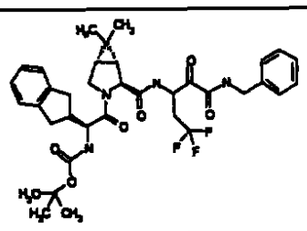
	652	B
	714	A
	561	B
	561	B
	685	B

Table5

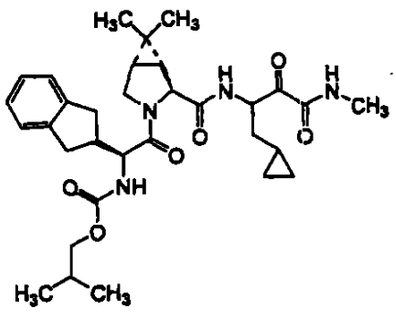
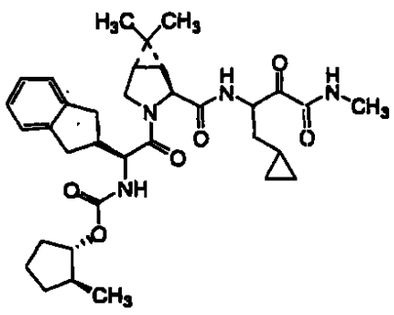
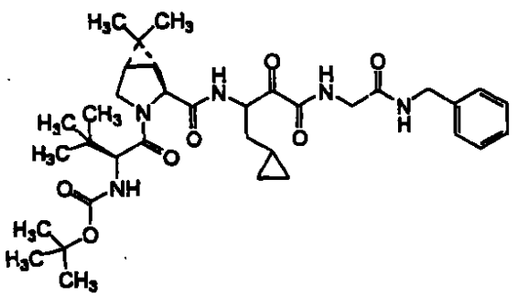
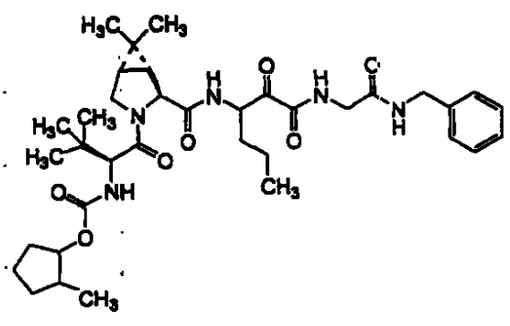
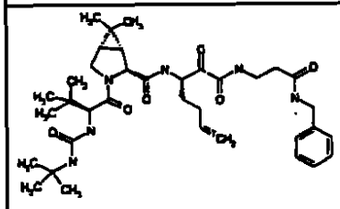
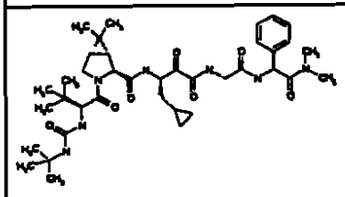
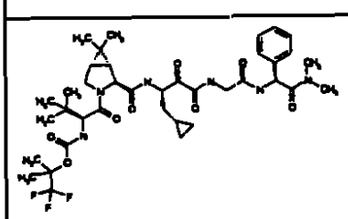
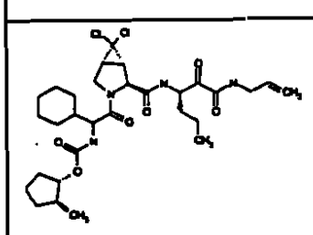
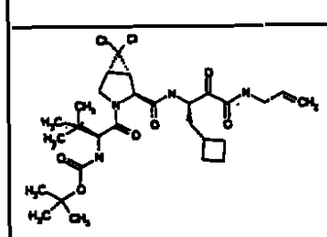
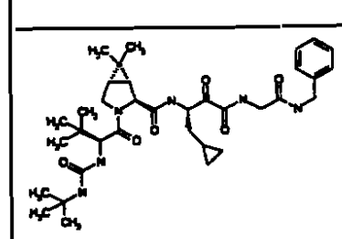
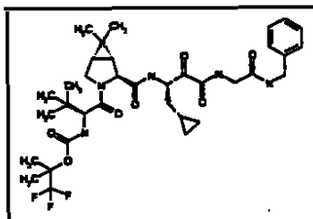
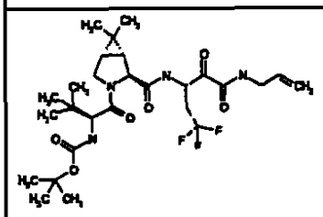
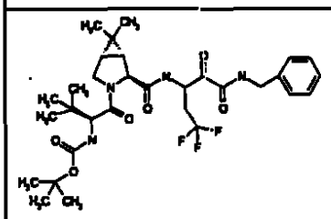
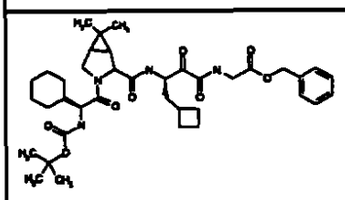
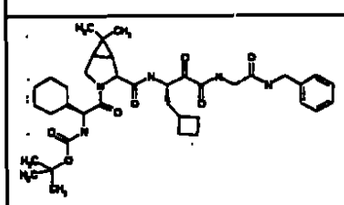
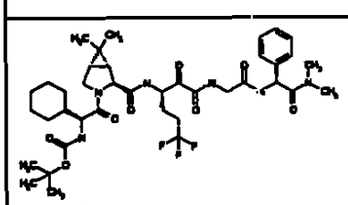
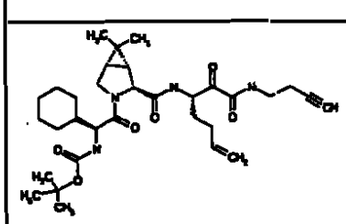
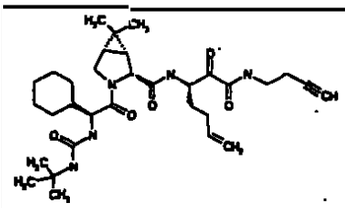
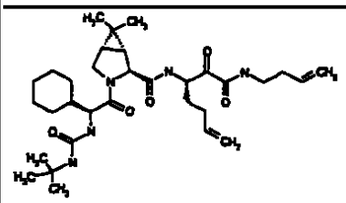
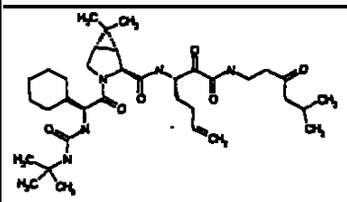
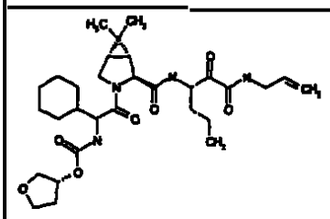
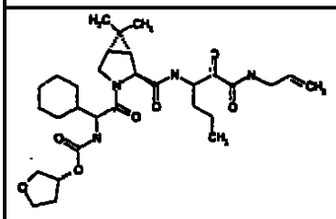
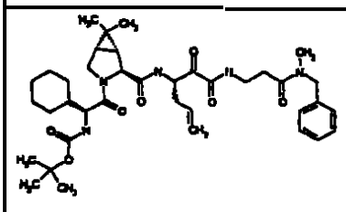
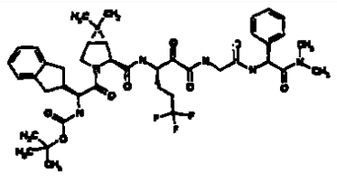
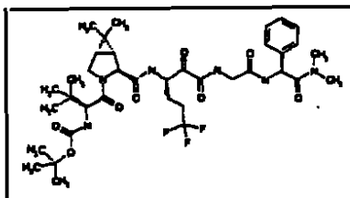
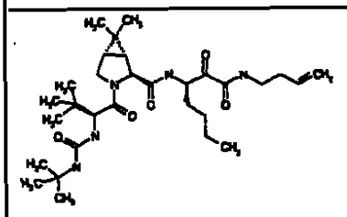
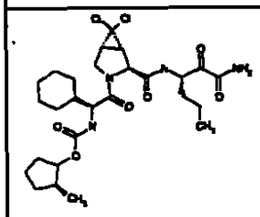
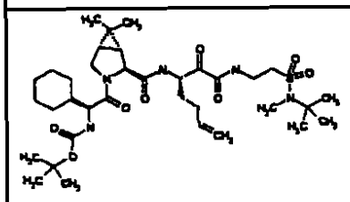
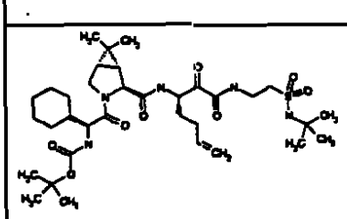
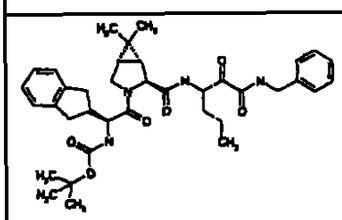
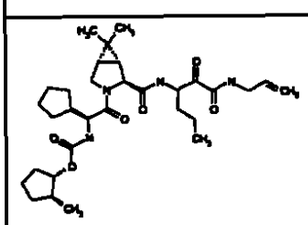
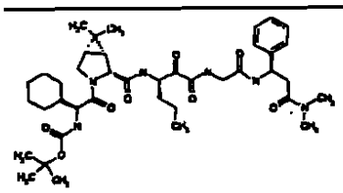
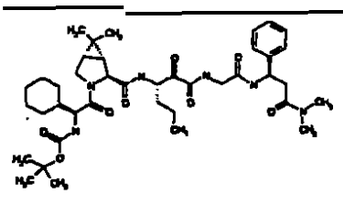
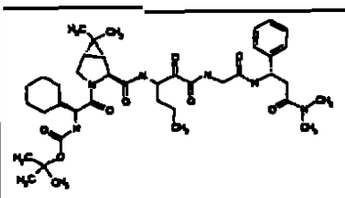
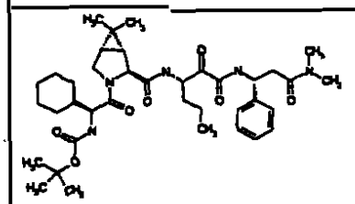
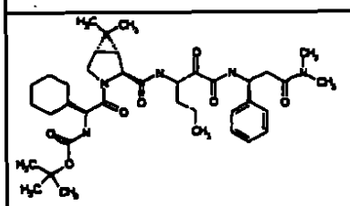
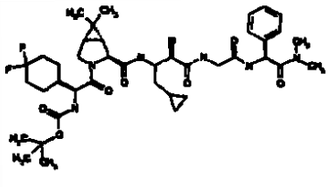
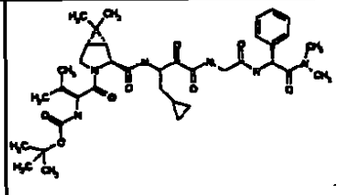
Structure	MW	Ki* Range
	580	A
	606	A
	653	A
	667	A

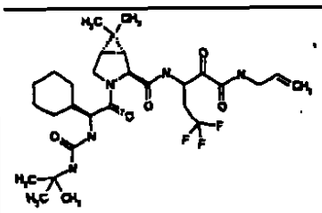
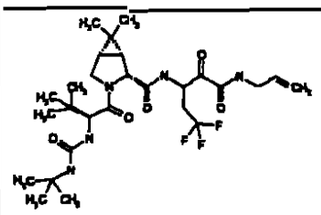
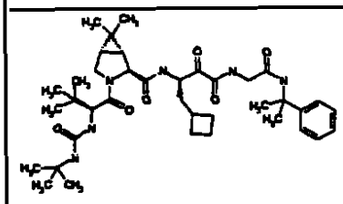
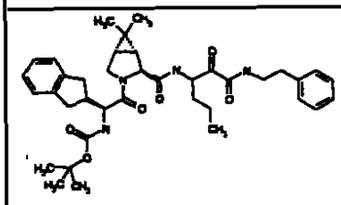
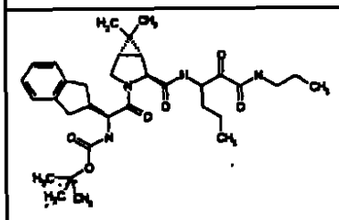
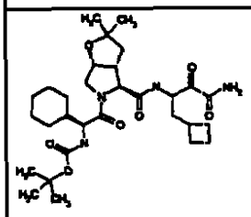
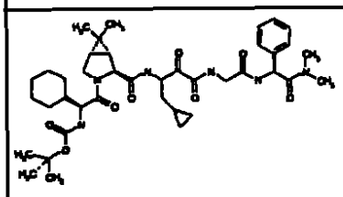
TABLE 6		
STRUCTURE	MW	Ki* (nM)
	666.87	A
	723.92	A
	778.88	A
	627.61	A
	601.58	B
	652.84	A

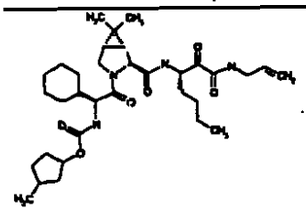
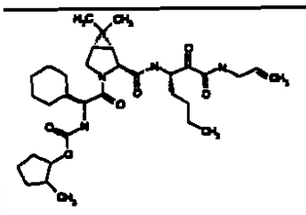
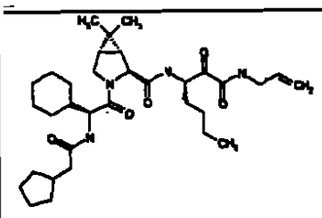
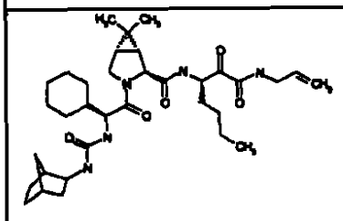
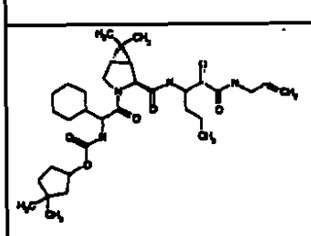
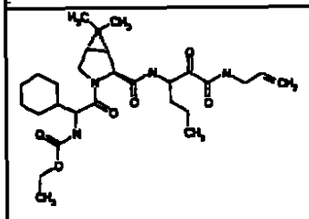
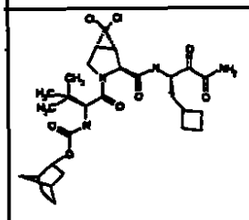
	707.80	A
	574.65	B
	624.71	B
	694.88	A
	693.89	B
	792.90	A
	584.76	A

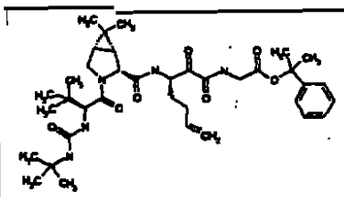
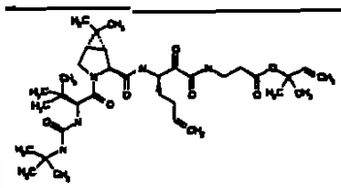
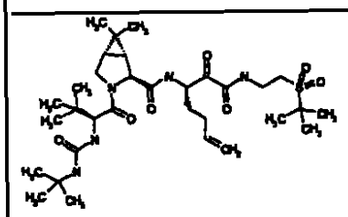
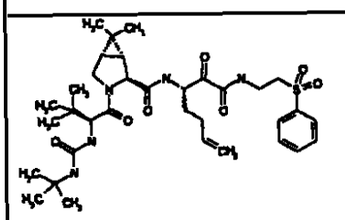
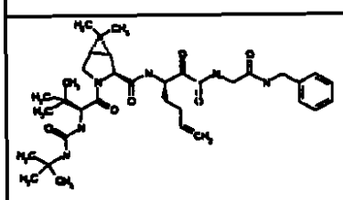
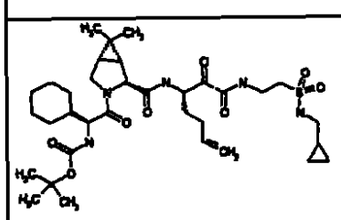
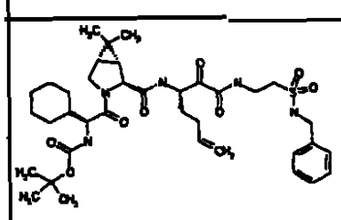
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	585.79	A
	643.87	A
	574.72	B
	574.72	B
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	826.92	A

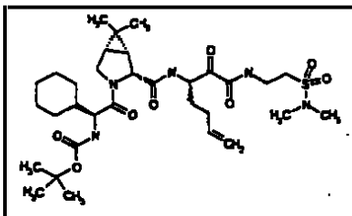
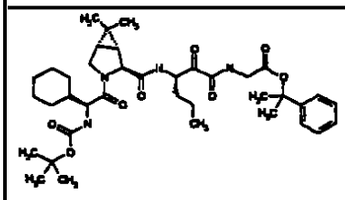
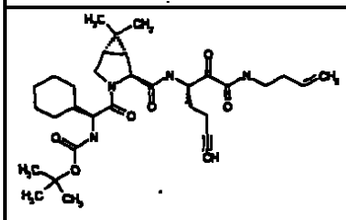
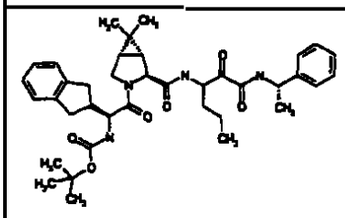
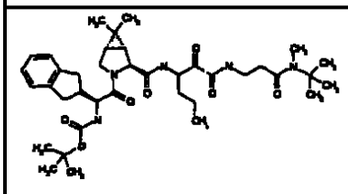
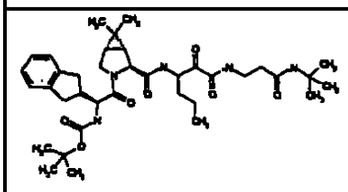
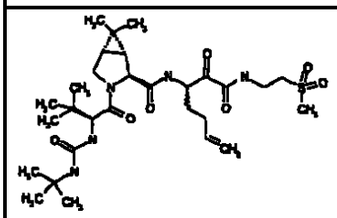
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	561.77	B
	587.55	A
	709.95	A
	695.93	B
	644.82	B
	572.75	A

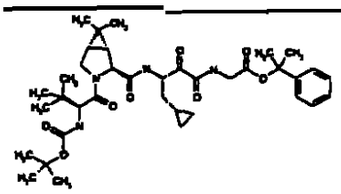
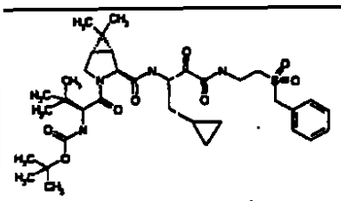
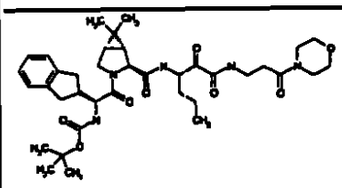
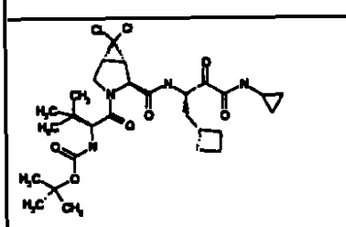
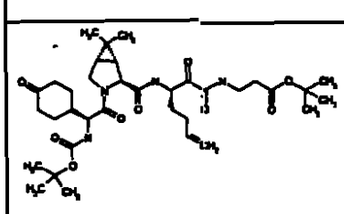
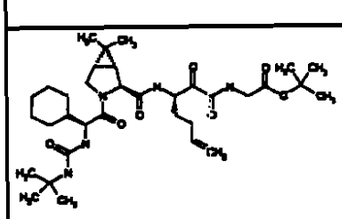
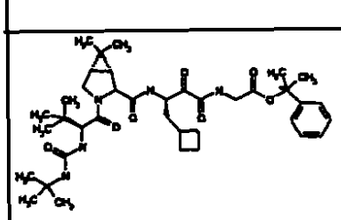
	752.96	A
	752.96	A
	752.96	A
	695.91	C
	695.91	B
	786.92	A
	710.88	A

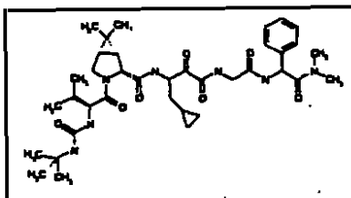
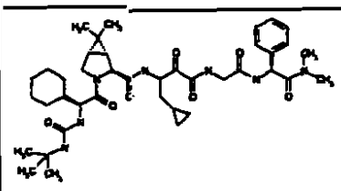
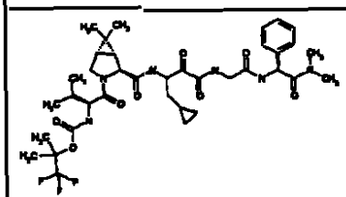
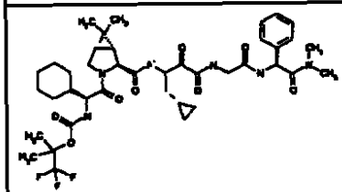
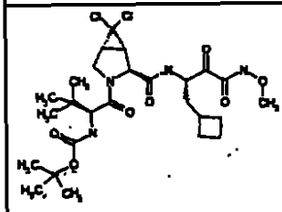
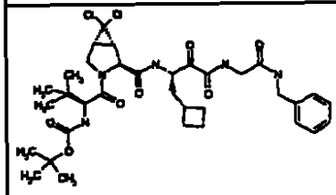
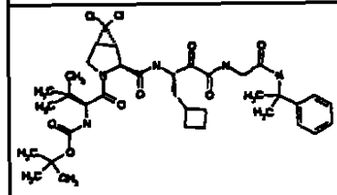
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	573.66	B
	694.92	B
	658.85	B
	596.77	B
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	750.94	A

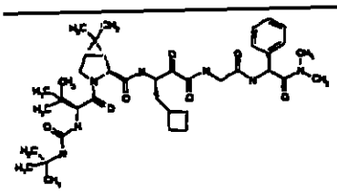
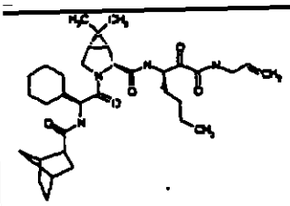
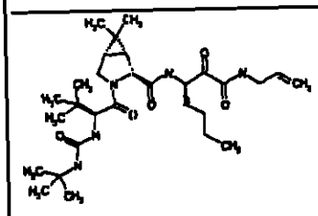
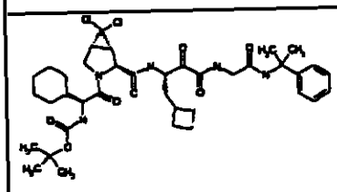
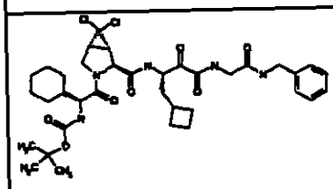
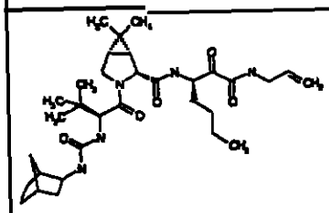
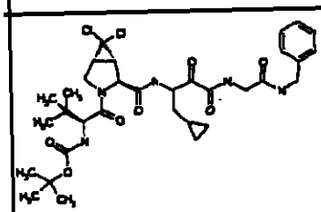
	600.81	B
	600.81	B
	584.81	B
	611.83	A
	600.81	B
	532.69	B
	599.56	A

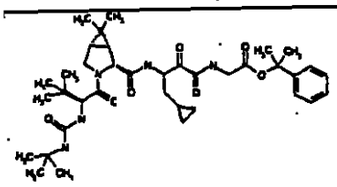
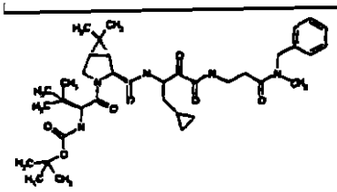
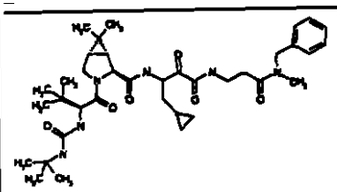
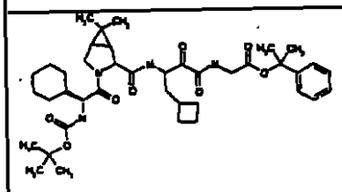
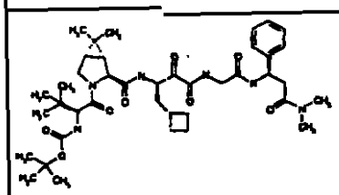
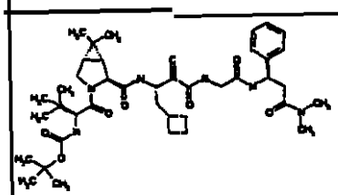
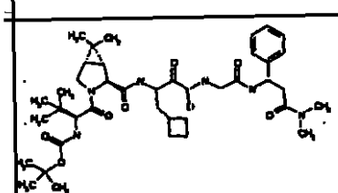
	681.88	A
	645.85	A
	653.89	B
	673.88	A
	652.84	A
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	729.94	A

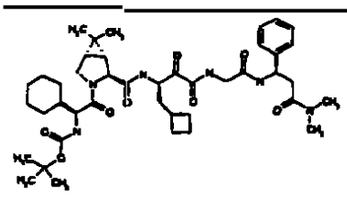
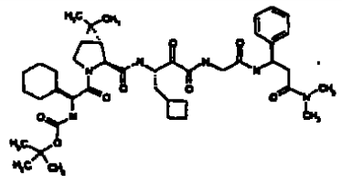
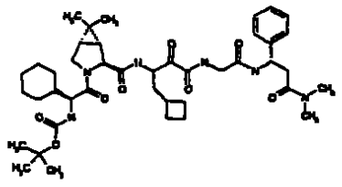
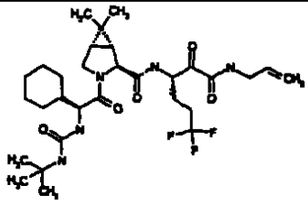
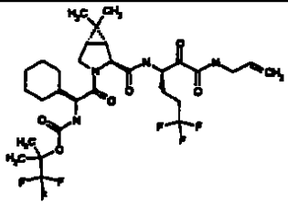
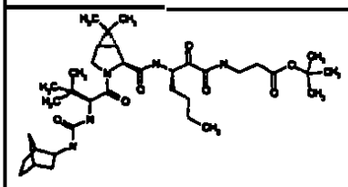
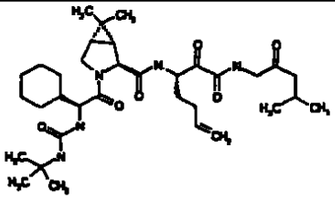
	667.87	A
	696.89	A
	584.76	A
	658.85	A
	695.91	B
	681.88	B
	611.81	B

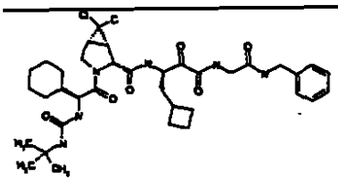
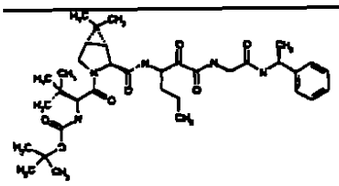
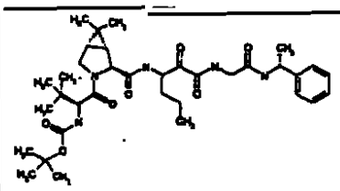
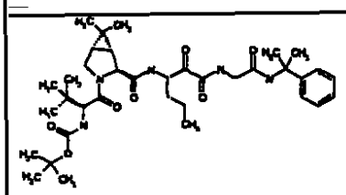
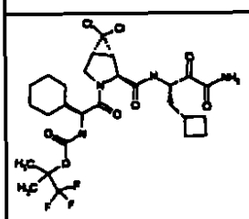
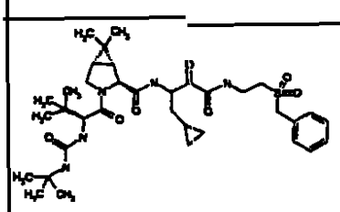
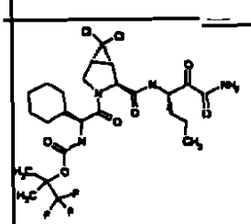
	682.87	A
	688.89	A
	695.86	B
	601.58	B
	674.84	A
	645.85	B
	695.91	A

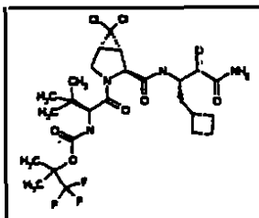
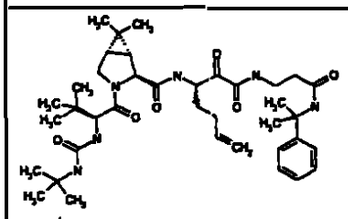
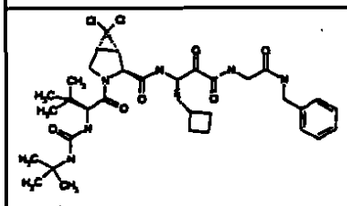
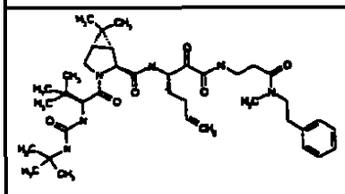
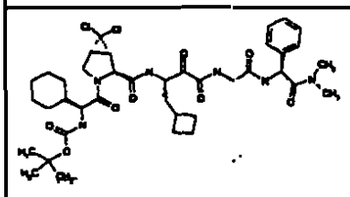
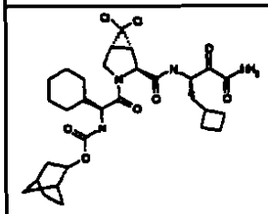
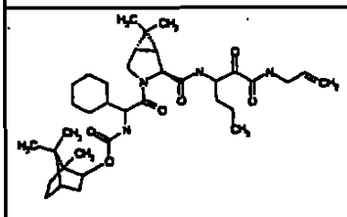
	709.89	A
	749.96	A
	764.85	A
	804.92	A
	591.54	A
	708.69	C
	736.74	C

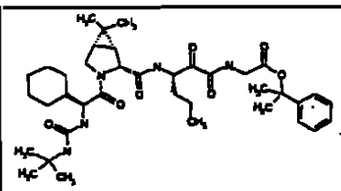
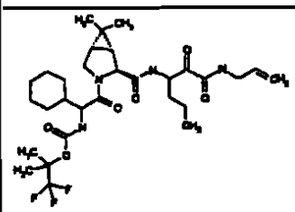
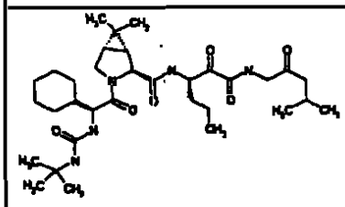
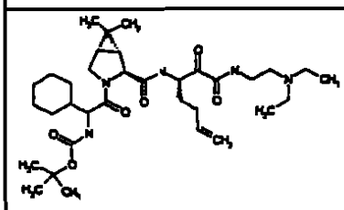
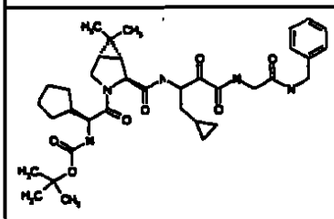
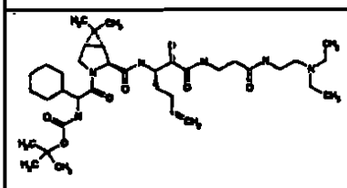
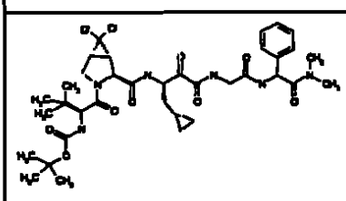
	737.95	A
	596.82	B
	547.74	B
	762.78	C
	734.73	A
	585.79	B
	694.66	A

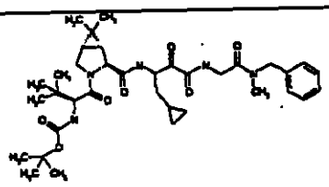
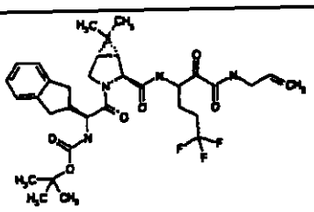
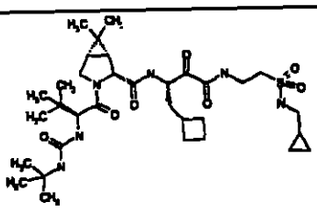
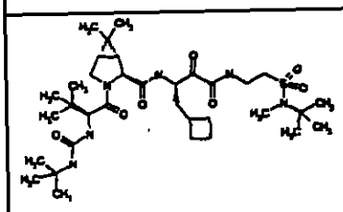
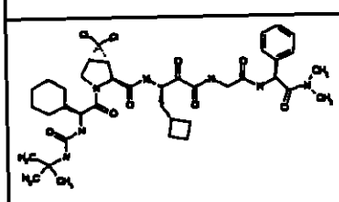
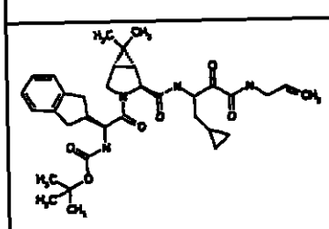
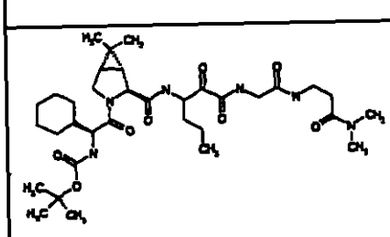
	681.88	A
	681.88	B
	680.90	B
	722.93	C
	752.96	A
	752.96	A
	752.96	A

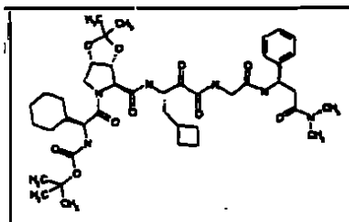
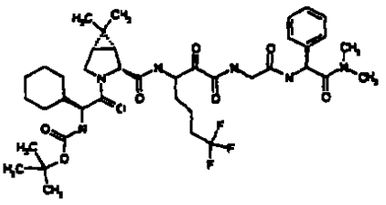
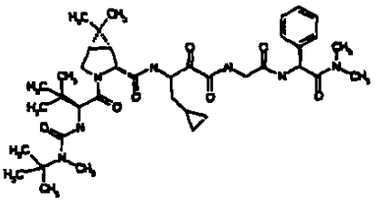
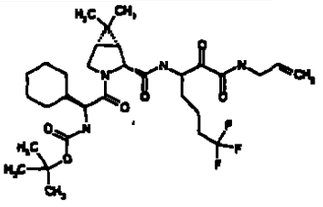
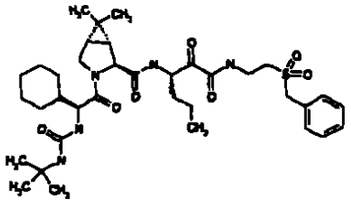
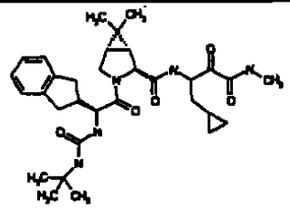
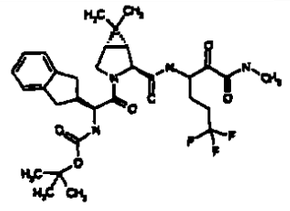
	779.00	A
	779.00	A
	779.00	A
	613.73	C
	668.68	A
	673.90	B
	629.85	B

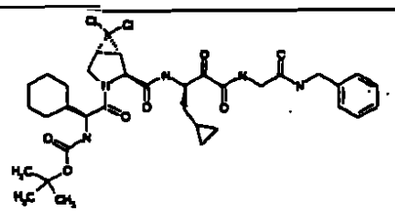
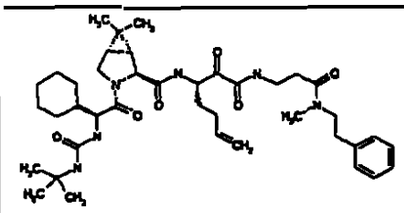
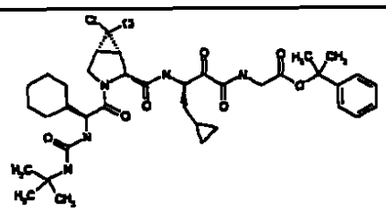
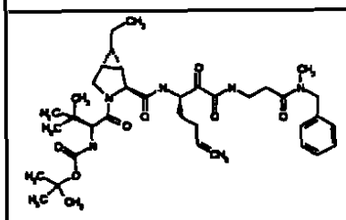
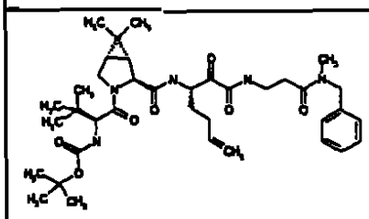
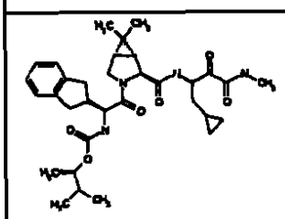
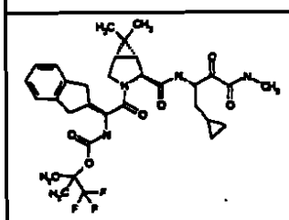
	733.74	B
	655.84	B
	655.84	B
	669.87	B
	641.52	B
	687.91	A
	615.48	A

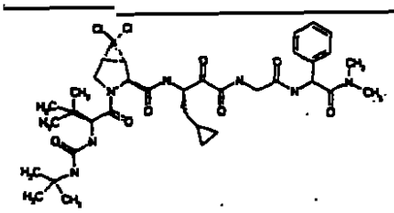
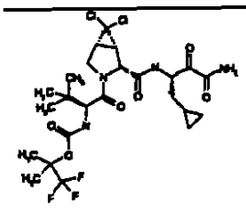
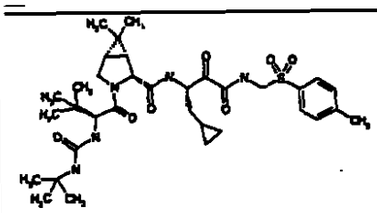
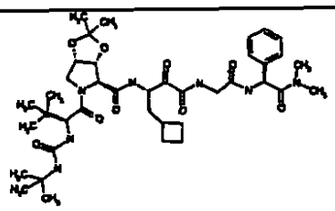
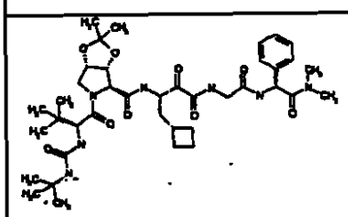
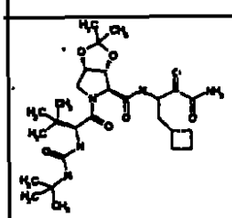
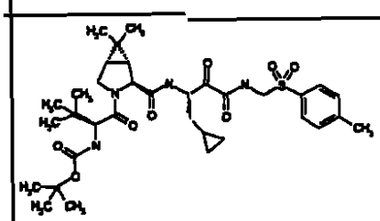
	615.48	A
	694.92	B
	707.70	A
	694.92	A
	805.81	A
	625.60	A
	640.87	B

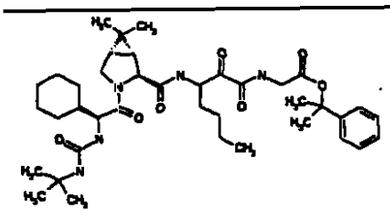
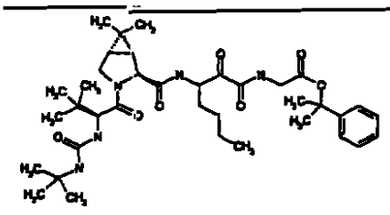
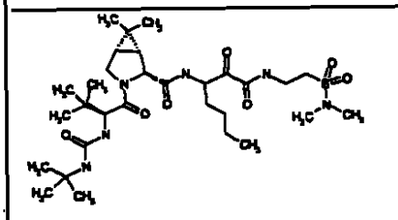
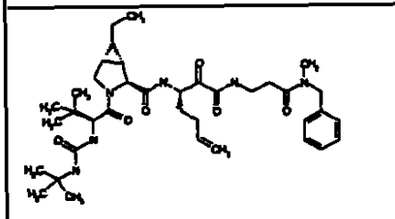
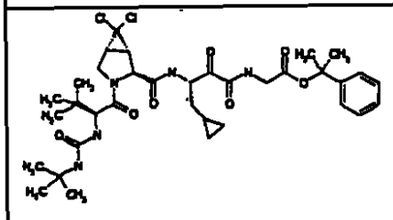
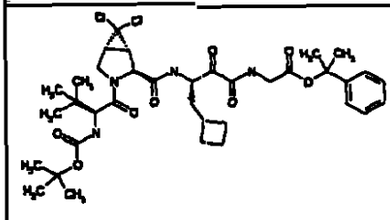
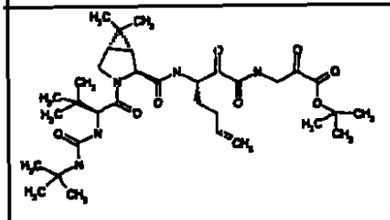
	695.91	A
	614.71	B
	617.84	B
	631.86	C
	665.84	A
	702.94	C
	765.74	A

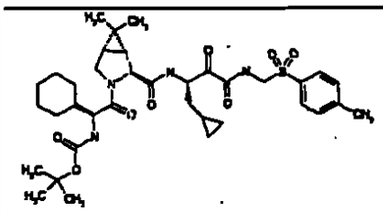
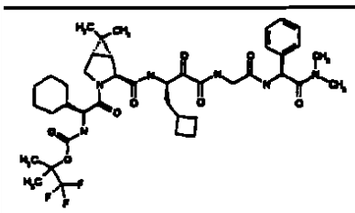
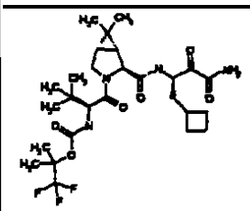
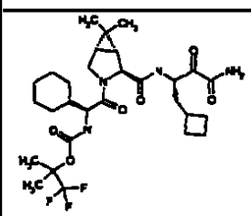
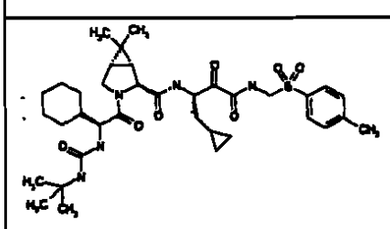
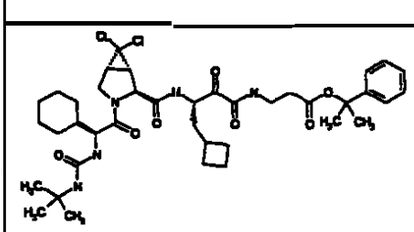
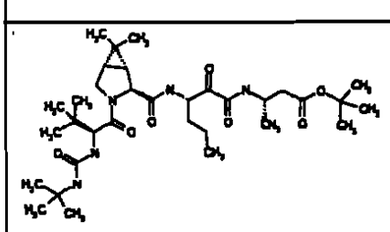
	667.85	C
	648.73	A
	680.91	B
	696.96	C
	804.82	A
	606.77	B
	676.86	A

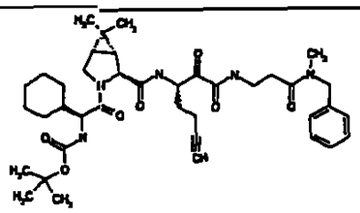
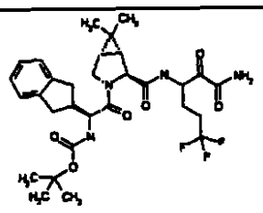
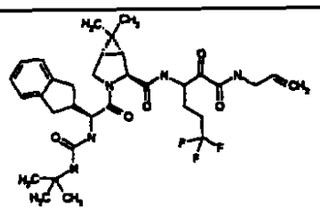
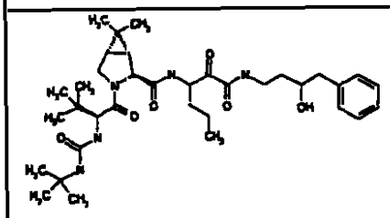
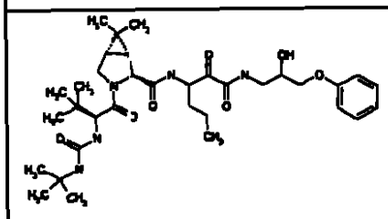
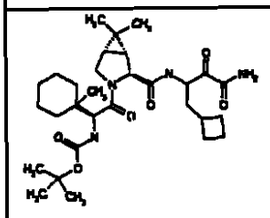
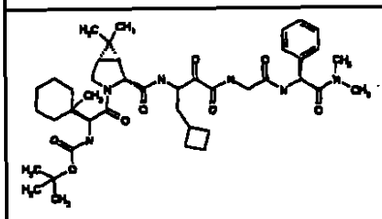
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	806.93	A
	737.95	A
	628.74	B
	701.93	A
	579.75	B
	622.69	B

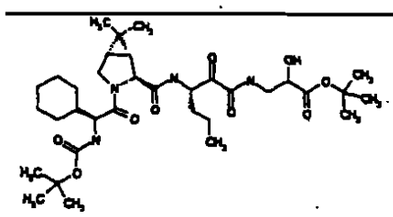
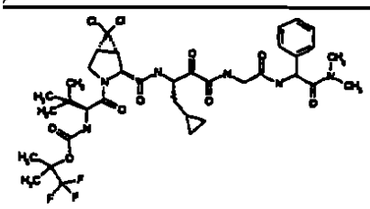
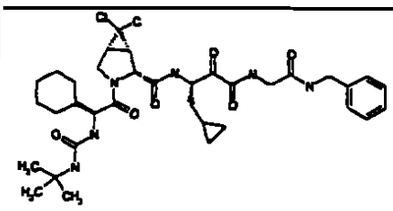
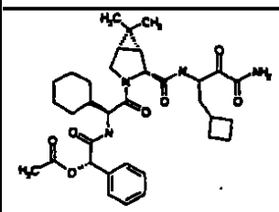
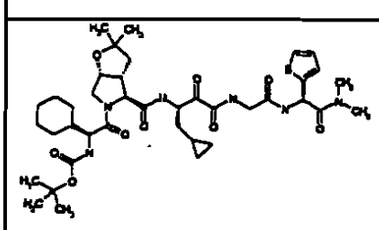
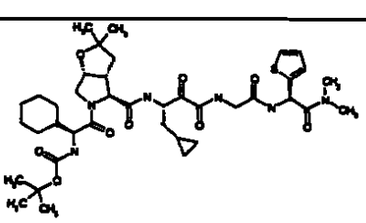
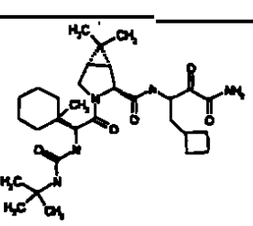
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	720.96	A
	748.75	A
	681.88	B
	681.88	B
	594.76	A
	634.70	A

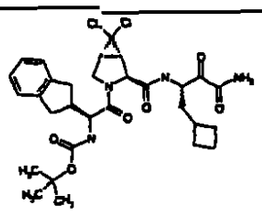
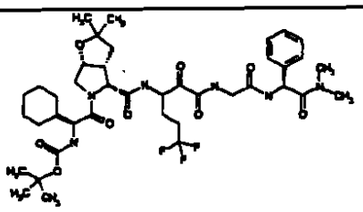
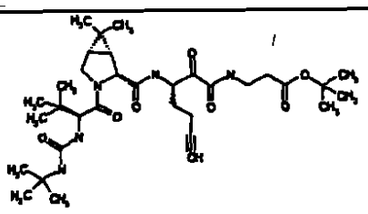
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	601.46	A
	673.88	A
	769.95	B
	769.95	A
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	674.86	B

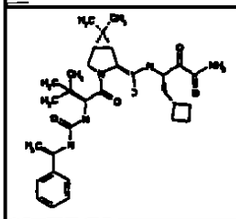
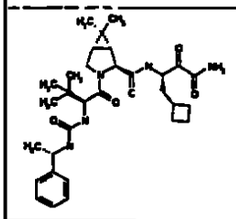
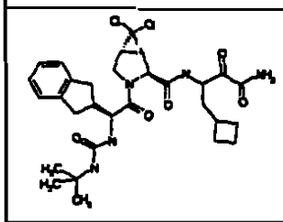
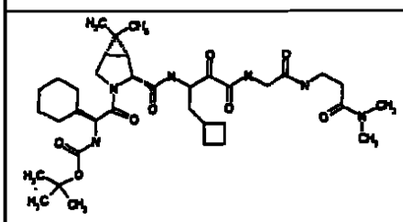
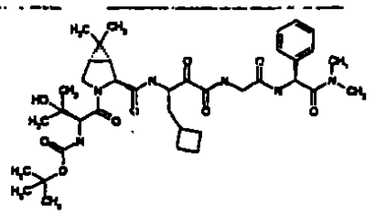
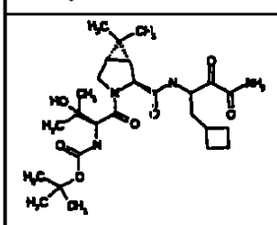
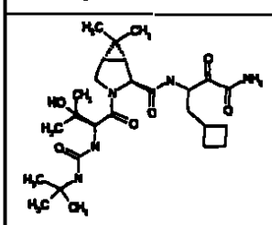
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	683.90	B
	642.87	B
	680.90	B
	722.72	A
	737.73	B
	647.82	B

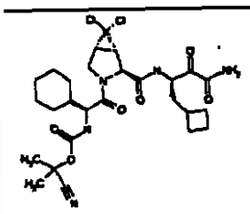
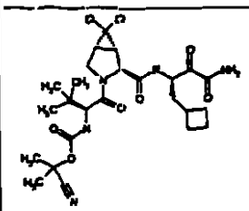
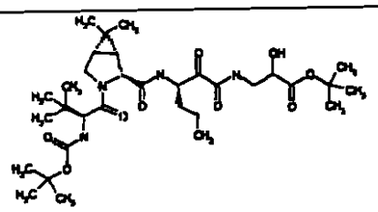
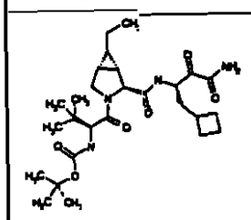
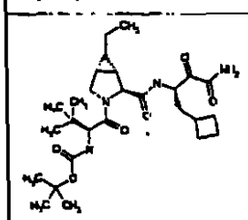
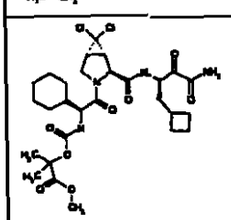
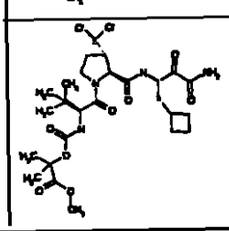
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	818.94	A
	574.65	B
	600.68	A
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	776.81	B
	635.85	A

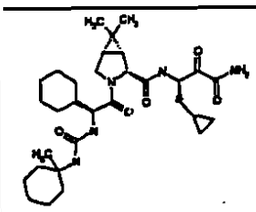
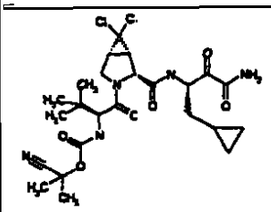
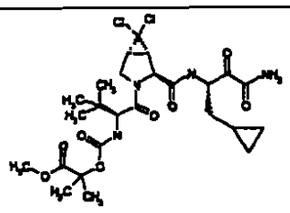
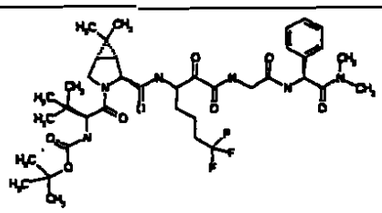
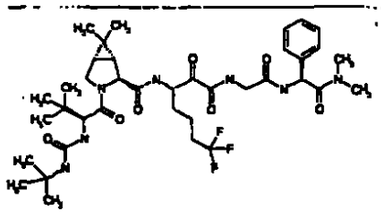
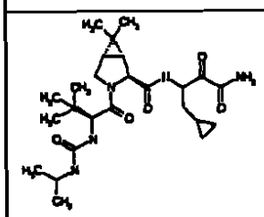
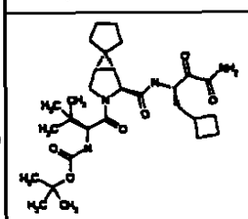
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	608.66	A
	647.74	A
	641.86	B
	643.83	B
	560.74	B
	779.00	A

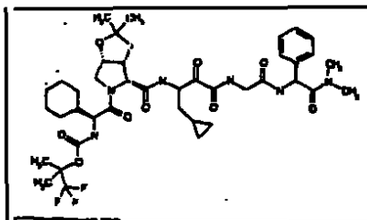
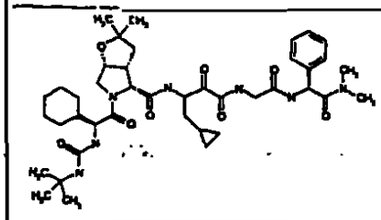
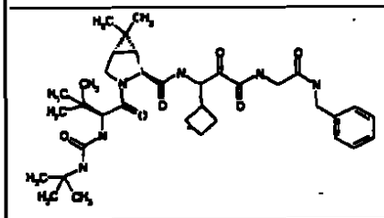
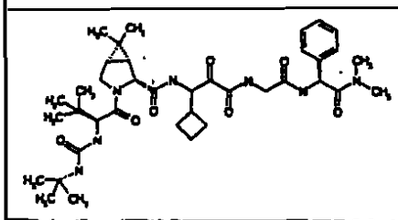
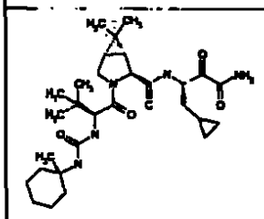
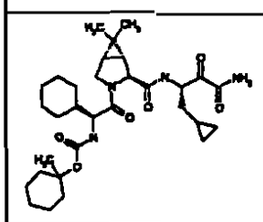
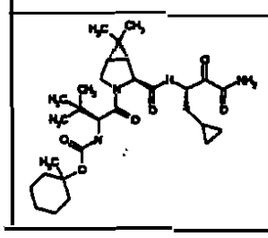
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	819.71	A
	719.72	A
	622.77	A
	787.00	A
	787.00	A
	559.76	A

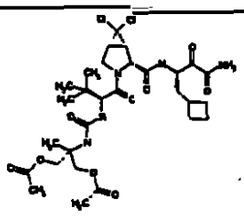
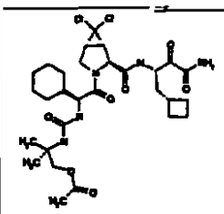
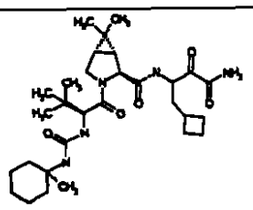
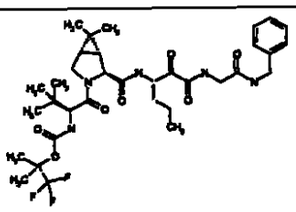
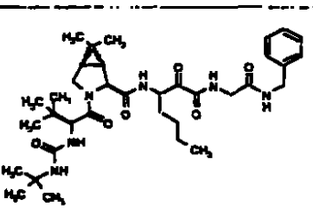
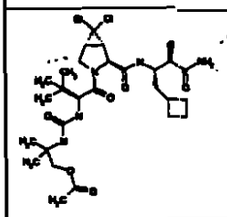
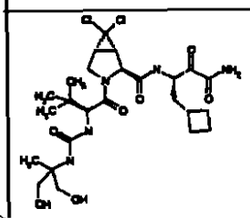
	621.57	A
	822.93	A
	631.82	A

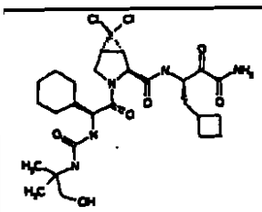
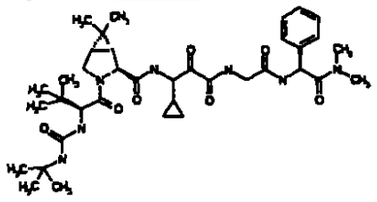
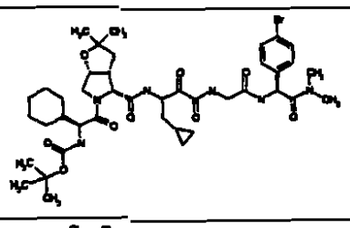
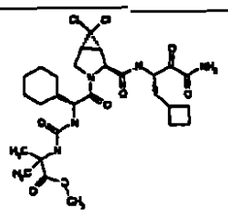
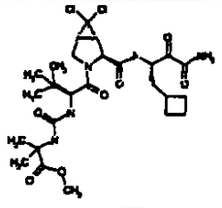
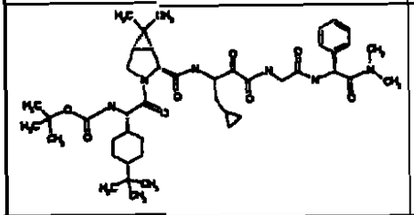
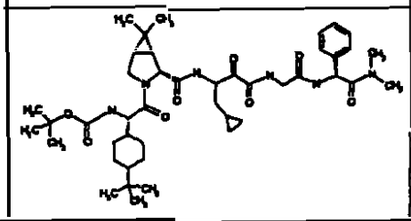
STRUCTURE	MW	Ki* (nM)
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	567.74	A
	620.58	A
	702.90	A
	740.91	A
	522.65	B
	521.66	B

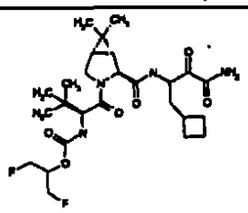
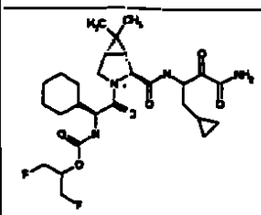
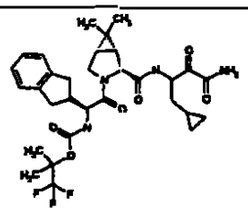
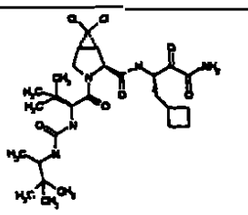
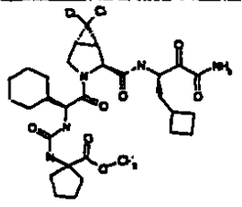
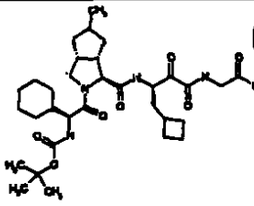
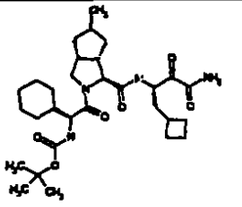
	598.53	B
	572.49	B
	638.81	B
	520.68	C
	520.68	B
	631.56	B
	605.52	B

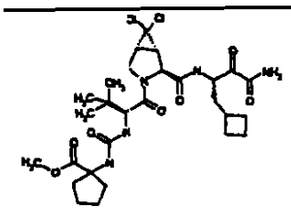
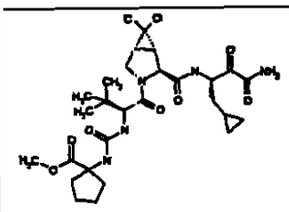
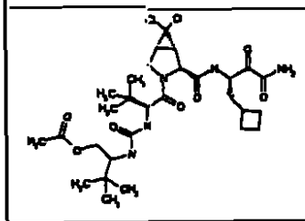
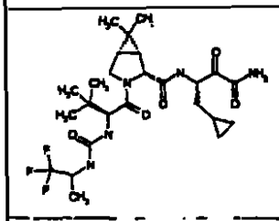
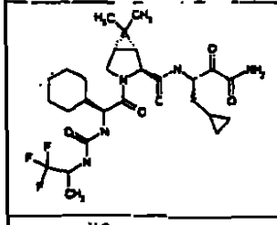
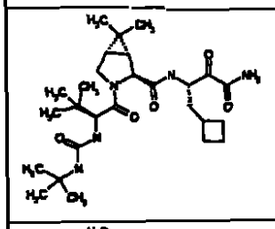
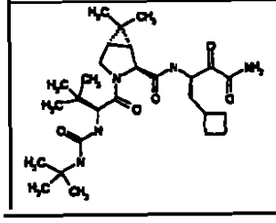
	571.77	A
	558.47	A
	591.49	A
	780.89	A
	779.91	A
	491.64	B
	546.71	B

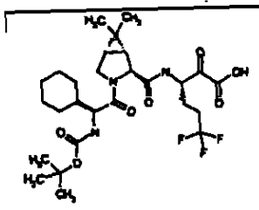
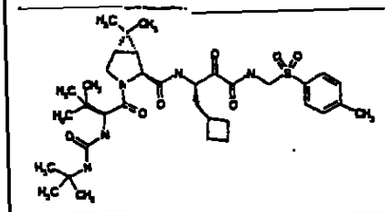
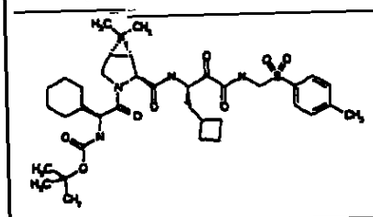
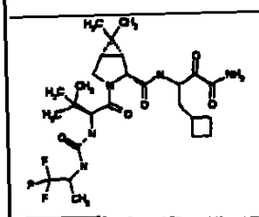
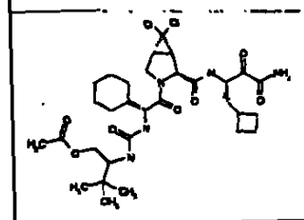
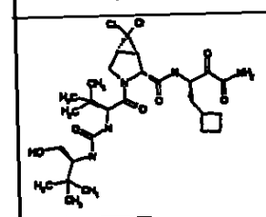
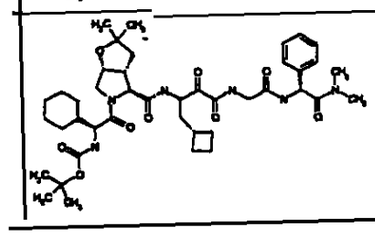
	834.94	A
	779.99	A
	852.84	A
	723.92	A
	545.73	A
	572.75	A
	546.71	A

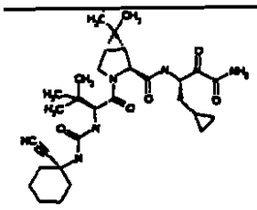
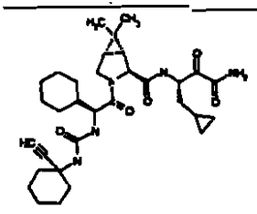
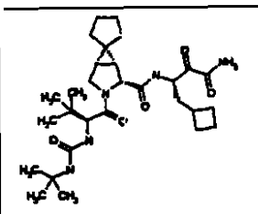
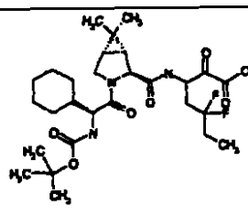
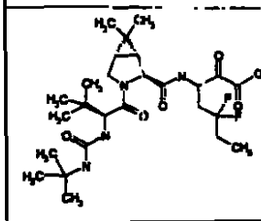
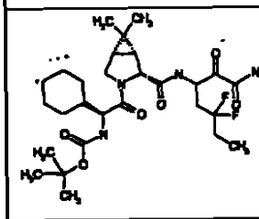
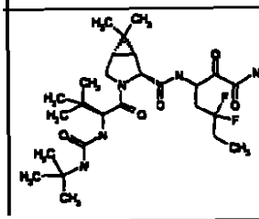
	676.60	B
	644.60	B
	559.76	A
	695.79	A
	654.86	A
	618.56	B
	592.53	B

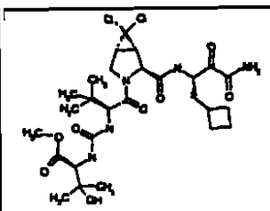
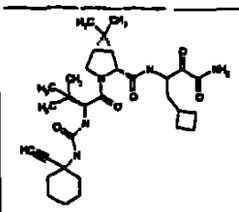
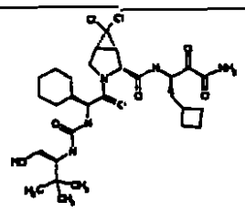
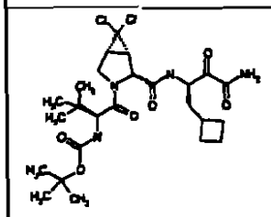
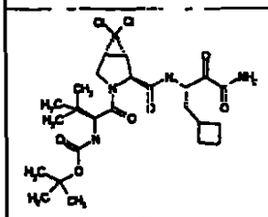
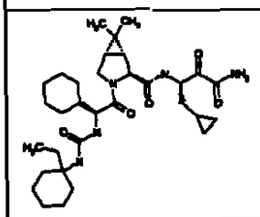
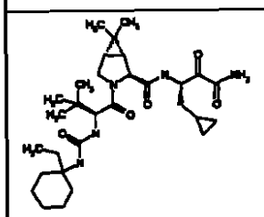
	602.56	B
	709.89	A
	859.87	A
	630.57	A
	604.54	A
	807.05	A
	807.05	A

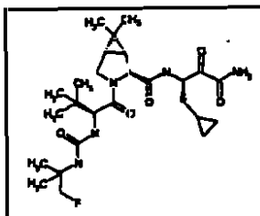
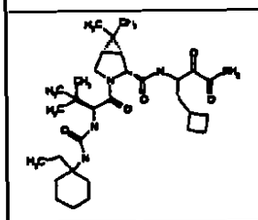
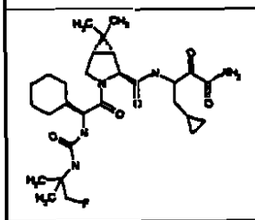
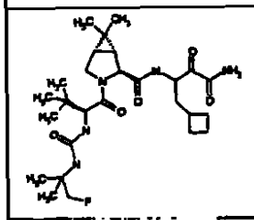
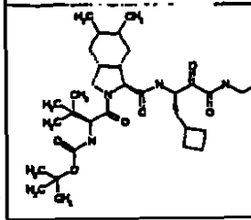
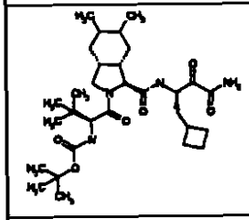
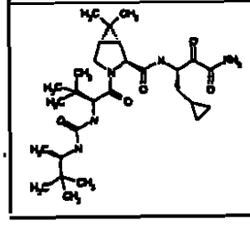
	542.63	B
	554.64	A
	620.68	A
	588.58	A
	656.61	B
	779.00	A
	560.74	B

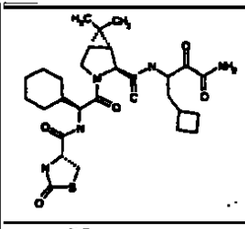
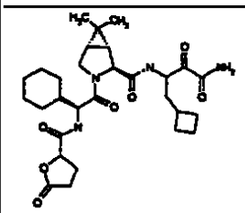
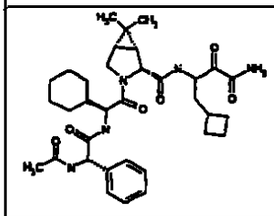
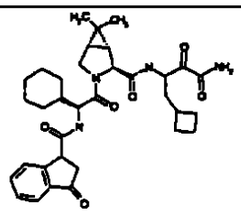
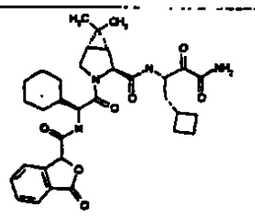
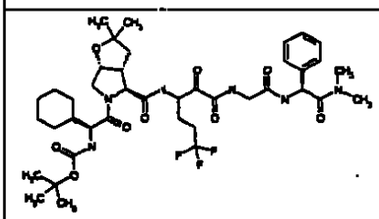
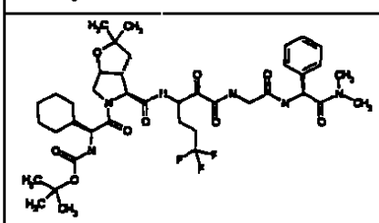
	630.57	B
	616.55	B
	646.62	A
	545.61	B
	571.65	B
	519.69	A
	519.69	B

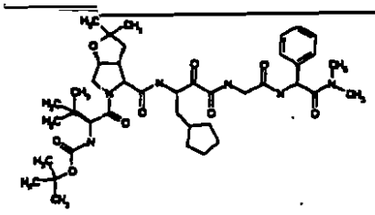
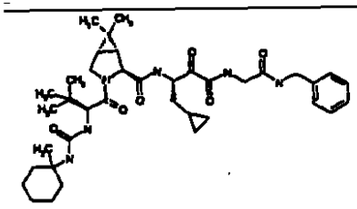
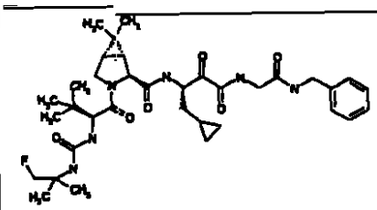
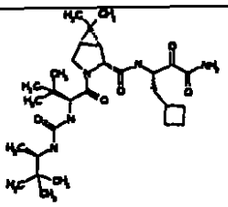
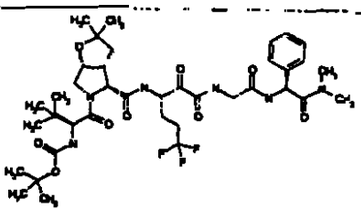
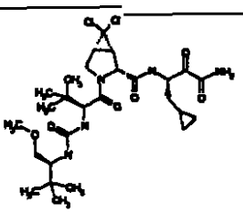
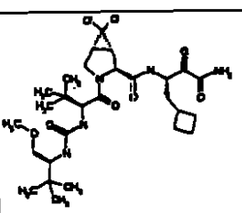
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	714.93	B
	559.63	A
	672.66	A
	604.58	B
	795.00	A

	555.72	A
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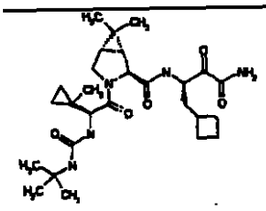
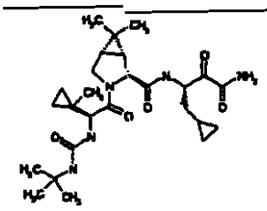
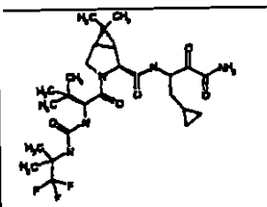
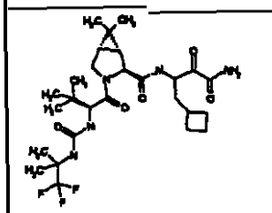
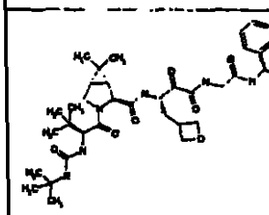
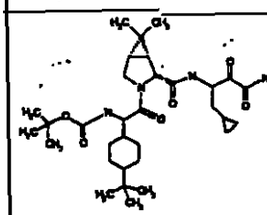
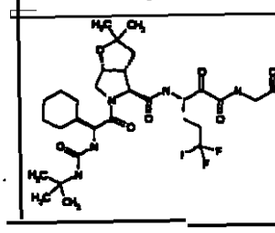
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	561.51	C
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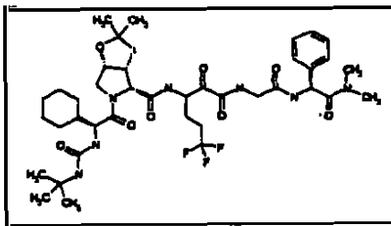
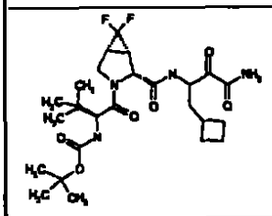
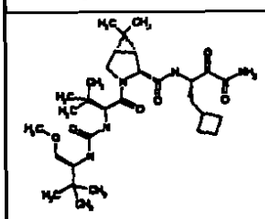
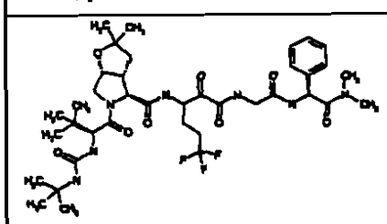
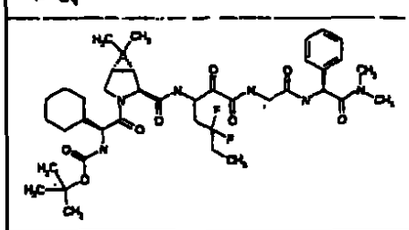
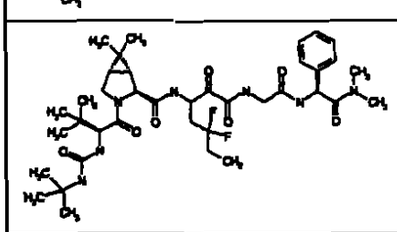
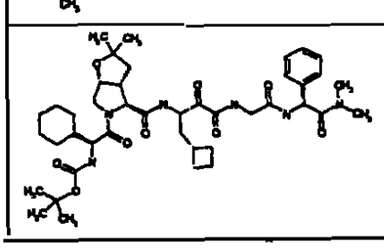
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	549.69	A
	537.68	A
	781.01	A
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	533.72	A

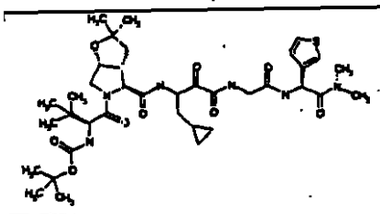
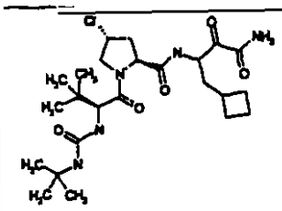
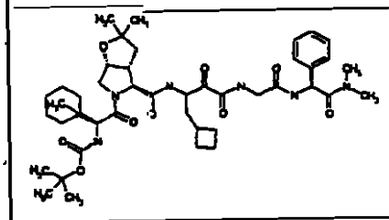
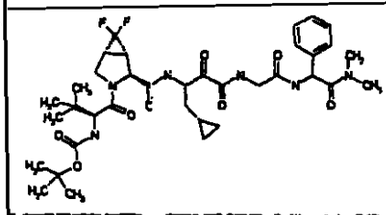
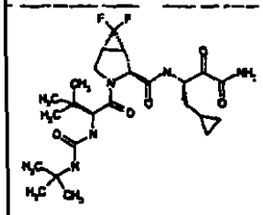
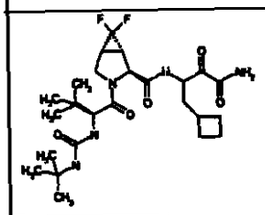
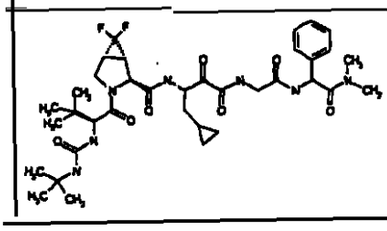
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	621.78	A
	604.75	B
	606.73	A
	822.93	A
	822.93	A

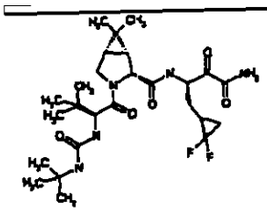
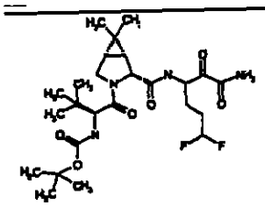
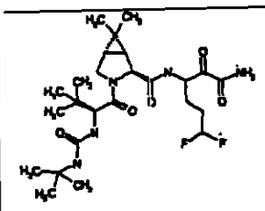
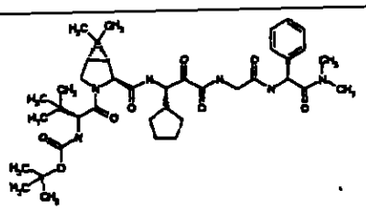
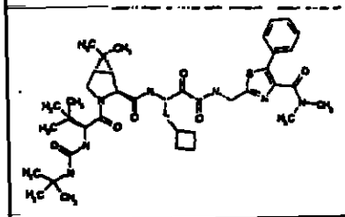
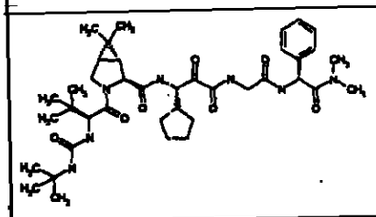
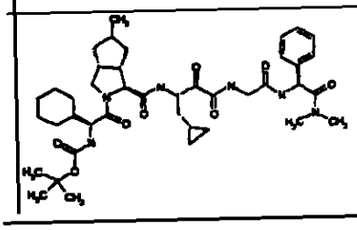
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	547.74	A
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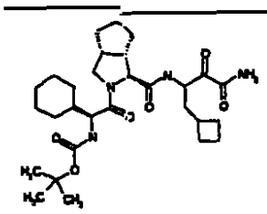
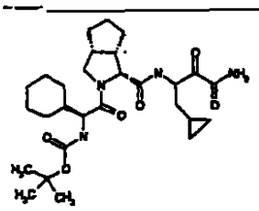
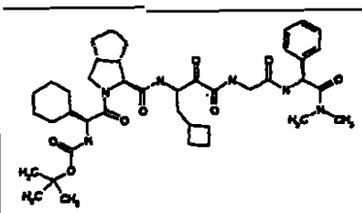
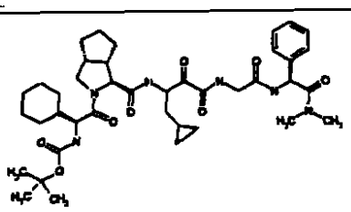
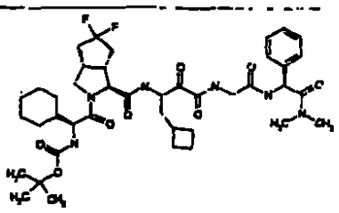
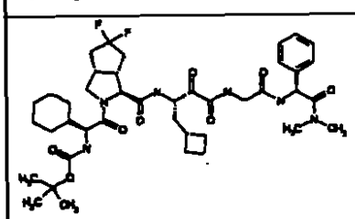
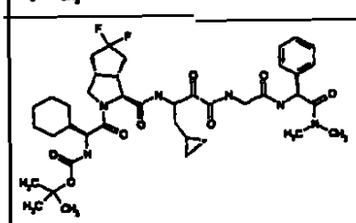
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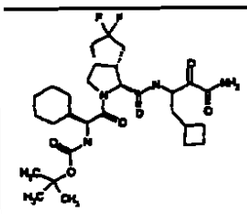
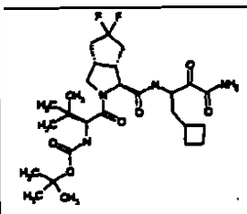
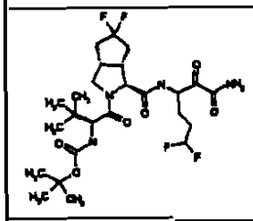
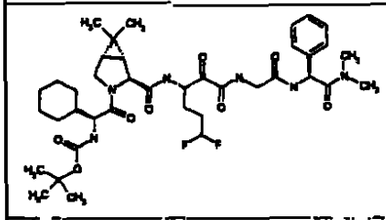
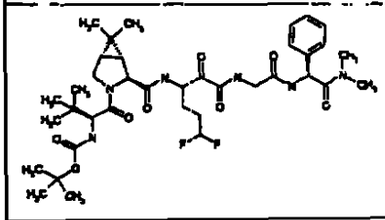
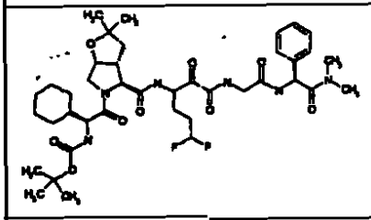
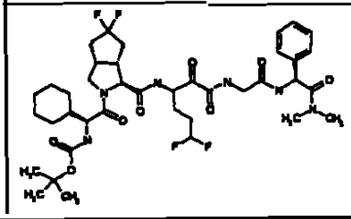
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	503.65	B
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	573.68	A
	739.92	A
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	821.95	A

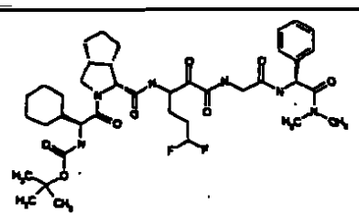
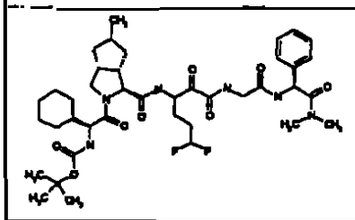
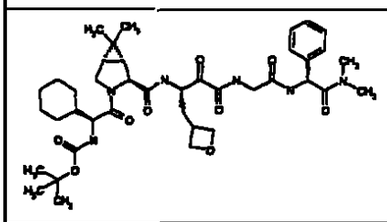
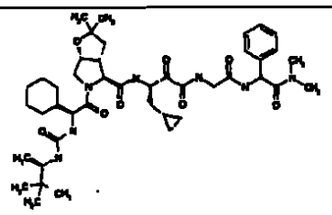
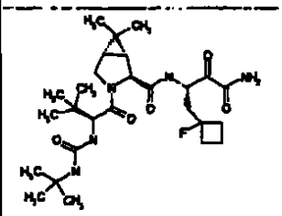
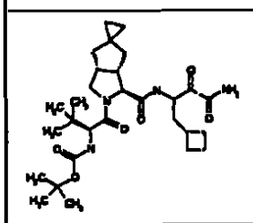
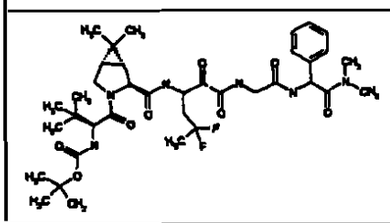
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	528.60	B
	577.77	B
	795.91	A
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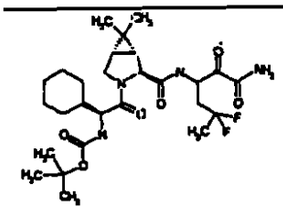
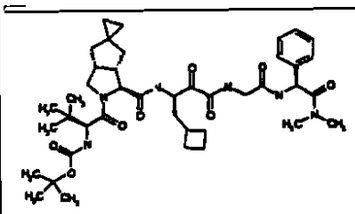
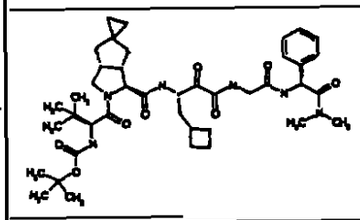
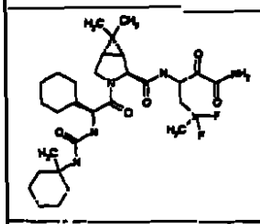
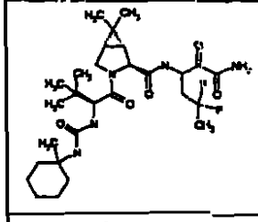
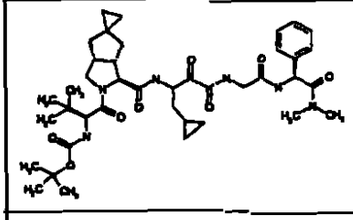
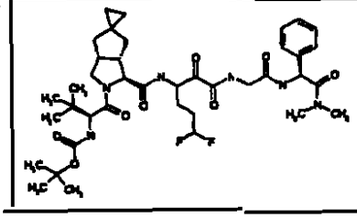
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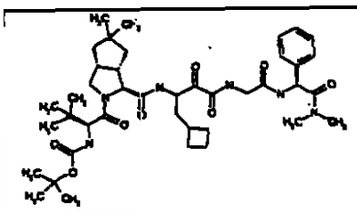
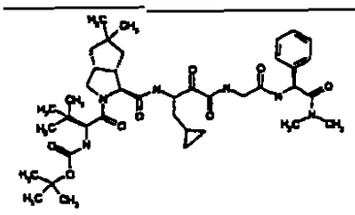
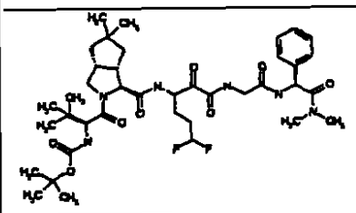
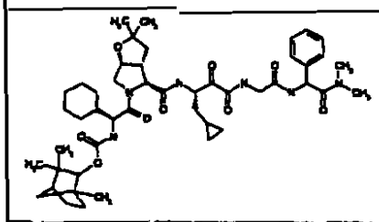
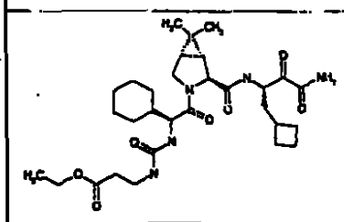
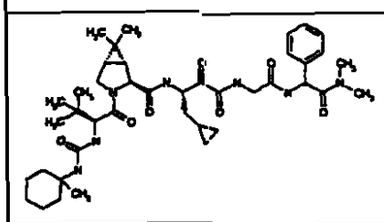
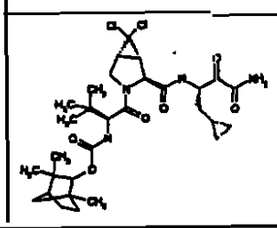
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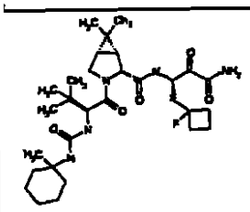
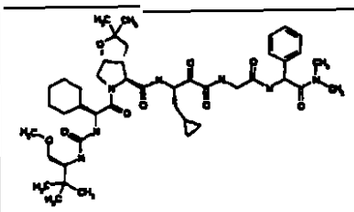
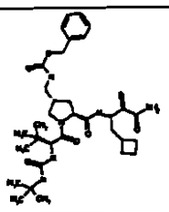
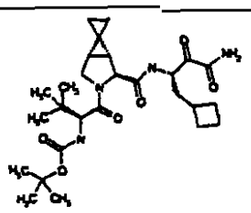
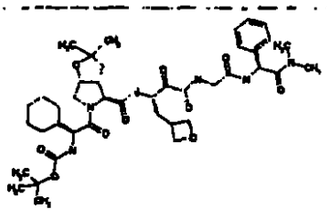
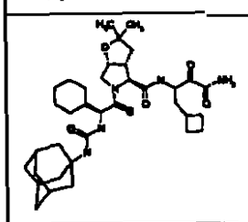
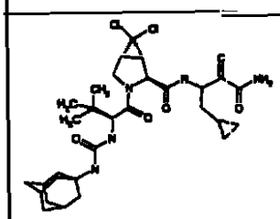
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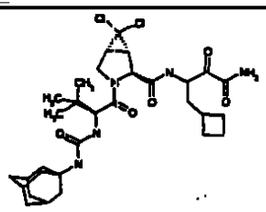
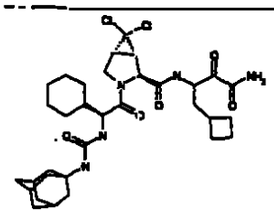
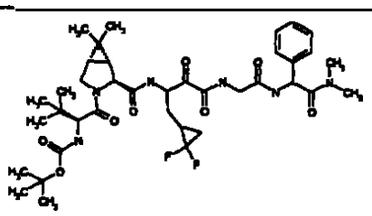
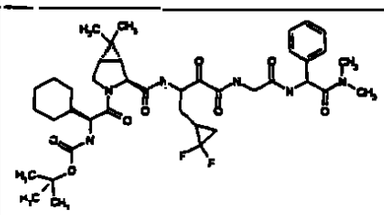
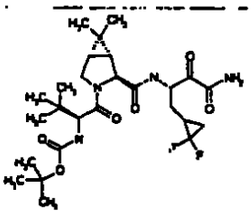
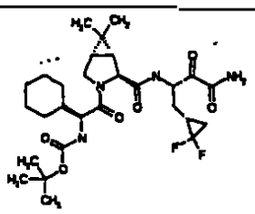
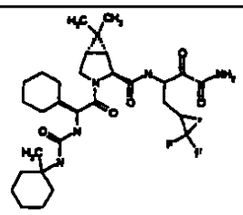
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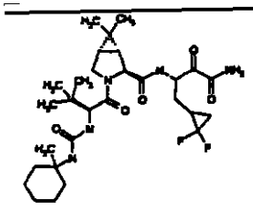
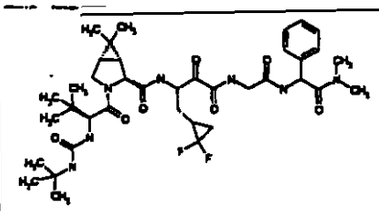
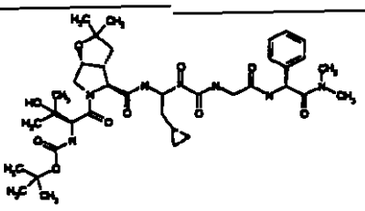
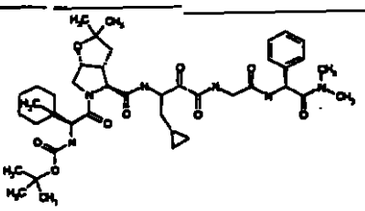
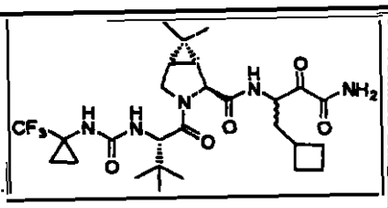
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	766.94	A
	808.04	A
	537.68	B
	546.71	B
	748.88	B

	556.66	B
	764.97	B
	764.97	A
	595.74	B
	569.70	A
	750.94	A
	774.91	A

	766.99	A
	752.96	A
	776.93	A
	861.10	A
	589.74	A
	763.99	A
	627.61	A

	577.75	A
	838.07	A
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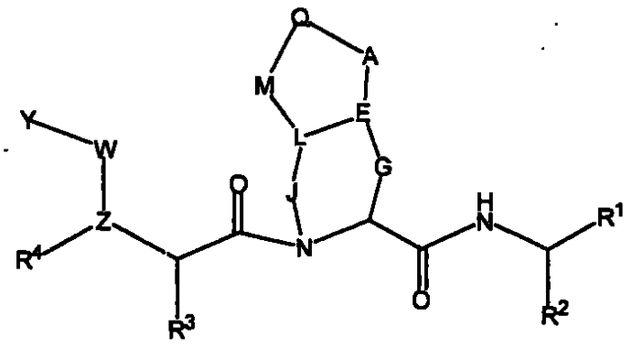
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	664.68	A
	760.89	A
	786.92	A
	542.63	A
	568.67	A
	607.75	A

	581.71	A
	759.90	A
	756.90	A
	795.00	A
	571.63	A

Claims

What is claimed is:

1. A compound, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound having the general structure shown in Formula I:



Formula I

wherein:

Y is selected from the group consisting of alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkyloxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino, with the proviso that Y maybe optionally substituted with X^{11} or X^{12};

X^{11} is alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkyl-alkyl, heterocyclyl, heterocyclylalkyl, aryl, alkylaryl, arylalkyl, heteroaryl, alkylheteroaryl, or heteroarylalkyl, with the proviso that X^{11} may be additionally optionally substituted with X^{12};

X^{12} is hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, alkylsulfonamido, arylsulfonamido, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halogen, cyano, or nitro, with the proviso that said alkyl, alkoxy, and

aryl may be additionally optionally substituted with moieties independently selected from X^{12};

R^1 is $-C(O)R^5$;

R^5 is H, -OH, $-C(O)OR^8$, $-C(O)NR^9R^{10}$;

Z is selected from O, N, C(H) or C(R);

W maybe present or absent, and if W is present, W is selected from C(=O), C(=S), C(=N-CN), or $S(O_2)$;

Q maybe present or absent, and when Q is present, Q is C(H), N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, NR, S, or SO_2; and when Q is absent, M may be present or absent; when Q and M are absent, A is directly linked to L;

A is O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, N(R), S, $S(O_2)$ or a bond;

E is CH, N, CR, or a double bond towards A, L or G;

G may be present or absent, and when G is present, G is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$; and when G is absent, J is present and E is directly connected to the carbon atom in Formula I as G is linked to;

J maybe present or absent, and when J is present, J is $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$, $S(O_2)$, N(H), N(R) or O; and when J is absent, G is present and E is directly linked to N shown in Formula I as linked to J;

L may be present or absent, and when L is present, L is C(H), C(R), O, S or N(R); and when L is absent, then M may be present or absent; and if M is present with L being absent, then M is directly and independently linked to E, and J is directly and independently linked to E;

M may be present or absent, and when M is present, M is O, NR, S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, or $(CRR')_p$;

p is a number from 0 to 6; and

R, R', R^2, R^3 and R^4 can be the same or different and are independently selected from the group consisting of H; C_1-C_{10} alkyl; C_2-C_{10} alkenyl; C_3-C_8 cycloalkyl; C_3-C_8 heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen;

(cycloalkyl)alkyl and (heterocycloalkyl)alkyl, wherein said cycloalkyl is made of three to eight carbon atoms, and zero to six oxygen, nitrogen, sulfur, or phosphorus atoms, and said alkyl is of one to six carbon atoms; aryl; heteroaryl; alkyl-aryl; and alkyl-heteroaryl;

wherein said alkyl, heteroalkyl, alkenyl, heteroalkenyl, aryl, heteroaryl, cycloalkyl and heterocycloalkyl moieties may be optionally and chemically-suitably substituted, with said term "substituted" referring to optional and chemically-suitable substitution with one or more moieties selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, aralkyl, cycloalkyl, heterocyclic, halogen, hydroxy, thio, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, sulfonamido, sulfoxide, sulfone, sulfonyl urea, hydrazide, and hydroxamate;

further wherein said unit N-C-G-E-L-J-N in Formula I represents either a five-membered cyclic ring structure or a six-membered cyclic ring structure with the proviso that when said unit N-C-G-E-L-J-N represents a five-membered cyclic ring structure, or when the bicyclic ring structure in Formula I comprising N, C, G, E, L, J, N, A, Q, and M represents a five-membered cyclic ring structure, then said five-membered cyclic ring structure lacks a carbonyl group as part of the cyclic ring.

2. The compound of claim 1, wherein R^1 is $-C(O)C(O)NR^9R^{10}$;

R^9 is H;

R^{10} is H, $-R^{14}$, $-[CH(R^{1'})]_pC(O)OR^{11}$, $-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$, $-[CH(R^{1'})]_pS(O_2)R^{11}$, $-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$, $-[CH(R^{1'})]_pC(O)R^{11}$, $-CH(R^{1'})C(O)N(H)C(H)(R^{2'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})CONR^{12}R^{13}$, or $-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$, wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaralkyl.

3. The compound of claim 2, wherein R^{10} is H, $-R^{14}$, $-CH(R^{1'})C(O)OR^{11}$, $-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$, $-CH(R^{1'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$, $-CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})C(O)R^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$, or

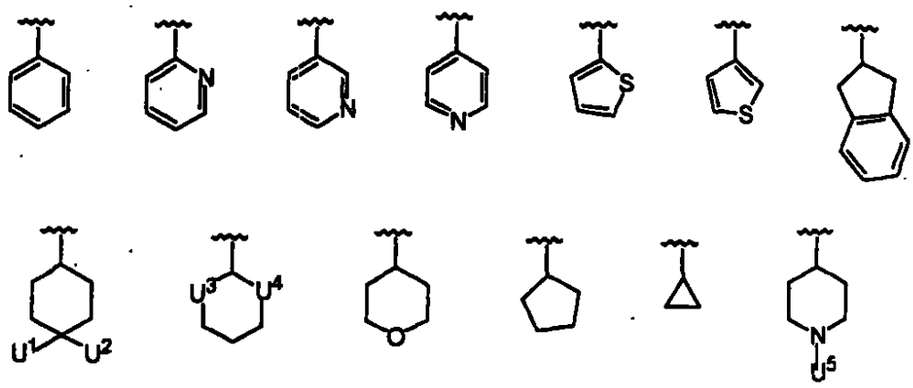
$-CH(R^{1'})C(O)N(H)CH(R^{2'})(R')$, wherein $R^{1'}$ is H or alkyl, and $R^{2'}$ is phenyl, substituted phenyl, hetero atom-substituted phenyl, thiophenyl, cycloalkyl, piperidyl or pyridyl.

4. The compound of claim 3, wherein $R^{1'}$ is H.

5. The compound of claim 4, wherein R^{11} is H, methyl, ethyl, allyl, *tert*-butyl, benzyl, α-methylbenzyl, α,α-dimethylbenzyl, 1-methylcyclopropyl or 1-methylcyclopentyl;

R' is hydroxymethyl or $-CH_2C(O)NR^{12}R^{13}$;

$R^{2'}$ is independently selected from the group consisting of:



wherein:

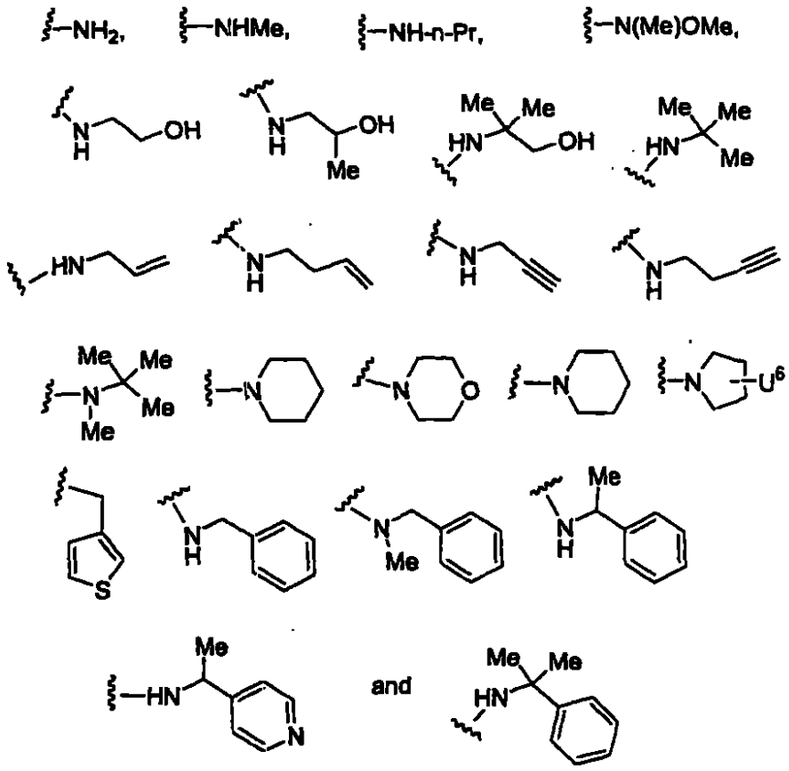
U^1 and U^2 maybe same or different and are selected from H, F, $-CH_2C(O)OH$, $-CH_2C(O)OMe$, $-CH_2C(O)NH_2$, $-CH_2C(O)NHMe$, $-CH_2C(O)NMe_2$, azido, amino, hydroxyl, substituted amino, substituted hydroxyl;

U^3 and U^4 maybe same or different and are selected from O and S;

U^5 is selected from the group consisting of alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl,

arylaminocarbonyl, heteroarylaminocarbonyl or a combination thereof;

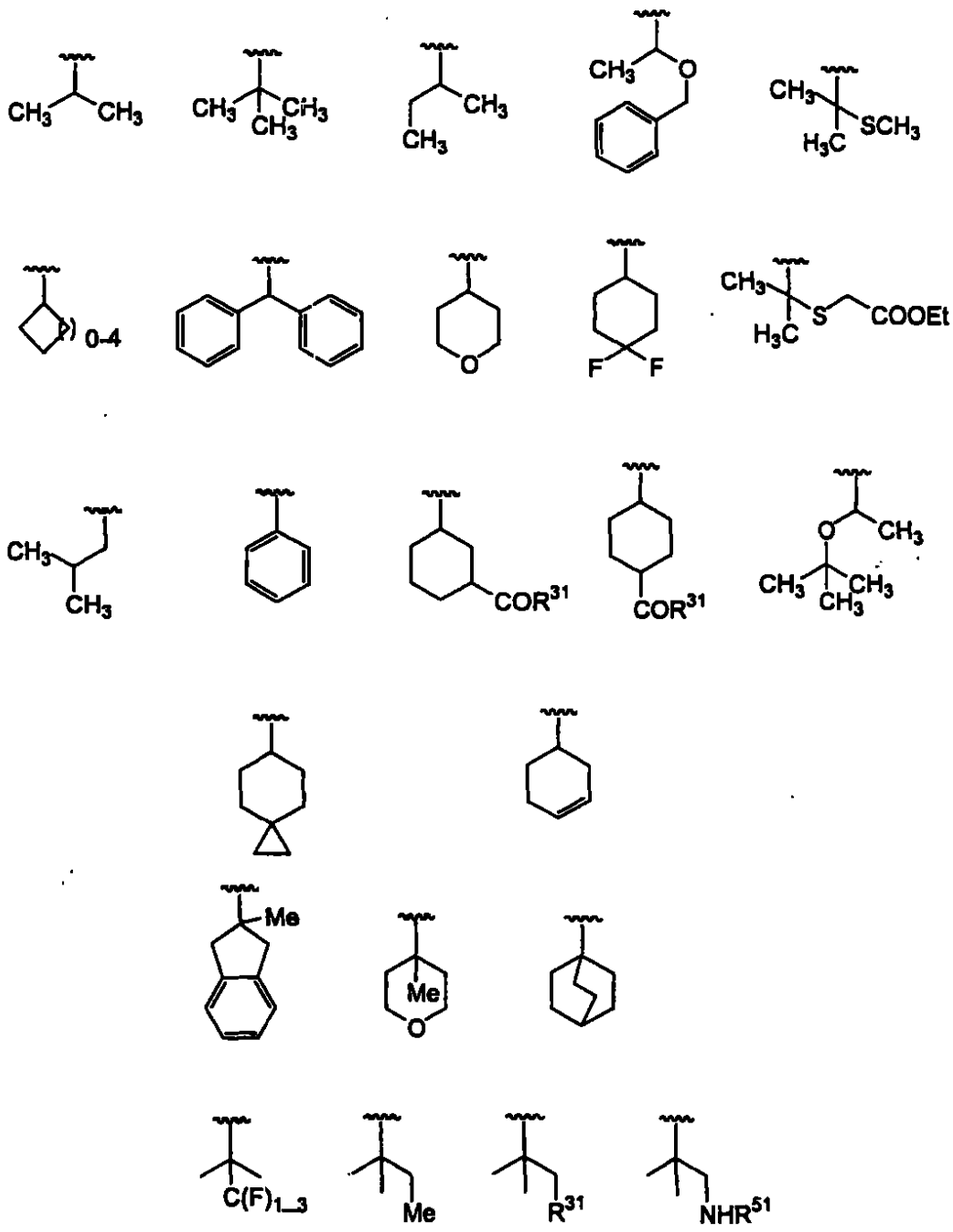
and $NR^{12}R^{13}$ is selected from the group consisting of:



wherein U^6 is H, OH, or CH_2OH, and

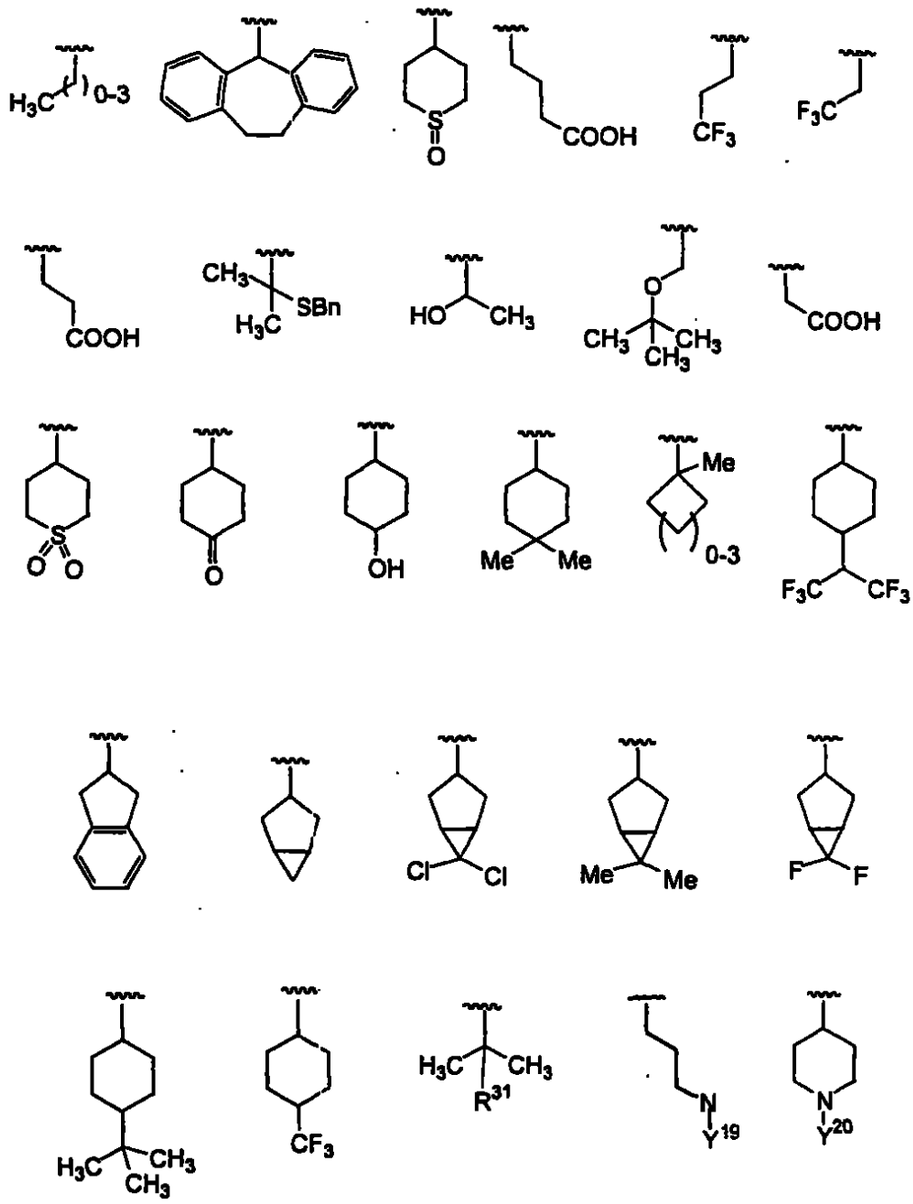
R^{14} is selected from the group consisting of: H, Me, Et, *n*-propyl, methoxy, cyclopropyl, *n*-butyl, 1-but-3-ynyl, benzyl, α-methylbenzyl, phenethyl, allyl, 1-but-3-enyl, OMe and cyclopropylmethyl.

6. The compound of claim 5, wherein R^3 is selected from the group consisting of:



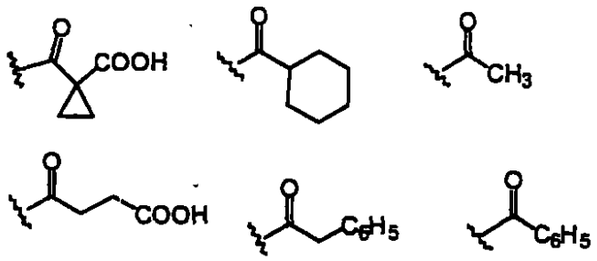
wherein R^{51} = H, $COCH_3$, COOtBu or CONHtBu;

5

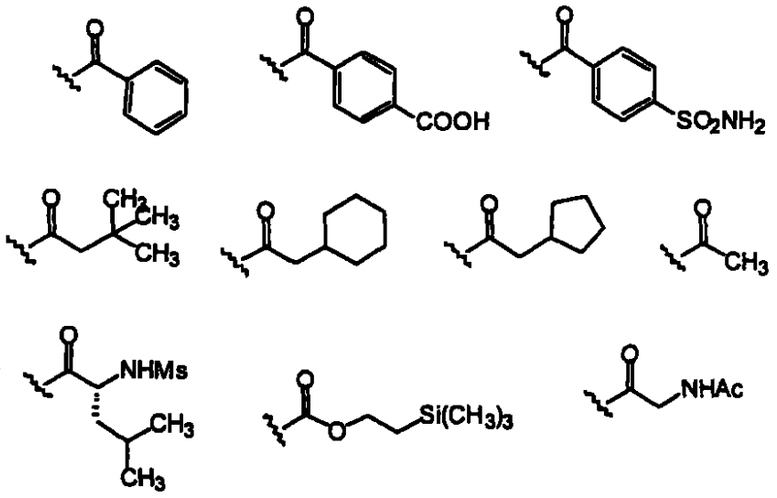


wherein R^{31} = OH or O-alkyl;

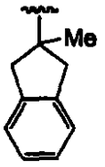
Y^{19} is selected from the following moieties:



and Y^{20} is selected from the following moieties:



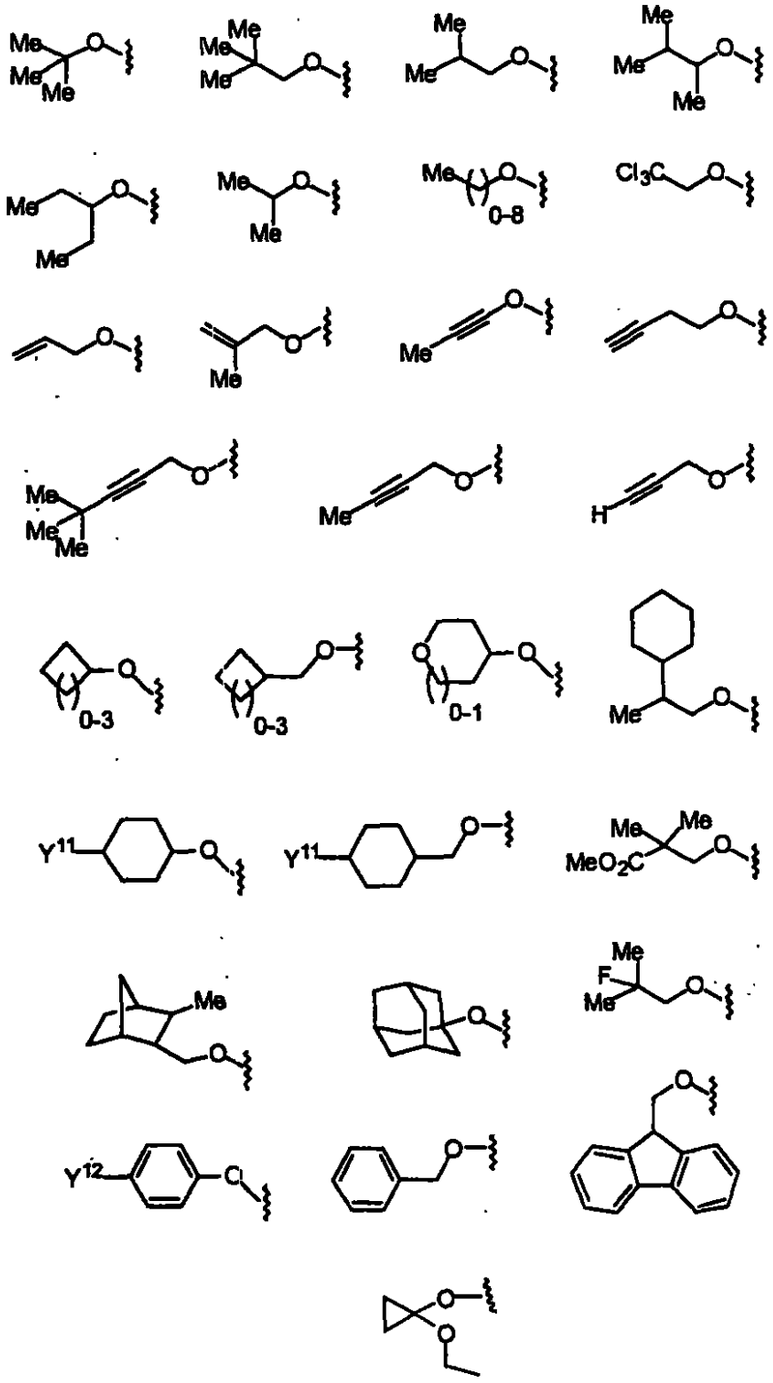
7. The compound of claim 6, wherein R^3 is:

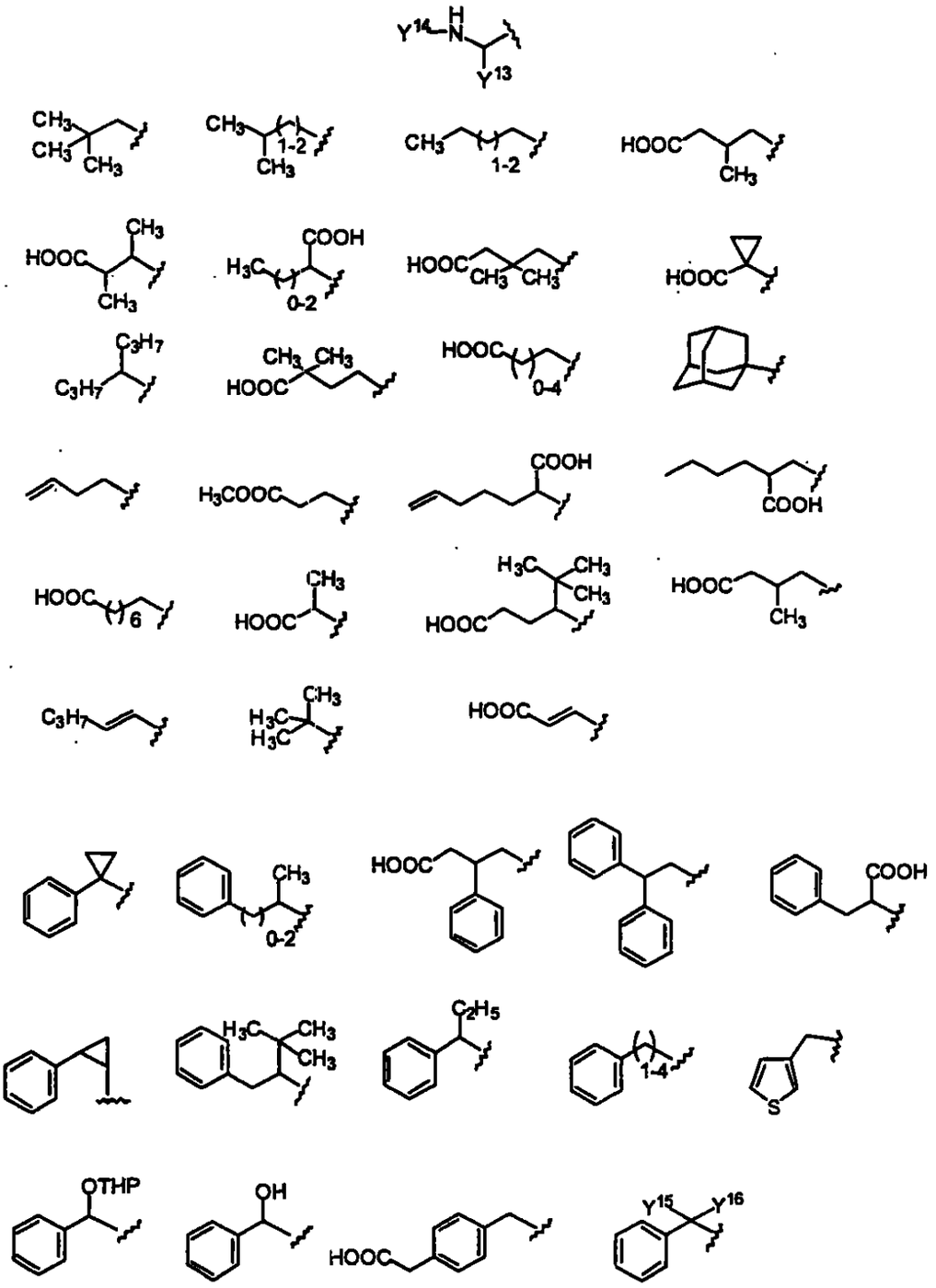


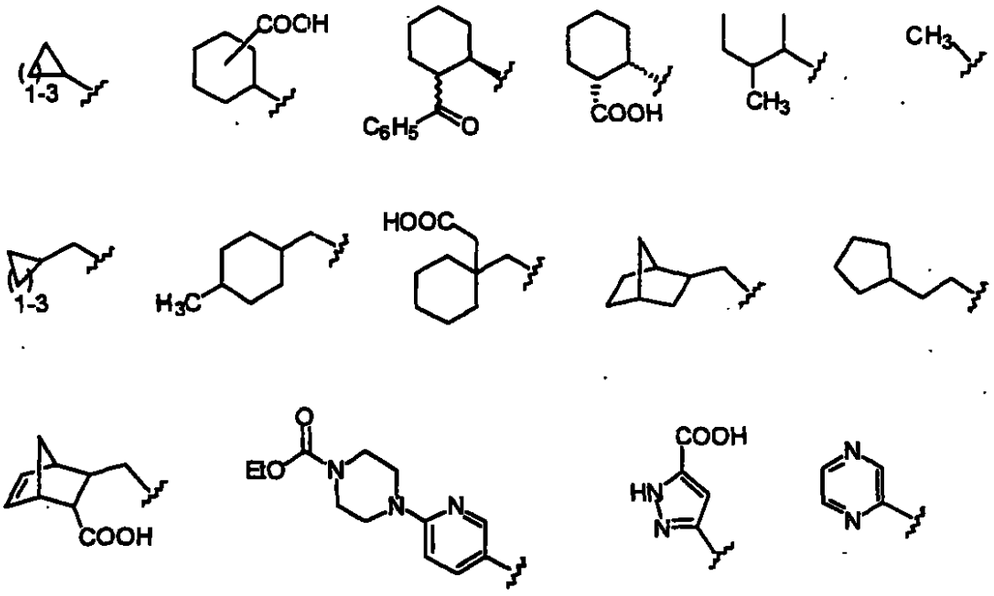
8. The compound of claim 6, wherein Z is N and R^4 is H.

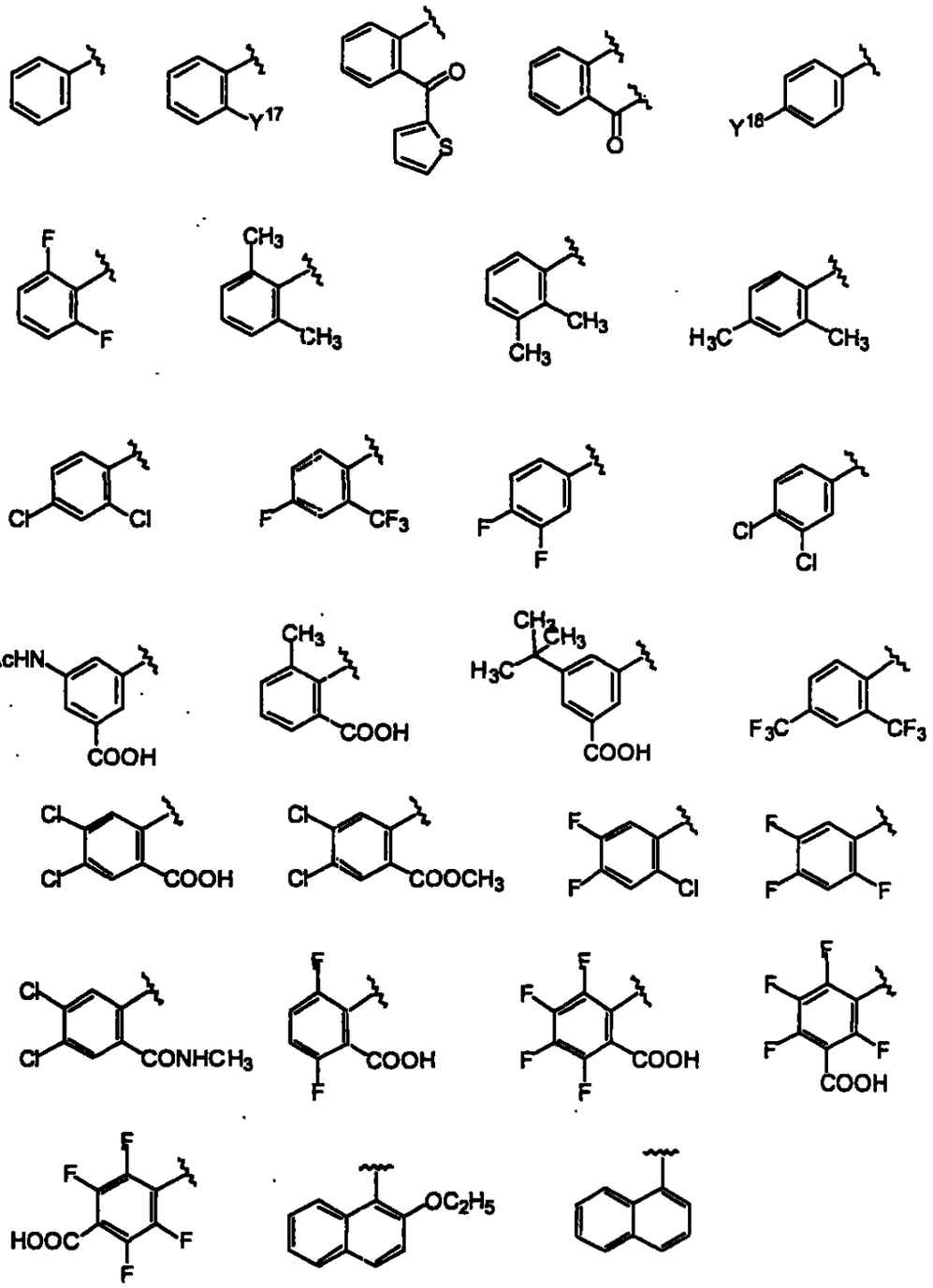
9. The compound of claim 8, wherein W is C=O.

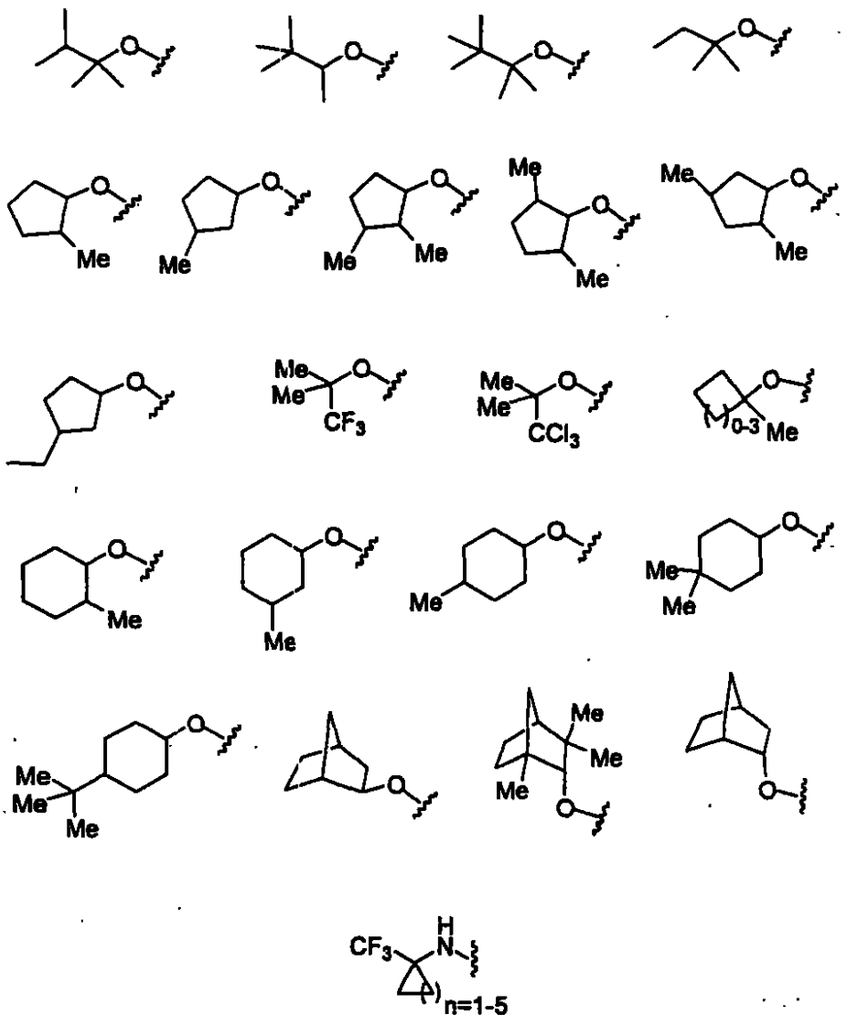
10. The compound of claim 9, wherein Y is selected from the following moieties:

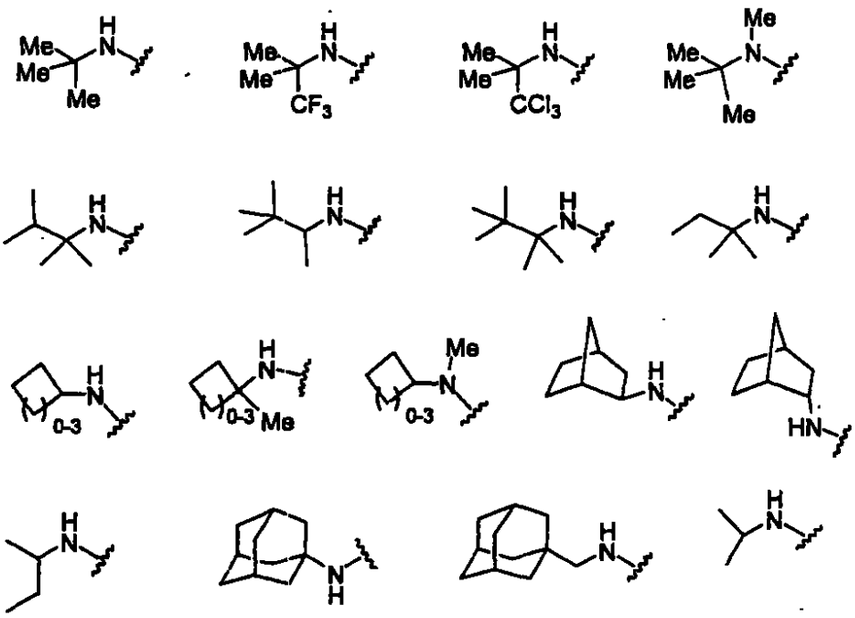

Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
0-8
Cl3C
Me
Me
Me
Me
Me
Me
Me
H
0-3
0-3
0-1
Me
Y11
Y11
Me
Me
MeO2C
Me
Me
F
Me
Y12
Cl




1-3
COOH
C_6H_5
O
COOH
CH_3
CH_3
1-3
H_3C
HOOC
COOH
EtO
N
N
N
COOH
HN
N
N
N


Y17
O
S
O
Y18
F
F
CH3
CH3
CH3
CH3
CH3
H3C
CH3
Cl
Cl
F
CF3
F
F
Cl
Cl
AcHN
COOH
CH3
COOH
CH3
H3C
COOH
F3C
CF3
Cl
Cl
COOH
Cl
Cl
COOCH3
F
F
Cl
F
F
F
Cl
CONHCH3
F
COOH
F
F
F
COOH
F
F
F
F
F
COOH
F
F
F
HOOC
OC2H5


Me
Me
Me
Me
Me
Me
Me
Me
Me
CF3
Me
Me
CCl3
0-3
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
CF3
H
N
n=1-5

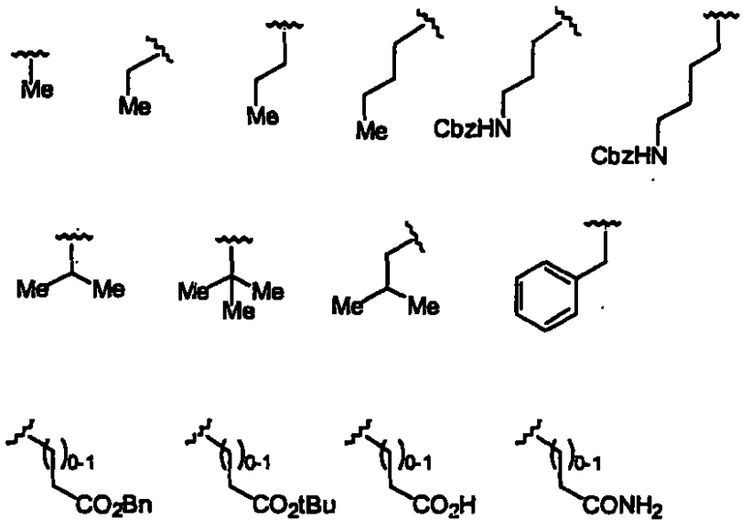


wherein:

Y^{11} is selected from the group consisting of H, -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 H, -C(O)OH, -C(O)OMe, -OMe, F, Cl, and Br;

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



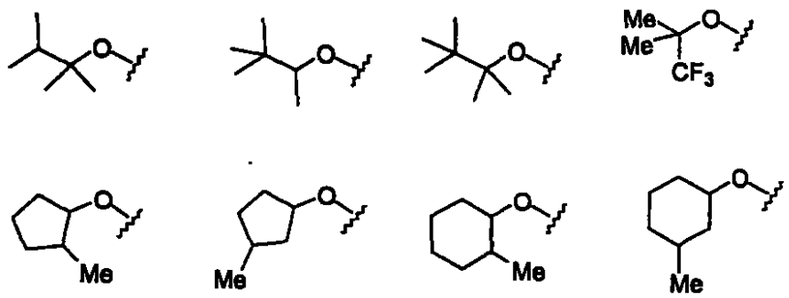
Y^{14} is $MeS(O_2)$-, -Ac, -Boc, -iBoc, -Cbz, or -Alloc;

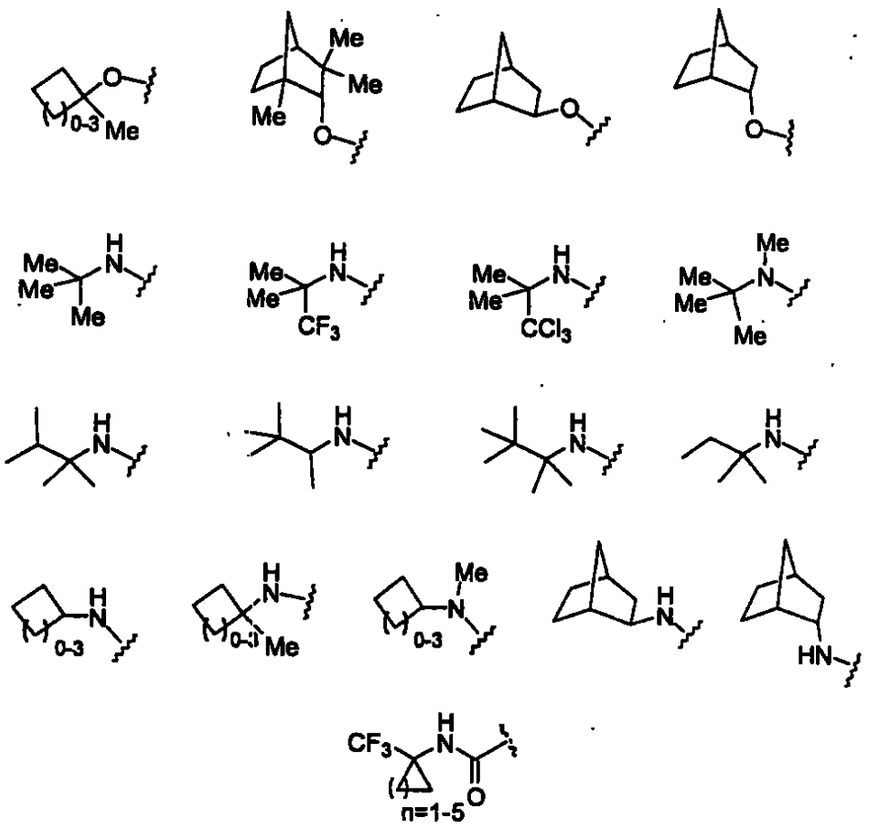
Y^{15} and Y^{16} can be the same or different and are independently selected from alkyl, aryl, heteroalkyl, and heteroaryl;

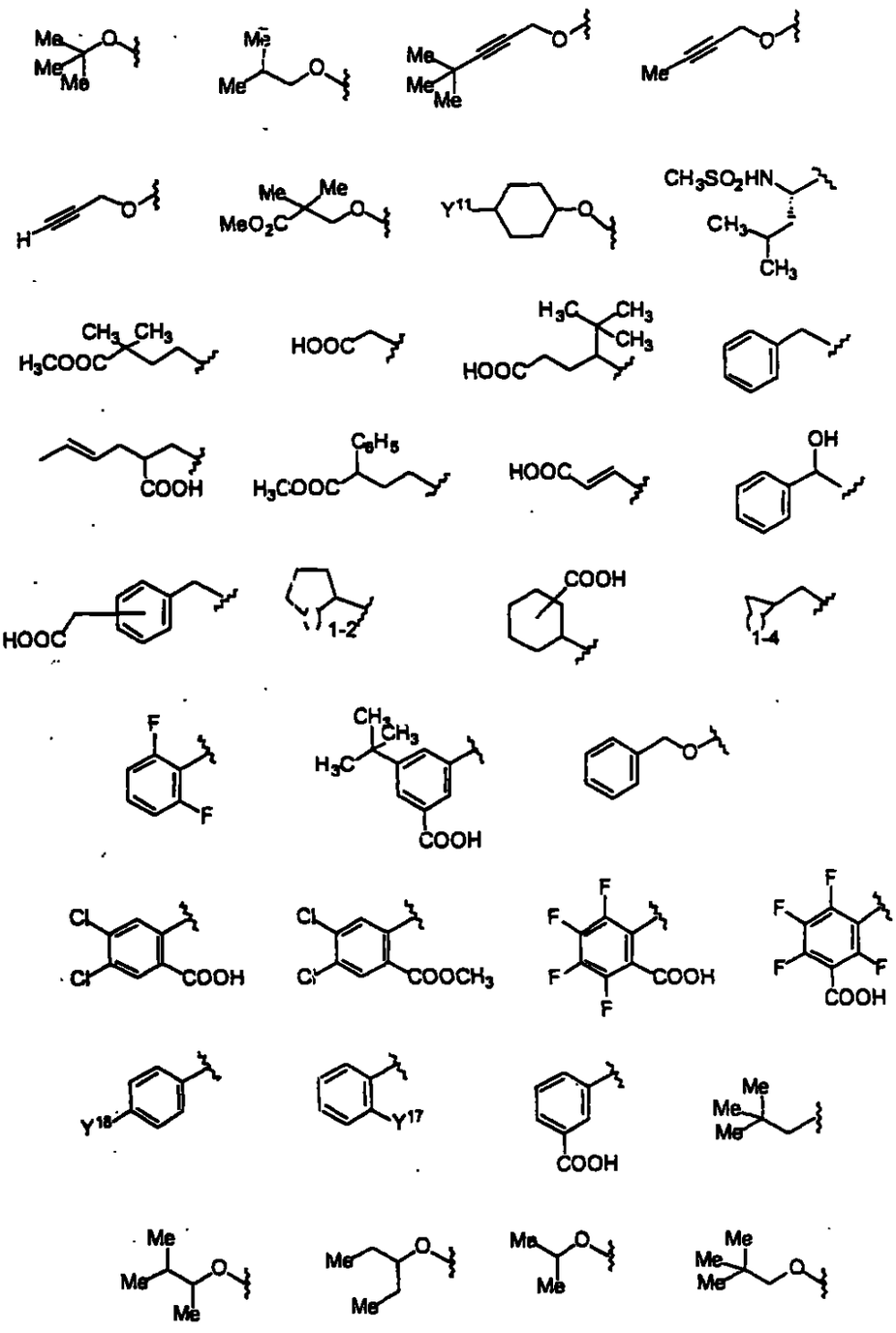
Y^{17} is $-CF_3$, $-NO_2$, $-C(O)NH_2$, -OH, $-C(O)OCH_3$, $-OCH_3$, $-OC_6H_5$, $-C_6H_5$, $-C(O)C_6H_5$, $-NH_2$, or –C(O)OH; and

Y^{18} is $–C(O)OCH_3$, $-NO_2$, $-N(CH_3)_2$, F, $-OCH_3$, $-C(H_2)C(O)OH$, -C(O)OH, $-S(O_2)NH_2$, or $–N(H)C(O)CH_3$.

11. The compound of claim 10, wherein Y is selected from the group consisting of:

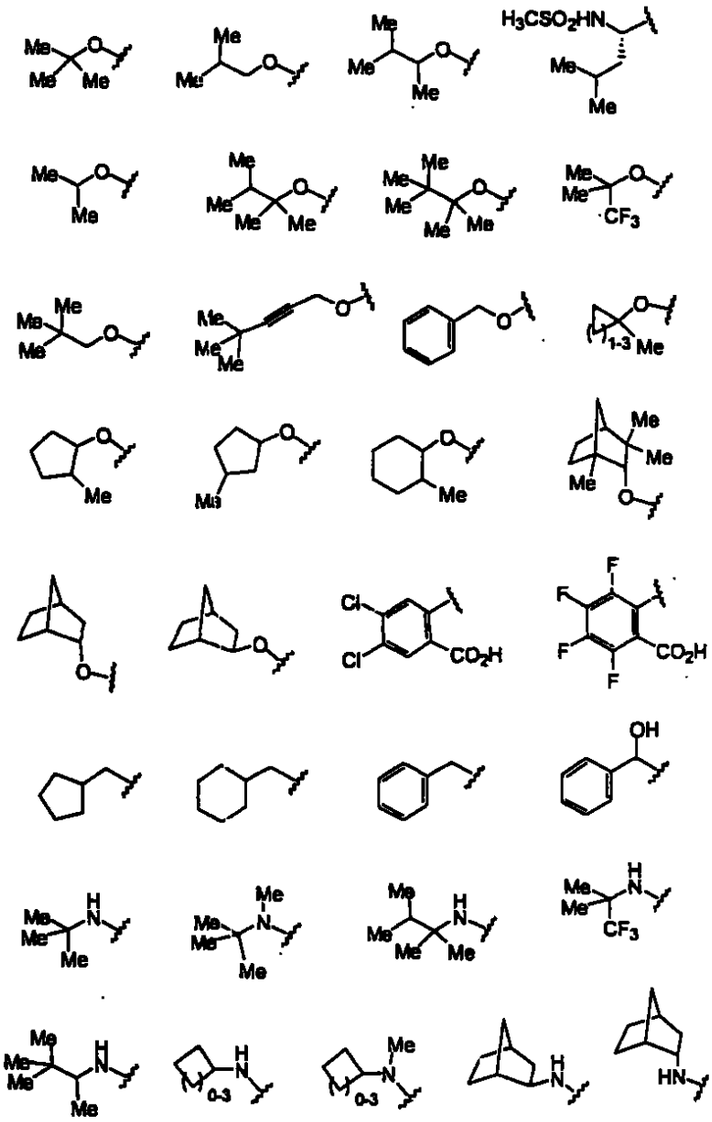



0-3
Me
Me
Me
Me
O
O
O
Me
Me
Me
H
N
Me
Me
CF3
Me
Me
CCl3
Me
Me
N
Me
Me
H
N
H
N
H
N
H
N
0-3
H
N
0-1
Me
Me
N
0-3
H
N
HN
CF3
H
N
(4)
O
n=1-5



wherein:
Y^{17} = CF_3, NO_2, $CONH_2$, OH, NH_2, or COOH;
Y^{18}= F, COOH,

12. The compound of claim 11, wherein Y is selected from the group consisting of:

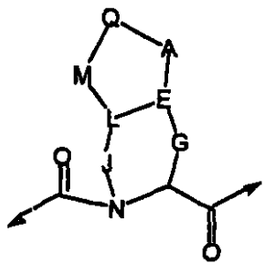


13. The compound of claim 12, wherein L and M are absent, and J is directly linked to E.

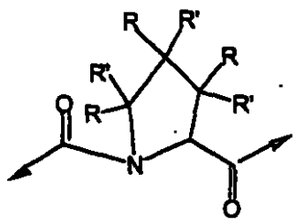
14. The compound of claim 12, wherein L, J and M are absent and E is directly linked to N.

15. The compound of claim 12, wherein G and M are absent.

16. The compound of claim 12, wherein the moiety:

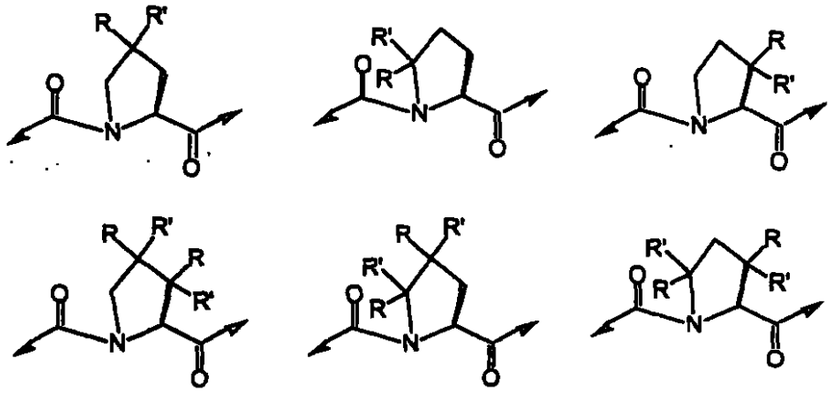


is

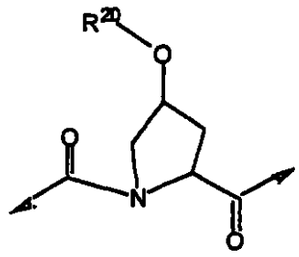


a

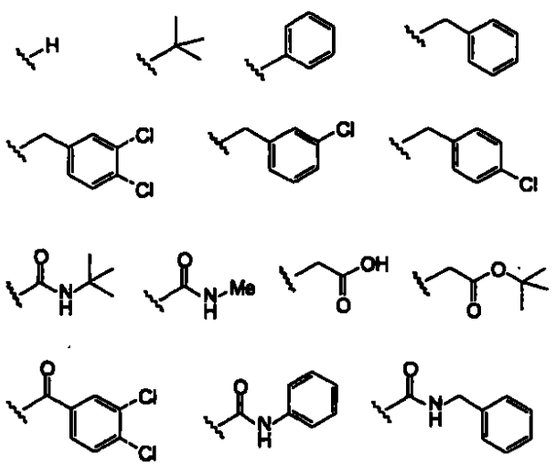
17. The compound of claim 16, wherein structure a is selected from the following structures:



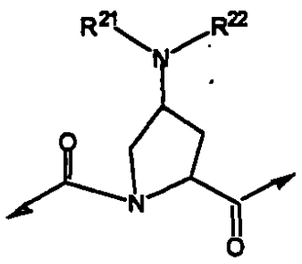
18. The compound of claim 16, wherein structure a is:



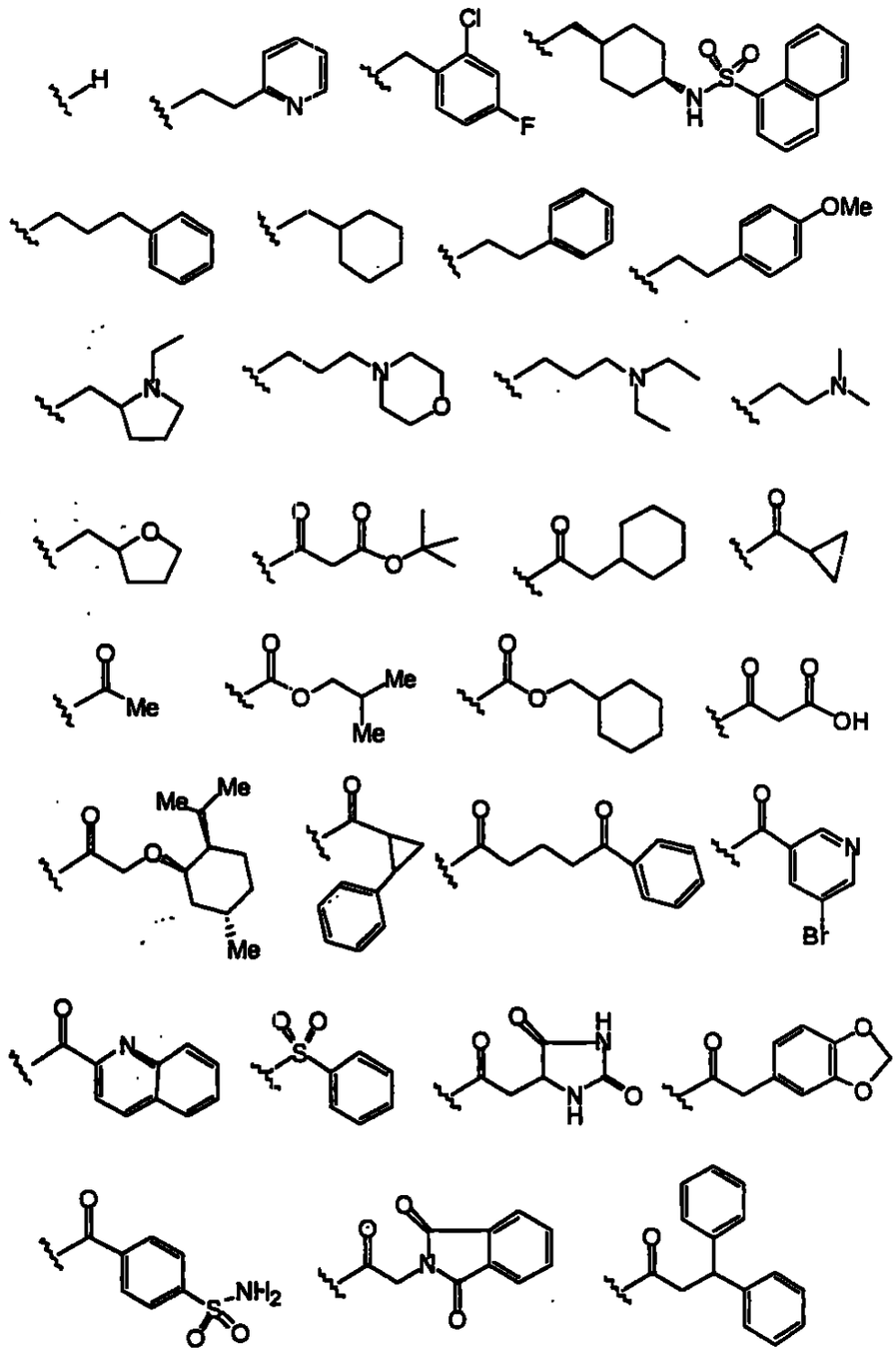
wherein R^{20} is selected from the following structures:



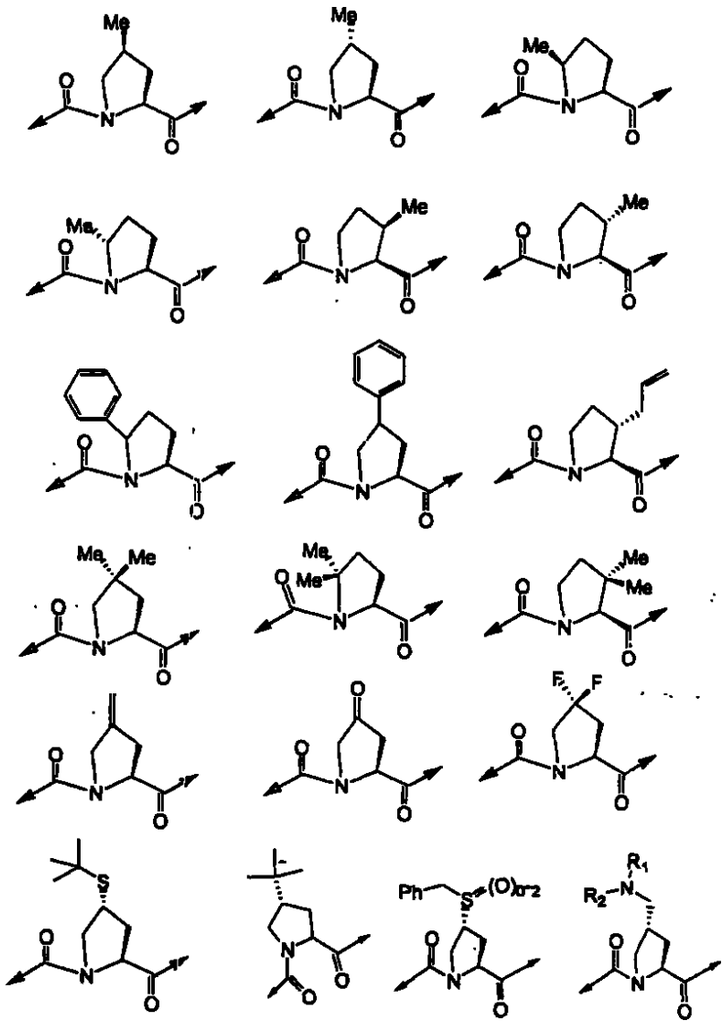
19. The compound of claim 16, wherein structure a is:



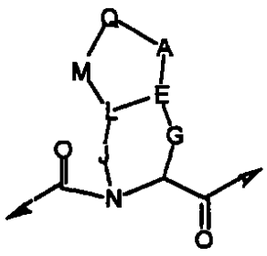
wherein R^{21} and R^{22} may be the same or different and are independently selected from the group consisting of the following structures:



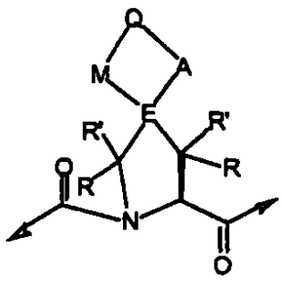
20. The compound of claim 16, wherein structure a is selected from the group consisting of the following structures:



21. The compound of claim 12, wherein:



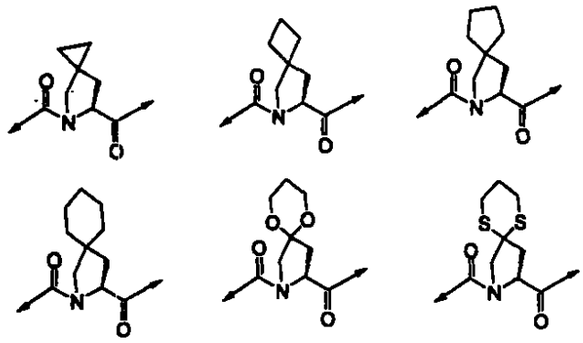
is

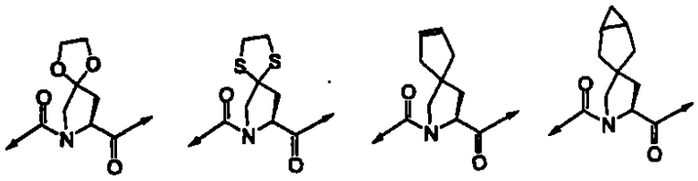


b

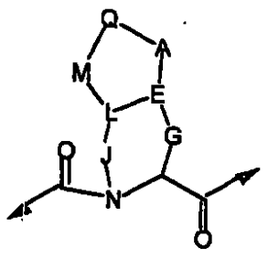
wherein Q may be present or absent, and if Q is absent, M is directly linked to A.

22. The compound of claim 21, wherein structure b is selected from the following structures:

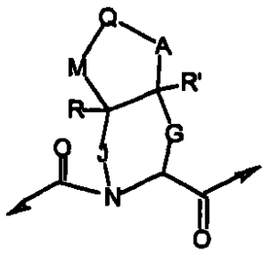




23. The compound of claim 12, wherein:



is



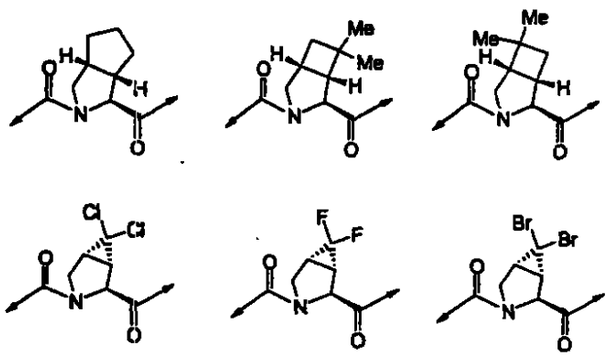
c

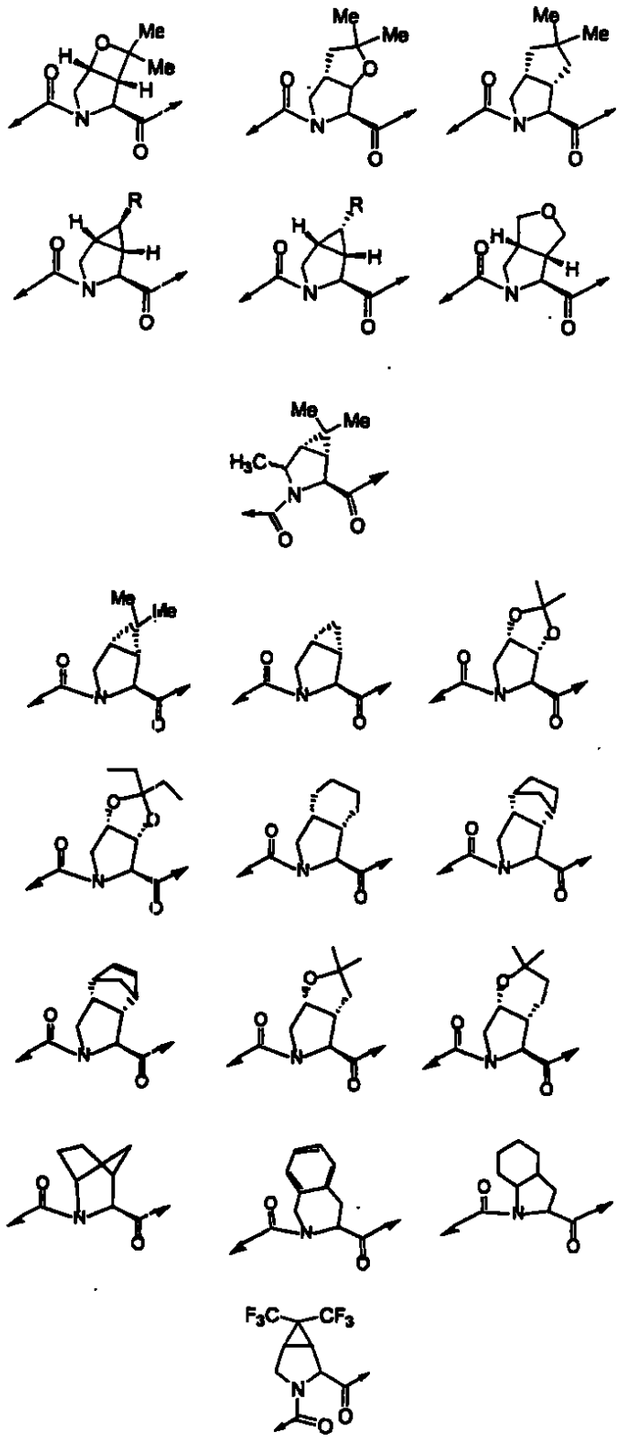
wherein G and J can be the same or different and are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$;

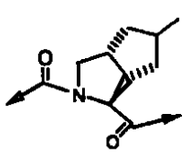
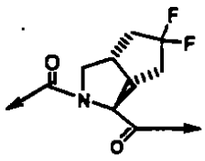
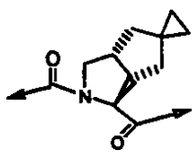
A and M can be the same or different and are independently selected from the group consisting of O, S, $S)O_2)$, N(R), $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; and

Q is CH_2, CH(R), C(RR'), N(H), N(R), O, S, $S(O_2)$, N(R), $(CH_2)_p$, $(CHR)_p$, or $(CRR')_p$.

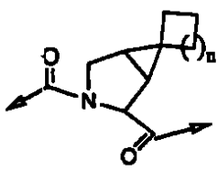
24. The compound of claim 23, wherein structure c is selected from the following structures:



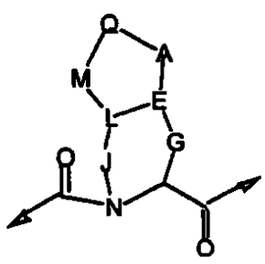


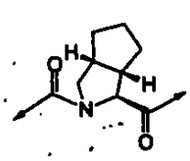
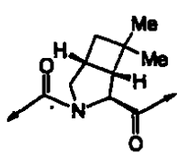
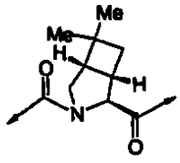
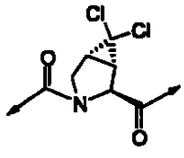
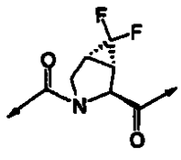
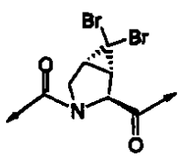
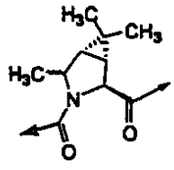
and

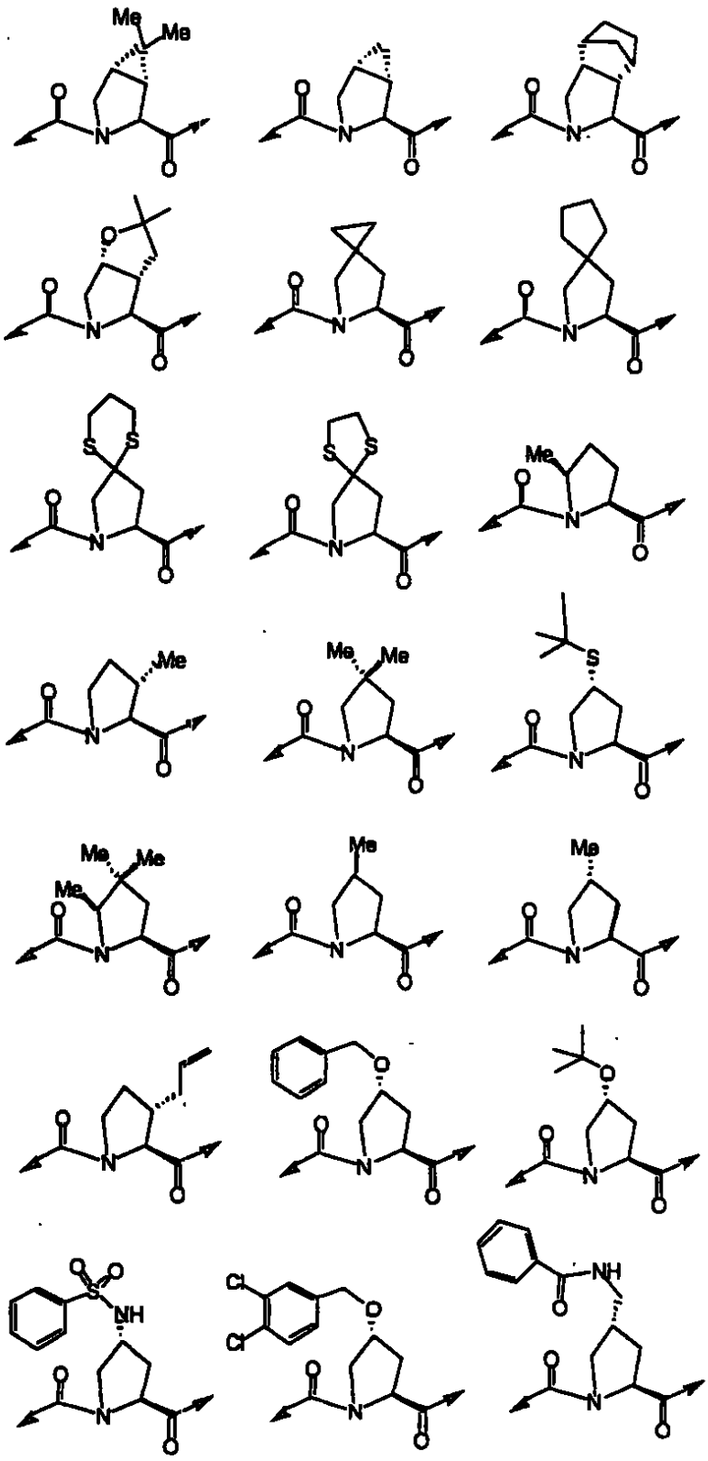

where n= 0-4.

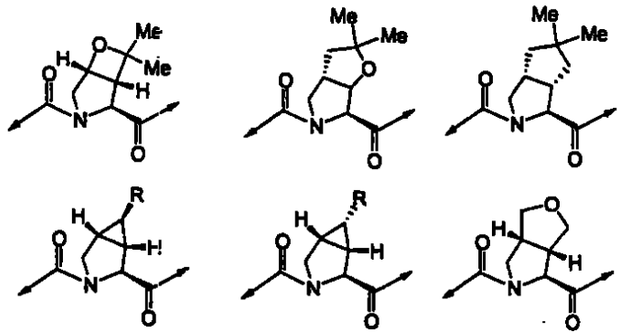
25. The compound of claim 12, wherein:



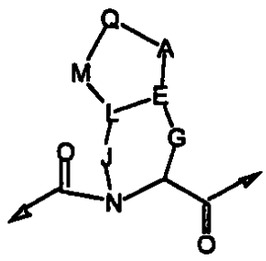
is selected from the following structures:

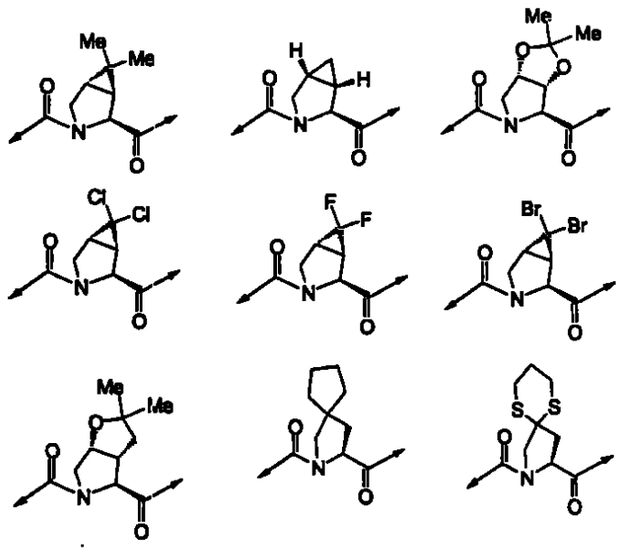




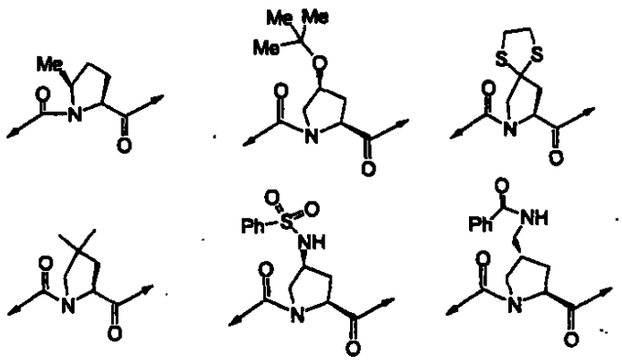
26. The compound of clairn 25, wherein:



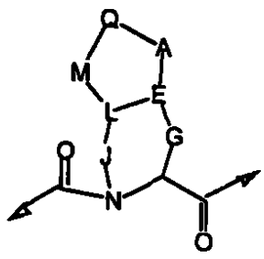
is selected from the following structures:



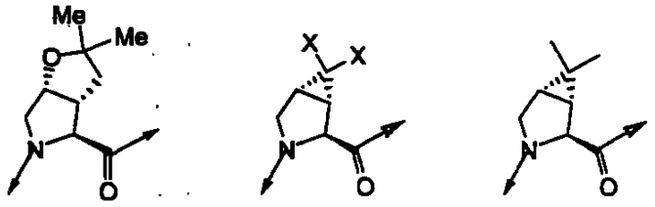
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27. The compound of claim 25, wherein:

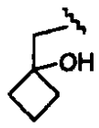


is selected from the following structures:



X= F, Cl, Br

28. The compound of claim 1, wherein R^2 is the moiety:



29. A pharmaceutical composition comprising as an active ingredient at least one compound of compound of claim 1.

30. The pharmaceutical composition of claim 29 for use in treating disorders associated with HCV.

31. The pharmaceutical composition of claim 29 additionally comprising a pharmaceutically acceptable carrier.

32. The pharmaceutical composition of claim 31, additionally containing at least one antiviral agent.

33. The pharmaceutical composition of claim 32, still additionally containing an interferon.

34. The pharmaceutical composition of claim 33, wherein said antiviral agent is ribavirin and said interferon is α-interferon or pegylated interferon.

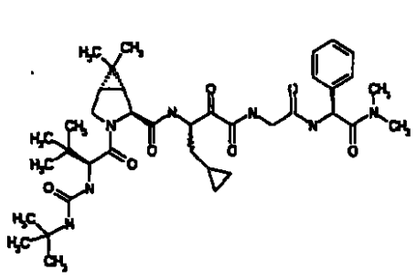
35. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1.

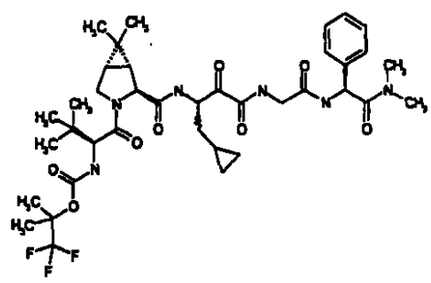
36. The method of claim 35, wherein said administration is oral or subcutaneous.

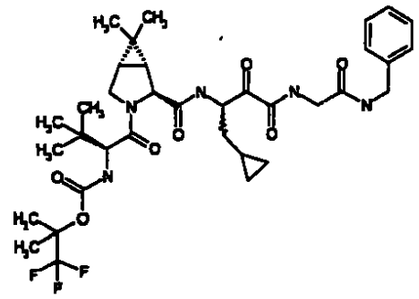
37. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV.

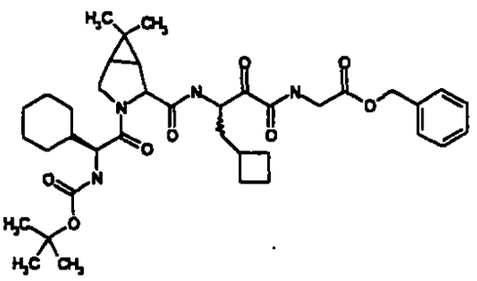
38. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV, said method comprising bringing into intimate contact at least one compound of claim 1 and a pharmaceutically acceptable carrier.

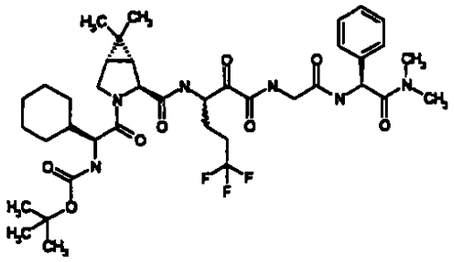
39. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates and prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being selected from the compounds of structures listed below:

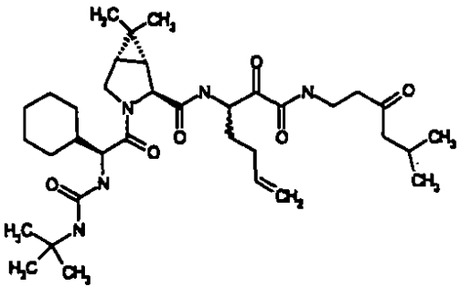


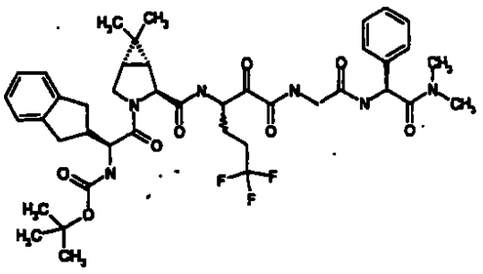


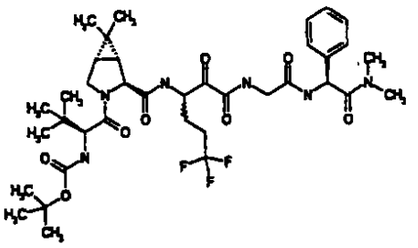


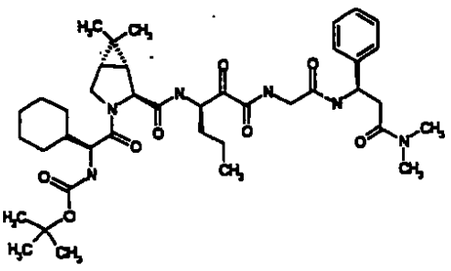


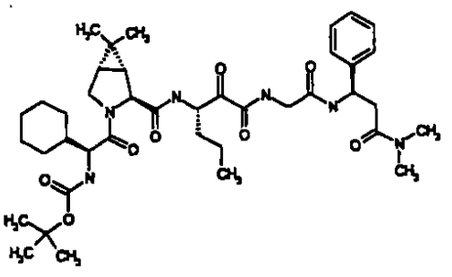


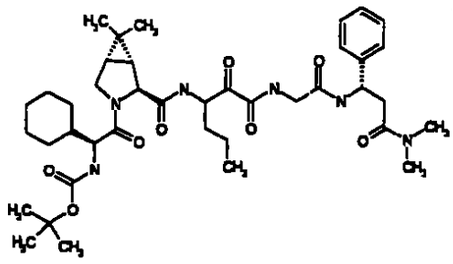


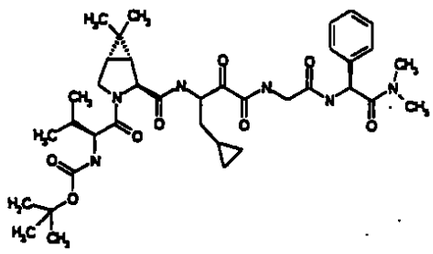


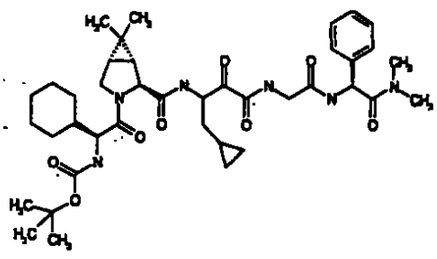


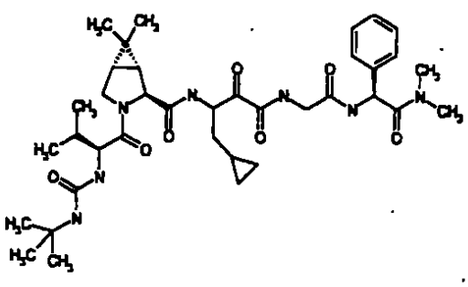


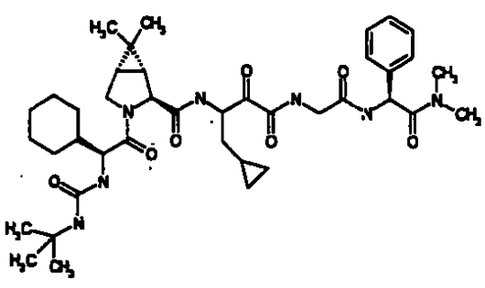


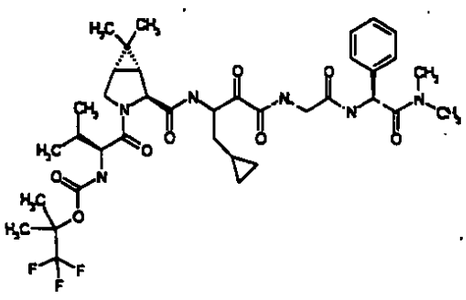




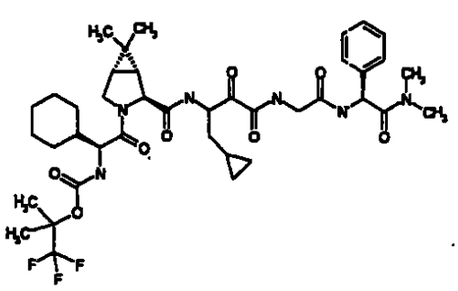


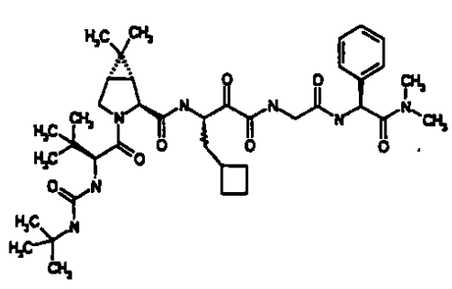


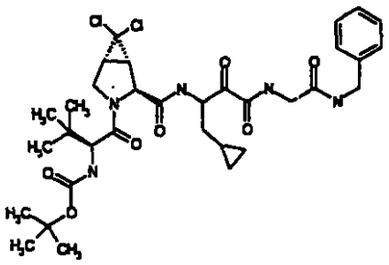


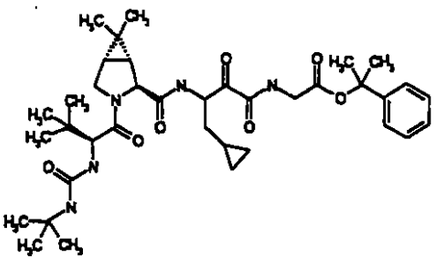


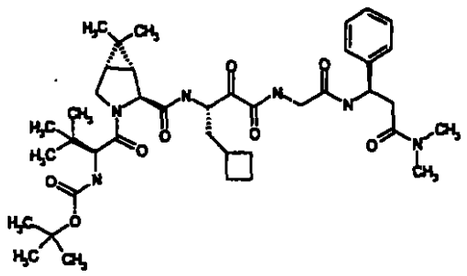
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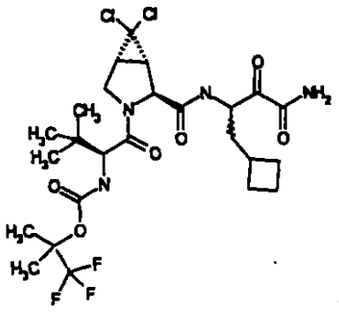


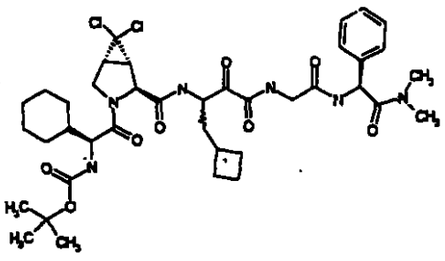


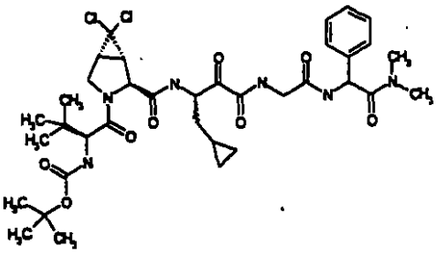


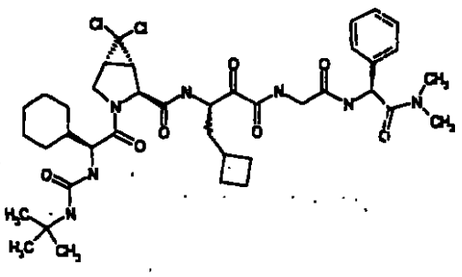


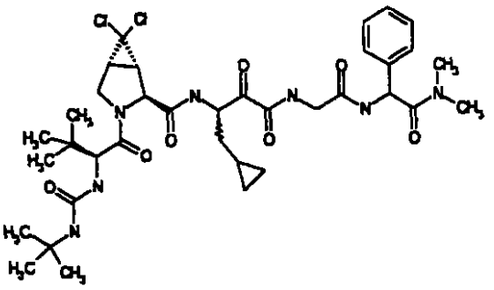


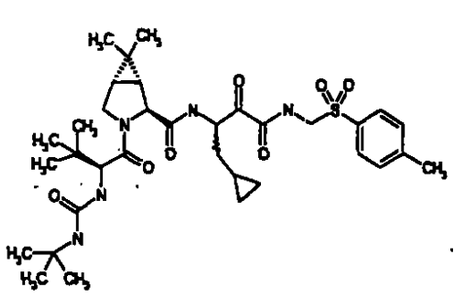


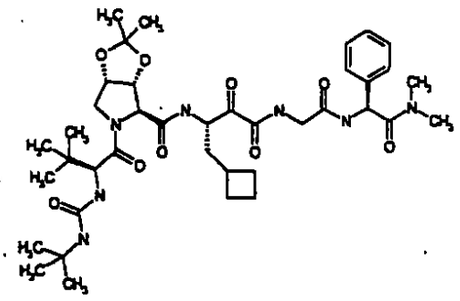


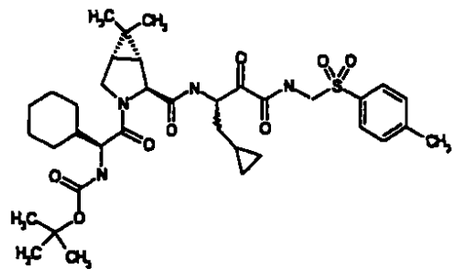


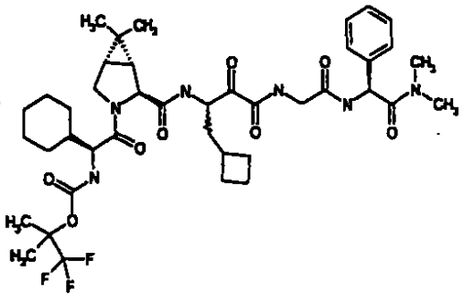


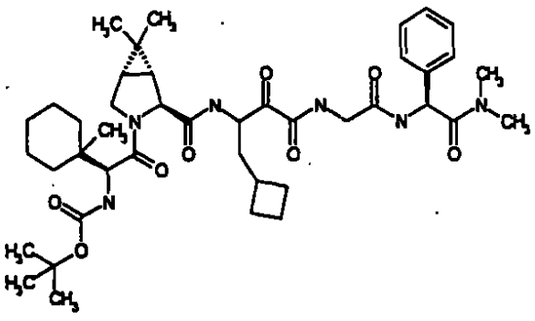


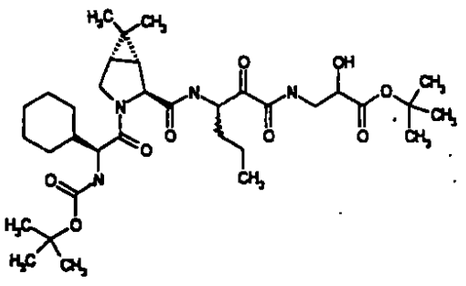


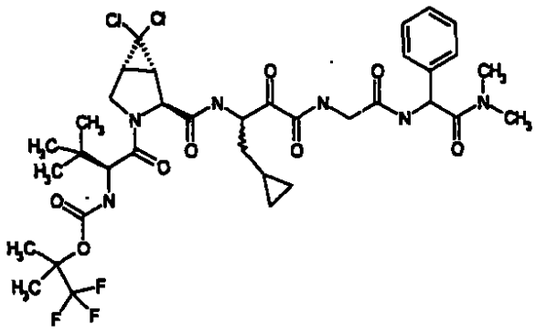


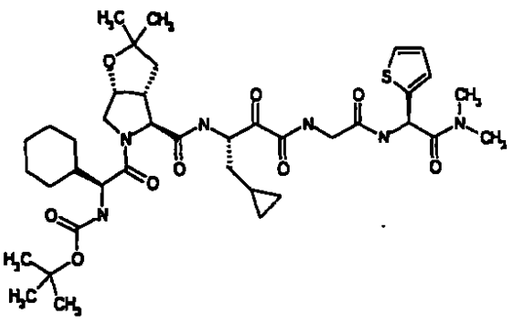


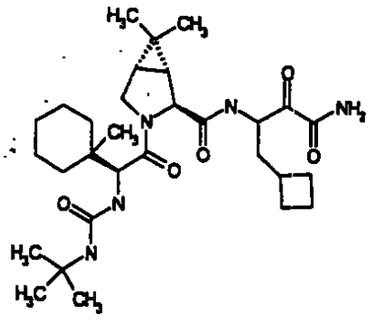


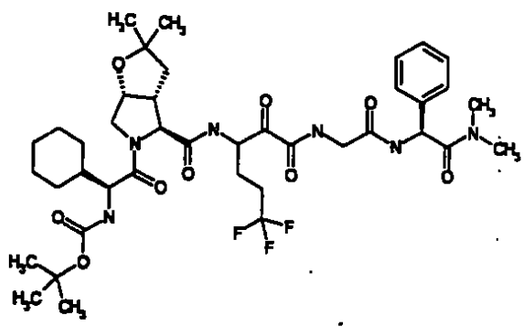


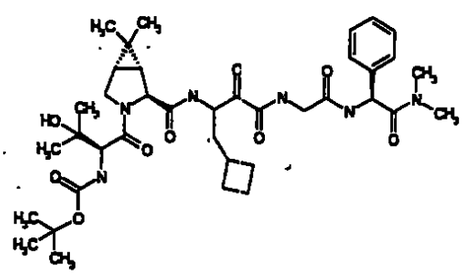


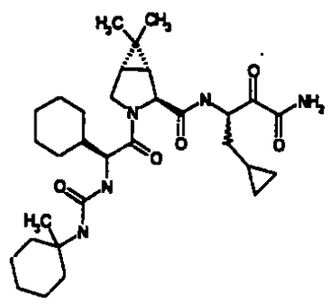




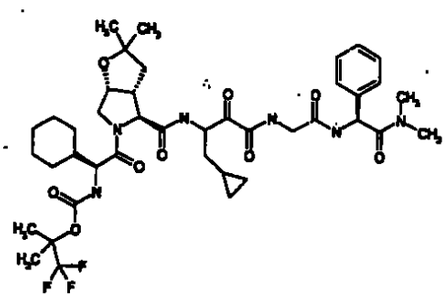


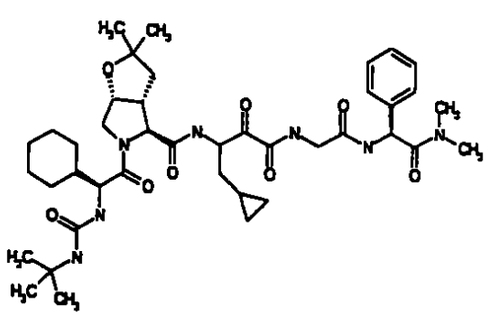


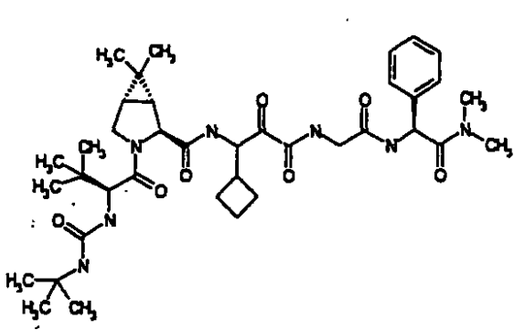


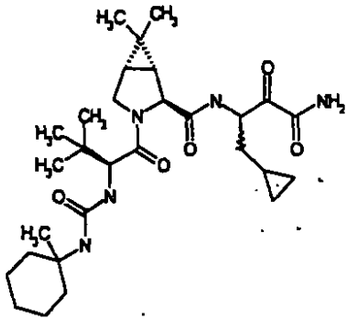


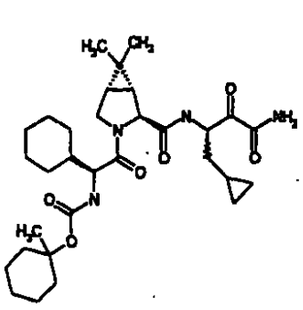
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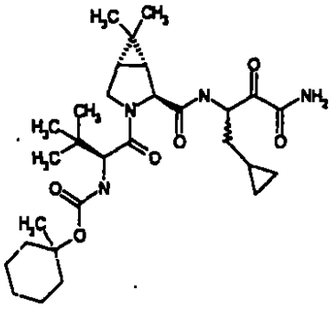


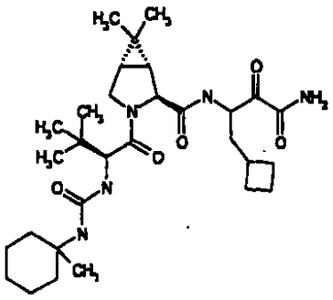


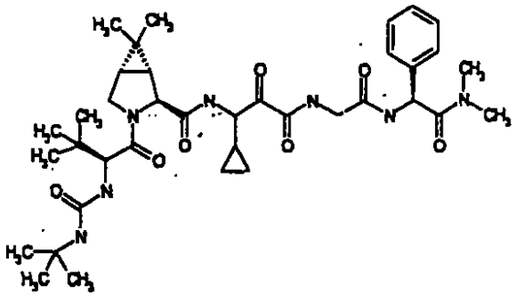


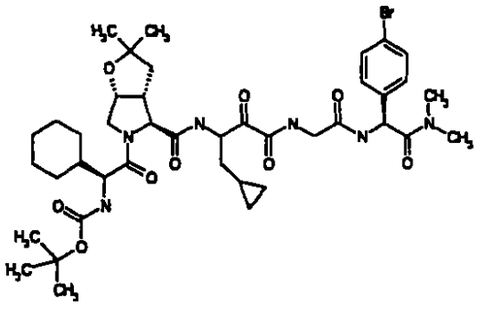


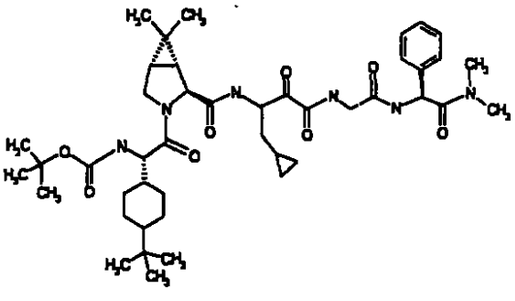


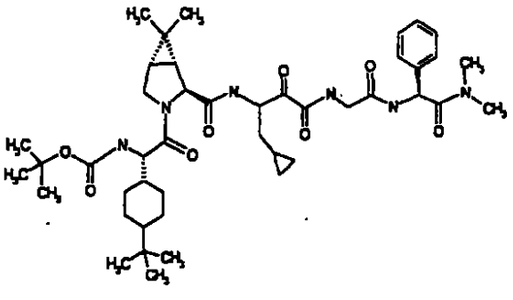


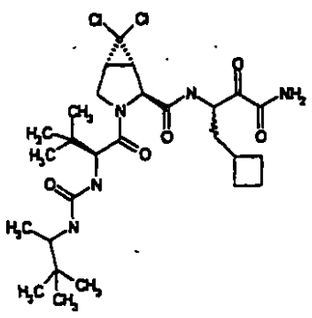


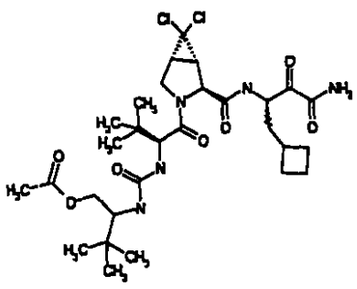


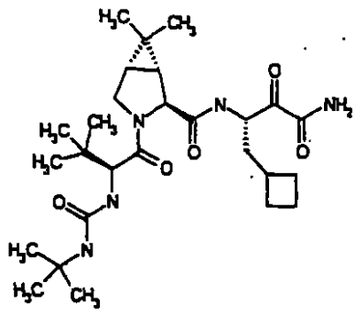


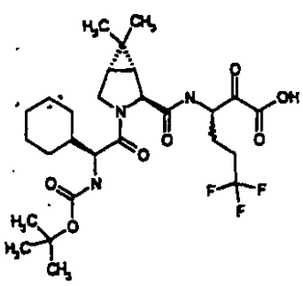


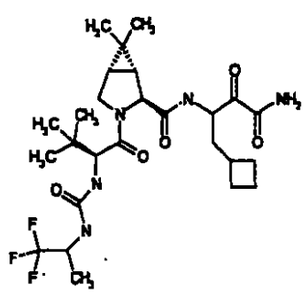


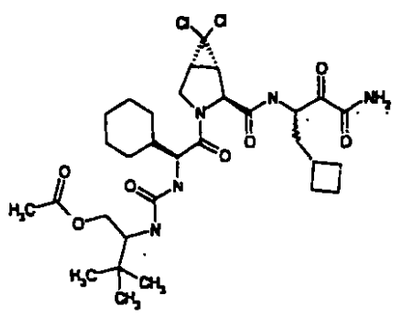




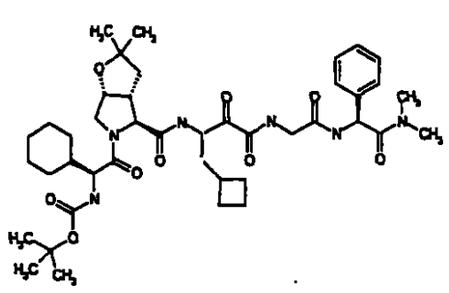


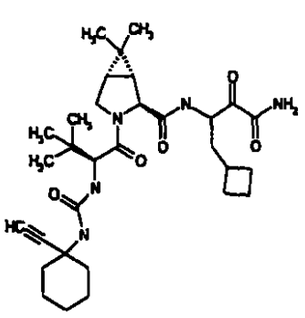


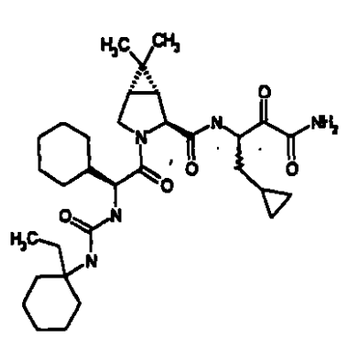


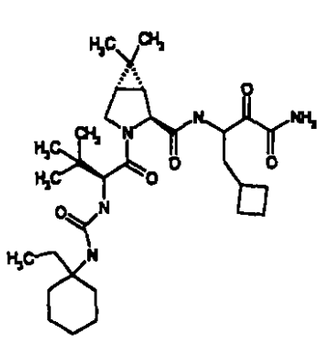


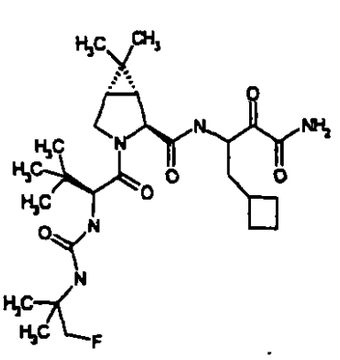
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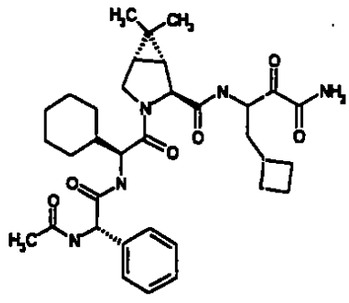


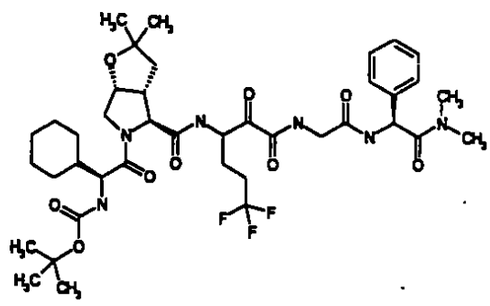


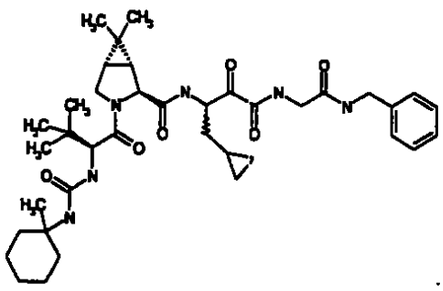


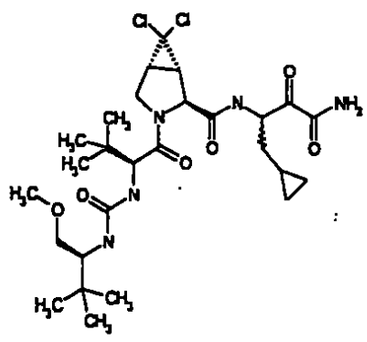


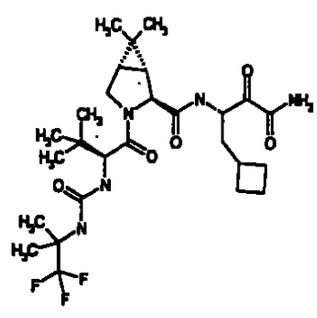


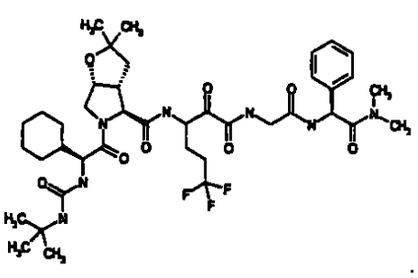


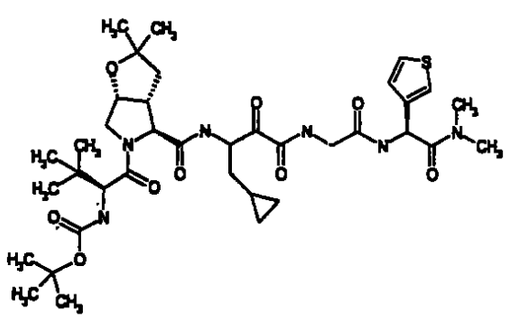


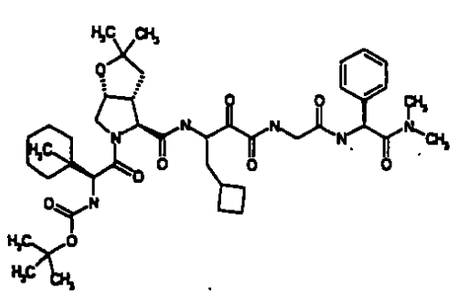


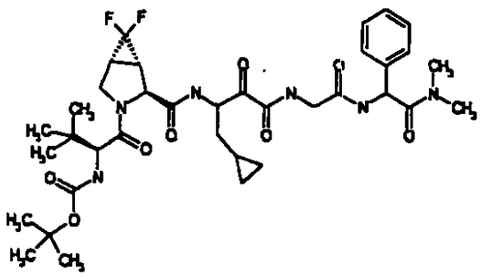


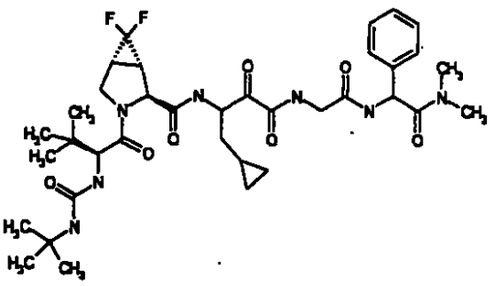


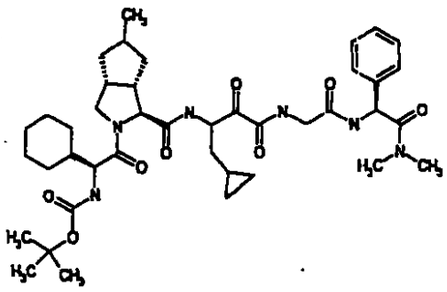


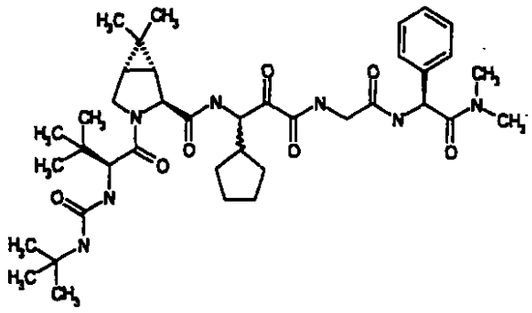




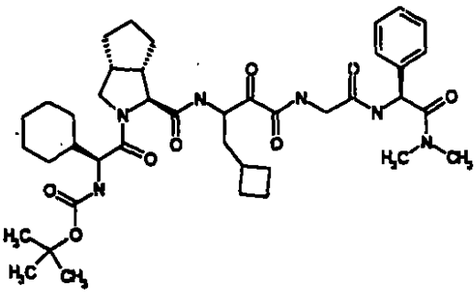


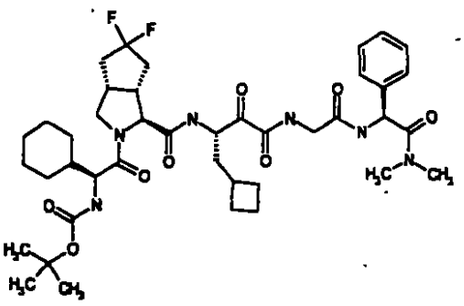


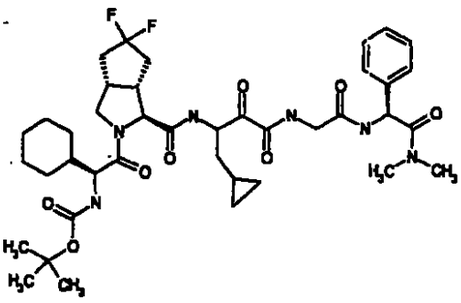


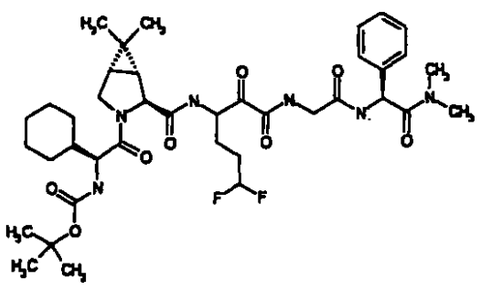


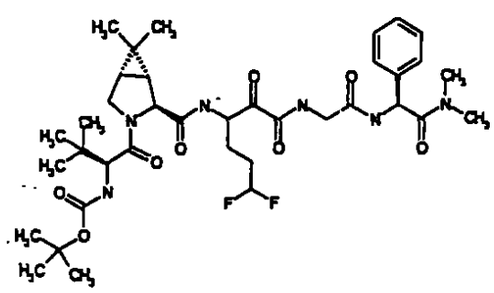
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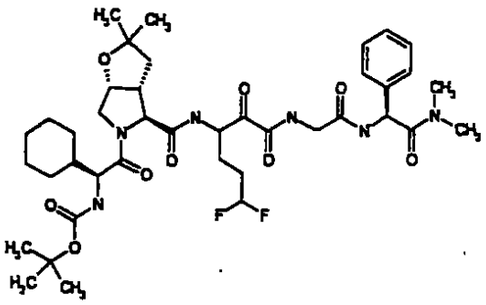


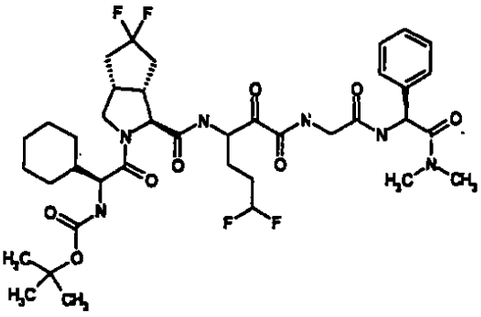


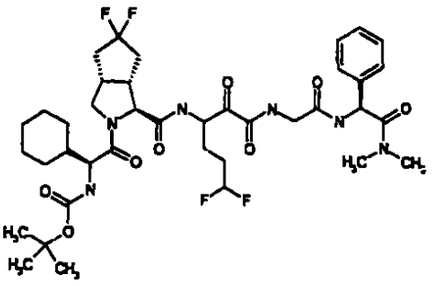




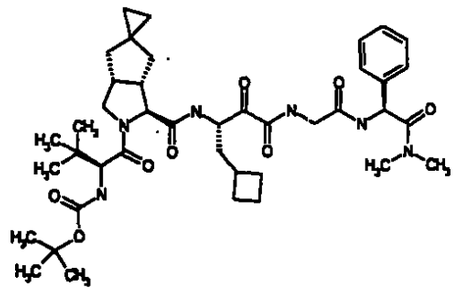


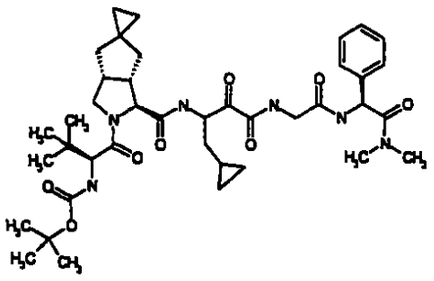


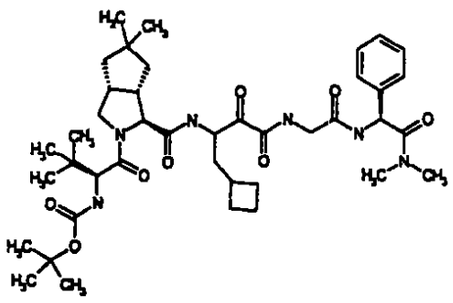


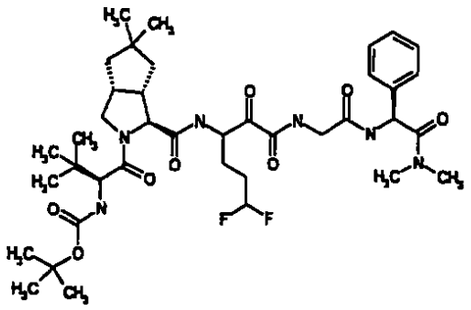


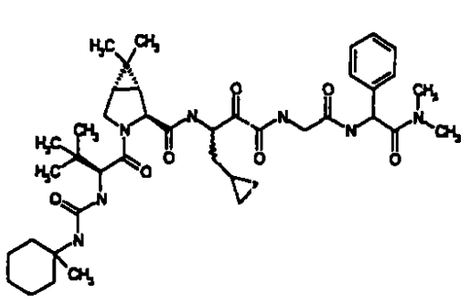
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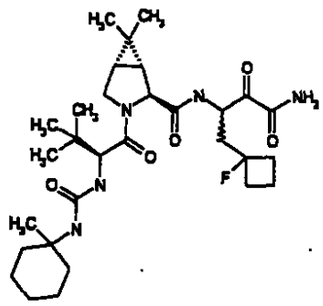


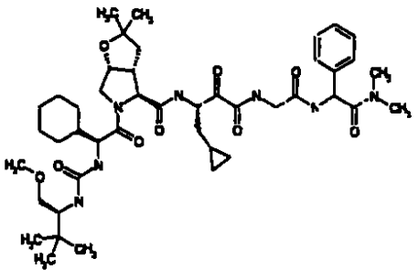


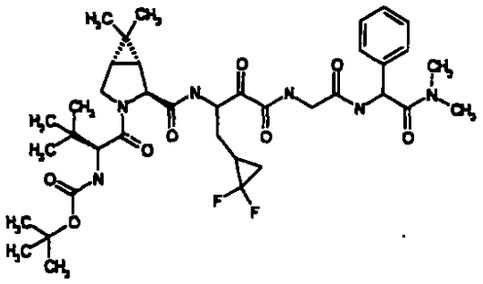


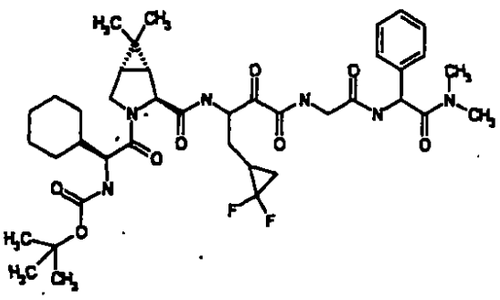


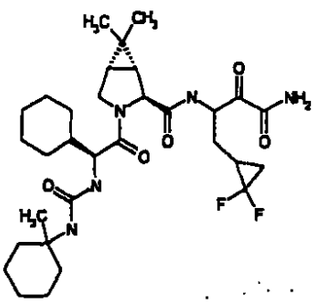


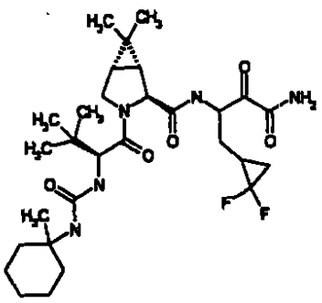


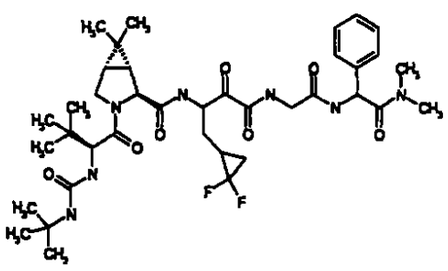


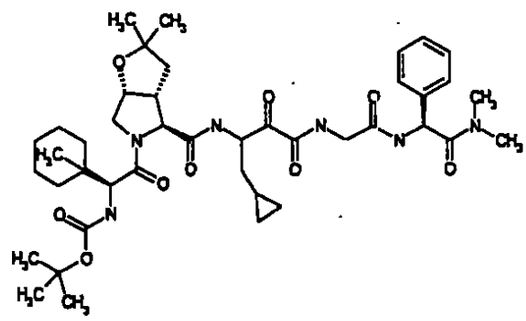




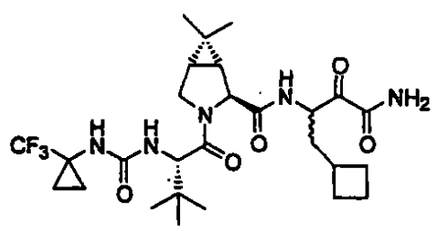








and



40. A pharmaceutical composition for treating disorders associated with the HCV, said composition comprising therapeutically effective amount of one or more compounds in claim 39 and a pharmaceutically acceptable carrier.

41. The pharmaceutical composition of claim 40, additionally containing an antiviral agent.

42. The pharmaceutical composition of claim 41, still additionally containing an interferon or PEG-interferon alpha conjugate.

43. The pharmaceutical composition of claim 42, wherein said antiviral agent is ribavirin and said interferon is α-interferon.

44. A method of treatment of a hepatitis C virus associated disorder, comprising administering an effective amount of one or more compounds of claim 39.

45. A method of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more compounds of claim 39.

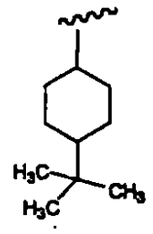
46. A method of treating, preventing, or ameliorating one or more symptoms of hepatitis C, comprising administering an effective amount of one or more compounds of claim 39.

47. The method of claim 46, wherein the HCV protease is the NS3/NS4a protease.

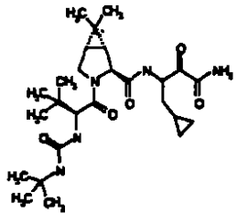
48. The method of claim 46, wherein the compound or compounds inhibit HCV NS3/NS4a protease.

49. A method of modulating the processing of hepatitis C virus (HCV) polypeptide, comprising contacting a composition containing the HCV polypeptide under conditions in which the polypeptide is processed with one or more compounds of claim 39.

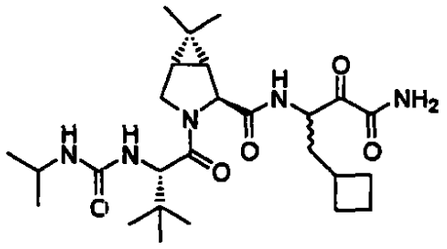
50. The compound of claim 6, wherein R^3 is:



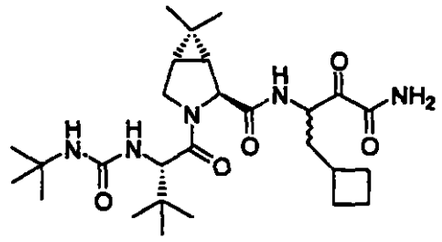
51. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:



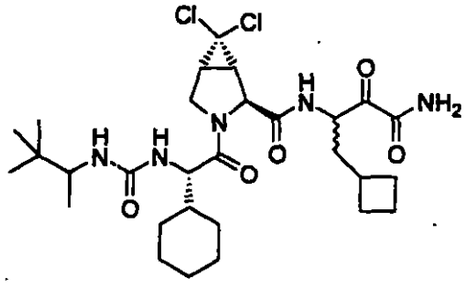
52. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:



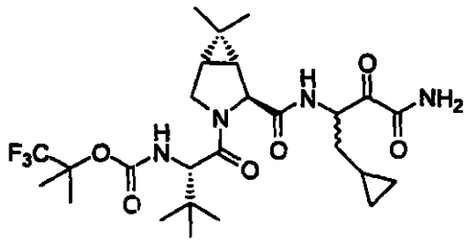
53. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:



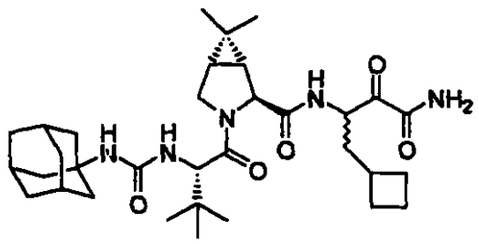
54. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:



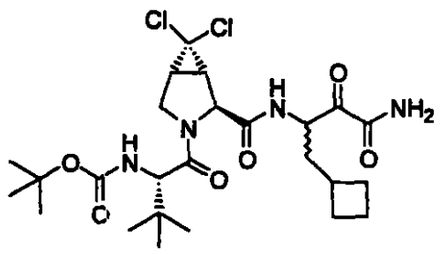
55. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:



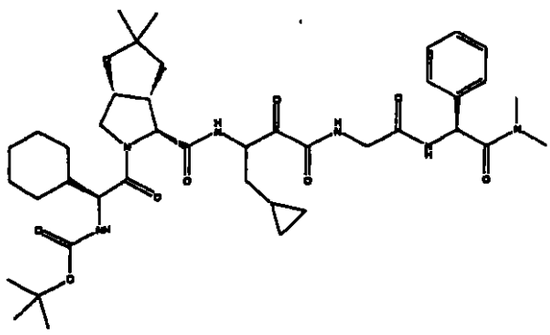
56. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:



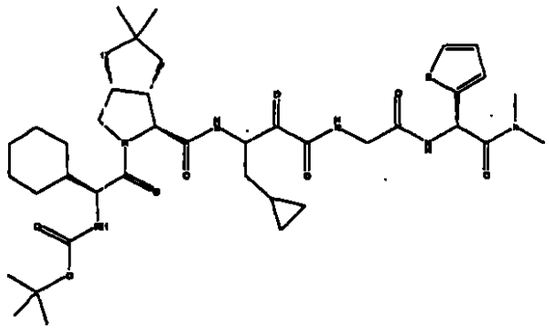
57. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:



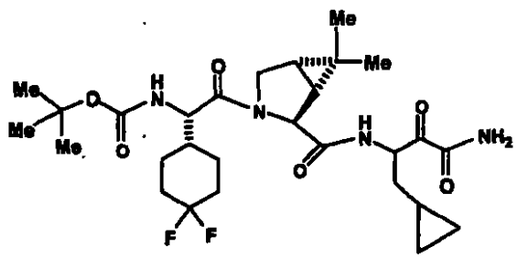
58. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:



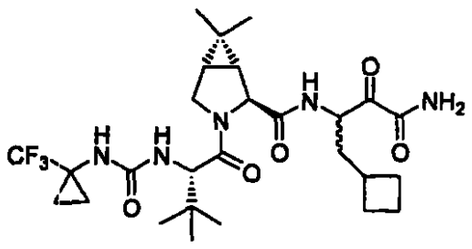
59. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:



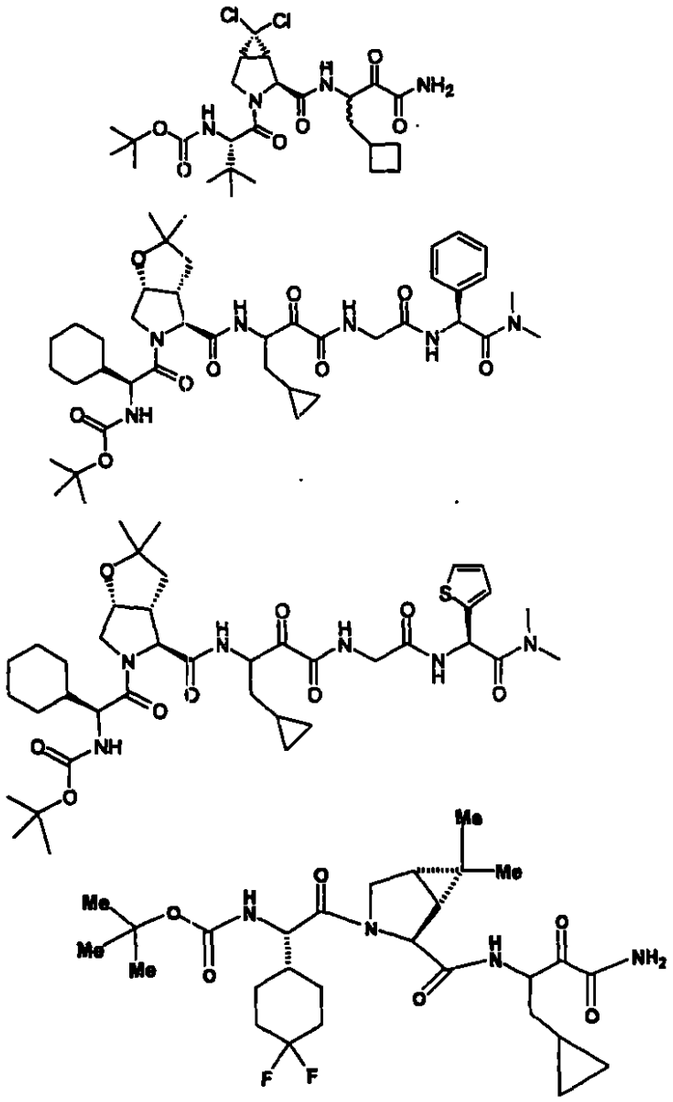
60. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:

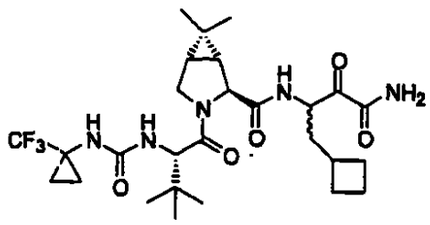


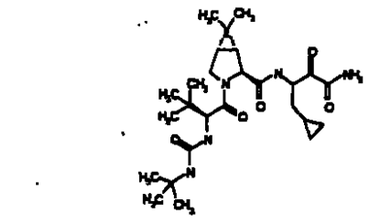
61. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being the compound of structure shown below:

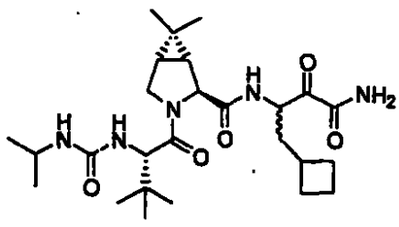


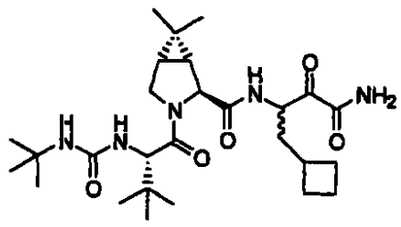
62. A pharmaceutical composition comprising as an active ingredient a compound, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being selected from the following:

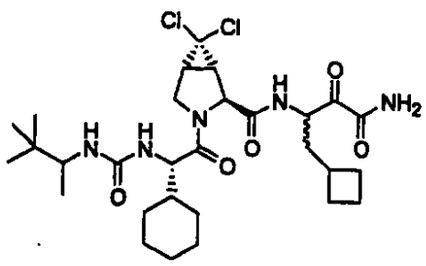


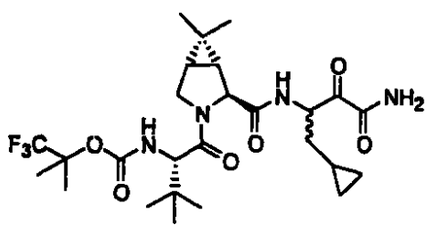

CF3
H
N
O
H
N
O
N
O
H
N
O
NH2
O

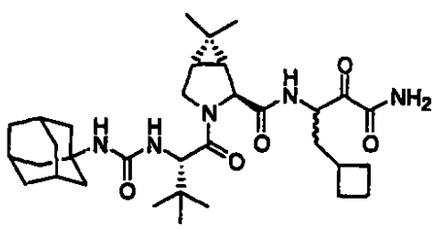










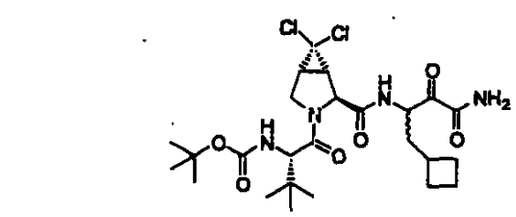


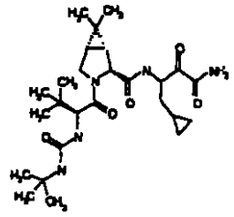
63. The pharmaceutical composition of claim 62, additionally containing an antiviral agent.

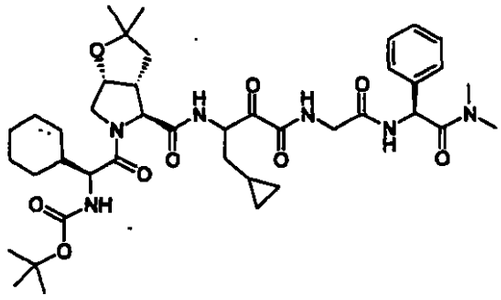
64. The pharmaceutical composition of claim 63, still additionally containing an interferon or PEG-interferon alpha conjugate.

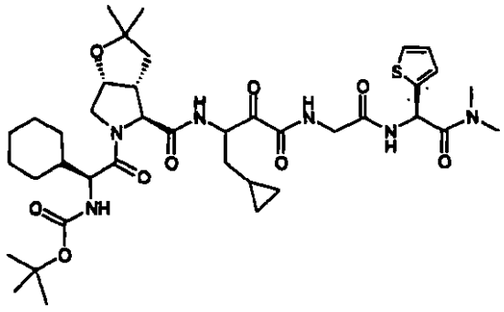
65. The pharmaceutical composition of claim 64, wherein said antiviral agent is ribavirin and said interferon is α-interferon.

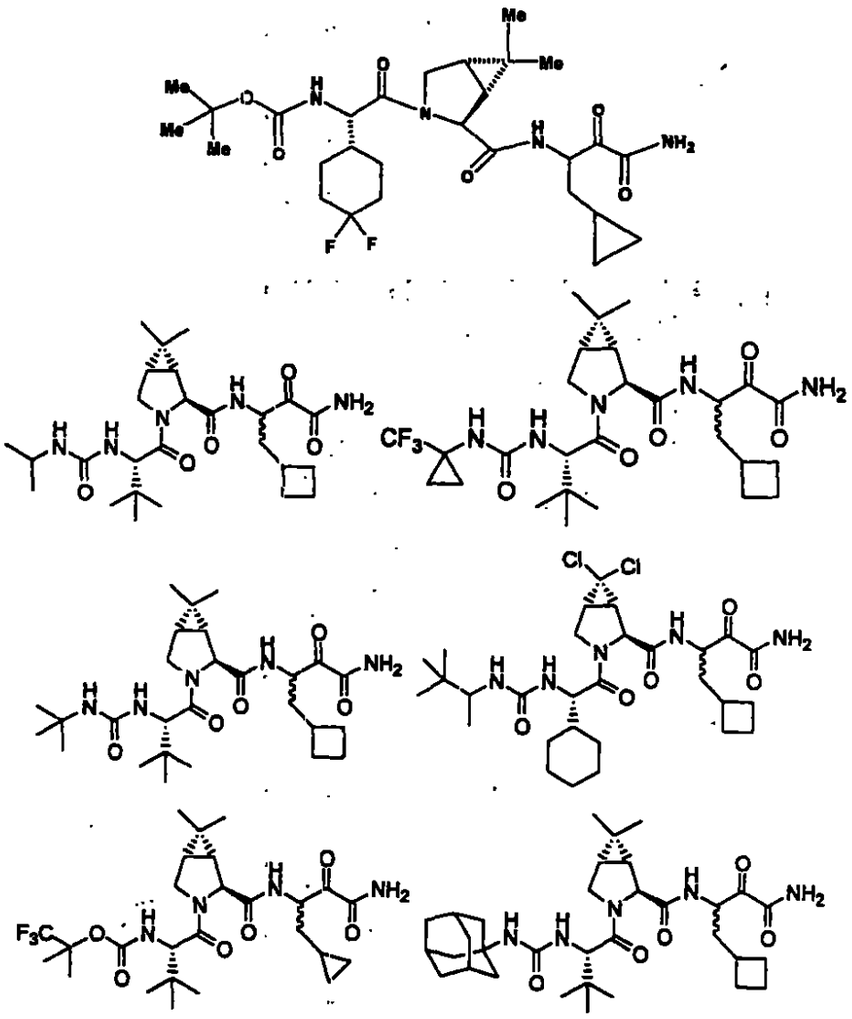
66. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment, a pharmaceutical composition which comprises therapeutically effective amounts of a compound, or enantiomers, stereoisomers, rotamers, tautomers, racemates or prodrug of said compound, or pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being selected from the following:











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Nuevos Péptidos como Inhibidores de la Proteasa Serina NS3 del Virus de la Hepatitis C

Campo de la Invención

La presente invención se refiere a nuevos inhibidores de la proteasa del virus de la hepatitis C ("HCV"), composiciones farmacéuticas que contienen uno o más de dichos inhibidores, métodos para preparar dichos inhibidores y métodos de uso de dichos inhibidores para tratar la hepatitis C y otros trastornos relacionados. Esta invención describe en forma específica nuevos compuestos peptídicos como inhibidores de la proteasa serina NS3/NS4a del HCV. La prioridad de la invención se basa en las solicitudes de Patentes de los Estados Unidos con Número de Serie 60/220.108, presentada el 21 de julio de 2000, y Número de Serie 09/908.955, presentada el 19 de julio de 2001.

Fundamento de la Invención

El virus de la hepatitis C es un virus con ARN de una hebra de sentido (+) que se ha relacionado como el agente causativo mayor de la hepatitis no A, no B (NANBH), en particular en la NANBH asociada con la sangre (BB-NANBH) (ver, Publicación de la Solicitud de Patente Internacional No. WO 89/04669 y la Publicación de la Solicitud de Patente Europea No. EP 381 216). La NANBH debe distinguirse de otros tipos de enfermedad hepática inducida por virus, como el virus de la hepatitis A (HAV), el virus de la hepatitis B (HBV), el virus de la hepatitis delta (HDV), el citomegalovirus (CMV) y el virus de Epstein-Barr (EBV), como también de otras formas de enfermedades hepáticas como el alcoholismo y la cirrosis biliar primaria.

Recientemente, se ha identificado, clonado y expresado una proteasa del HCV necesaria para el procesamiento polipeptídico y la replicación viral; (ver, por ej., la Patente de los Estados Unidos No. 5.712.145). Esta poliproteína de aproximadamente 3.000 aminoácidos contiene, desde la extremidad amino hasta la extremidad carboxi, una proteína nucleocapsídica (C), proteínas codificadas

(E1 y E2) y varias proteínas no estructurales (NS1, 2, 3, 4a, 5a y 5b). La 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 la proteasa serina formado por aproximadamente 200 de los animoácidos N-terminales; y (b) un dominio de ATPasa ARN-dependiente en la extremidad C de la proteína. La proteasa NS3 se considera un miembro de la familia de quimiotripsina debido a sus similitudes en la secuencia de la proteína, la estructura tridimensional general y el mecanismo de catálisis. Otras enzimas con aspecto de quimiotripsina son la elastasa, el factor Xa, la trombina, la tripsina, la plasmina, la uroquinasa, tPA y PSA. La proteasa serina NS3 del HCV es responsable de la proteólisis del polipéptido (poliproteína) en las uniones NS3/NS4a, NS4a/NS4b, NS4b/NS5a y NS5a/NS5b y, por consiguiente, es responsable de generación de cuatro proteínas virales durante la replicación viral. Esto ha logrado que la proteasa serina NS3 del HCV sea un blanco atractivo para la quimioterapia antiviral.

Se ha determinado que la proteína NS4a, un polipéptido de aproximadamente 6 kda, es un co-factor de la actividad de la proteasa serina de NS3. La autodisociación de la unión NS3/NS4a a través de la proteasa serina NS3/NS4a ocurre dentro de la molécula (es decir, *cis*) mientras que los otros sitios de disociación se procesan entre las moléculas (es decir, *trans*).

El análisis de los sitios de disociación natural para la proteasa del HCV reveló la presencia de cisteína en P1 y serina en P1' y que estos residuos se conservan en forma estricta en las uniones NS4a/NS4b, NS4/NS5a y NS5a/NS5b. La unión NS3/NS4a contiene una treonina en P1 y una serina en P1'. La sustitución Cys → Thr en NS3/NS4a se postula como explicación del requerimiento del procesamiento de *cis* en lugar de *trans* en esta unión. Ver, por ej., Pizzi et al. (1994) Proc. Natl. Acad. Sci (USA) 91: 888-892, Failla et al (1996) Folding & Design 1: 35-42. El sitio de disociación de NS3/NS4a también es más

tolerante de mutagénesis que los otros sitios. Ver, por ej. Kollykhalov et al. (1994) J. Virol. 68: 7525-7533. Se ha encontrado, además, que los residuos ácidos en la región ascendente del sitio de disociación se requieren para lograr una disociación eficiente. Ver, por ej., Komoda et al. (1994) J. Virol. 68: 7351-7357.

Los inhibidores de la proteasa del HCV que se han reportado incluyen antioxidantes (ver la Publicación de la Solicitud de Patente Internacional No. WO 98/14181), ciertos péptidos y análogos de péptidos (ver la Publicación de la Solicitud de Patente Internacional No. WO 98/17679, Landro et al. (1997) Biochem. 36: 9340-9348, Ingallinella et al. (1998) Biochem. 37 8906-8914, Llinàs-Brunet et al. (1998) Bioorg. Med. Chem. Lett. 8: 1713-1718), inhibidores basados en la eglina c polipeptídica de 70 aminoácidos (Martin et al. (1998) Biochem. 37: 11459-11468, afinidad por los inhibidores seleccionados del inhibidor de tripsina de secreción pancreática humana (hPSTI-C3) y repertorios de mini-cuerpos (MBip) (DIMASI et al. (1997) J. Virol. 71: 7461-7469), cV_HE2 (un fragmento del anticuerpo "camelizado" de dominio variable) (Martin et al. (1997) Protein Eng. 10: 607-614), y α1-antiquimiotripsina (ACT) (Elzouki et al.) (1997) J. Hepat. 27: 42-28). Una ribozima diseñada para destruir en forma selectiva el ARN del virus de la hepatitis C se ha descrito recientemente (ver, *BioWorld Today* 9(217): 4 (10 de noviembre de 1998)).

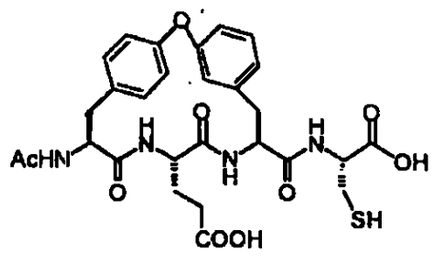
Además, se hace referencia a las Publicaciones de PCT, No. WO 98/17679, publicada el 30 de abril de 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496 publicada el 28 de mayo de 1998 (F. Hoffmann-La Roche AG); y WO 99/07734, publicada el 18 de febrero de 1999 (Boehringer Ingelheim Canada Ltd.).

El HCV se ha implicado en la cirrosis hepática y en la inducción del carcinoma hepatocelular. El pronóstico de los pacientes que sufren de infección por HCV es actualmente escaso. La infección por HCV es más difícil de tratar

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que otras formas de hepatitis debido a la falta de inmunidad o remisión asociadas con la infección por HCV. Los datos actuales indican una tasa menor del 50% de supervivencia después de 4 años del diagnóstico de cirrosis. Los pacientes que reciben un diagnóstico de carcinoma hepatocelular localizado que puede eliminarse por cirugía presentan una tasa de supervivencia a los 5 años del 10-30%, mientras que aquellos con carcinoma hepatocelular que no puede eliminarse por cirugía presentan una tasa de supervivencia a los cinco años inferior al 1%.

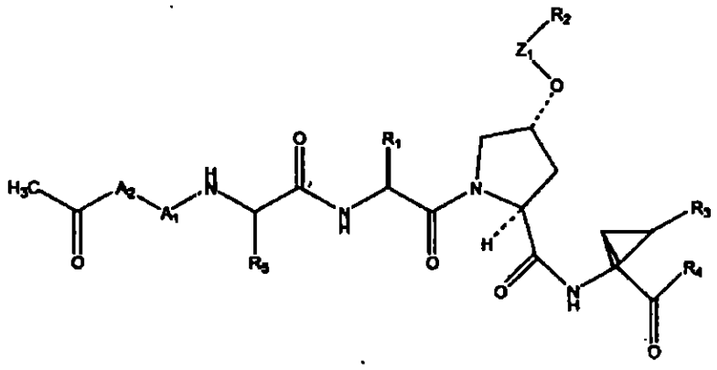
Se hace referencia a A. Marchetti *et al, Synlett*, S1, 1000-1002 (1999) que describe la síntesis de los análogos bicíclicos de un inhibidor de la proteasa NS3 del HCV. Allí se describe un compuesto que tiene la fórmula:



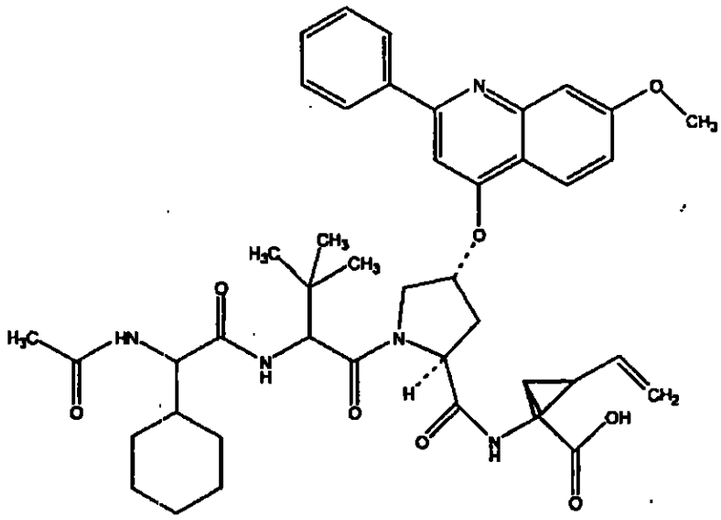
Además, se hace referencia a W. Han *et al, Bioorganic & Medicinal Chem. Lett*, (2000) 10, 711-713, que describe la preparación de ciertas α-cetoamidas, ciertos α-cetoésteres y ciertas α-dicetonas que contienen grupos funcionales alilo y etilo.

Además se hace referencia a la WO 00/09558 (Cesionario: Boehringer Ingelheim Limited; Publicada el 24 de febrero de 2000) que describe derivados peptídicos de la fórmula:

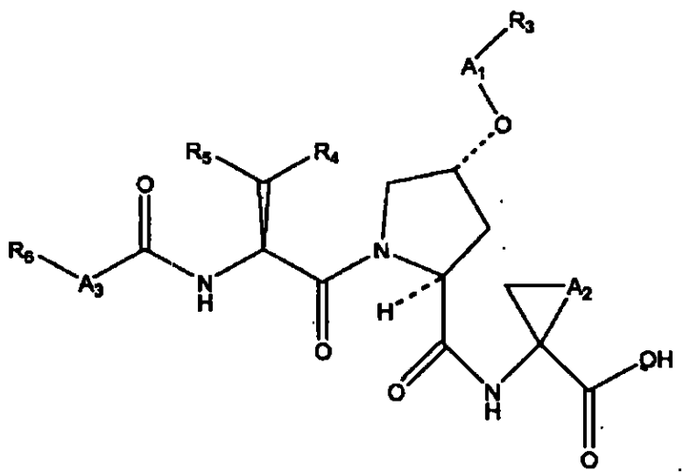
153



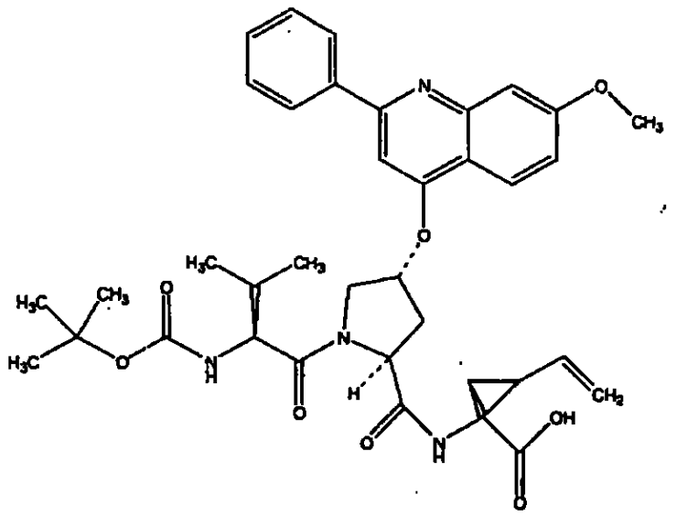
en la cual los diferentes elementos se definen en esa referencia. Un compuesto ilustrativo de esa serie es:



Además se hace referencia a la WO 00/09543 (Cesionario: Boehringer Ingelheim Limited; Publicada el 24 de febrero de 2000) que describe derivados peptídicos de la fórmula:



en la cual los diferentes elementos se definen en esa referencia. Un compuesto ilustrativo de esa serie es:



Los tratamientos actuales para la hepatitis C incluyen la terapia con interferón-α (INF_α) y la terapia combinada con ribavirina e interferón. Ver, por ej., Beremguer et al. (1998) Proc. Assoc. Am. Physicians 110(2): 98-112. Estas terapias sufren de una baja tasa de liberación prolongada y frecuentes efectos colaterales. Ver, por ej., Hoofnagle et al. (1997) N. Engl. J. Med. 336: 347. Actualmente, no se encuentra disponible ninguna vacuna para la infección por HCV.

Las solicitudes de Patente de los Estados Unidos pendientes y co-pendientes, No. de Serie 60/194.607, presentada el 5 de abril de 2000, y No. de serie 60/198.204, presentada el 19 de abril de 2000, No. de serie 60/220.110, presentada el 21 de julio de 2000, No. de serie 60/220.109, presentada el 21 de julio de 2000, No. de serie 60/220/107, presentada el 21 de julio de 2000, No. de serie 60/254.869, presentada el 12 de diciembre de 2000, y No. de serie 60/220.101, presentada el 21 de julio de 2000, describen varios tipos de péptidos y/u otros compuestos como inhibidores de la proteasa serina NS-3 del virus de la hepatitis C.

Existe una necesidad de lograr nuevos tratamientos y nuevas terapias para la infección por HCV. Por lo tanto, es un objetivo de esta invención proveer compuesto útiles en el tratamiento o la prevención o el alivio de uno o más síntomas de la hepatitis C.

Un objetivo adicional de la invención es proveer métodos de tratamiento o prevención o alivio de uno o más síntomas de la hepatitis C.

Aún otro objetivo de la presente invención es proveer métodos para modular la actividad de las proteasas serinas, en particular la proteasa serina NS3/NS4a del HCV, usando los compuestos provistos aquí.

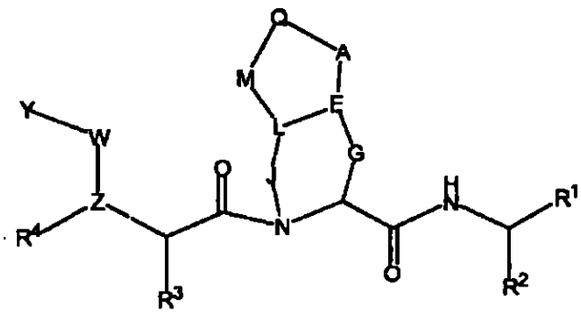
Otro objetivo de la invención es proveer métodos para modular el procesamiento del polipéptido del HCV usando los compuestos provistos aquí.

Breve Descripción de la Invención

En sus muchas realizaciones, la presente invención provee una nueva clase de inhibidores de la proteasa del HCV, composiciones farmacéuticas que contienen uno o más de los compuestos, métodos para preparar formulaciones farmacéuticas que comprenden uno o más de dichos compuestos, y métodos de tratamiento, prevención o alivio de uno o más de los síntomas de la hepatitis C. Además, se proveen métodos para modular la interacción del polipéptido del HCV con la proteasa del HCV. Entre los compuestos provistos aquí, se prefieren los

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compuestos que inhiben la actividad de la proteasa serina NS3/NS4a del HCV. La presente solicitud describe un compuesto, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra en la Fórmula I:



Fórmula I

donde: Y se selecciona del grupo formado por alquilo, alquil-arilo, heteroalquilo, heteroarilo, aril-heteroarilo, alquil-heteroarilo, cicloalquilo, alquiloxi, alquil-ariloxi, ariloxi, heteroariloxi, heterocicloalquiloxi, cicloalquiloxi, alquilamino, arilamino, alquil-arilamino, arilamino, heteroarilamino, cicloalquilamino y heterocicloalquilamino, con la salvedad de que Y puede estar sustituido en forma opcional con X^{11} o X^{12};

X^{11} es alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquil-alquilo, heterociclilo, heterociclilalquilo, arilo, alquilarilo, arilalquilo, heteroarilo, alquilheteroarilo, o heteroarilalquilo, con la salvedad de que X^{11} puede estar sustituido adicionalmente en forma opcional con X^{12}; X^{12} es hidroxi, alcoxi, ariloxi, tio, alquiltio, ariltio, amino, alquilamino, arilamino, alquilsulfonilo, arilsulfonilo, alquilsulfonamido, arilsulfonamido, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halógeno, ciano, o nitro, con la salvedad de que dicho alquilo, alcoxi, y arilo pueden estar sustituidos

adicionalmente en forma opcional con restos seleccionados en forma independiente de X^{12};

R^1 es $-C(O)R^5$ o $-B(OR)_2$, donde R^5 es H, -OH, $-OR^8$, $-NR^9R^{10}$, $-CF_3$, $-C_2F_5$, $-C_3F_7$, $-CF_2R_6$, $-R^6$, o $-C(O)R^7$ donde R^7 es H, -OH, $-OR^8$, $-CHR^9R^{10}$, o $-NR^9R^{10}$, donde R6, R^8, R^9 y R^{10} se seleccionan en forma independiente del grupo formado por H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, cicloalquilo, arilalquilo, heteroarilalquilo, $-[CH(R^{1'})]_pC(O)OR^{11}$, $-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$, $-[CH(R^{1'})]_pS(O_2)R^{11}$, $-[CH(R^{1'})]_pC(O)R^{11}$, $-[CH(R^{1'})]_pCH(OH)R^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})R'$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)OR11$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)N(H)CH(R^{5'})C(O)OR^{11}$ y $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)N(H)CH(R^{3'})C(O)N(H)CH(R^{4'})C(O)N(H)CH(R^{5'})C(O)NR^{12}R^{13}$, donde $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, y R' se seleccionan en forma independiente del grupo formado por H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquil y heteroaralquilo;

Z se selecciona de O, N, C(H) o C(R);

W puede estar presente o ausente, y si W está presente, W se selecciona de C(=O), C(=S), C(=N-CN), o $S(O_2)$;

Q puede estar presente o ausente, y cuando Q está presente, Q es C(H), N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, NR, S, o SO_2; y cuando Q está ausente, M puede estar presente o ausente; cuando Q y M están ausentes, A está ligado directamente a L;

A es O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, N(R), S, $S(O_2)$ o un enlace;

E es CH, N, CR, o un enlace doble hacia A, L o G;

G puede estar presente o ausente, y cuando G está presente, G es $(CH_2)_p$, $(CHR)_p$, o $(CRR')_p$; y cuando G está ausente, J está presente y E está conectado directamente al átomo de carbono en la Fórmula I como está ligado G;

J puede estar presente o ausente, y cuando J está presente, J es $(CH_2)_p$, $(CHR)_p$, o $(CRR')_p$, $S(O_2)$, N(H), N(R) u O; y cuando J está ausente, G está presente y E está ligado directamente a N como se muestra en la Formula I ligado a J;

L puede estar presente o ausente, y cuando L está presente, L es C(H), C(R), O, S o N(R); y cuando L está ausente, entonces M puede estar presente o ausente; y si M está presente y L está ausente, entonces M está ligado directa e independientemente a E, y J está ligado directa e independientemente a E;

M puede estar presente o ausente, y cuando M está presente, M es O, NR, S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, o $(CRR')_p$;

p es un número desde 0 hasta 6; y

R, R', R^2, R^3 y R^4 pueden ser iguales o diferentes y se seleccionan independientemente del grupo formado por H; alquilo de C_1-C_{10}; alquenilo de C_2-C_{10}; cicloalquilo de C_3-C_8; heterocicloalquilo de C_3-C_8, alcoxi, ariloxi, alquiltio, ariltio, amino, amido, éster, ácido carboxílico, carbamato, urea, cetona, aldehído, ciano, nitro, halógeno; (cicloalquil)alquilo y (heterocicloalquil)alquilo, donde dicho cicloalquilo está formado por tres hasta ocho átomos de carbono, y desde cero hasta seis átomos de oxígeno, nitrógeno, azufre o fósforo, y dicho alquilo tiene desde uno hasta seis átomos de carbono; arilo; heteroarilo; alquil-arilo; y alquil-heteroarilo;

donde dichos restos alquilo, heteroalquilo, alquenilo, heteroalquenilo, arilo, heteroarilo, cicloalquilo y heterocicloalquilo pueden estar sustituidos opcionalmente y en forma apropiada por medios químicos, donde dicho término "sustituido" se refiere a una sustitución opcional y apropiada químicamente con uno o más restos seleccionados del grupo formado por alquilo; alquenilo, alquinilo, arilo, aralquilo, cicloalquilo, heterocíclico, halógeno, hidroxi, tio, alcoxi, ariloxi, alquiltio, ariltio, amino, amido, éster, ácido carboxílico, carbamato, urea, cetona, aldehído, ciano, nitro, sulfonamido, sulfóxido, sulfona, sulfonil urea, hidrazida, y hidroxamato; además donde dicha unidad N-C-G-E-L-J-N en la Fórmula I representa tanto una estructura anular cíclica de cinco miembros como una estructura anular cíclica de seis miembros con la salvedad de que cuando dicha unidad N-C-G-E-L-J-N representa una estructura anular cíclica de cinco miembros, o cuando la estructura anular bicíclica en la Fórmula I que comprende N, C, G, E, L, J, N, A, Q, y M representa una estructura anular cíclica de cinco miembros, entonces dicha estructura anular cíclica de cinco miembros carece de un grupo carbonilo como parte del anillo cíclico.

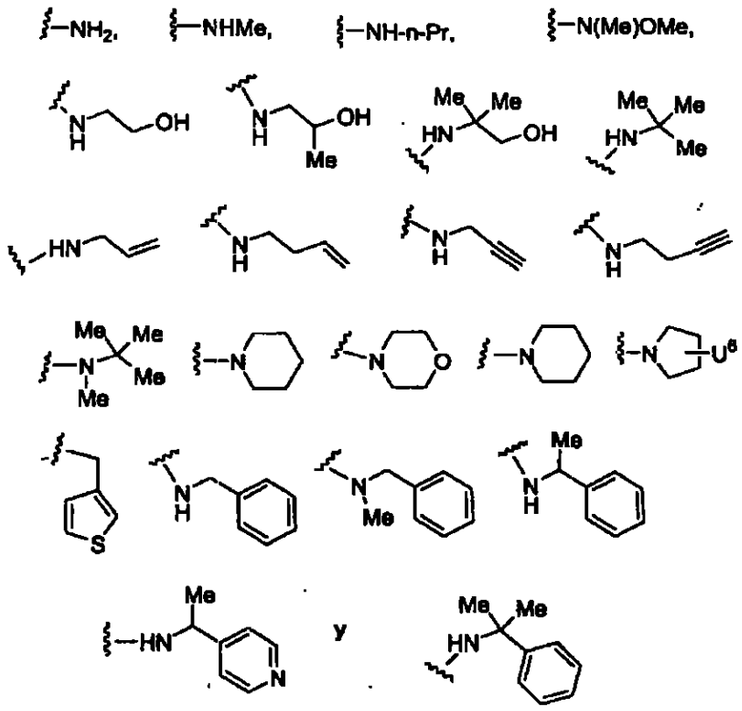
Entre las definiciones anteriores para los diferentes restos de Fórmula I, los grupos preferidos para los diferentes restos son de la siguiente manera: La definición preferida para R^1 es $-C(O)R^5$ donde R^5 es H, -OH, $-C(O)OR^8$ o $-C(O)NR^9R^{10}$, donde R^8, R^9 y R^{10} se definieron con anterioridad. El resto aún más preferido para R^1 es $-C(O)C(O)NR^9R^{10}$, donde R9 es H; y R^{10} es H, $-R^{14}$, $-[CH(R^{1'})]_pC(O)OR^{11}$, $-[CH(R^{11})]_pC(O)NR^{12}R^{13}$, $-[CH(R^{1'})]_pS(O_2)R^{11}$, $-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$, $-[CH(R^{1'})]_pC(O)R^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$, o $-CH(R^{1'})C(O)N(H)CH(R^{2'})$ (R'), donde R^{14} es H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo, alquenilo, alquinilo o heteroaralquilo.

Entre los anteriores para R^{10}, los restos preferidos para R^{10} are: H, $-R^{14}$, $-CH(R^{1'})C(O)OR^{11}$, $-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$, $-CH(R^{1'})C(O)NR^{12}R^{13}$,

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-CH($R^{1'}$)CH($R^{1'}$)C(O)N$R^{12}R^{13}$, -CH($R^{1'}$)CH($R^{1'}$)S(O_2)R^{11}, -CH($R^{1'}$)CH($R^{1'}$)S(O_2)N $R^{12}R^{13}$, -CH($R^{1'}$)CH($R^{1'}$)C(O)R^{11}, -CH($R^{1'}$)C(O)N(H)CH($R^{2'}$)C(O)OR^{11}, -CH($R^{1'}$)C(O)N(H)CH($R^{2'}$)C(O)N$R^{12}R^{13}$, o -CH($R^{1'}$)C(O)N(H)CH($R^{2'}$) (R'), donde $R^{1'}$ es H o alquilo, y $R^{2'}$ es fenilo, fenilo sustituido, fenilo sustituido con un heteroátomo, tiofenilo, cicloalquilo, piperidilo o piridilo.

Los restos más preferidos son: para $R^{1'}$ es H, para R^{11} es H, metilo, etilo, alilo, tertbutilo, bencilo, α-metilbencilo, α,α-dimetilbencilo, 1-metilciclopropilo o 1-metilciclopentilo; para R' es hidroximetilo o -CH_2C(O)N$R^{12}R^{13}$ donde N$R^{12}R^{13}$ se selecciona del grupo formado por:

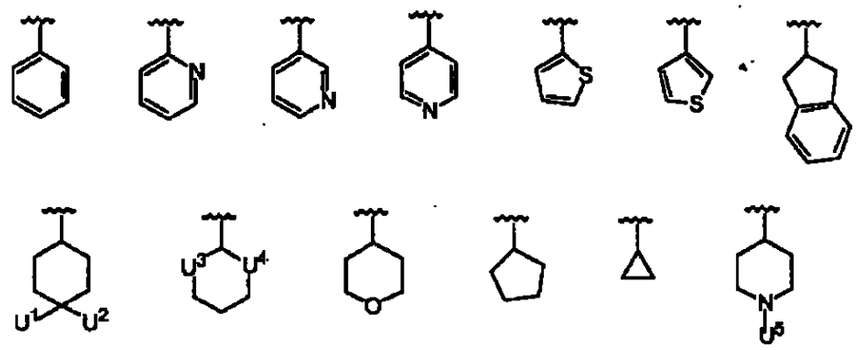


donde U^6 es H, OH, o CH_2OH;

R^{14} se selecciona, con preferencia, del grupo formado por: H, Me, Et, *n*-propilo, metoxi, ciclopropilo, *n*-butilo, 1-but-3-inilo, bencilo, α-metilbencilo, fenetilo, alilo, 1-but-3-enilo, OMe y ciclopropilmetilo;

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y $R^{2'}$ se selecciona, con preferencia, en forma independiente, del grupo formado por:



donde

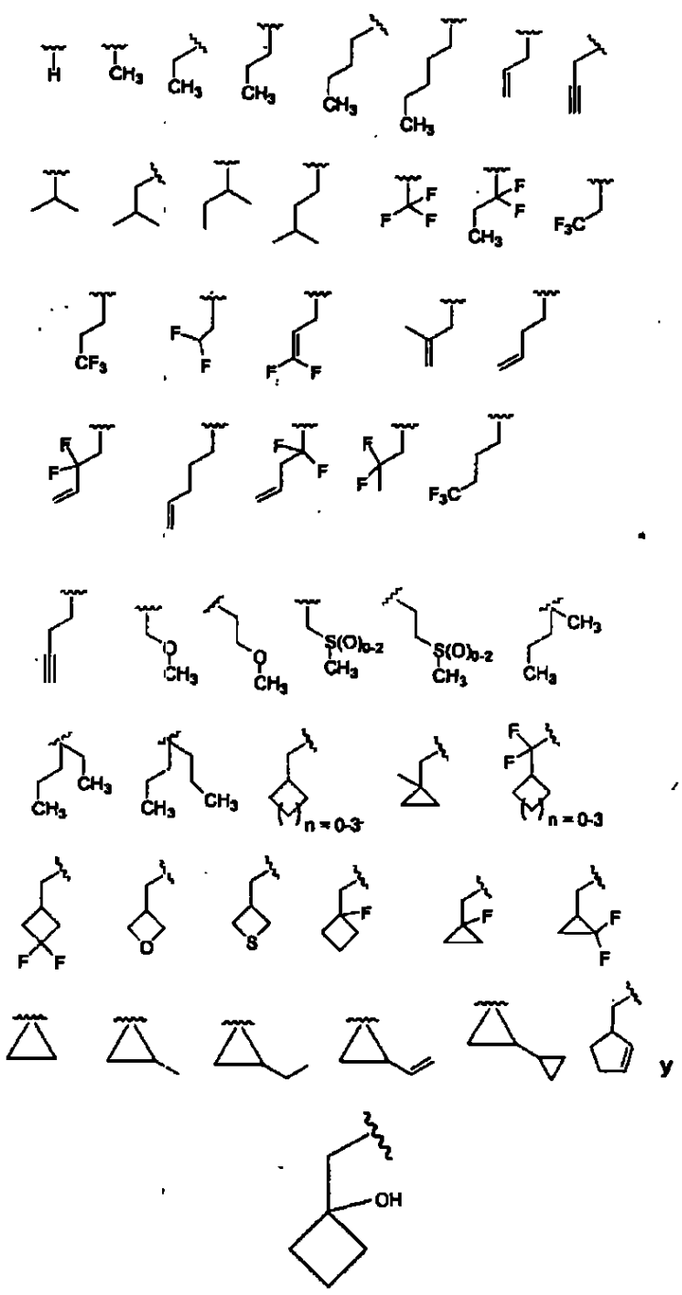
U^1 y U^2 pueden ser iguales o diferentes y se seleccionan del grupo formado por H, F, CH_2COOH, CH_2COOMe, CH_2CONH_2, $CH_2CONHMe$, CH_2CONMe_2, azido, amino, hidroxilo, amino sustituido e hidroxilo sustituido;

U^3 y U^4 pueden ser iguales o diferentes y se seleccionan de O y S;

U^5 se selecciona de los restos formados por alquilsulfonilo, arilsulfonilo, heteroalquilsulfonilo, heteroarilsulfonilo, alquilcarbonilo, arilcarbonilo, heteroalquilcarbonilo, heteroarilcarbonilo, alcoxicarbonilo, ariloxicarbonilo, heteroariloxicarbonilo, alquilaminocarbonilo, arilaminocarbonilo, heteroarilaminocarbonilo o una de sus combinaciones.

Los restos preferidos para R^2 son:

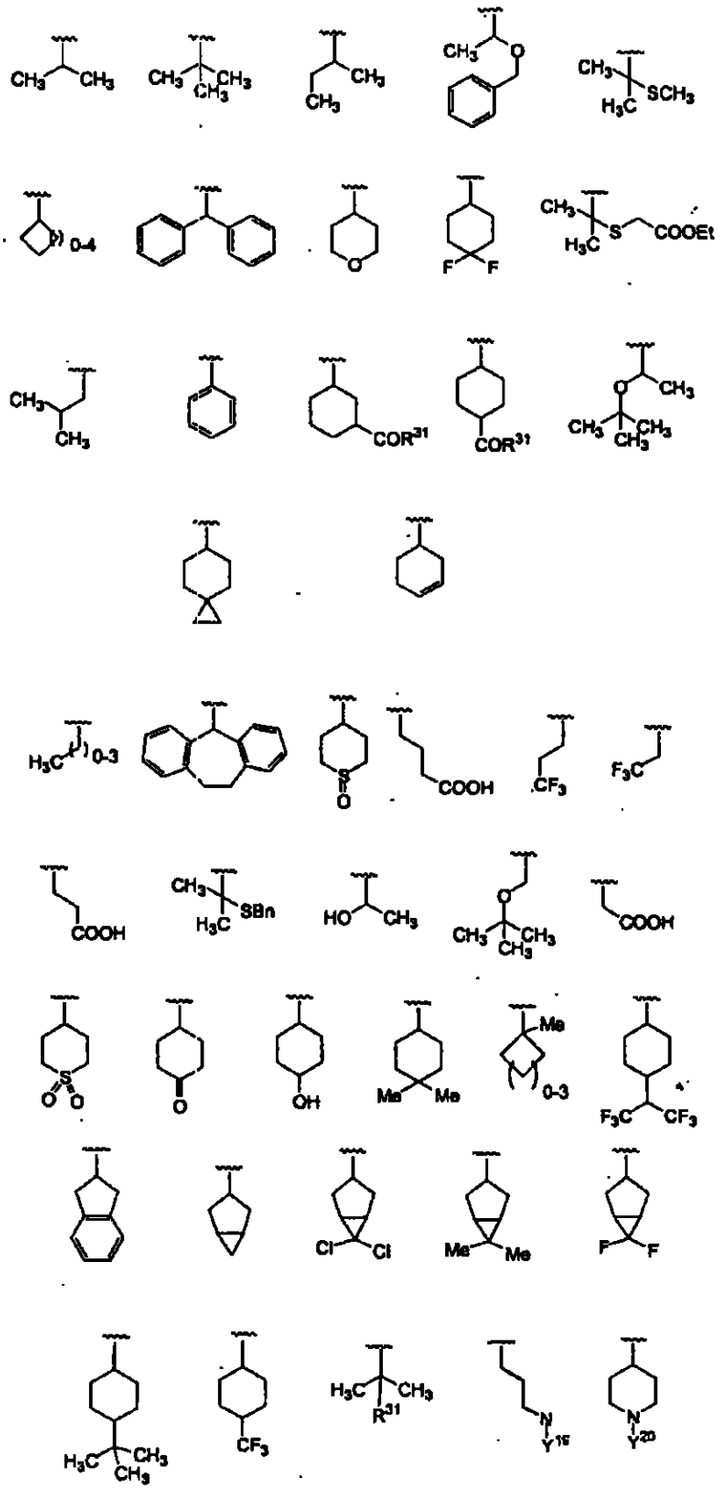
662



y

Los restos preferidos para R^3 son:

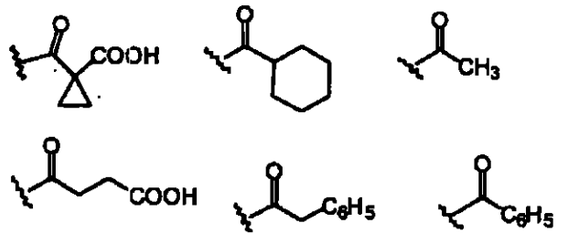
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0-4
COOEt
COR31
COR31
0-3
COOH
CF3
COOH
SBn
COOH
Me
0-3
Cl
Cl
Me
Me
F
F
R31
N
Y15
N
Y20

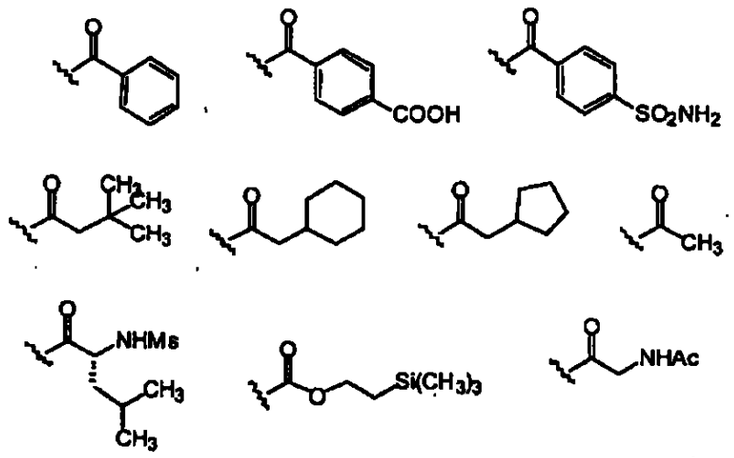
664

donde R^{31} = OH u OH-alquilo;

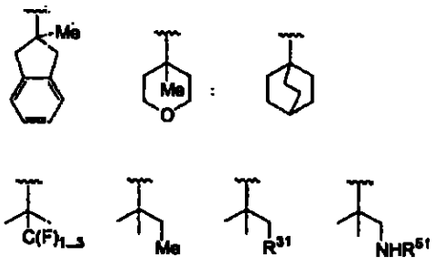
Y^{19} se selecciona de los siguientes restos:



y Y^{20} se selecciona de los siguientes restos:

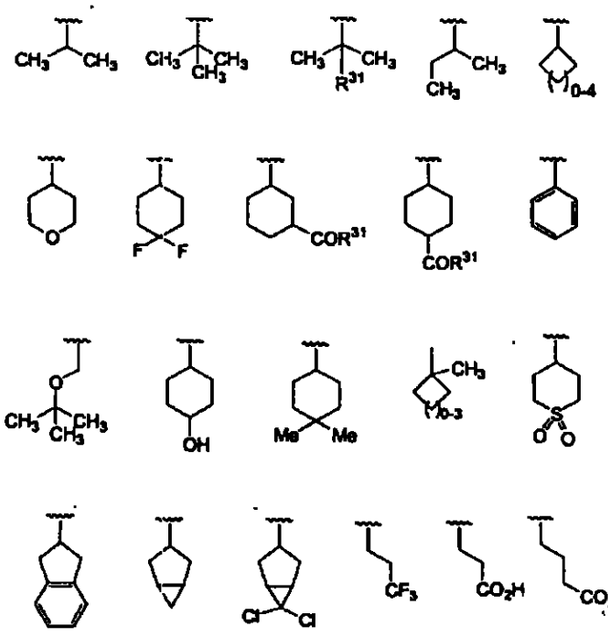


Los restos más preferidos para R^3 son:

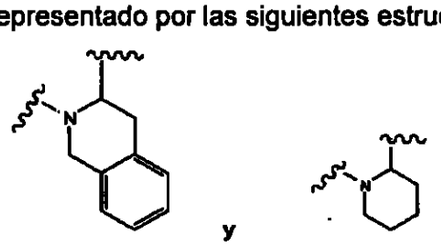


donde R^{51} = H, -$COCH_3$, -COOtBu o -CONHtBu.

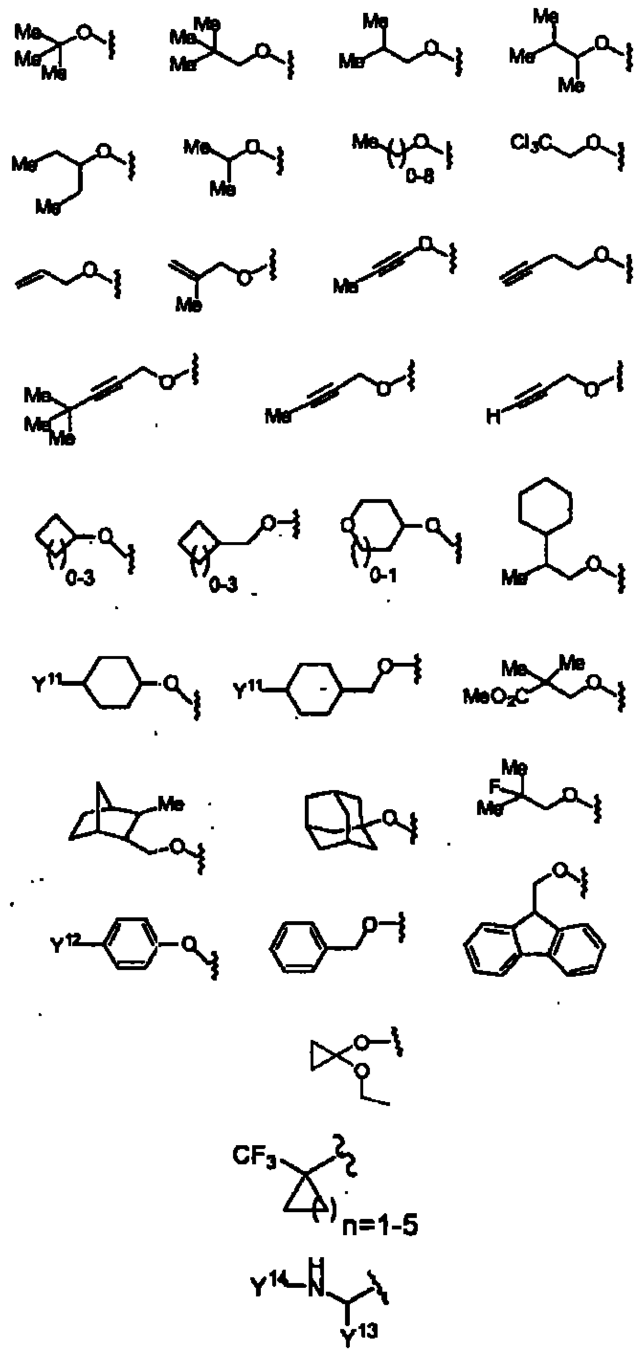
Los restos más preferidos para R^3 son:

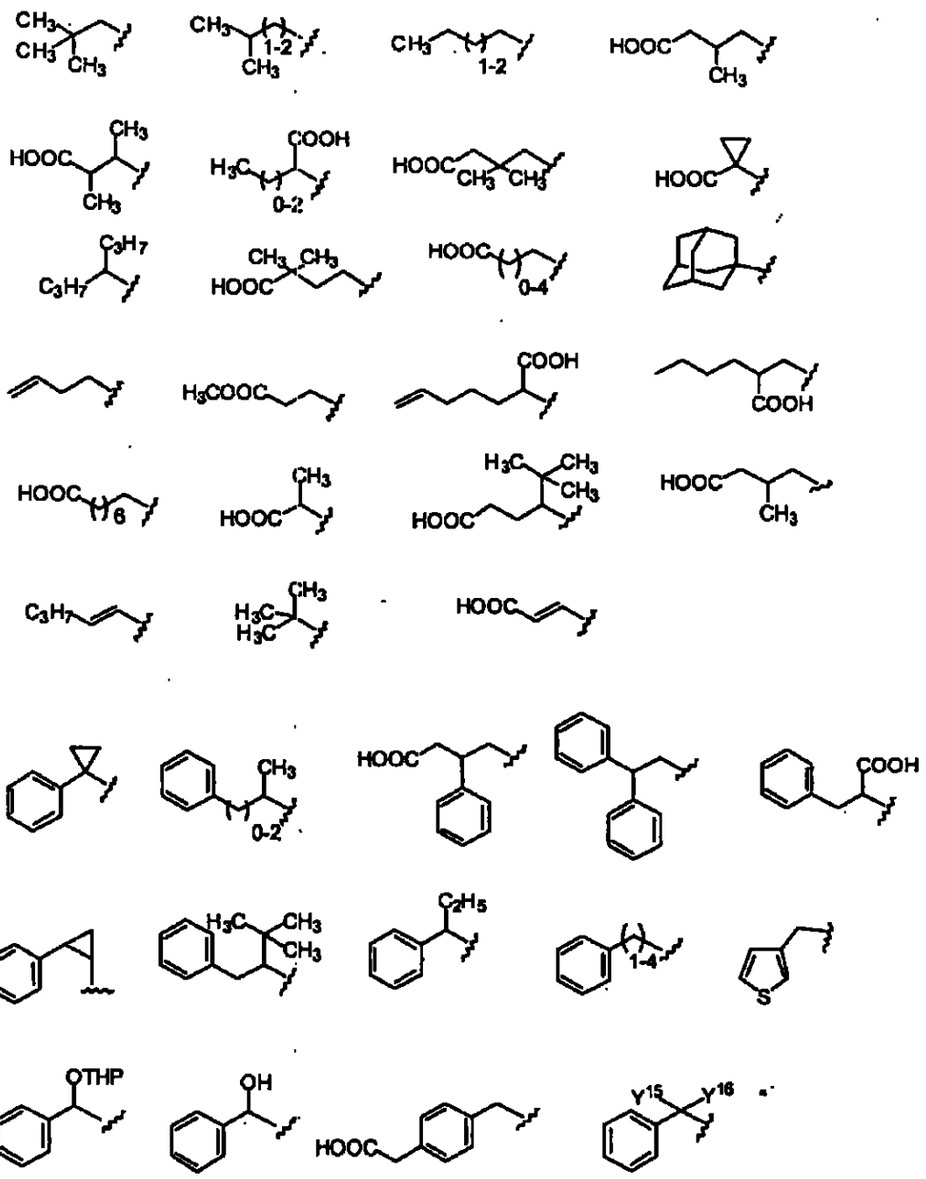


Algunos otros restos preferidos son: para Z es N, para R^4 es H, y para W es C=O. En forma adicional, el resto Z-C-R^3 en la Fórmula I, cuando R^4 está ausente, puede estar representado por las siguientes estructuras:

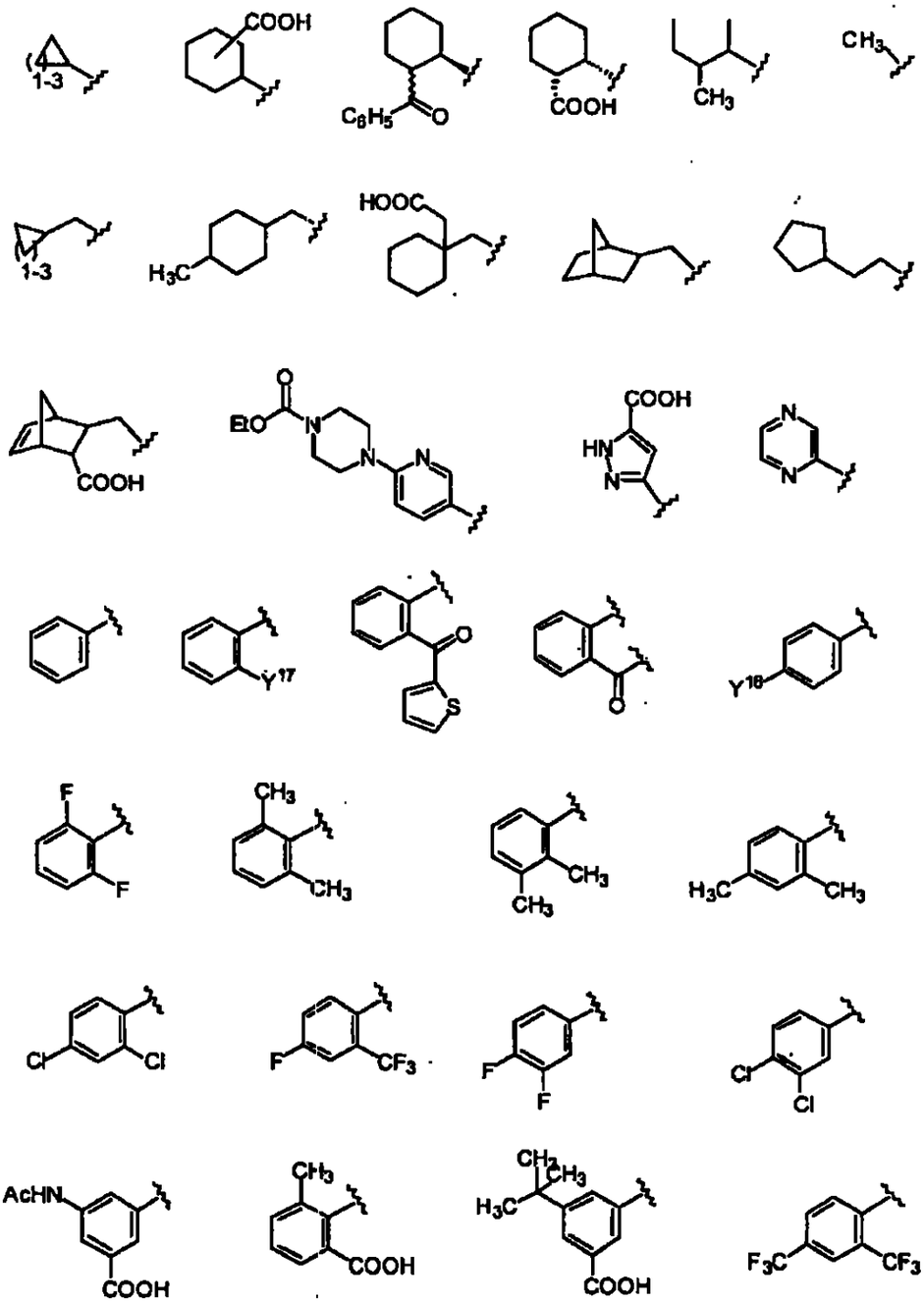


Los restos preferidos para Y son:

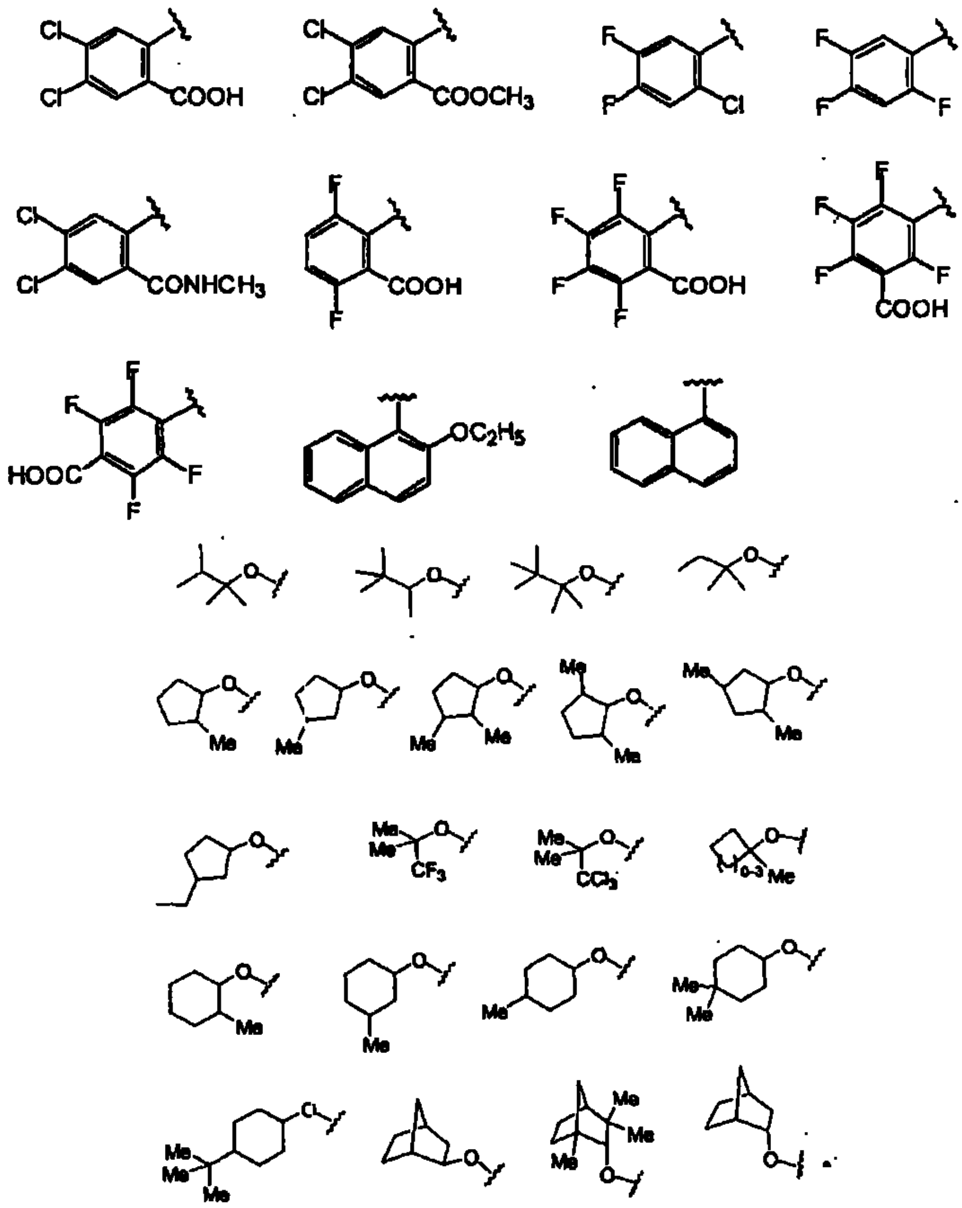

0-8
Cl_3C
0-3
0-3
0-1
Y^{11}
Y^{11}
MeO_2C
F
Y^{12}
CF_3
n=1-5
Y^{14}
Y^{13}

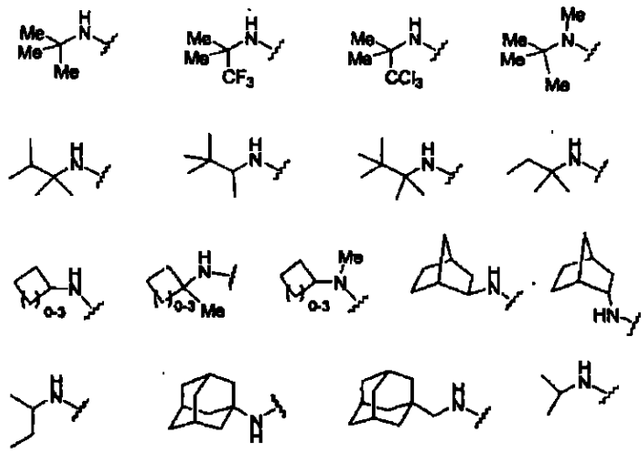


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(4
1-3
COOH
C_8H_5
O
COOH
CH_3
CH_3
1-3
H_3C
HOOC
COOH
EtO
N
N
N
COOH
HN
N
N
N
Y17
O
S
O
Y18
F
F
CH_3
CH_3
CH_3
CH_3
H_3C
CH_3
Cl
Cl
F
CF_3
F
F
Cl
Cl
AcHN
COOH
CH_3
COOH
CH_2
CH_3
H_3C
COOH
F_3C
CF_3

669



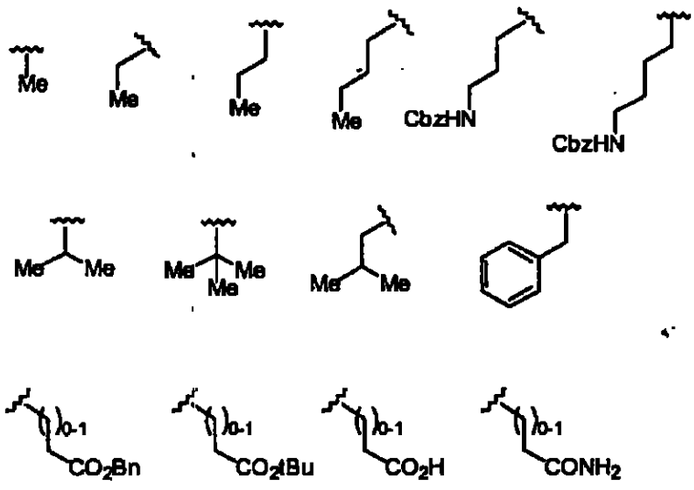


donde:

Y^{11} se selecciona de H, COOH, COOEt, OMe, Ph, OPh, NHMe, NHAc, NHPh, $CH(Me)_2$, 1-triazolilo, 1-imidazolilo, y $NHCH_2COOH$;

Y^{12} se selecciona de H, COOH, COOMe, OMe, F, Cl, o Br;

Y^{13} se selecciona de los siguientes restos:



Y^{14} se selecciona de $MeS(C)_2$, Ac, Boc, iBoc, Cbz, o Alloc;

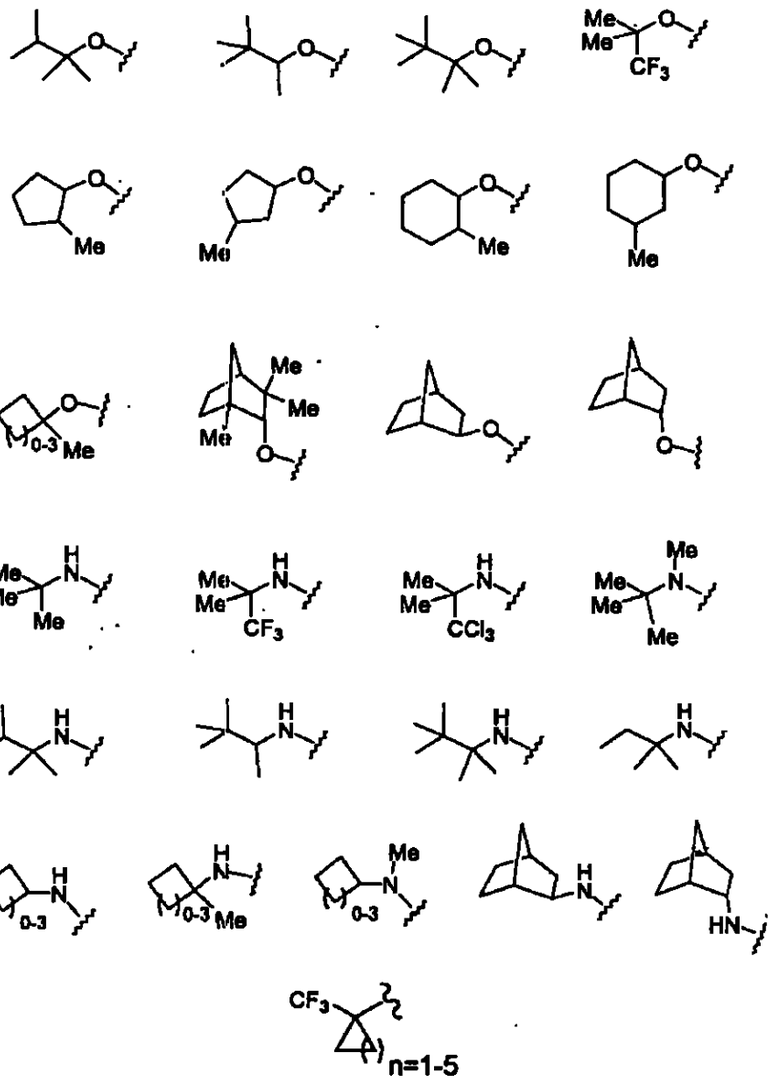
Y^{15} e Y^{16} se seleccionan en forma independiente de alquilo, arilo, heteroalquilo y heteroarilo;

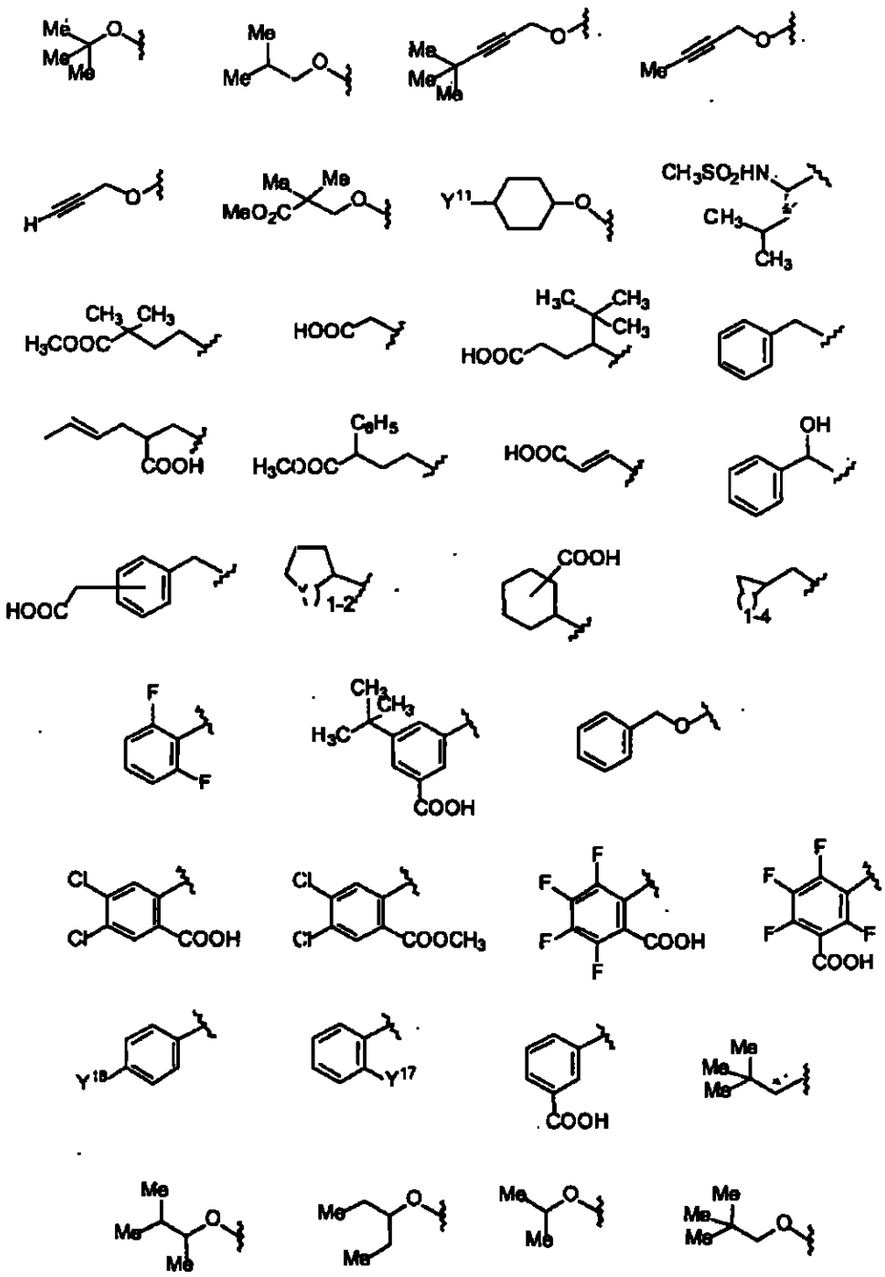
Y^{17} es $-CF_3$, $-NO_2$, $-C(O)NH_2$, -OH, $-C(O)OCH_3$, $-OCH_3$, $-OC_6H_5$, $-C_6H_5$, $-C(O)C_6H_5$, $-NH_2$, o -C(O)OH; e

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Y^{18} es $-C(O)OCH_3$, $-NO_2$, $-N(CH_3)_2$, F, $-OCH_3$, $-CH_2C(O)OH$, $-C(O)OH$, $-S(O_2)NH_2$, o $-NHCOCH_3$.

Y puede estar representado con mayor preferencia por:


Me
Me
CF3
Me
Me
Me
Me
0-3
Me
Me
Me
Me
Me
Me
CF3
Me
Me
CCl3
Me
Me
Me
0-3
0-3
Me
0-3
HN
CF3
n=1-5

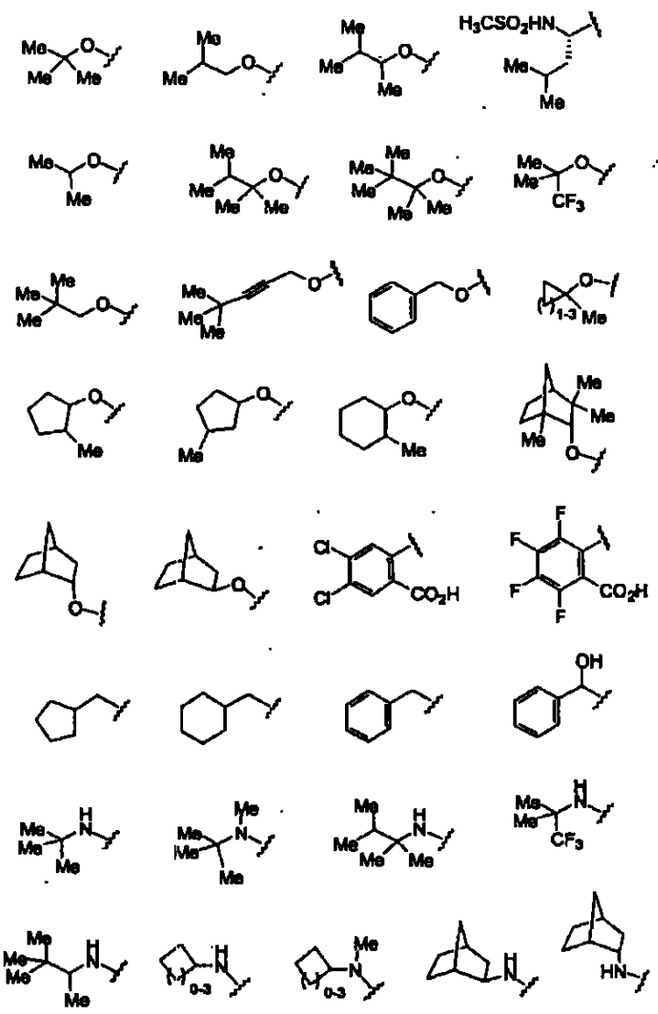


donde:

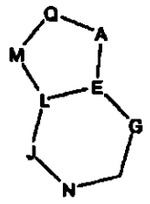
Y^{17} = CF_3, NO_2, $CONH_2$, OH, NH_2, o COOH;

Y^{18} = F, COOH.

Los restos aún más preferidos para Y son:

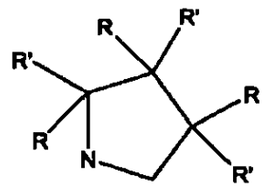


Como se muestra en la Fórmula I, la unidad:

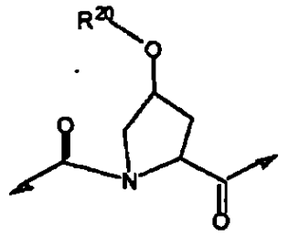


representa una estructura anular cíclica, que puede ser una estructura anular de cinco miembros o de seis miembros. Cuando ese anillo cíclico representa un anillo cíclico de cinco miembros, un requerimiento de esta invención es que el anillo cíclico de cinco miembros no contenga un grupo carbonilo como parte de la

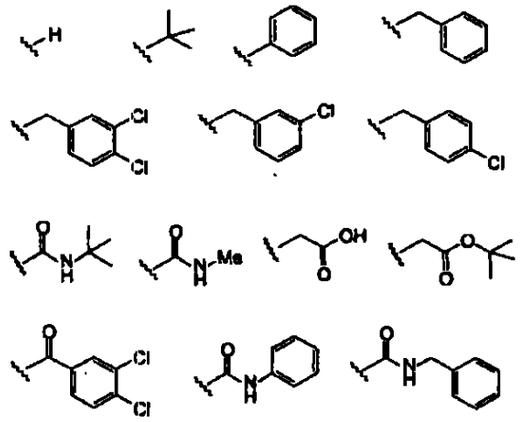
estructura anular cíclica. Con preferencia, ese anillo de cinco elementos tiene la estructura:



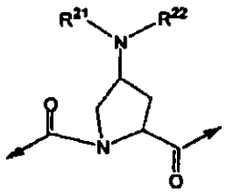
donde R y R' son como se los definió con anterioridad. Las representaciones preferidas para la estructura anular cíclica de cinco miembros es:



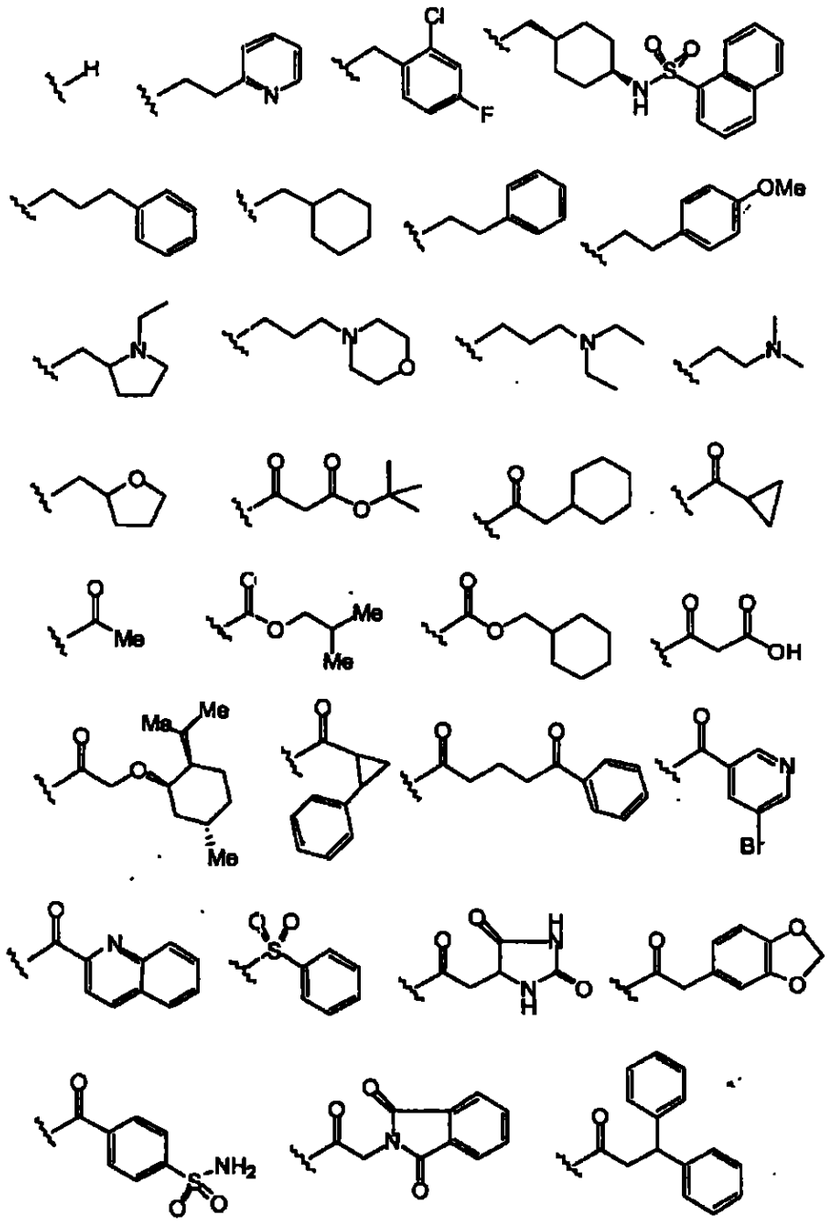
donde R^{20} se selecciona de los siguientes restos:



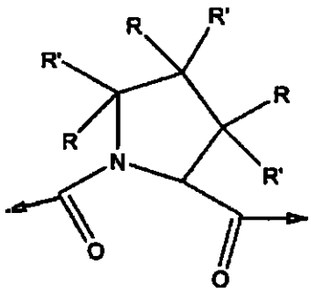
Además, ese anillo de cinco miembros, junto con sus dos carbonilos exocíclicos adyacentes, puede esta representado de la siguiente manera:



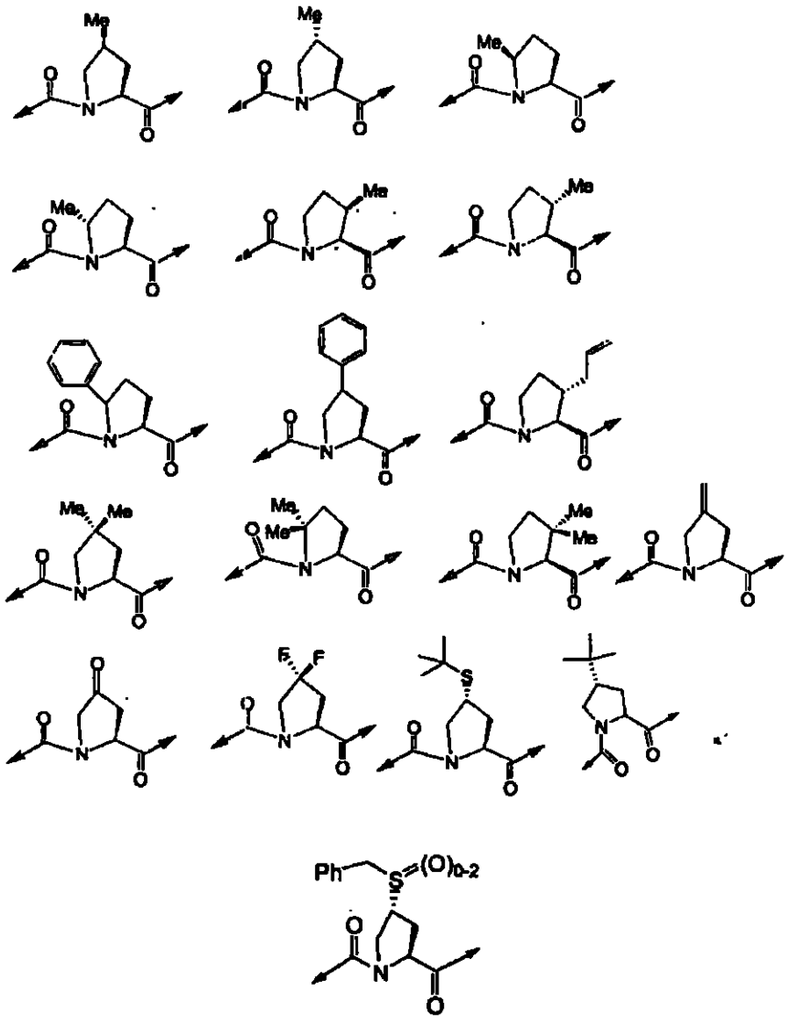
en cuyo caso, R^{21} y R^{22} pueden ser iguales o diferentes y se seleccionan en forma independiente de los siguientes restos:



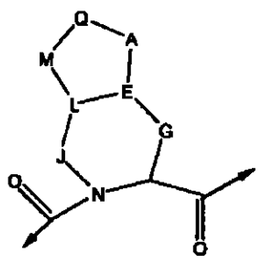
Algunas ilustraciones para la estructura anular de cinco miembros:



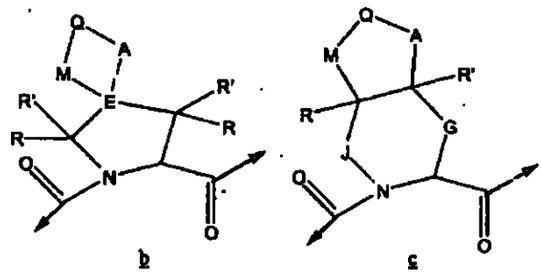
son las siguientes:



En forma adicional, la unidad:

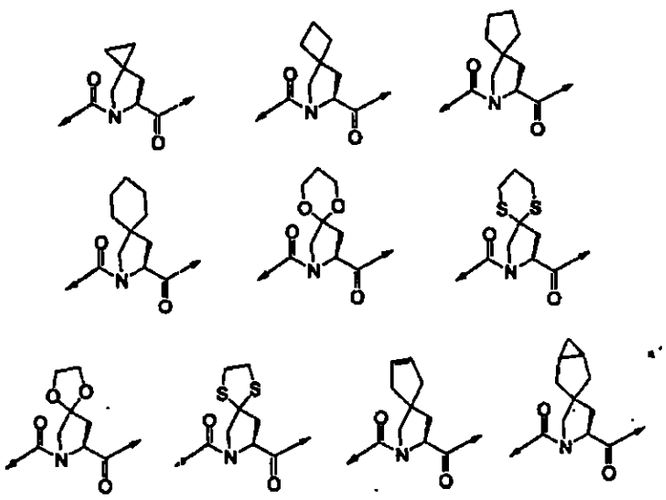


en la fórmula I puede estar representada por las siguientes estructuras b y c:



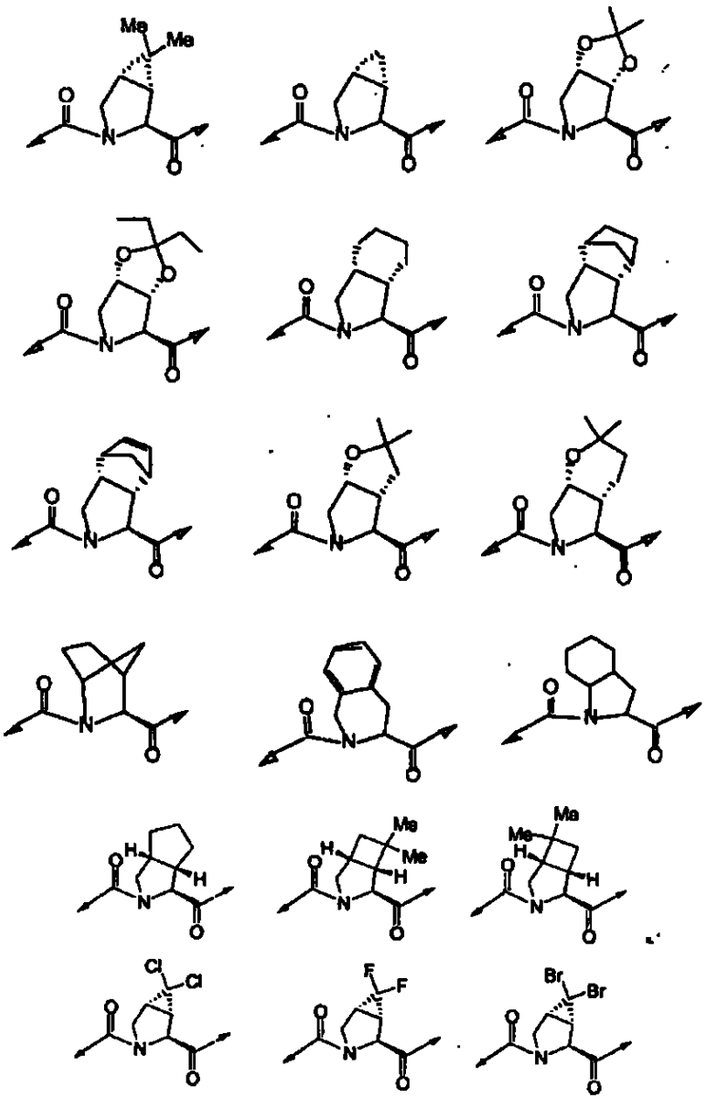
b c

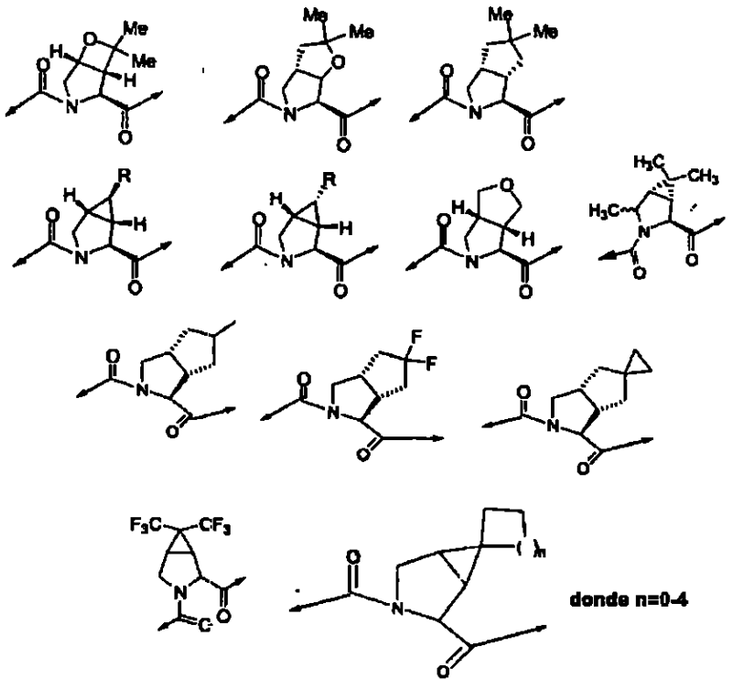
Las definiciones preferidas para b son:



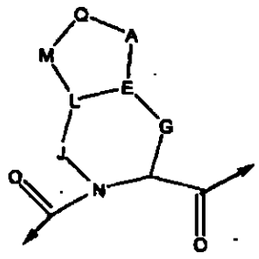
En c, G y J se seleccionan en forma independiente del grupo formado por $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ y $(CRR')_p$; A y M se seleccionan en forma independiente del grupo formado por O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, y $(CRR')_p$ y Q es CH_2, CHR, CRR', NH, NR, O, S, SO_2, NR $(CH_2)_p$, $(CHR)_p$ y $(CRR')_p$. Las definiciones preferidas para c son:

680

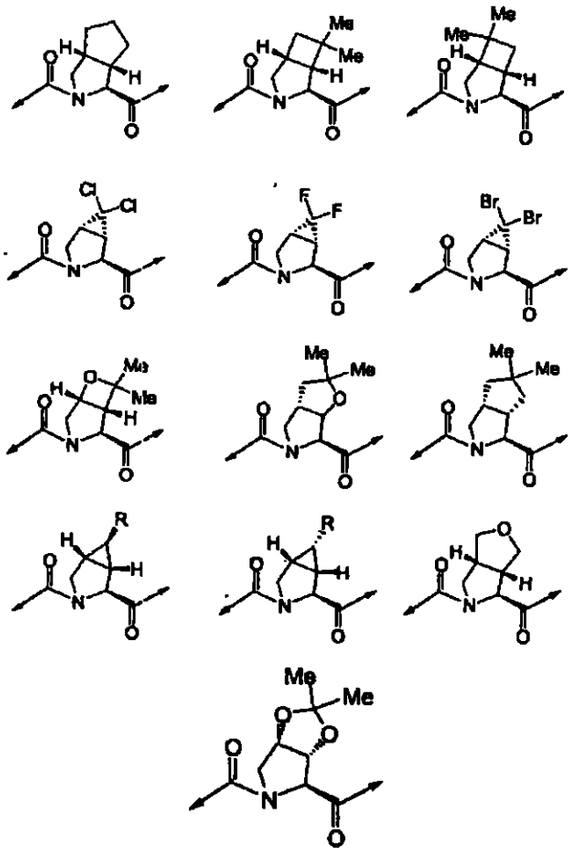


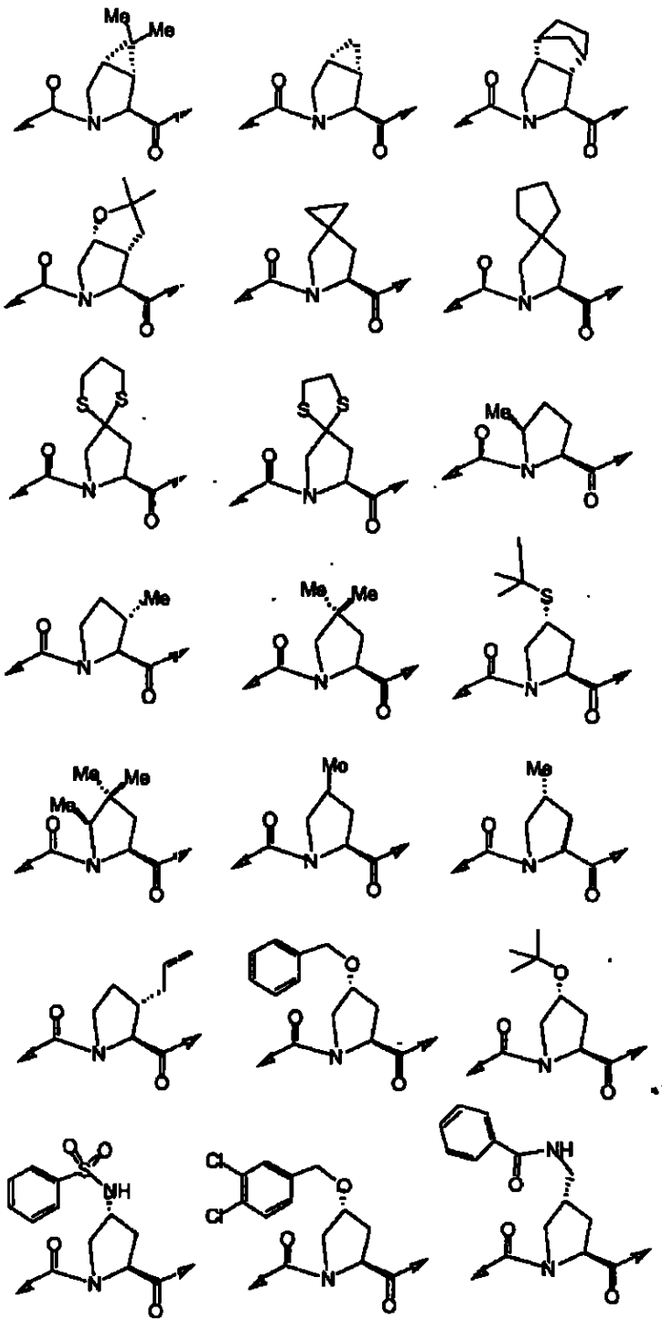


Cuando la estructura anular cíclica se presenta como:

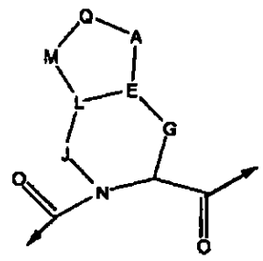


las ilustraciones más preferidas son las siguientes:

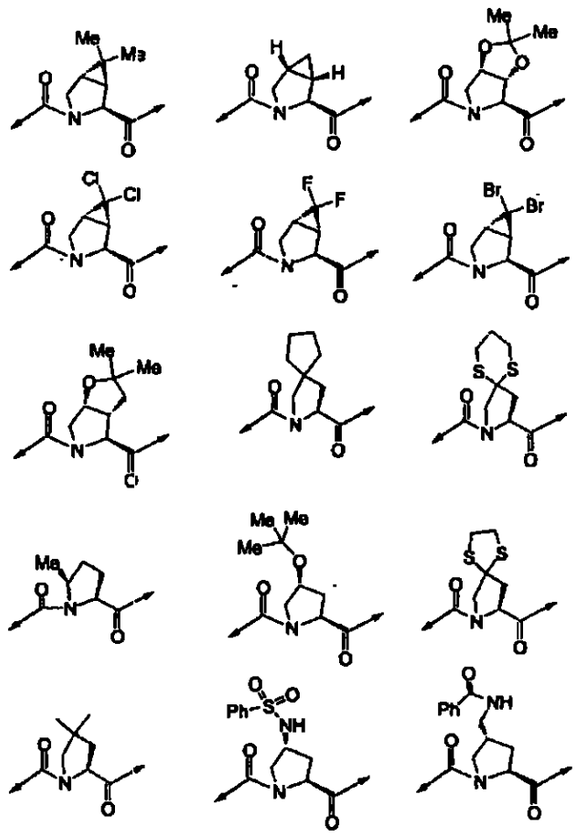




Algunos de los restos aún preferidos para la unidad:



que se mostró anteriormente son:



Salvo que se defina lo contrario, todos los términos técnicos y científicos usados aquí tienen el mismo significado que las personas expertas en el arte al cual la invención pertenece le asignan comúnmente. Así, por ejemplo, el término alquilo (que incluye las porciones alquílicas del alcoxi) se refiere a un grupo monovalente derivado de un hidrocarburo saturado de cadena recta o ramificada

a través de la eliminación de un solo átomo que tiene desde 1 hasta 8 átomos de carbono, con preferencia desde 1 hasta 6;

arilo - representa un grupo carbocíclico que tiene desde 6 hasta 14 átomos de carbono y que tiene por lo menos un anillo bencenoide, con todos los átomos de carbono aromáticos sustituibles disponibles considerados como posibles puntos de unión. Los grupos arilo preferidos incluyen fenilo, 1-naftilo, 2-naftilo e indanilo, y especialmente fenilo y fenilo sustituido;

aralquilo - representa un resto que tiene un grupo arilo ligado a través de un alquilo inferior;

alquilarilo - representa un resto que contiene un alquilo inferior ligado a través de un grupo arilo;

cicloalquilo - representa un anillo carbocíclico saturado que tiene desde 3 hasta 8 átomos de carbono, con preferencia 5 ó 6, opcionalmente sustituido.

heterocíclico - representa, además de los grupos heteroarilo definidos a continuación, grupos orgánicos cíclicos saturados o insaturados que tienen por lo menos un átomo de O, S y/o N interrumpiendo una estructura anular carbocíclica formada por un anillo o dos anillos fusionados, donde cada anillo tiene 5, 6 ó 7 miembros y puede o no tener enlaces dobles que carecen de electrones pi no localizados, cuya estructura anular tiene desde 2 hasta 8, con preferencia desde 3 hasta 6 átomos de carbono, por ej., 2- ó 3-piperidinilo, 2- ó 3-piperazinilo, 2- ó 3-morfolinilo o 2- ó 3-tiomorfolinilo;

halógeno - representa flúor, cloro, bromo y yodo;

heteroarilo - representa un grupo orgánico cíclico que tiene por lo menos un átomo de O, S y/o N interrumpiendo una estructura anular carbocíclica y tiene un número suficiente de electrones pi no localizados para dar el carácter aromático, donde el grupo heterocíclico aromático tiene desde 2 hasta 14, con preferencia 4 ó 5 átomos de carbono, por ej., 2-, 3-, ó 4-piridilo, 2- ó 3-furilo, 2-ó 3-tienilo, 2-, 4- ó 5-tiazolilo, 2- ó 4-imidazolilo, 2-, 4- ó 5-pirimidinilo, 2-pirazinilo ó

3- ó 4-piridazinilo, etc. Los grupos heteroarilo preferidos son 2-, 3- y 4-piridilo; dichos grupos heteroarilo pueden estar, además, sustituidos en forma opcional. Adicionalmente, salvo que se defina lo contrario en forma específica, como se indicó con anterioridad, el término "sustituido o no sustituido", o "sustituido en forma opcional" se refiere al resto sujeto que está sustituido en forma opcional y apropiado para la química con un resto perteneciente a R^{12} o R^{13}. Según se usa aquí, "profármaco" se refiere a compuestos que son precursores de fármacos que, luego de la administración a un paciente, liberan el fármaco *in vivo* a través de algunos procesos químicos o fisiológicos (por ej., un profármaco que luego de llevarse al pH fisiológico o a través de la acción enzimática se convierte en la forma de fármaco deseada).

Además, se incluyen en la invención los tautómeros, los rotámeros, los enantiómeros y otros isómeros ópticos, como también los profármacos, de los compuestos de Fórmula I, como también sus sales, solvatos y sus derivados aceptables para uso farmacéutico.

Una característica adicional de la invención es la de composiciones farmacéuticas que contienen como ingrediente activo un compuesto de Fórmula I (o sus sales, solvatos o isómeros) junto con un vehículo o excipiente aceptable para uso farmacéutico.

La invención provee, además, métodos para preparar compuestos de fórmula I, como también métodos para tratar enfermedades como, por ejemplo, el HCV, el SIDA (Síndrome de Inmuno Deficiencia Adquirida), y trastornos relacionados. Los métodos para el tratamiento comprenden la administración a un paciente que sufre de dicha enfermedad o enfermedades de una cantidad terapéuticamente efectiva de un compuesto de Fórmula I, o composiciones que comprenden un compuesto de Fórmula I.

Se describe, además, el uso de un compuesto de Fórmula I para la fabricación de un medicamento para el tratamiento del HCV, del SIDA y trastornos relacionados.

Se describe, además, un método para el tratamiento de un trastorno asociado con el virus de la hepatitis C, que comprende la administración de una cantidad efectiva de uno o más de los compuestos de la invención.

Se describe, además, un método para modular la actividad de la proteasa del virus de la hepatitis C (HCV), que comprende el contacto de la proteasa del HCV con uno o más compuestos de la invención.

Se describe, además, un método para tratar, prevenir, o aliviar uno o más de los síntomas de la hepatitis C, que comprende la administración de una cantidad efectiva de uno o más compuestos de la invención. La proteasa del HCV es la proteasa NS3 ó NS4a. Los compuestos de la invención inhiben dicha proteasa. Éstos además modulan el procesamiento del polipéptido del virus de la hepatitis C (HCV).

Descripción Detallada de las Realizaciones Preferidas

En una realización, la presente invención describe compuestos de fórmula I como inhibidores de la proteasa del HCV, en especial la proteasa serina NS3/NS4a del HCV, o uno de sus derivados aceptables para uso farmacéutico, donde las diferentes definiciones se proveyeron con anterioridad.

Los compuestos representativos de la invención, que presentan excelente actividad de inhibición de la proteasa del HCV se enumeran a continuación en las **Tablas 1 hasta 5** junto con su actividad (rangos de los valores Ki* en nanomolar, nM). Varios compuestos, como también compuestos adicionales, se describen en forma adicional en las Reivindicaciones.

Tabla 1: Compuestos y Resultados Continuos de Valoración de la Proteasa del HCV

Compuesto del Ejemplo No.	Rango de Ki*
1	C
2	C
3	C
4	C
5	C
6	C
7	C
8	C
9	C
10	C
11	C
12	C
13	C
14	C
15	C
16	C
17	C
18	C
19	C
20	C
21	C
22	C
23	C
24	C
25	C
26	C
27	C
28	C
29	C
30	C
31	C
32	C
33	C
34	C
35	C
36	C
37	C
38	C
39	C
40	C
41	C
42	C
43	C
44	C
45	C

Compuesto del Ejemplo No.	Rango de Ki*
46	C
47	C
48	C
49	C
50	C
51	C
52	C
53	C
54	C
55	C
56	C
57	C
58	C
59	C
60	C
61	C
62	C
63	C
64	C
65	C
66	C
67	C
68	B
69	C
70	C
71	B
72	C
73	B
74	C
75	C
76	A
77	B
78	A
79	C
80	A
81	C
82	A
83	B
84	C
85	C
86	B
87	B
88	A
89	B
90	C

690

Compuesto del Ejemplo No.	Rango de Ki*
91	C
92	C
93	C
94	C
95	C
96	C
97	C
98	B
99	B
100	A
101	A
102	C
103	C
104	C
105	C
106	C
107	B
108	A
109	A
110	A
111	A
112	A
113	B
114	A
115	B
116	A
117	A
118	A
119	A
120	A
121	B
122	B
123	A
124	B
125	B
126	B
127	A
128	A
129	A
130	B
131	A
132	A
133	A
134	B
135	A

Compuesto del Ejemplo No.	Rango de Ki*
136	A
137	A
138	A
139	A
140	B
141	A
142	A
143	B
144	B
145	C
146	A
147	A
148	B
149	A
150	A
151	A
152	A
153	A
154	A
155	B
156	B
157	B
158	C
159	B
160	A
161	A
162	A
163	C
164	A
165	C
166	B
167	A
168	C
169	B
170	B
171	A
172	A
173	A
174	A
175	A
176	B
177	B
178	A
179	A
180	B

692

Compuesto del Ejemplo No.	Rango de Ki*
181	A
182	B
183	A
184	A
185	A
186	A
187	A
188	A
189	B
190	B
191	B
192	A
193	A
194	B
195	A
196	B
197	A
198	A
199	A
200	A
201	B
202	A
203	B
204	B
205	B
206	B
207	B
208	A
209	A
210	A
211	A
212	A
213	B
214	B
215	B
216	B
217	C
218	A
219	A
220	A
221	A
222	A
223	B
224	C
225	C

693

Compuesto del Ejemplo No.	Rango de Ki*
226	A
227	A
228	C
229	A
230	A
231	A
232	C
233	C
234	C
235	C
236	B
237	C
238	A
239	C
240	A
241	C
242	B
243	C
244	B
245	C
246	B
247	A
248	A
249	C
250	C
251	B
252	C
253	C
254	B
255	B
256	A
257	C
258	A
259	A
260	C
261	C
262	A
263	B
264	B
265	C
266	B
267	A
268	C
269	A
270	C

Compuesto del Ejemplo No.	Rango de Ki*
271	A
272	C
273	C
274	C
275	C
276	A
277	B
278	A
279	B
280	A
281	C
282	C
293	C
284	C
285	C
286	C
287	C
288	B
289	B
290	C
291	C
292	C
293	C
294	C
295	C
296	B
297	C
298	C
299	B
300	B
301	C
302	C
303	B
304	C
305	C
306	C
307	B
308	B
309	C
310	C
311	C
312	C
313	B
314	A
315	B

695

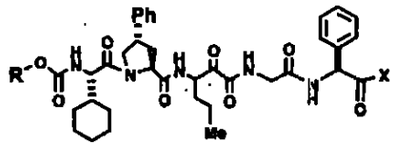
Compuesto del Ejemplo No.	Rango de Ki*
316	B
317	A
318	A
319	A
320	A
321	C
322	C
323	C
324	C
325	A
326	A
327	C
328	B
329	B
330	A
331	A
332	A
333	B
334	B
335	B
336	A
337	A
338	C
339	A
340	C
341	C
342	C
343	A
344	C
345	C
346	C
347	B
348	B
349	C
350	C
351	C
352	C
353	C
354	C
355	C
356	A
357	A
358	C
359	A
360	B

361	B
362	C

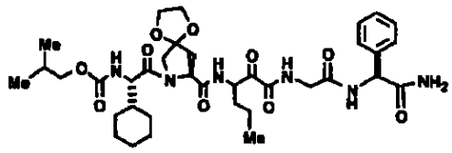
Rango de Ki* de valoración continua de HCV.

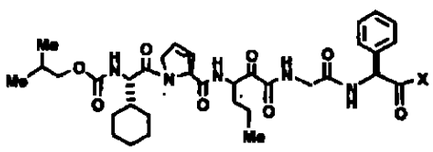
Categoría A = 1-100 nM; Categoría B = 101-1.000 nm; Categoría C > 1.000 nM.

Algunos de los tipos de los compuestos de la invención y los métodos para sintetizar los diferentes tipos de los compuestos de la invención de Fórmula I se enumeran a continuación, luego se describen en forma esquemática, seguido de los Ejemplos ilustrativos.

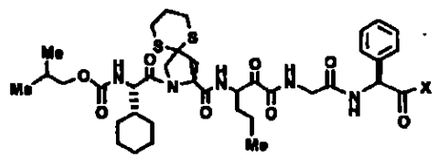


(R = t-butile, X = NH2)
(R = isobutile, X = NH2)
(R = t-butile, X = OH)
(R = tricloroetile, X = OH)

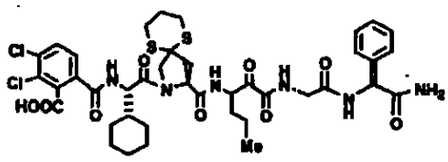


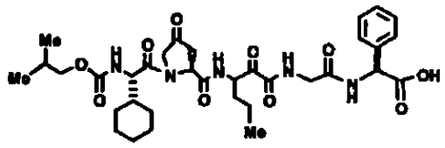


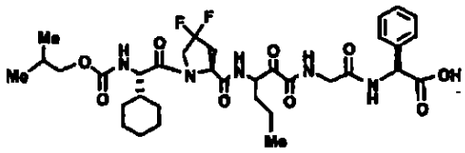
(X = O^{t}Bu)
(X = OH)

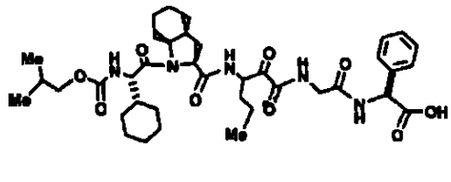


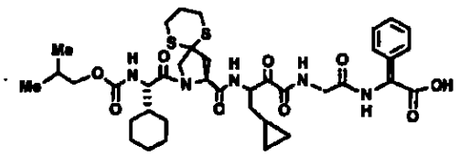
(X = OH)
(X = O^{t}Bu)
(X = NH_2)
(X = NHMe)
(X = NMe_2)

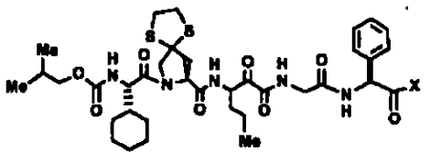




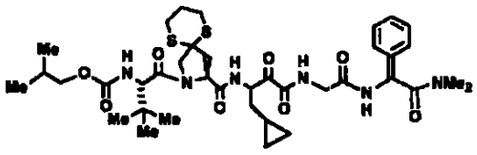


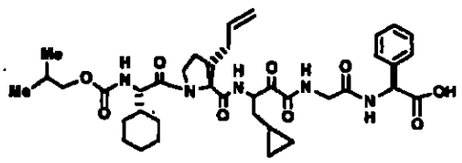


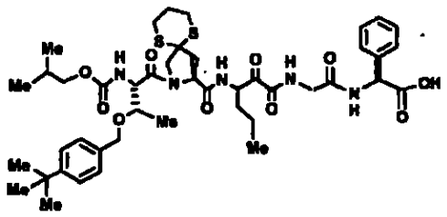


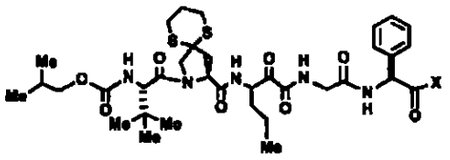


(X = NH_2)
(X = NMe_2)
(X = NHMe)
(X = OH)

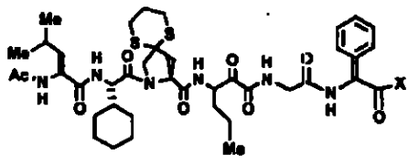




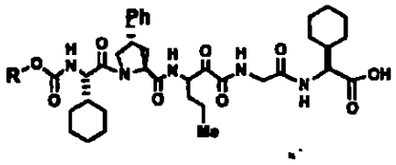




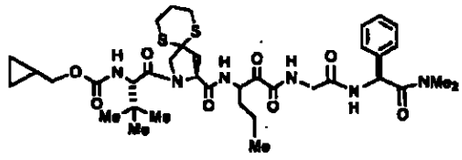
(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)

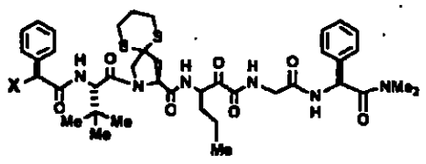


(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)
(X = NMeOMe)

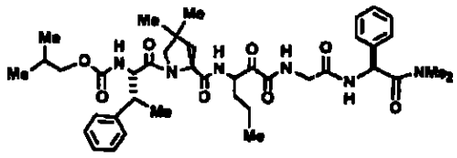


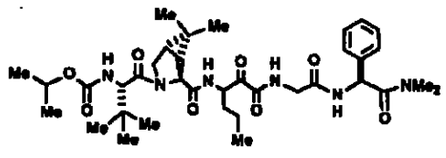
(R = t-butilo)
(R = isobutilo)

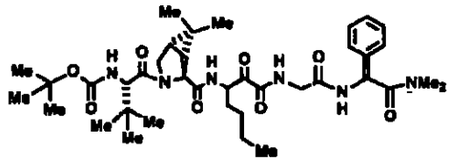


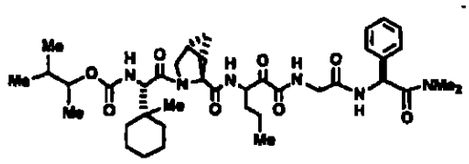


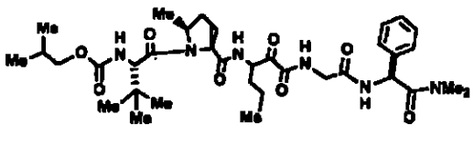
(X = Me, Y = CH_2Me)
(X = OAc, Y = Me)

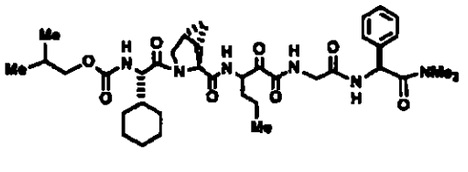


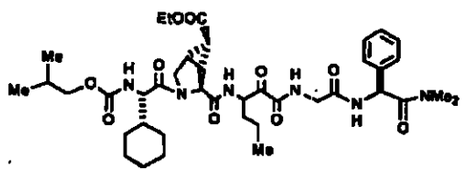


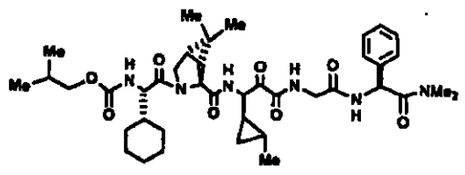


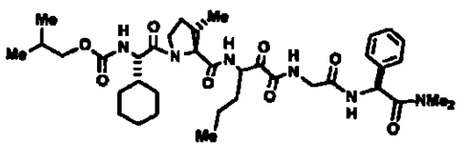


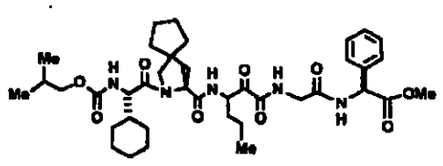


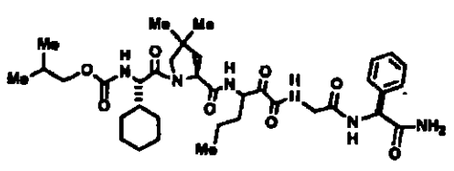


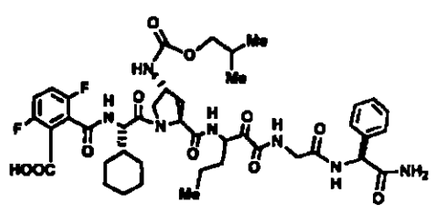


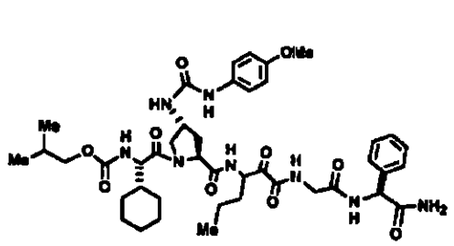


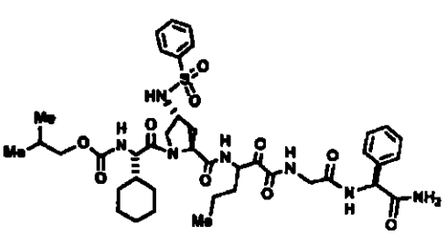


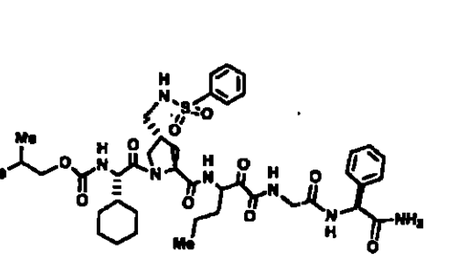


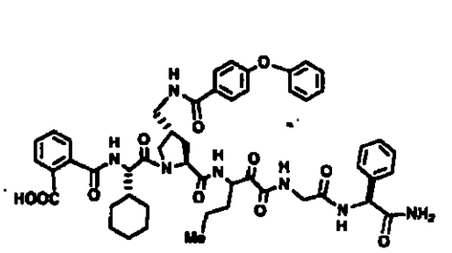


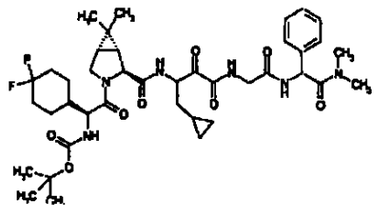


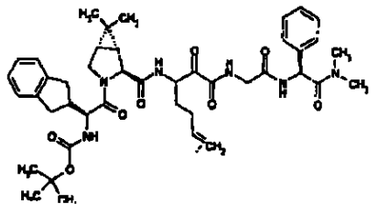


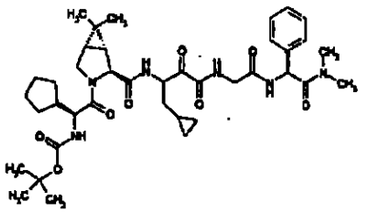


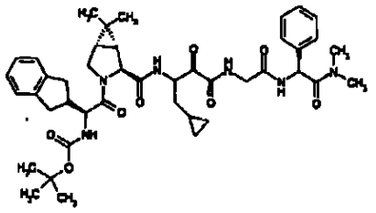


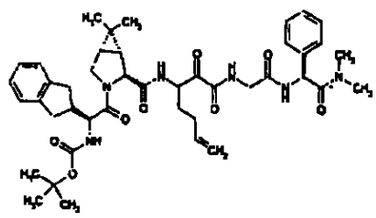


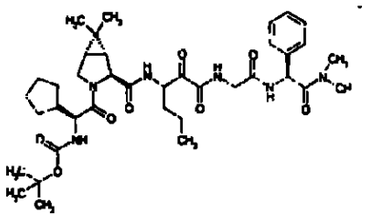


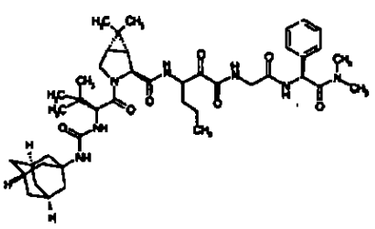


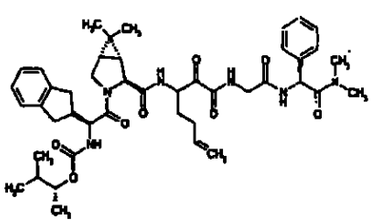


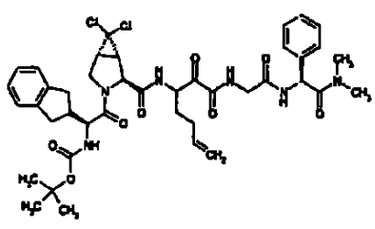


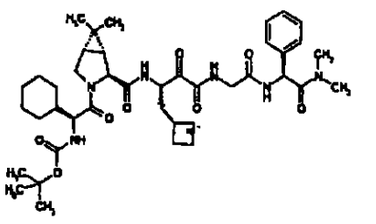


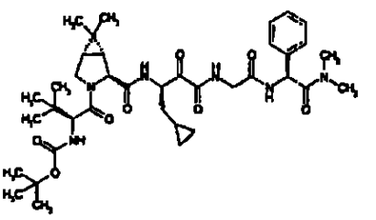


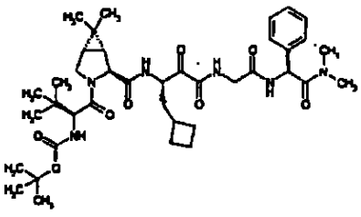


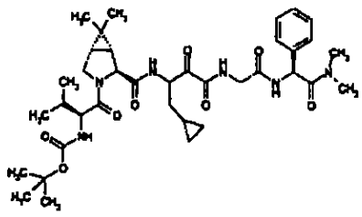


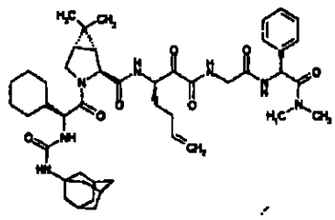


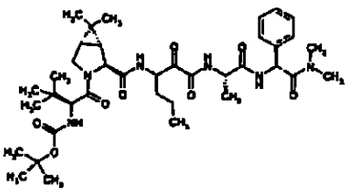


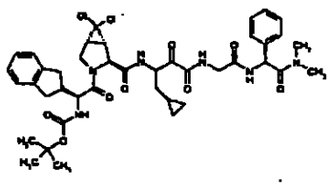


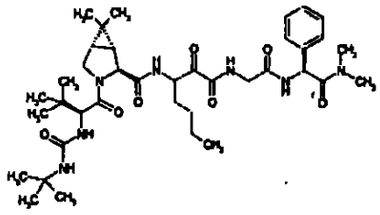


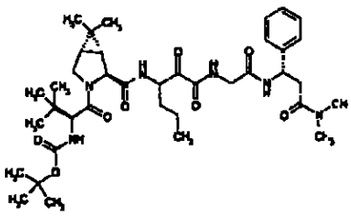


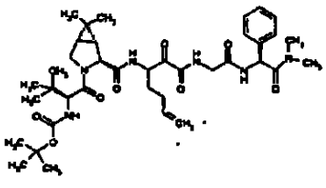


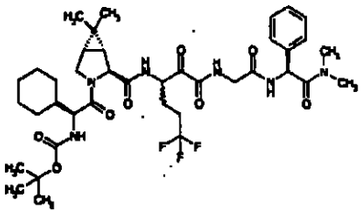


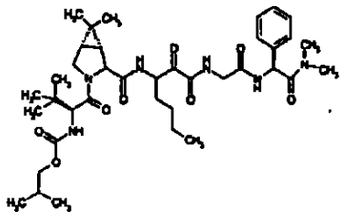


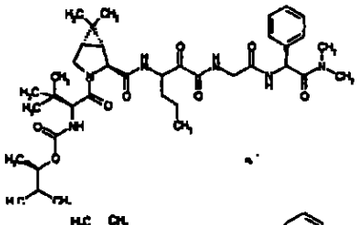


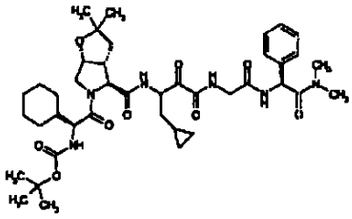


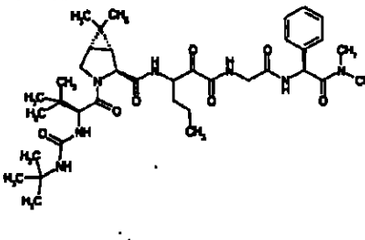




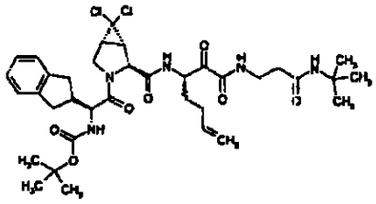


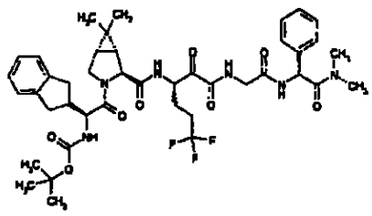


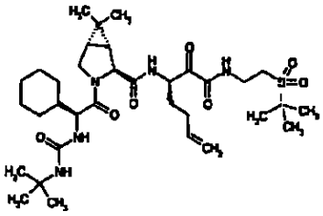


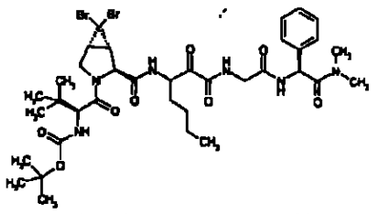


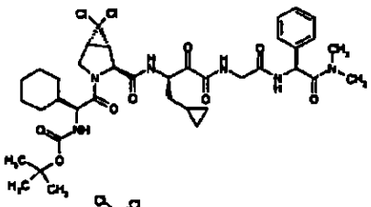


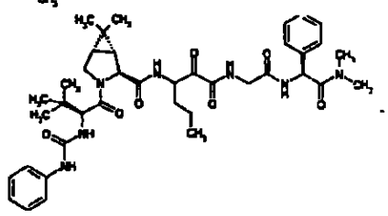


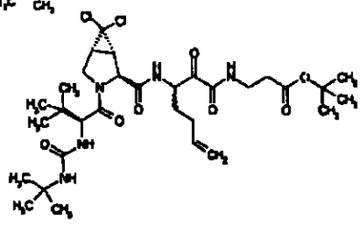


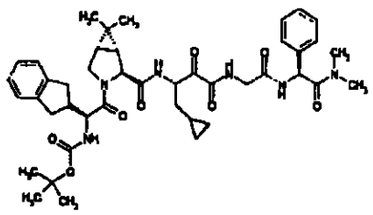


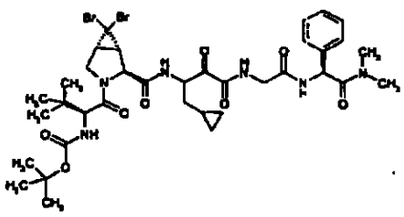


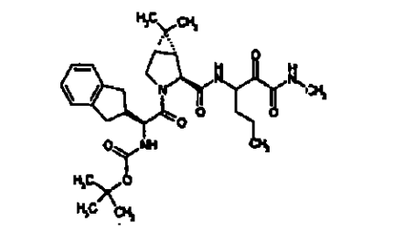


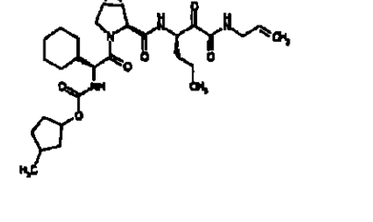


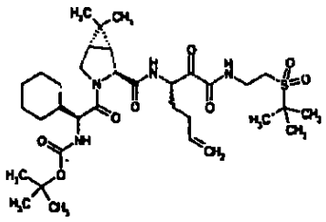


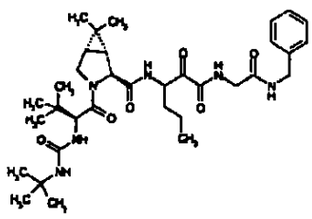


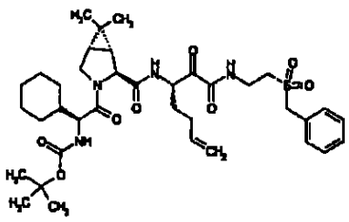


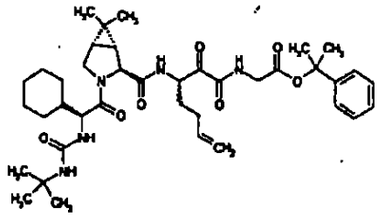


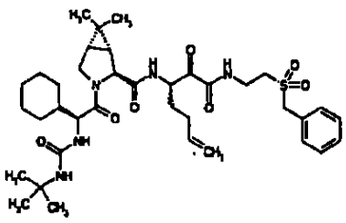


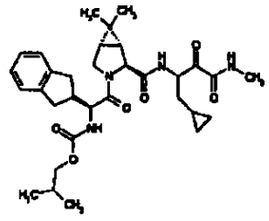


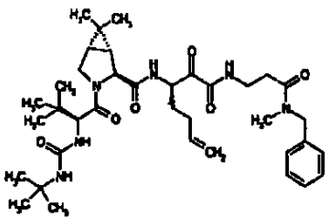


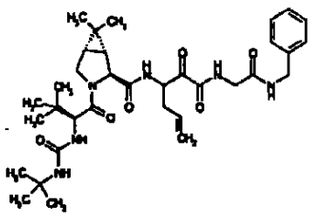


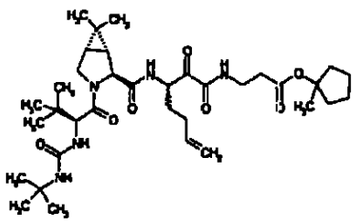


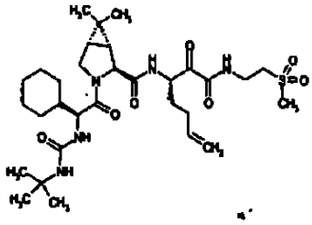


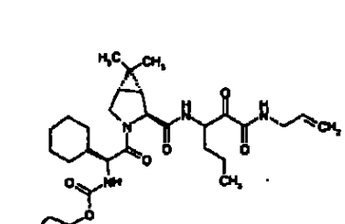


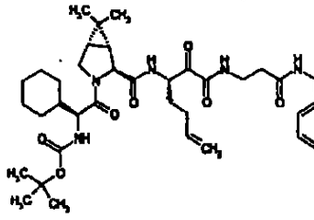


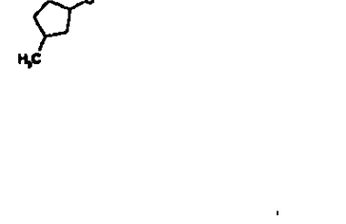




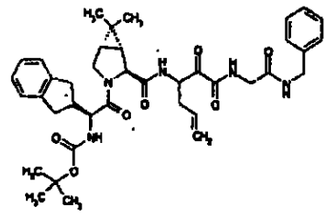


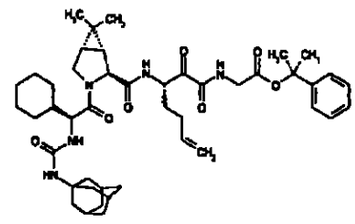


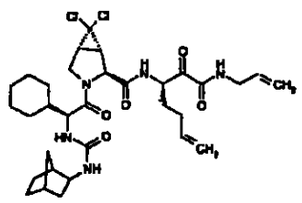


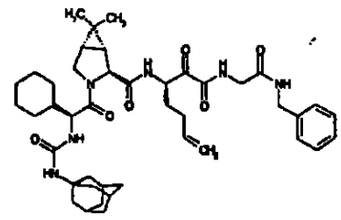


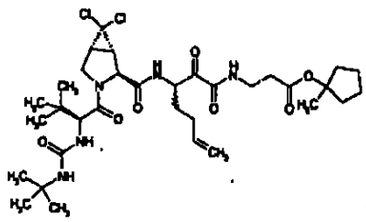
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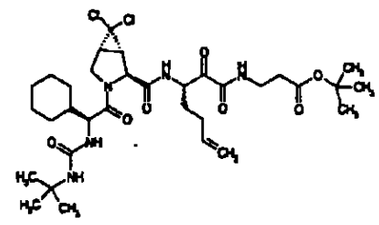


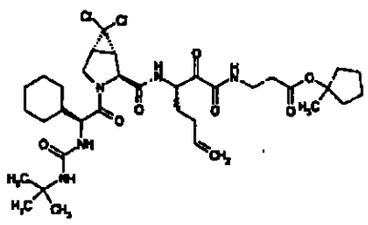


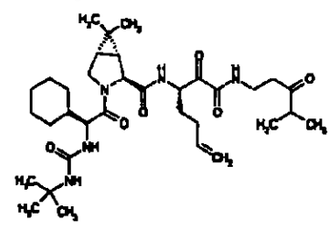


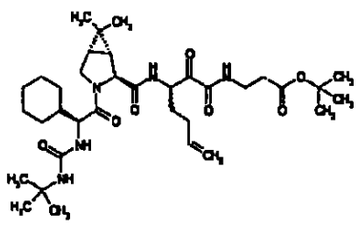


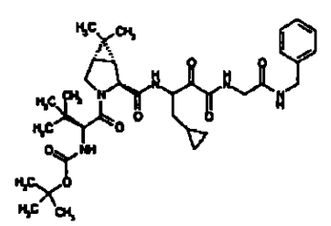


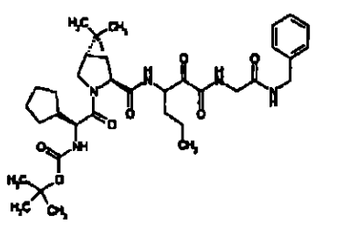


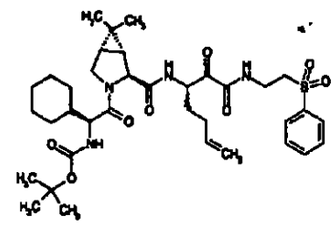


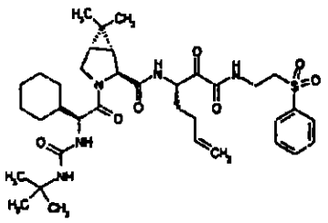


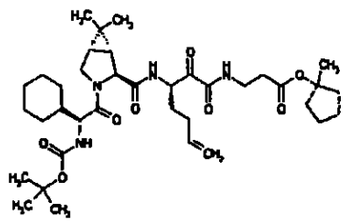


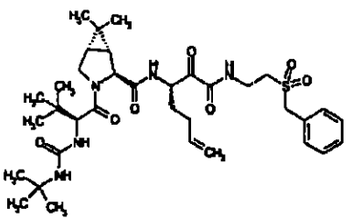


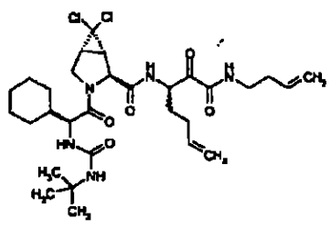


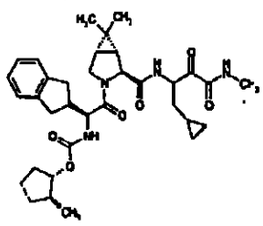


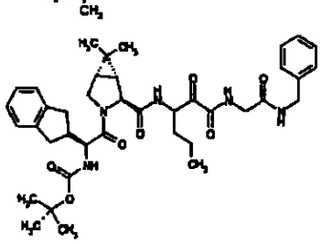


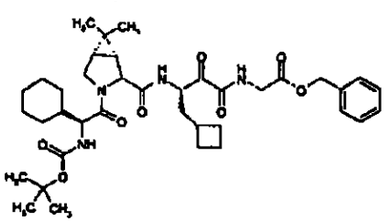


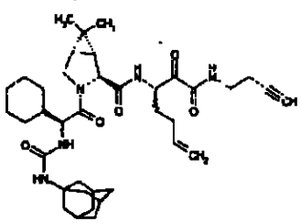


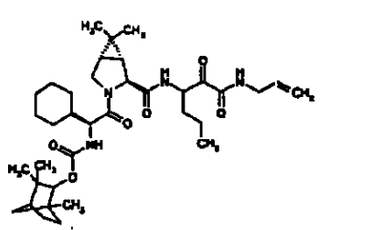


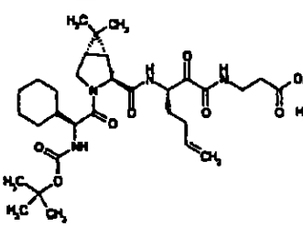


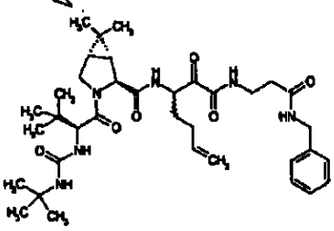


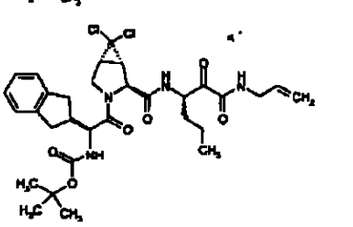


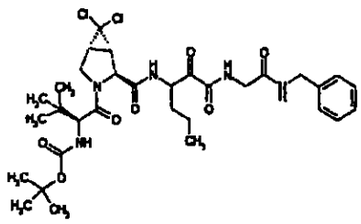


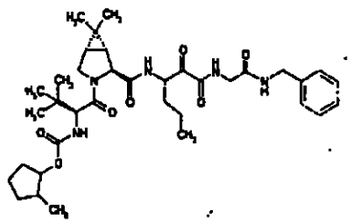


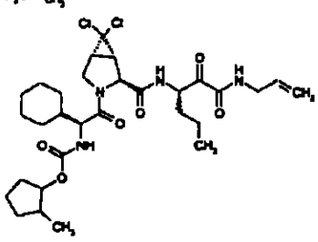


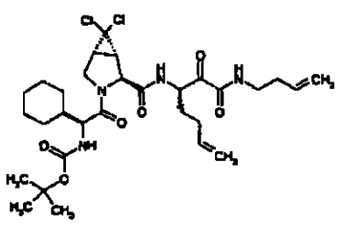


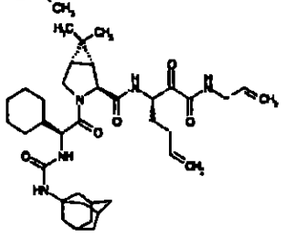


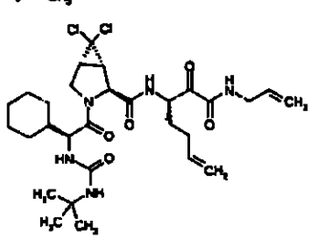


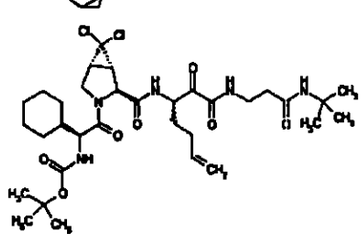


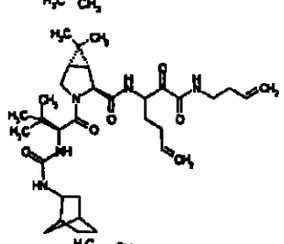


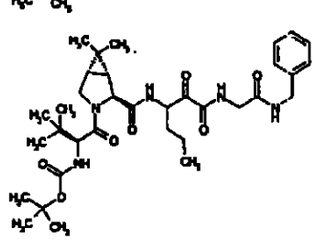


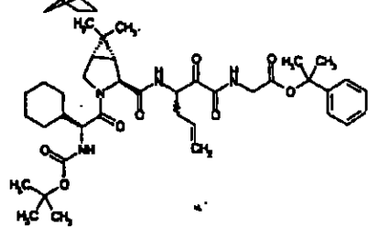


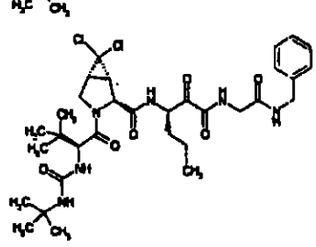


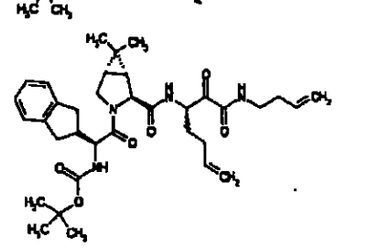




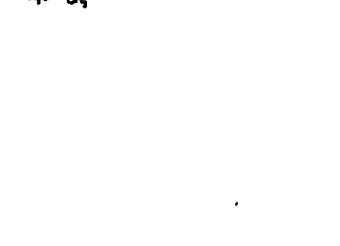


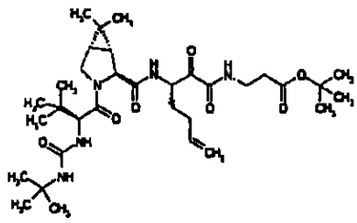


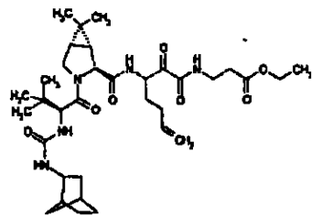


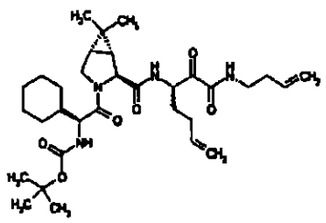


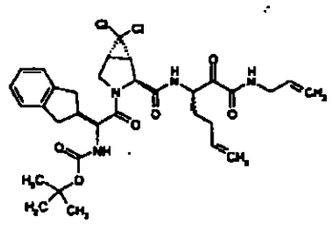


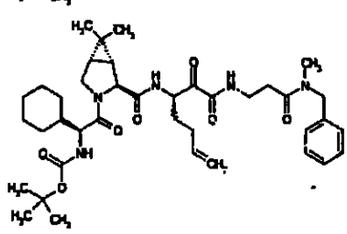


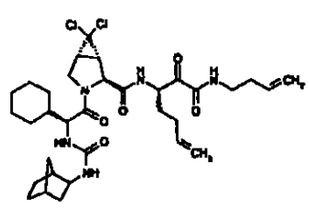


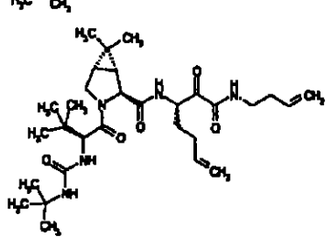


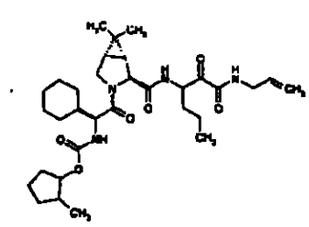


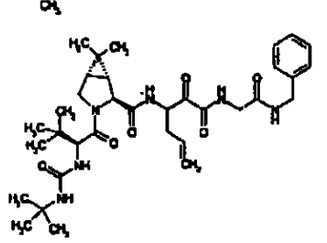


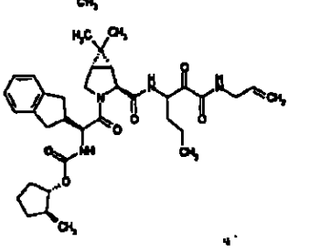


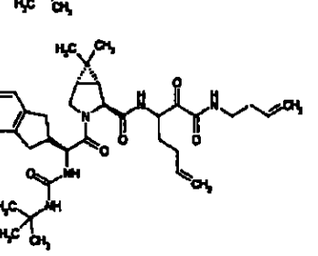


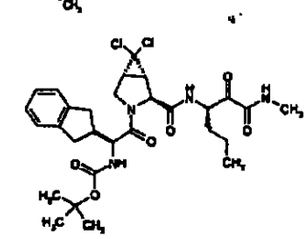




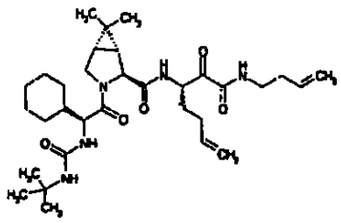


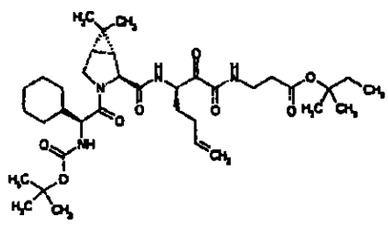


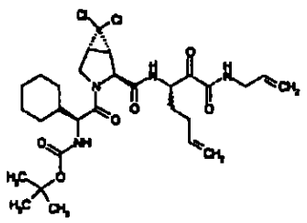


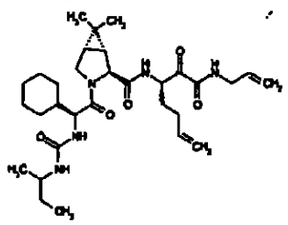


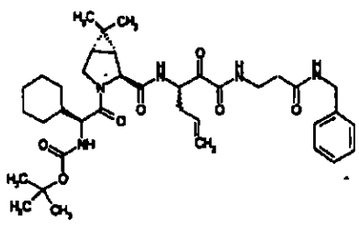


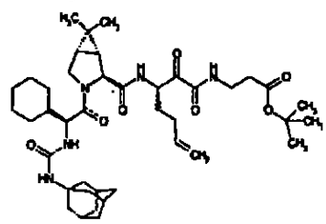


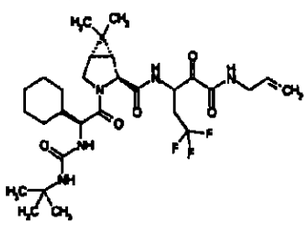


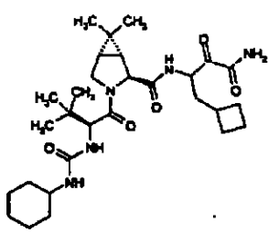


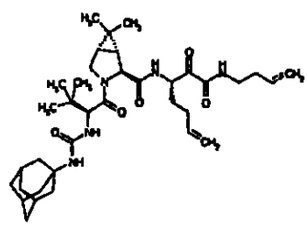


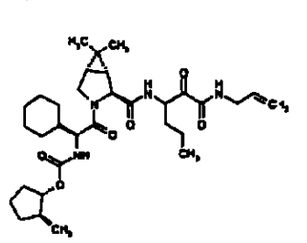


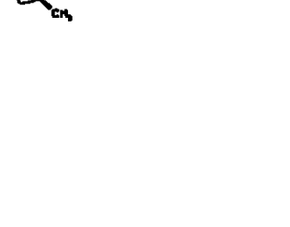


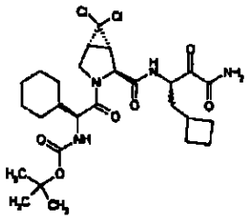


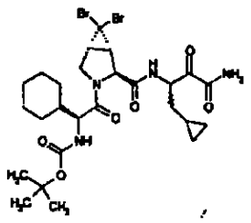


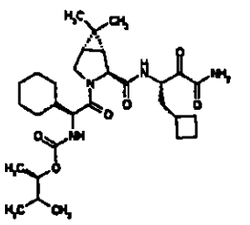


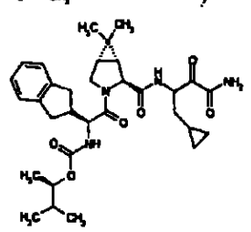


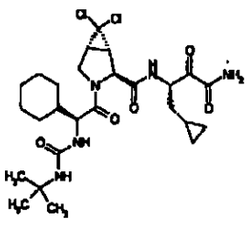


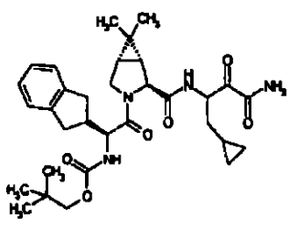


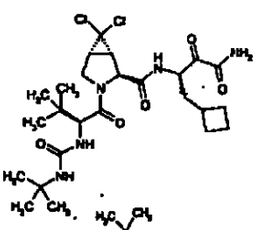


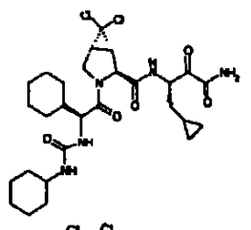


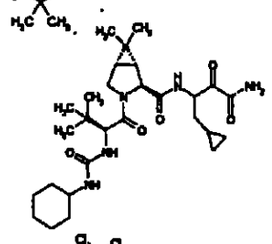


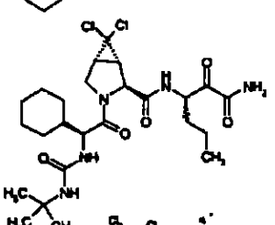


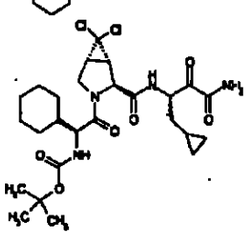


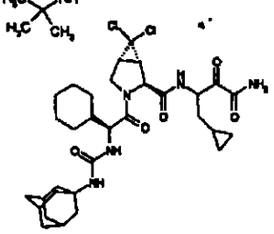




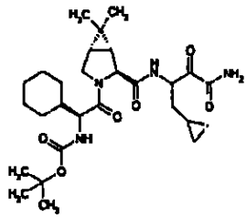


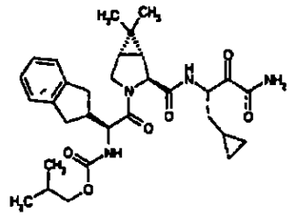


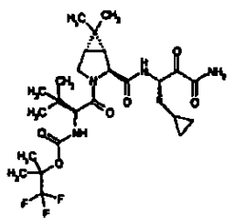


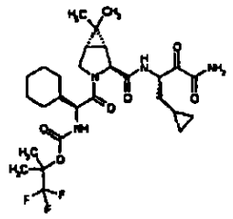


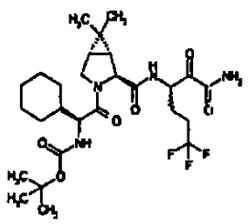
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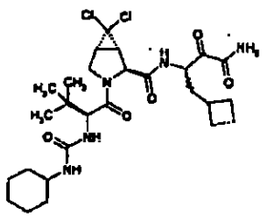


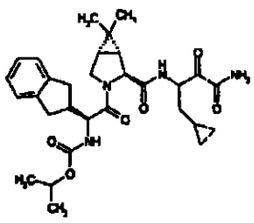


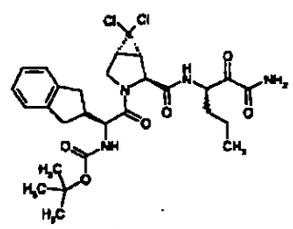


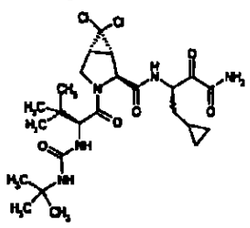


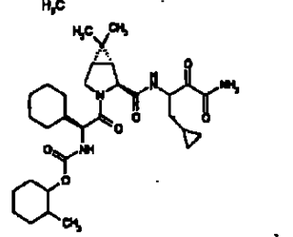


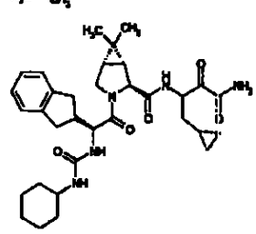


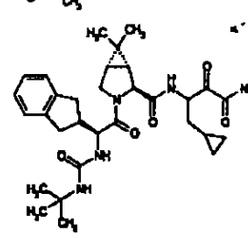


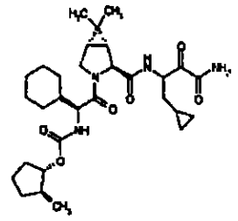


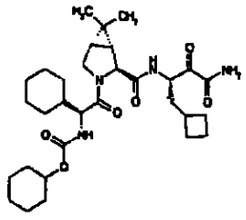


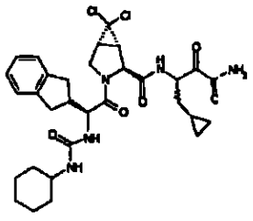


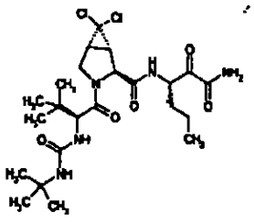


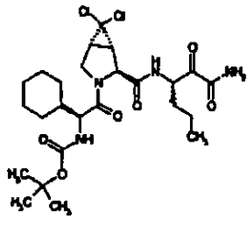


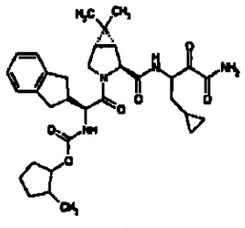


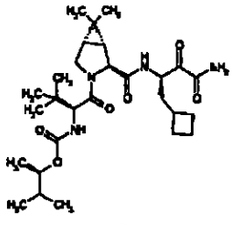


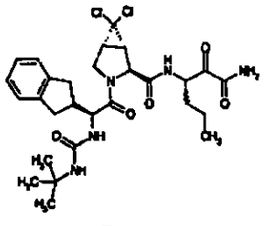


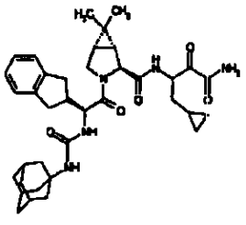


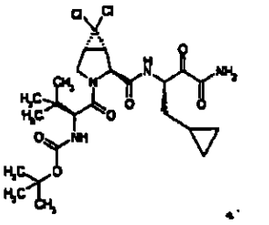


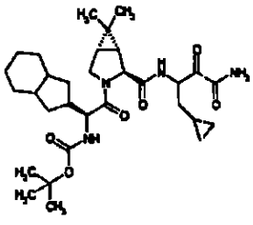


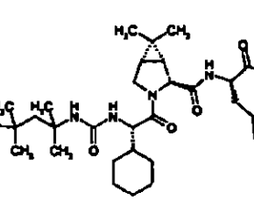


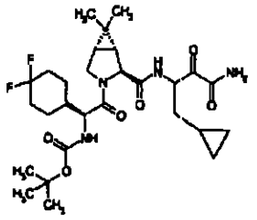


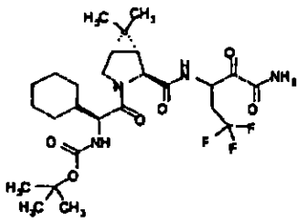


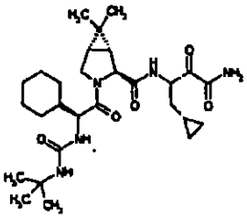


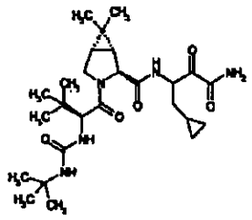


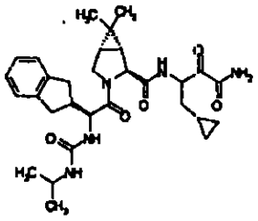


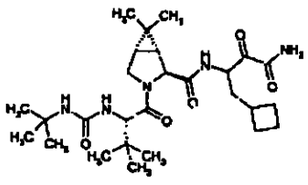


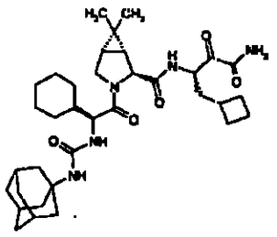


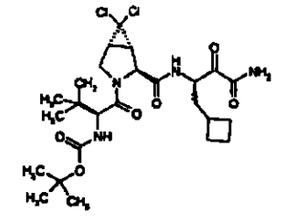


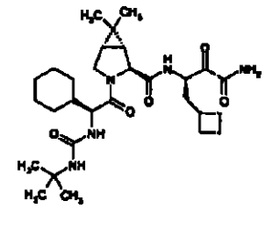


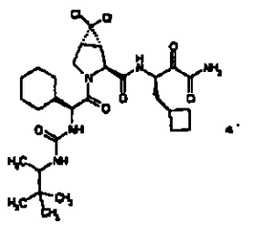


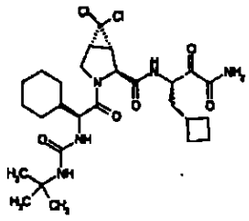


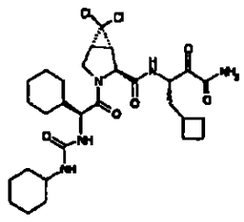


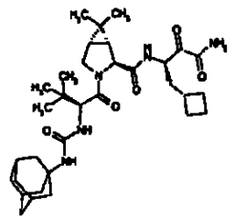


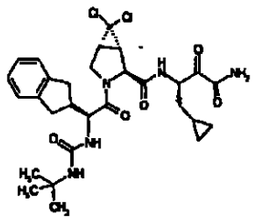


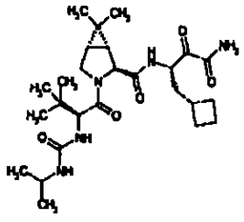


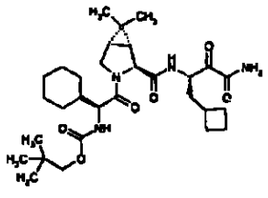


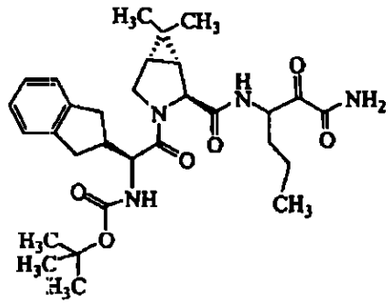


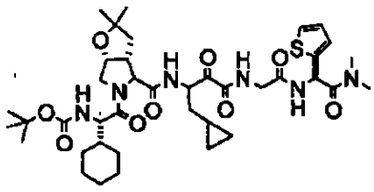


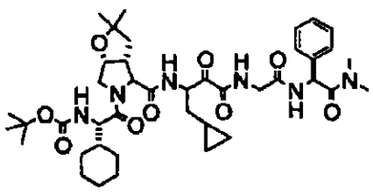


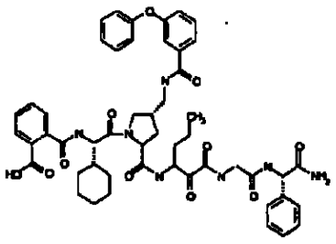


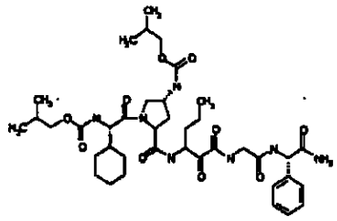


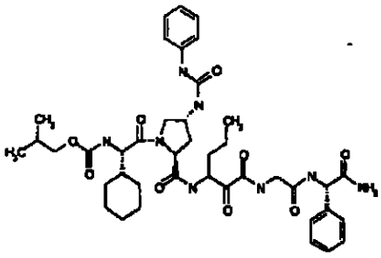


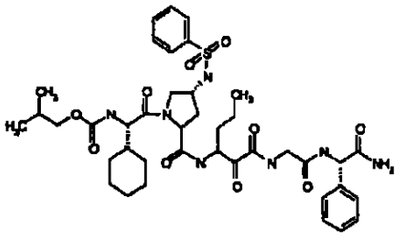


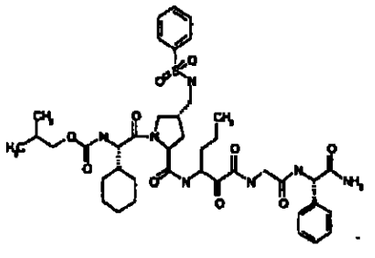


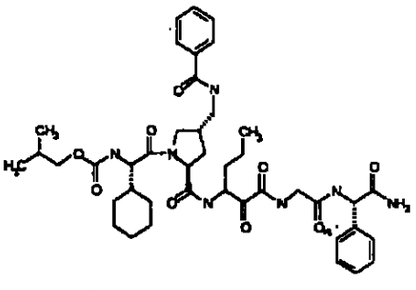


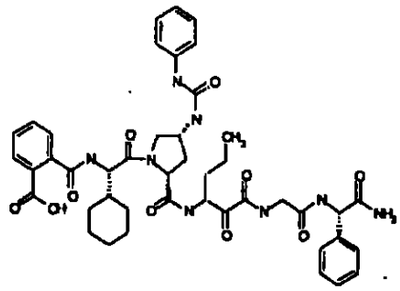


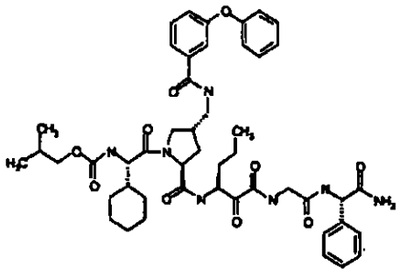


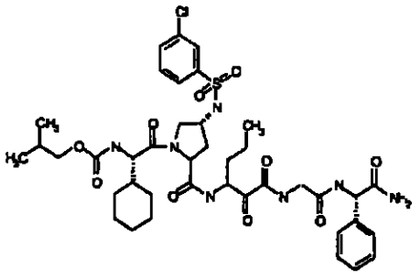


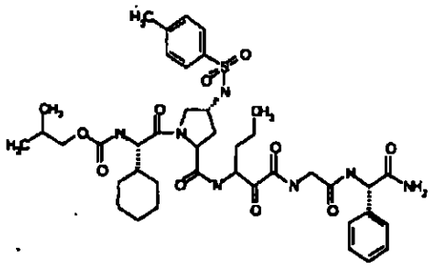


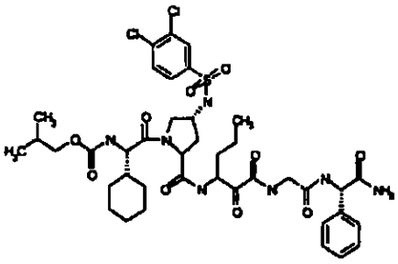


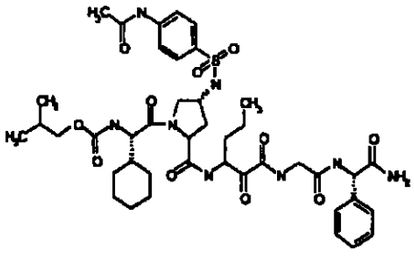


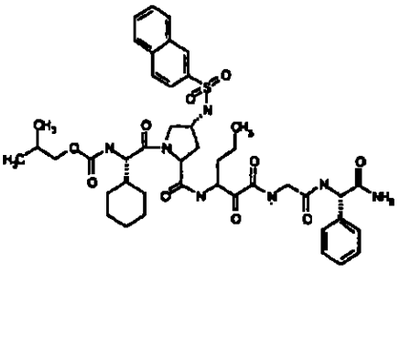


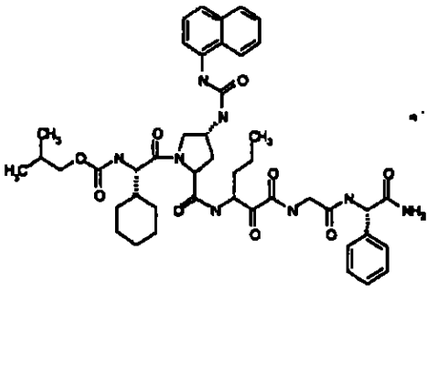


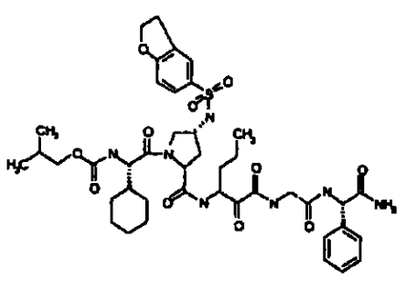


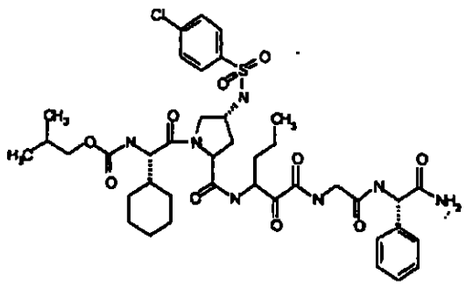


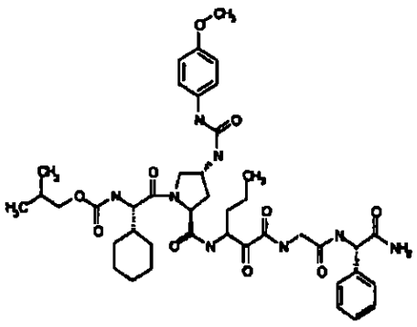


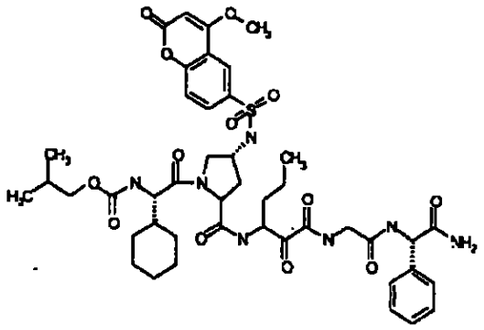


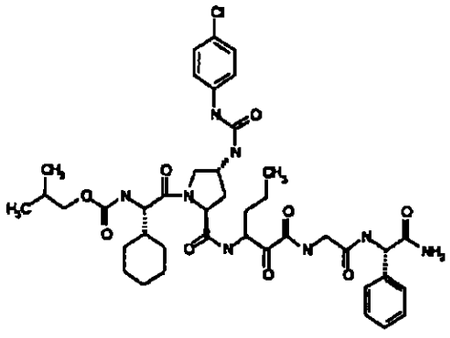


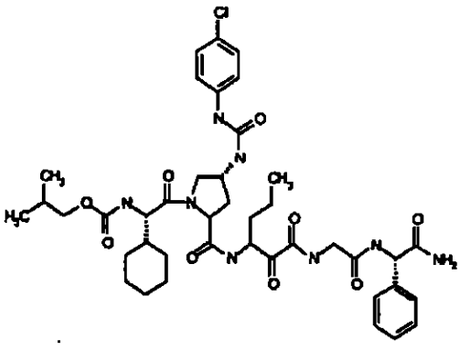




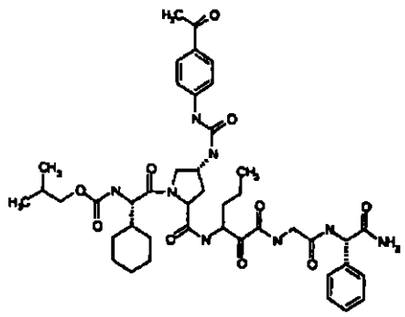


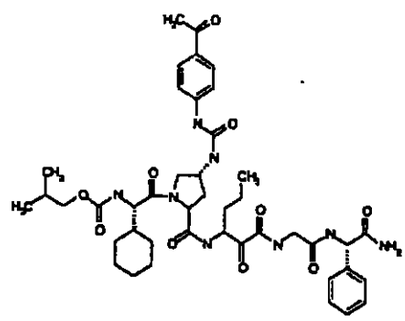


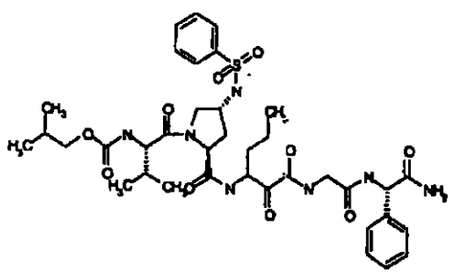


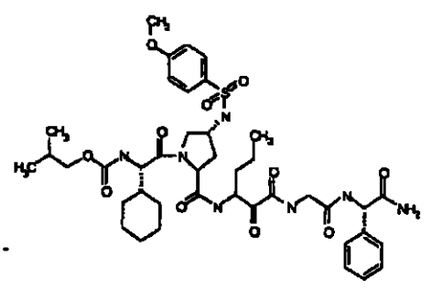


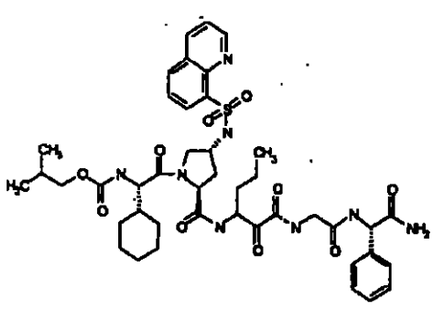
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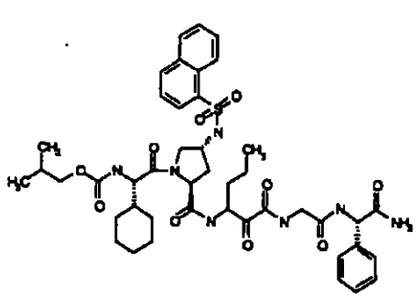


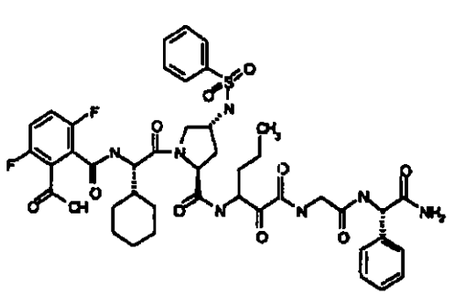


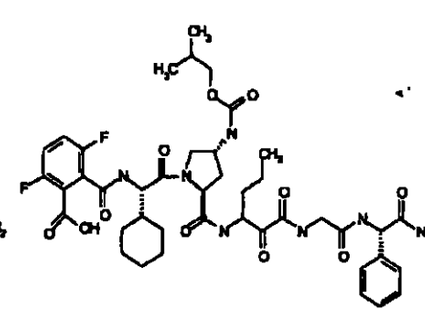


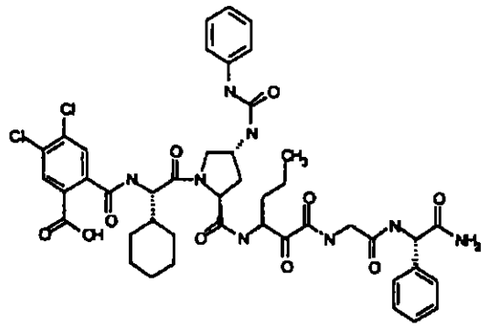


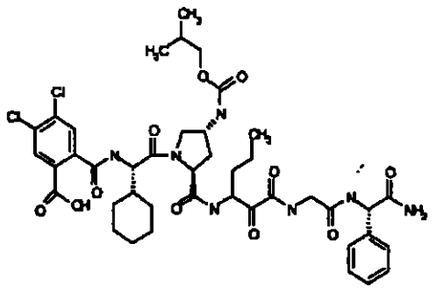


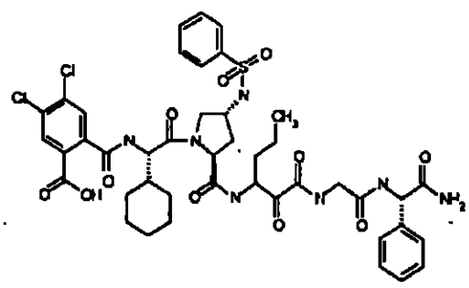


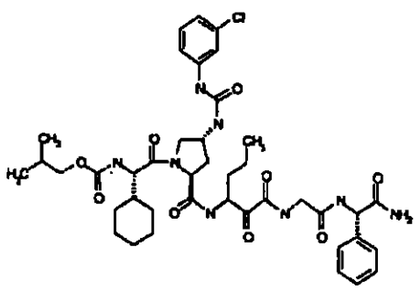


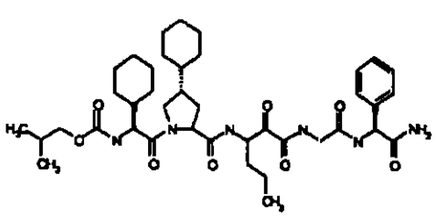


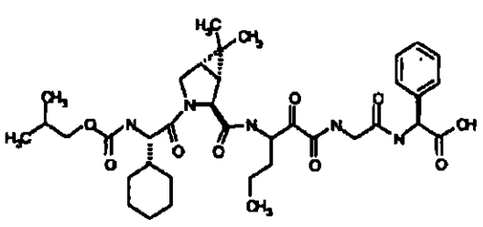


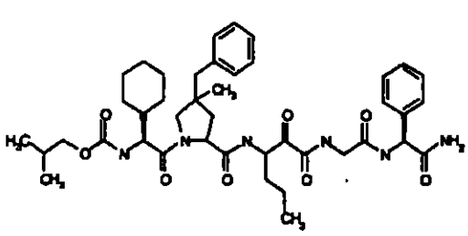


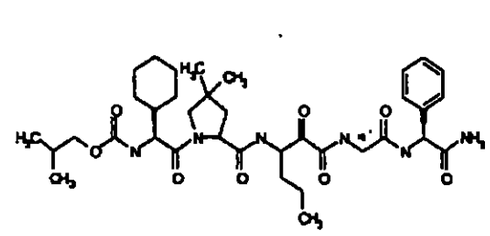


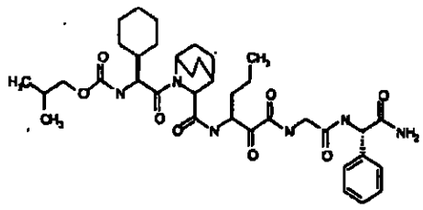


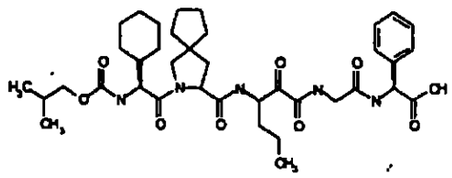


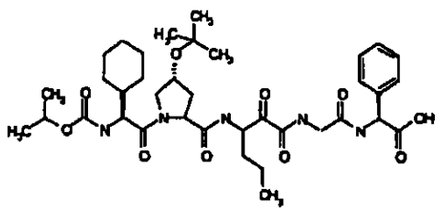


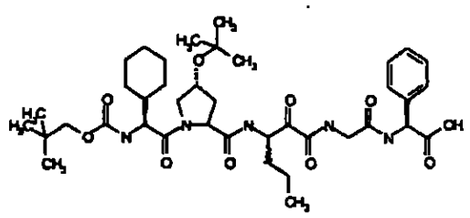


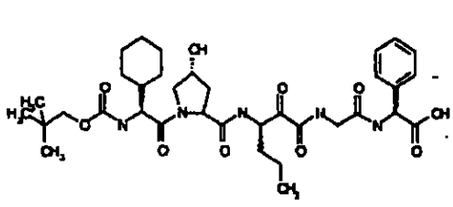


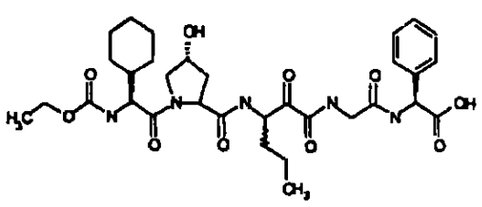


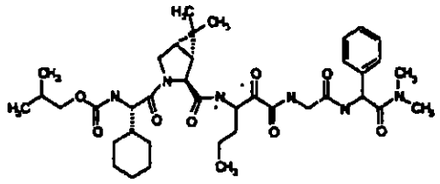


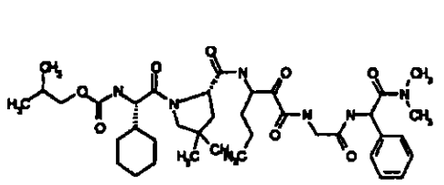


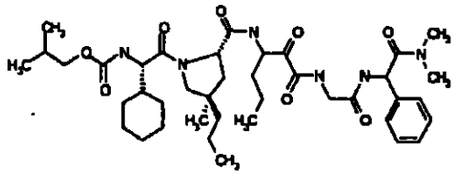


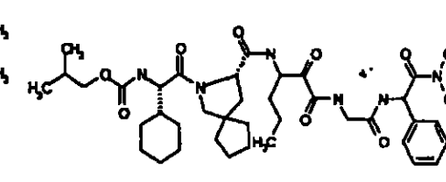


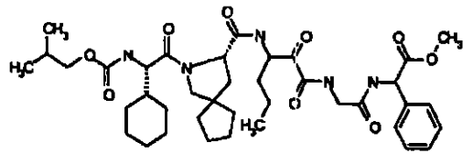


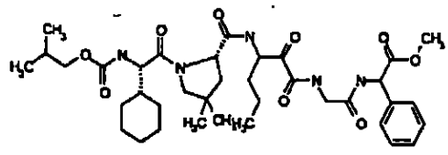


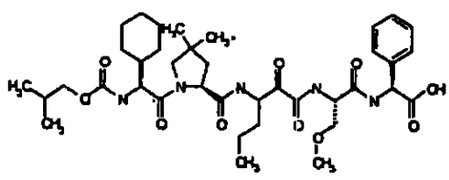


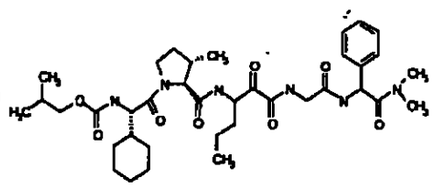


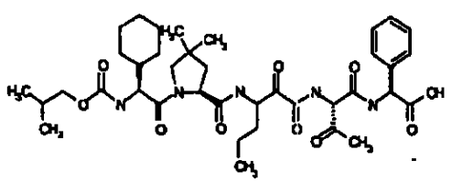


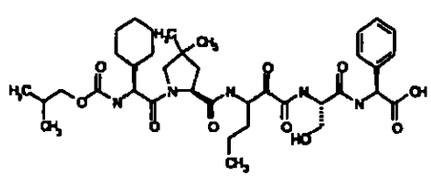


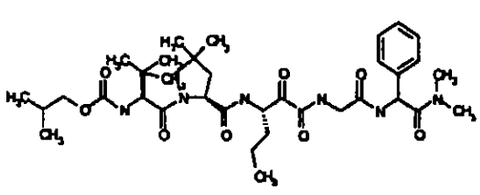


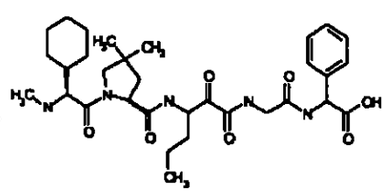


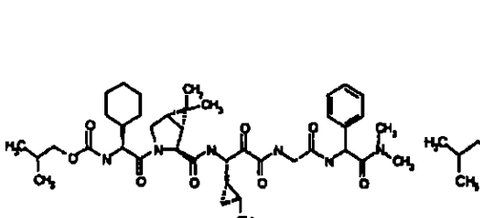


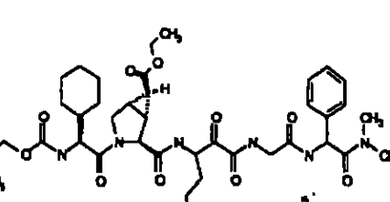


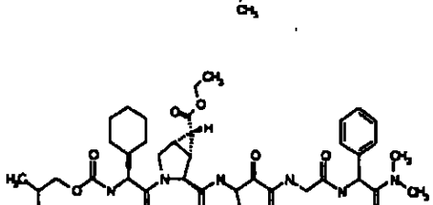


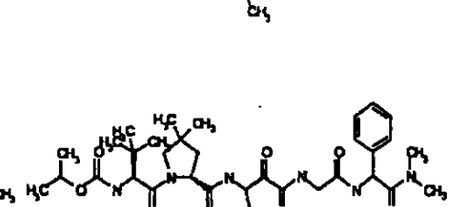


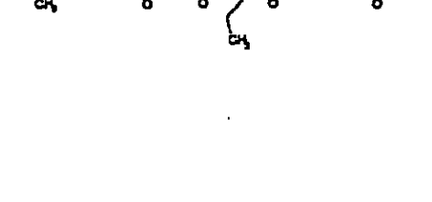


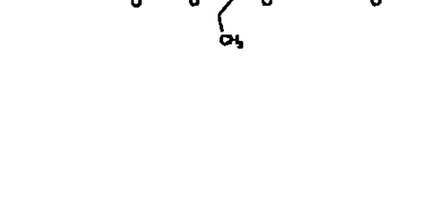


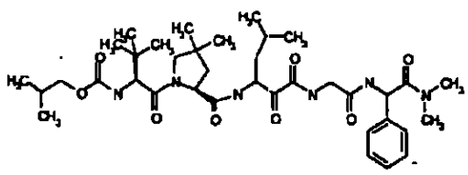


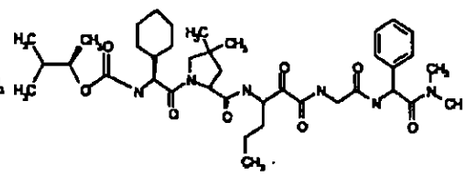


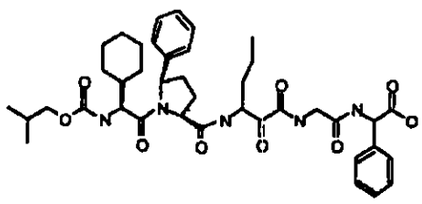


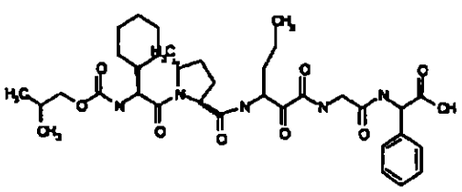


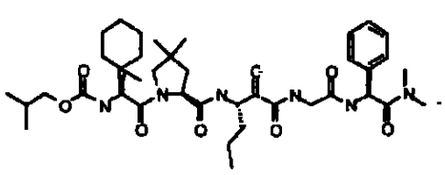


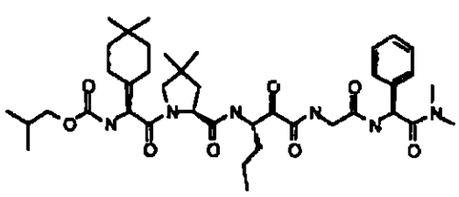


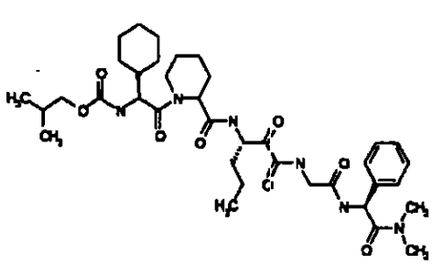


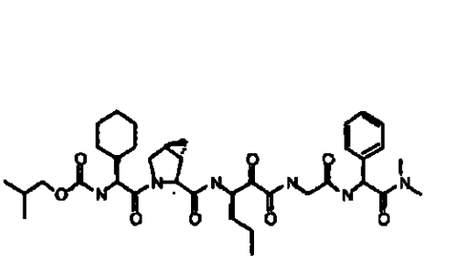


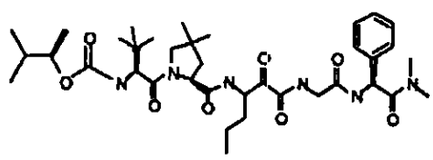


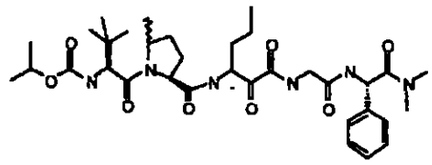


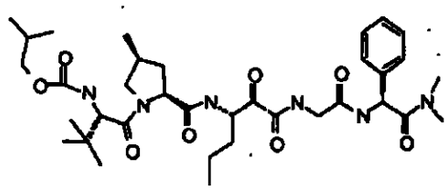


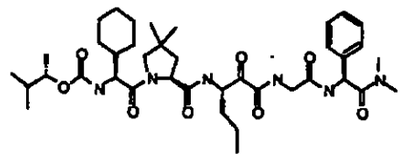


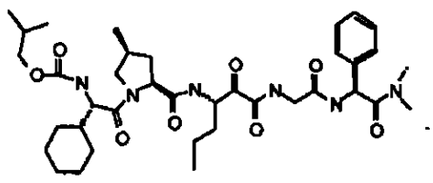


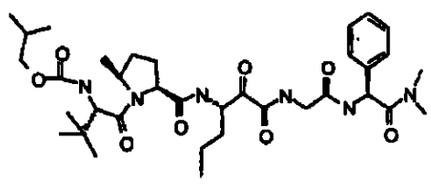


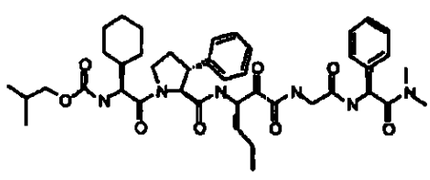


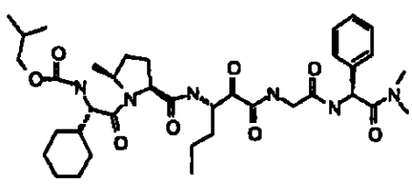


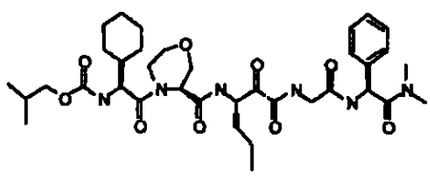


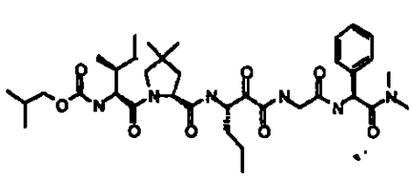


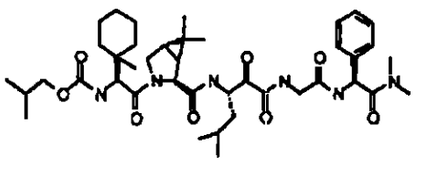


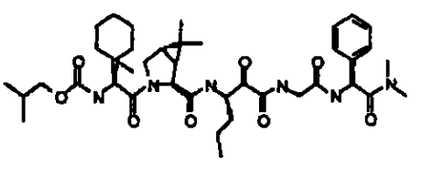




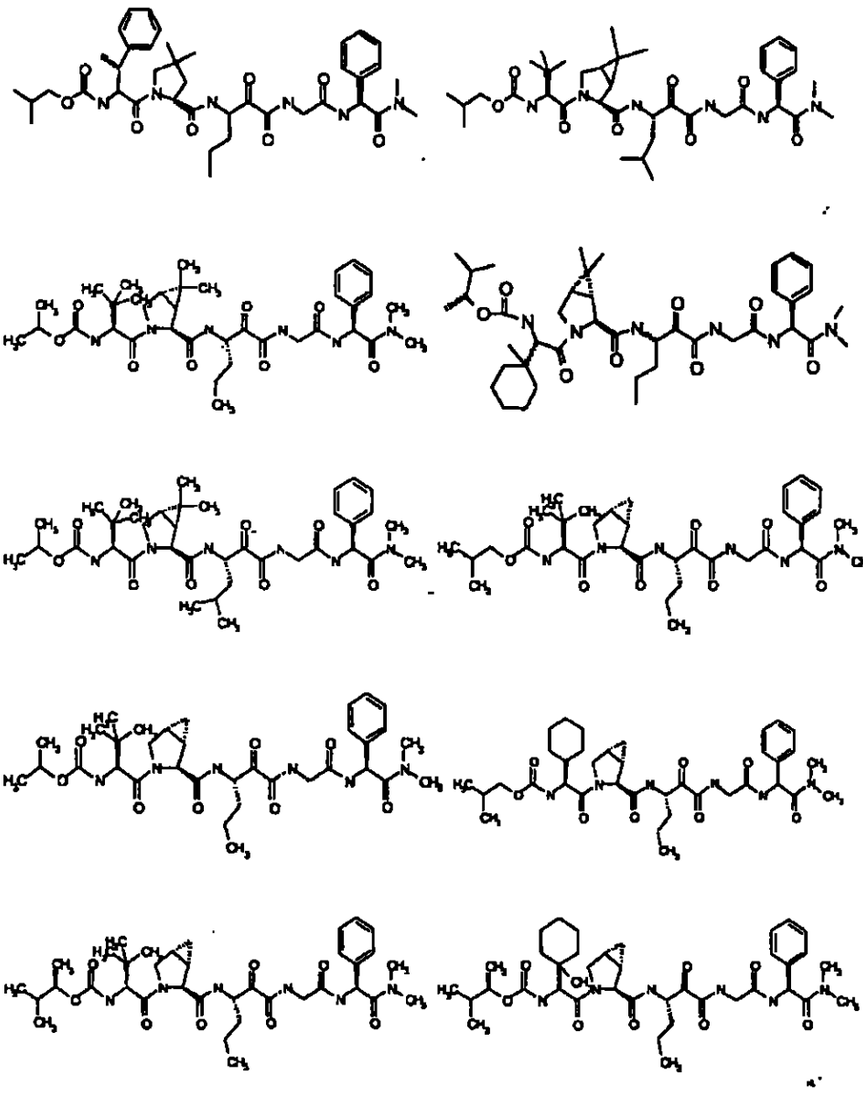












Dependiendo de su estructura; los compuestos de la invención pueden formar sales aceptables para uso farmacéutico con ácidos orgánicos o inorgánicos, o bases orgánicas o inorgánicas. Algunos ejemplos de ácidos apropiados para dicha formación de sales son los ácidos clorhídrico, sulfúrico, fosfórico, acético, cítrico, malónico, salicílico, málico, fumárico, succínico, ascórbico, maleico, metanisulfónico y otros ácidos minerales y carbocílicos conocidos por los expertos en el arte. Para la formación de sales con bases, las

bases apropiadas son, por ejemplo, NaOH, KOH, NH_4OH, hidróxido de tetraalquilamonio, y similares.

En otra realización, esta invención provee composiciones farmacéuticas que comprenden los péptidos de la invención como ingrediente activo. Las composiciones farmacéuticas comprenden, en general, en forma adicional, un diluyente vehículo, excipiente o vehículo aceptable para uso farmacéutico (denominados aquí en forma colectiva como materiales vehículo). Debido a su actividad como inhibidor del HCV, dichas composiciones farmacéuticas poseen utilidad en el tratamiento de la hepatitis C y trastornos relacionados.

Aún en otra realización, la presente invención describe métodos para preparar composiciones farmacéuticas que comprenden los compuestos de la invención como ingrediente activo. En las composiciones farmacéuticas y los métodos de la presente invención, los ingredientes activos se administrarán normalmente mezclados con materiales vehículos apropiados seleccionados en forma apropiada con respecto a la forma de administración pretendida, es decir, comprimidos orales, cápsulas (ya sea de relleno sólido, de relleno semi-sólido o de relleno líquido), polvos para constitución, geles orales, elixires, gránulos dispersables, jarabes, suspensiones y similares, y consistentes con las prácticas farmacéuticas convencionales. Por ejemplo, para administración oral en forma de comprimidos o cápsulas, el componente de fármaco activo puede combinarse con cualquier vehículo inerte no tóxico aceptable para uso farmacéutico, como lactosa, almidón, sacarosa, celulosa, estearato de magnesio, fosfato de dicalcio, sulfato de calcio, talco, manitol, alcohol etílico (formas líquidas) y similares. Más aún, cuando se desee o se necesite, pueden incorporarse también algunos agentes aglutinantes, lubricantes, agentes desintegrantes y agentes colorantes a la mezcla. Los polvos y los comprimidos pueden estar formados con aproximadamente 5 hasta aproximadamente 95 por ciento de composición de la invención. Los aglutinantes apropiados incluyen almidón, gelatina, azúcares

naturales, edulcorantes a base de maíz, gomas sintéticas y naturales como acacia, alginato de sodio, carboximetilcelulosa, polietilenglicol y ceras. Entre los lubricantes pueden mencionarse para uso en estas formas de dosificación el ácido bórico, el benzoato de sodio, el acetato de sodio, el cloruro de sodio, y similares. Los desintegrantes incluyen almidón, metilcelulosa, goma guar y similares.

También pueden incluirse agentes edulcorantes y saborizantes y preservantes cuando sea apropiado. Algunos de los términos indicados anteriormente, es decir, desintegrantes, diluyentes, lubricantes, aglutinantes y similares, se discuten en más detalle a continuación.

En forma adicional, las composiciones de la presente invención pueden formularse en forma de liberación prolongada para proveer la velocidad de liberación controlada de cualquiera de uno o más de los componentes o ingredientes activos para optimizar los efectos terapéuticos, es decir, la actividad de inhibición del HCV y similares. Las formas de dosificación apropiadas para la liberación prolongada incluyen los comprimidos en capas de velocidades variables de desintegración o matrices poliméricas de liberación controlada impregnadas con los componentes activos y con forma de comprimido o cápsulas que contienen dichas matrices poliméricas porosas impregnadas o encapsuladas.

Las preparaciones de forma líquida incluyen las soluciones, suspensiones y emulsiones. Como ejemplo pueden mencionarse las soluciones a base de agua o agua-propilenglicol para inyecciones parenterales o el agregado de edulcorantes y suavizantes para soluciones orales, suspensiones y emulsiones. Las preparaciones de forma líquida también pueden incluir soluciones para administración intranasal.

Las preparaciones en aerosol apropiadas para inhalación pueden incluir soluciones y sólidos en forma de polvo, que pueden combinarse con un vehículo aceptable para uso farmacéutico como un gas comprimido inerte, por ej.,

nitrógeno.

Para preparar supositorios, primero se funde una cera de bajo punto de fusión como mezcla de glicéridos de ácido graso como manteca de cacao, y se dispersa el ingrediente activo en forma homogénea agitando o con un mezclado similar. La mezcla fundida homogénea se vierte luego en moldes de tamaño conveniente, para enfriar y, por consiguiente, solidificar.

Además, se incluyen las preparaciones de forma sólida que tienen como finalidad convertirse, inmediatamente después de su uso, en preparaciones de forma líquida para administración oral o parenteral. Dichas formas líquidas incluyen soluciones, suspensiones, y emulsiones.

Los compuestos de la invención también pueden aplicarse por vía transdérmica. Las composiciones transdérmicas pueden tomar la forma de cremas, lociones, aerosoles, y/o emulsiones y pueden incluirse en un parche transdérmico del tipo de matriz o reservorio convencionales en el arte para este fin.

Con preferencia, el compuesto se administra por vía oral, intravenosa o subcutánea.

Con preferencia, la preparación farmacéutica se encuentra en una forma de dosificación unitaria. En dicha forma, la preparación se subdivide en dosis unitarias de tamaño apropiado que contienen las cantidades apropiadas de los componentes activos, por ejemplo, una cantidad efectiva para lograr el fin deseado.

La cantidad de composición activa de la invención en una dosis unitaria de preparación puede variar en general o ajustarse desde aproximadamente 1,0 miligramo hasta aproximadamente 1,000 miligramos, con preferencia, desde aproximadamente 1,0 hasta aproximadamente 950 miligramos, con mayor preferencia desde aproximadamente 1,0 hasta aproximadamente 500 miligramos, y normalmente desde aproximadamente 1 hasta aproximadamente 250

miligramos, de acuerdo con la aplicación en particular. La dosificación real empleada puede variar dependiendo de la edad del paciente, el sexo, el peso y la severidad de la condición tratada. Dichas técnicas son conocidas para los expertos en el arte.

En general, la forma de dosificación oral par humanos que contiene los ingredientes activos puede administrarse 1 ó 2 veces por día. La cantidad y la frecuencia de la administración se regulará de acuerdo con el criterio del clínico a cargo. Un régimen generalmente recomendado de dosificación oral para administración oral variará desde aproximadamente 1,0 miligramo hasta aproximadamente 1.000 miligramos por día, en una dosis única o dosis divididas.

A continuación se describen algunos términos útiles:

Cápsula - se refiere a un recipiente o recinto especial realizado de metilcelulosa, alcoholes polivinílicos, o gelatinas desnaturalizadas o almidón para contener o mantener las composiciones que comprenden los ingredientes activos. Las cápsulas de recubrimiento duro normalmente se realizan con mezclas de gelatinas de piel de cerdo o hueso de una resistencia de gel relativamente alta. La cápsula en sí misma puede contener pequeñas cantidades de colorantes, agentes opacantes, plastificadores y preservantes.

Comprimido - se refiere a una forma de dosificación sólida comprimida o moldeada que contiene los ingredientes activos con diluyentes apropiados. El comprimido puede prepararse por compresión de mezclas o granulaciones obtenidas por granulación en húmedo, granulación en seco, por compactación.

Gel oral - se refiere a los ingredientes activos dispersos o solubilizados en una matriz semi-sólida hidrofílica.

Polvo para constitución - se refiere a mezclas de polvos que contienen los ingredientes activos y diluyentes apropiados que pueden suspenderse en agua o jugos.

Diluyente - se refiere a sustancias que usualmente forman la mayor

porción de la composición o la forma de dosificación. Los diluyentes apropiados incluyen azúcares como lactosa, sacarosa, manitol y sorbitol; almidones derivados del trigo, el maíz, el arroz, y la papa; y celulosas como la celulosa microcristalina. La cantidad de diluyente en la composición puede variar desde aproximadamente 10 hasta aproximadamente 90% en peso de la composición total, con preferencia desde aproximadamente 25 hasta aproximadamente 75%, con mayor preferencia desde aproximadamente 30 hasta aproximadamente 60% en peso, aún con mayor preferencia desde aproximadamente 12 hasta aproximadamente 60%.

Desintegrante - se refiere a materiales agregados a la composición para ayudar a separar (desintegrar) y liberar los medicamentos. Los desintegrantes apropiados incluyen almidones; almidones modificados "solubles en agua fría" como almidón de carboximetilo sódico; gomas naturales y sintéticas como algarrobo, karaya, guar, tragacanto y agar; derivados de la celulosa como metilcelulosa y carboximetilcelulosa sódica; celulosas microcristalinas y celulosas microcristalinas entrecruzadas como croscarmelosa sódica; alginatos como ácido algínico y alginato de sodio; arcillas como las bentonitas; y mezclas efervescentes. La cantidad de desintegrante en la composición puede variar desde aproximadamente 2 hasta aproximadamente 15% en peso de la composición, con mayor preferencia desde aproximadamente 4 hasta aproximadamente 10% en peso.

Aglutinante - se refiere a sustancias que aglutinan o "adhieren" los polvos y los hacen cohesivos a través de la formación de gránulos, sirviendo así como "adhesivo" en la formulación. Los aglutinantes agregan fuerza cohesiva ya presente en el diluyente o agente a granel. Los aglutinantes apropiados incluyen los azúcares como la sacarosa; los almidones derivados del trigo, maíz, arroz, y papa; gomas naturales como la acacia, la gelatina y la goma tragacanto; derivados de algas marinas como ácido algínico, alginato de sodio y alginato

amónico de calcio; materiales celulósicos como metilcelulosa y carboximetilcelulosa sódica e hidroxipropilmetilcelulosa; polivinilpirrolidona; y materiales inorgánicos como silicato de aluminio y magnesio. La cantidad de aglutinante en la composición puede variar desde aproximadamente 2 hasta aproximadamente 20% en peso de la composición, con mayor preferencia desde aproximadamente 3 hasta aproximadamente 10% en peso, aún con mayor preferencia desde aproximadamente 3 hasta aproximadamente 6% en peso.

Lubricante - se refiere a una sustancia agregada a la forma de dosificación para permitir que los comprimidos, gránulos, etc., luego de comprimirse, se liberen del molde o matriz reduciendo la fricción o el desgaste. Los lubricantes apropiados incluyen estearatos metálicos como estearato de magnesio, estearato de calcio o estearato de potasio; ácido esteárico; ceras de punto de fusión elevado; y lubricantes solubles en agua, como cloruro de sodio, benzoato de sodio, acetato de sodio, oleato de sodio, polietilenglicoles y d'l-leucina. Los lubricantes usualmente se agregan en el último paso antes de la compresión, dado que deben estar presentes en las superficies de los gránulos y entre ellos, y las partes de la prensa para comprimidos. La cantidad de lubricante en la composición puede cariar desde aproximadamente 0,2 hasta aproximadamente 5% en peso de la composición, con preferencia desde aproximadamente 0,5 hasta aproximadamente 2%, con mayor preferencia desde aproximadamente 0,3 hasta aproximadamente 1,5% en peso.

Deslizante - material que evita la formación de torta y mejora las características de fluidez de las granulaciones, de modo que el flujo sea suave y uniforme. Los deslizantes apropiados incluyen dióxido de silicona y talco. La cantidad de deslizante en la composición puede cariar desde aproximadamente 0,1% hasta aproximadamente 5% en peso de la composición total, con preferencia, desde aproximadamente 0,5 hasta aproximadamente 2% en peso.

Agentes colorantes - excipientes que brindan coloración a la composición o

la forma de dosificación. Dichos excipientes pueden incluir colorantes de grado comestible y colorantes de grado comestible adsorbidos sobre un adsorbente apropiado como arcilla u óxido de aluminio. La cantidad de agente colorante puede variar desde aproximadamente 0,1 hasta aproximadamente 5% en peso de la composición, con preferencia desde aproximadamente 0,1 hasta aproximadamente 1%.

Biodisponibilidad - se refiere a la velocidad y el punto al cual el fármaco activo o el grupo terapéutico se absorbe en la circulación sistémica a partir de una forma de dosificación administrada, comparado con un estándar o control.

Los métodos convencionales para preparar comprimidos son conocidos. Dichos métodos incluyen métodos secos como la compresión directa y la compresión de la granulación producida por compactación, o métodos húmedos u otros procedimientos especiales. Los métodos convencionales para realizar otras formas de administración, por ejemplo, las cápsulas, los supositorios y similares, también son conocidos.

Otra realización de la invención describe el uso de las composiciones farmacéuticas descritas con anterioridad para el tratamiento de enfermedades como, por ejemplo, la hepatitis C y similares. El método comprende la administración de una cantidad terapéuticamente efectiva de la composición farmacéutica de la invención a un paciente que tiene una enfermedad o enfermedades y que necesita de dicho tratamiento.

Aún en otra realización, los compuestos de la invención pueden usarse para el tratamiento del HCV en humanos en modo de monoterapia o como tratamiento combinado (por ejemplo, combinación dual, combinación triple, etc.), como, por ejemplo, combinado con agentes antivirales y/o inmunomoduladores. Ejemplos de dichos agentes antivirales y/o inmunomoduladores incluyen Ribavirin (de Schering-Plough Corporation, Madison, New Jersey) y Levovirin™ (de ICN Pharmaceuticals, Costa Mesa, California); VP 50406™ (de Viropharm,

Incorporated, Exton, Pennsylvania), ISIS 14803™ (de ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (de Ribozyme Pharmaceuticals, Boulder, Colorado), VX 497™ (de Vertex Pharmaceuticals, Cambridge, Massachussets), Thymosin™ (de SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), micofenolato mofetilo (de Hoffman-LaRoche, Nutley, New Jersey), interferón (como, por ejemplo, el interferón alfa, conjugados PEG-interferón alfa) y similares. Los "conjugados PEG-interferón alfa" son las moléculas de interferón alfa unidas en forma covalente a una molécula de PEG. Los conjugados PEG-interferón alfa ilustrativos incluyen interferón alfa-2a (Roferon™, de Hoffman La-Roche, Nutley, New Jersey) en forma de interferón alfa-2a pegilado (por ejemplo, comercializado con el nombre Pegasys™), interferón alfa-2b (Intron™, de Schering-Plough Corporation) en forma de interferón alfa-2b pegilado (por ejemplo, comercializado con el nombre PEG-Intron™), interferón alfa-2c (Berofor Alpha™, de Boehringer Ingelheim, Ingelheim, Alemania) o el interferón de consenso, definido por la determinación de una secuencia de consenso de interferón alfa naturales (Infergen™, de Amgen, Thousand Oaks, California).

Como se indicó anteriormente, la invención incluye, además, los tautómeros, rotámeros, enantiómeros y otros estereoisómeros de los compuestos de la invención. Así, como lo aprecia un experto en el arte, algunos compuestos de la invención pueden existir en formas isoméricas apropiadas. Dichas variaciones están contempladas dentro del alcance de la invención.

Otra realización de la invención describe un método para fabricar los compuestos que se describen aquí. Los compuestos pueden prepararse a través de varias técnicas conocidas en el arte. Los procedimientos representativos ilustrativos se definen en los siguientes esquemas de reacción. Se debe entender que mientras que los siguientes esquemas ilustrativos describen la preparación de algunos compuestos representativos de la invención, la

sustitución apropiada de cualquiera de ambos, los aminoácidos naturales y no naturales, producirá la formación de los compuestos deseados en base a dicha sustitución. Dichas variaciones están contempladas dentro del alcance de la invención.

Las abreviaturas que se usan en las descripciones de los esquemas y en los ejemplos que siguen son:

THF: tetrahidrofurano.

DMF: *N,N*-Dimetilformamida

EtOAc: acetato de etilo

AcOH: ácido acético

HOOBt: 3-hidroxi-1,2,3-benzotriazin-4(3*H*)-ona

EDCI: clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida

NMM: *N*-metilmorfolina

ADDP: 1,1'-(Azodicarbonil)dipiperidina

DEAD: Dietilazodicarboxilato

MeOH: Metanol

EtOH: Etanol

Et_2O: Éter dietílico

DMSO: Dimetilsulfóxido

HOBt: N-hidroxibenzotriazol

PyBrOP: Hexafluorofosfato de bromo-*tris*-pirrolidinofosfonio

DCM: Diclorometano

DCC: 1,3-diciclohexilcarbodiimida

TEMPO: 2,2,6,6-tetrametil-1-piperidiniloxi

Phg: Fenilglicina

Chg: Ciclohexilglicina

Bn: Bencilo

Bzl: Bencilo

Et: Etilo

Ph: Fenilo

iBoc: isobutoxicarbonilo

iPr: isopropilo

^{t}Bu o Bu^{t}: *ter*-Butilo

Boc: ter-butiloxicarbonilo

Cbz: Benciloxicarbonilo

Cp: Ciclopentildienilo

Ts: p-toluensulfonilo

Me: Metilo

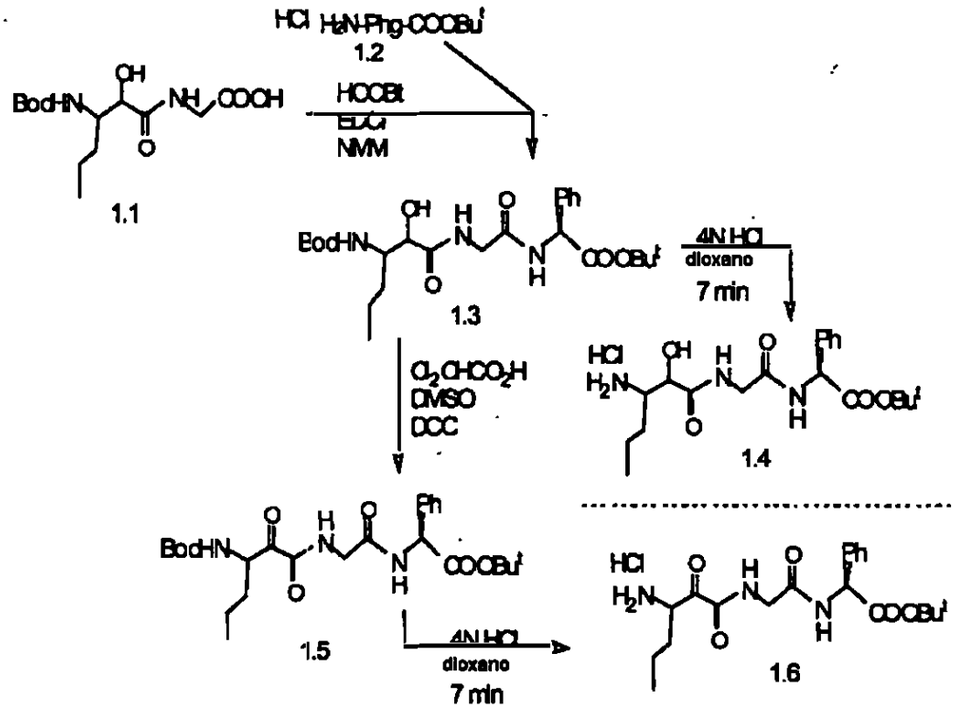
HATU: Hexafluorofosfato de O-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio

Bop: Benzotriazol-1-il-oxi-tris(dimetilamino)hexafluorofosfato

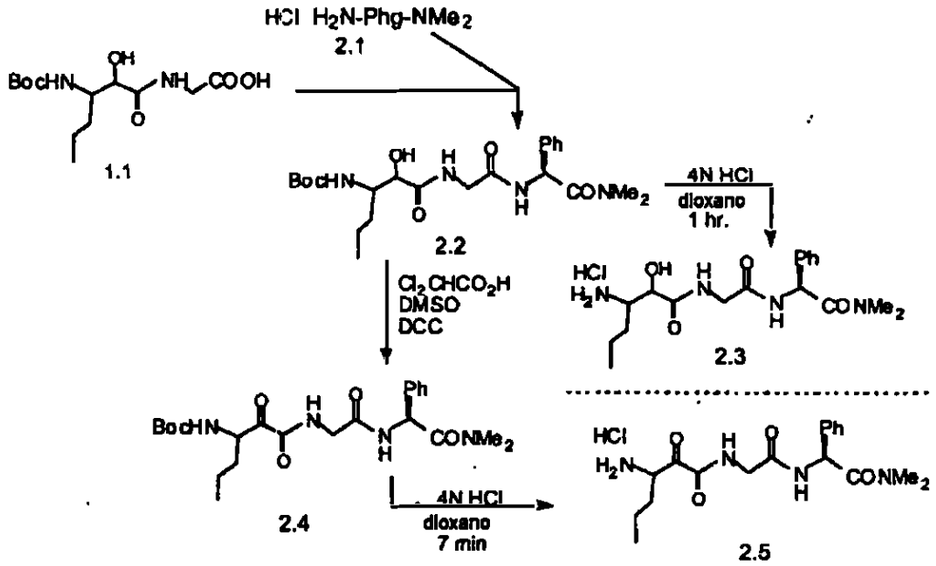
Esquemas de Preparación Generales:

Los siguientes esquemas describen los métodos de síntesis de los bloques de formación de intermediarios:

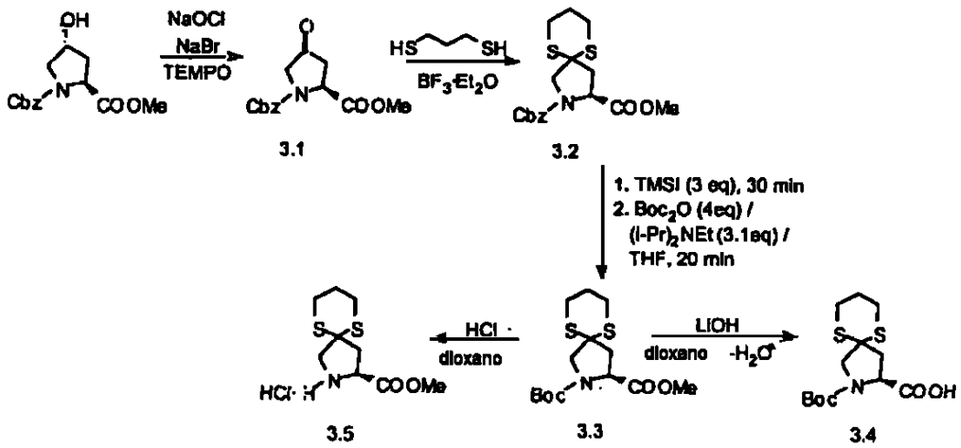
ESQUEMA 1



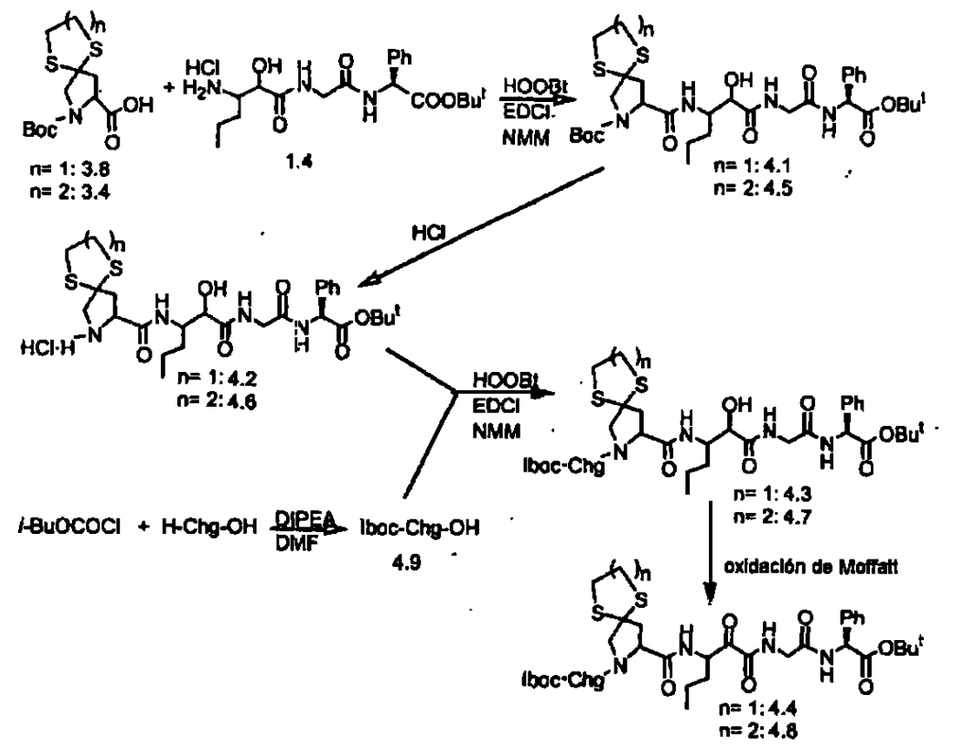
ESQUEMA 2



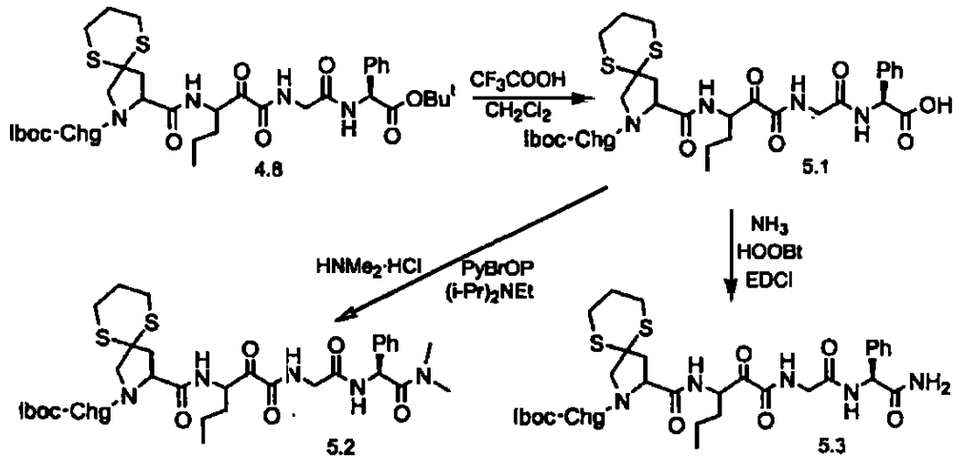
ESQUEMA 3



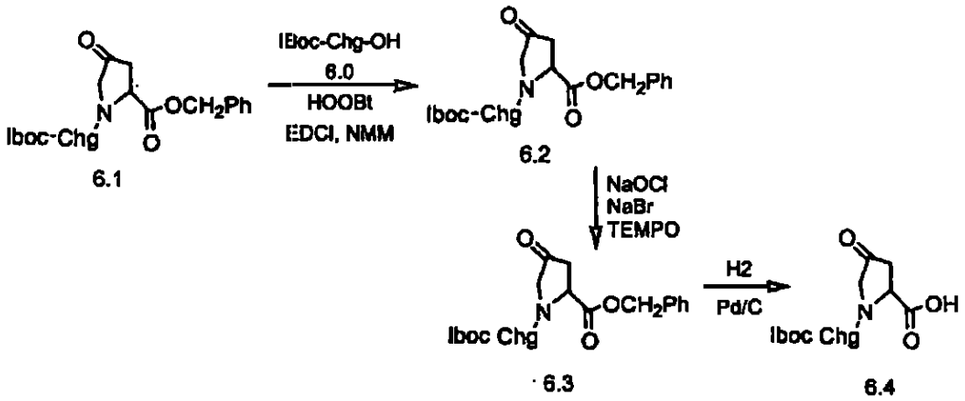
ESQUEMA 4



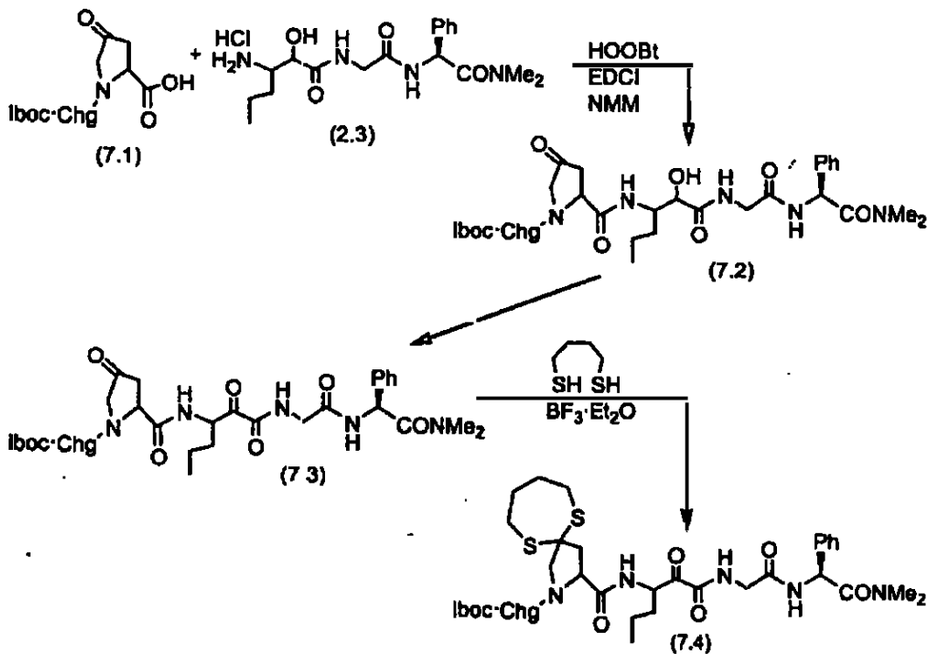
ESQUEMA 5



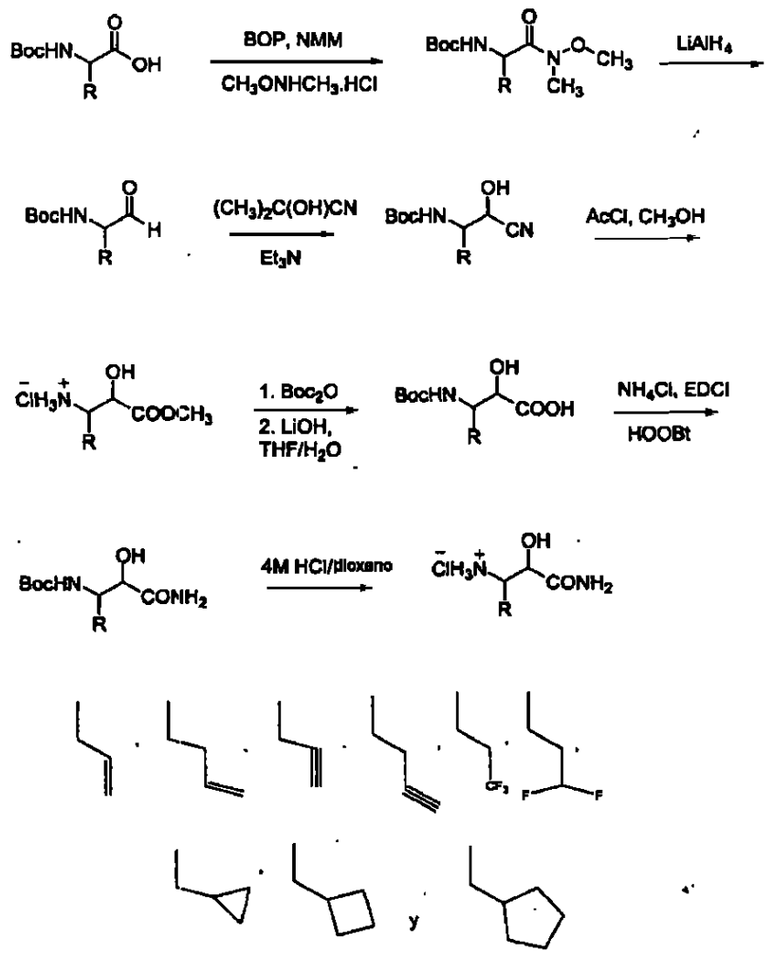
ESQUEMA 6



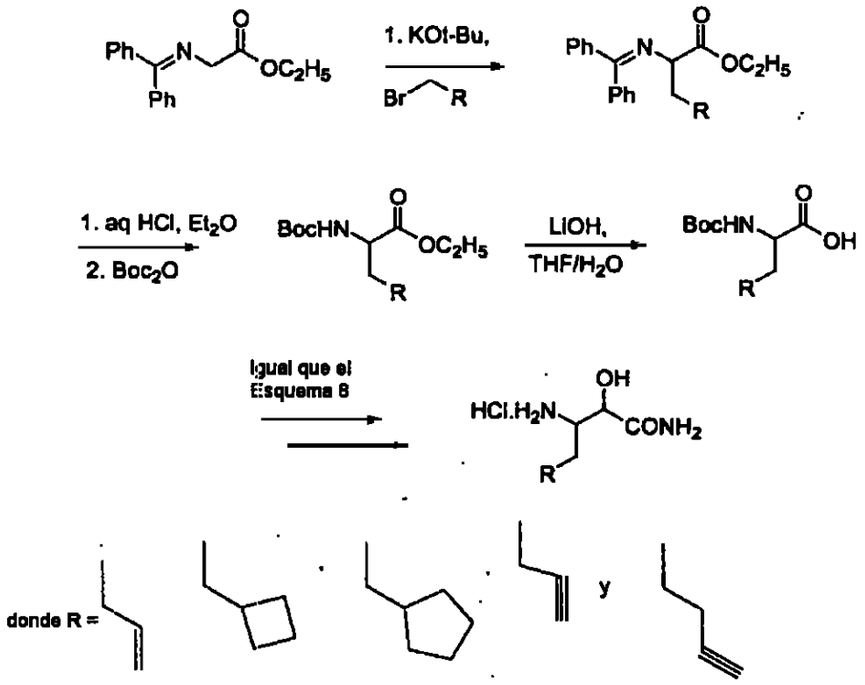
ESQUEMA 7


Iboc·Chg
(7.1)
HCl
(2.3)
HOOBt
EDCI
NMM
(7.2)
SH SH
BF3·Et2O
(7.3)
(7.4)
CONMe2
Ph

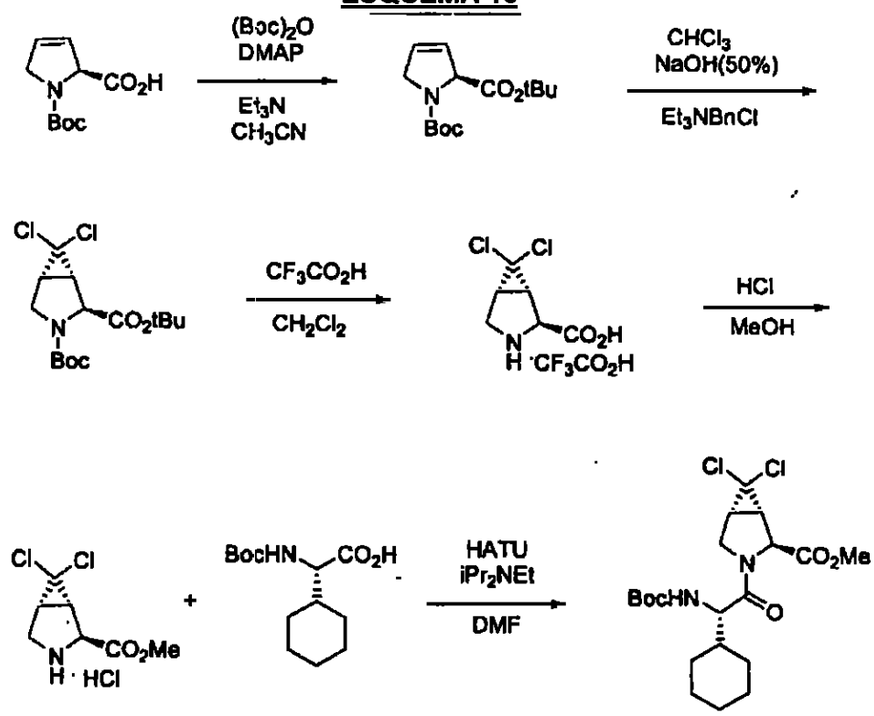
ESQUEMA 8


BocHN
OH
R
BOP, NMM
CH3ONHCH3.HCl
BocHN
N
O
CH3
CH3
R
LiAlH4
BocHN
H
R
(CH3)2C(OH)CN
Et3N
BocHN
OH
CN
R
AcCl, CH3OH
ClH3N
OH
COOCH3
R
1. Boc2O
2. LiOH,
THF/H2O
BocHN
OH
COOH
R
NH4Cl, EDCI
HOOBt
BocHN
OH
CONH2
R
4M HCl/dioxano
ClH3N
OH
CONH2
R
donde R =
CF3
F
F
y

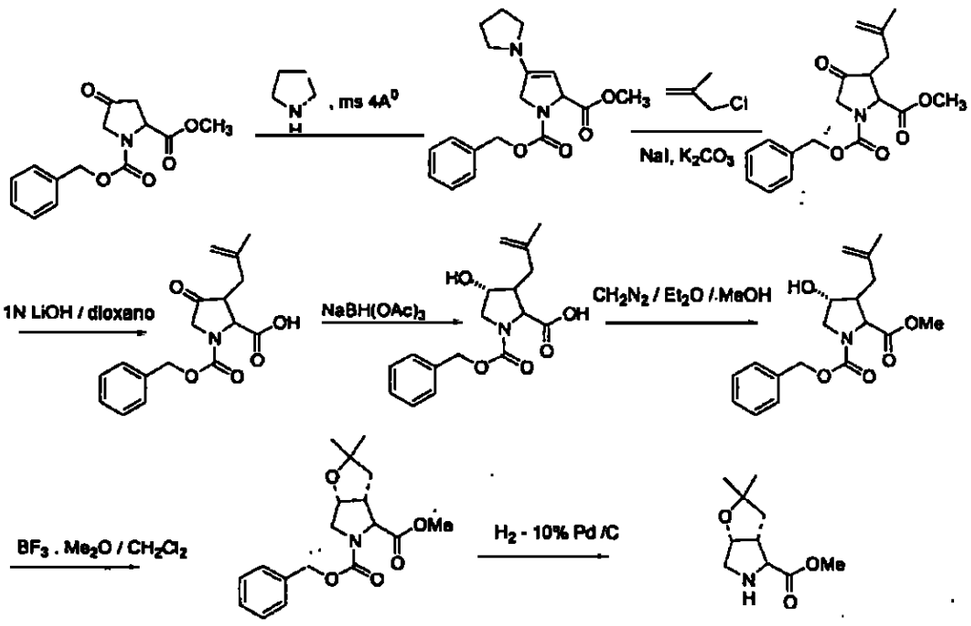
ESQUEMA 9



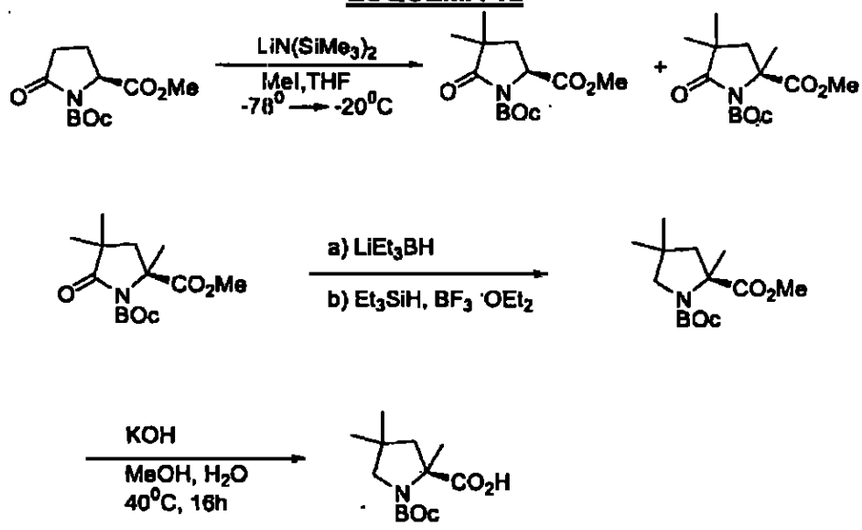
ESQUEMA 10



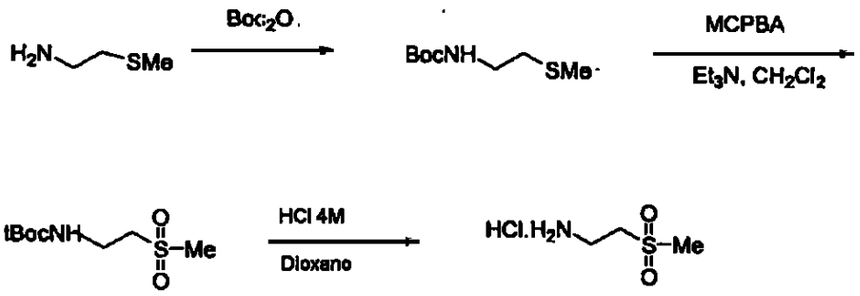
ESQUEMA 11



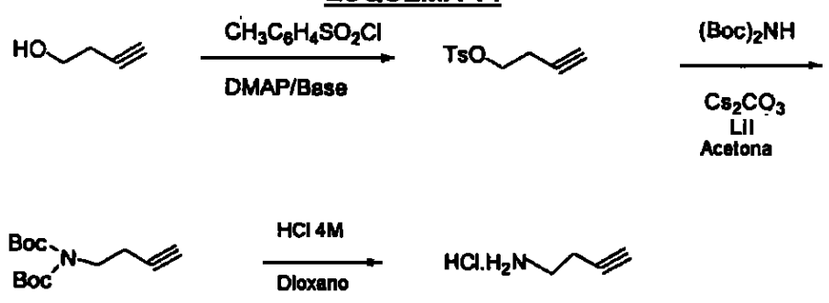
ESQUEMA 12



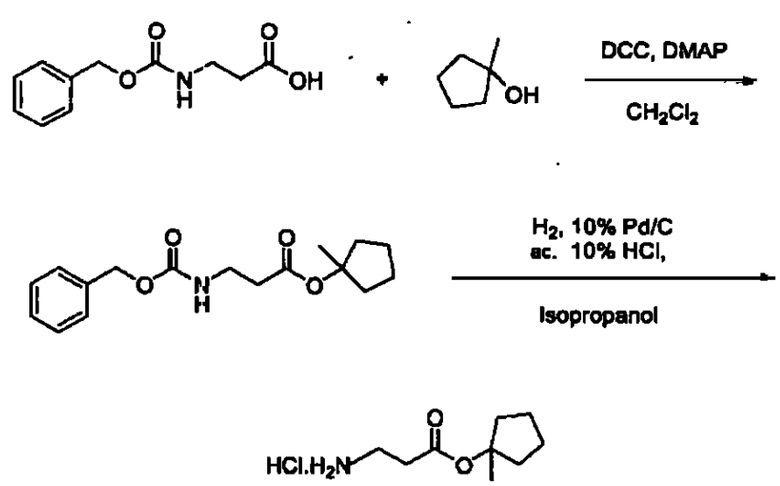
ESQUEMA 13



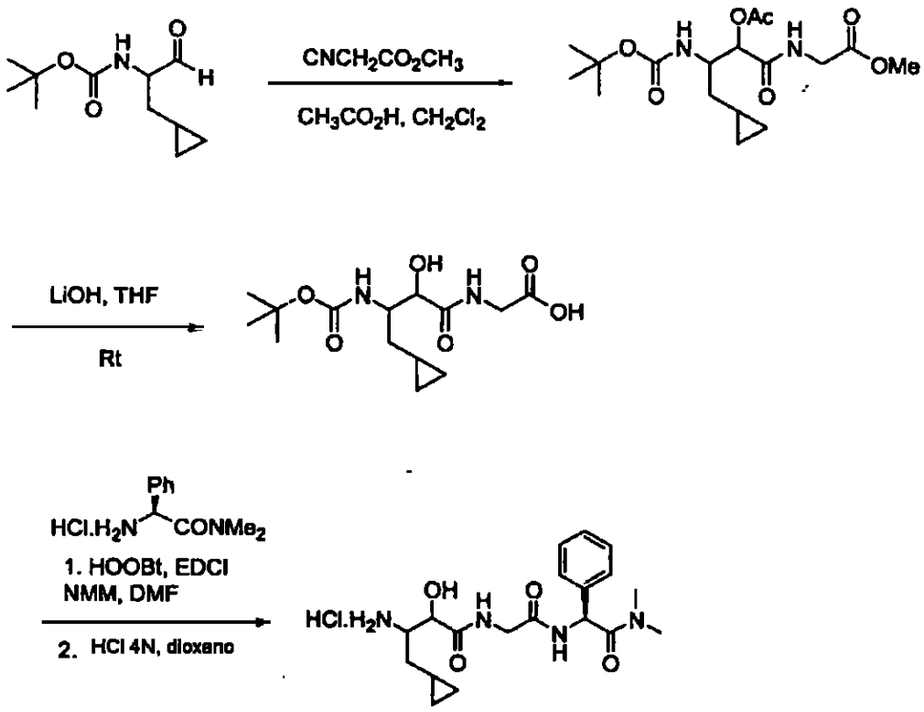
ESQUEMA 14



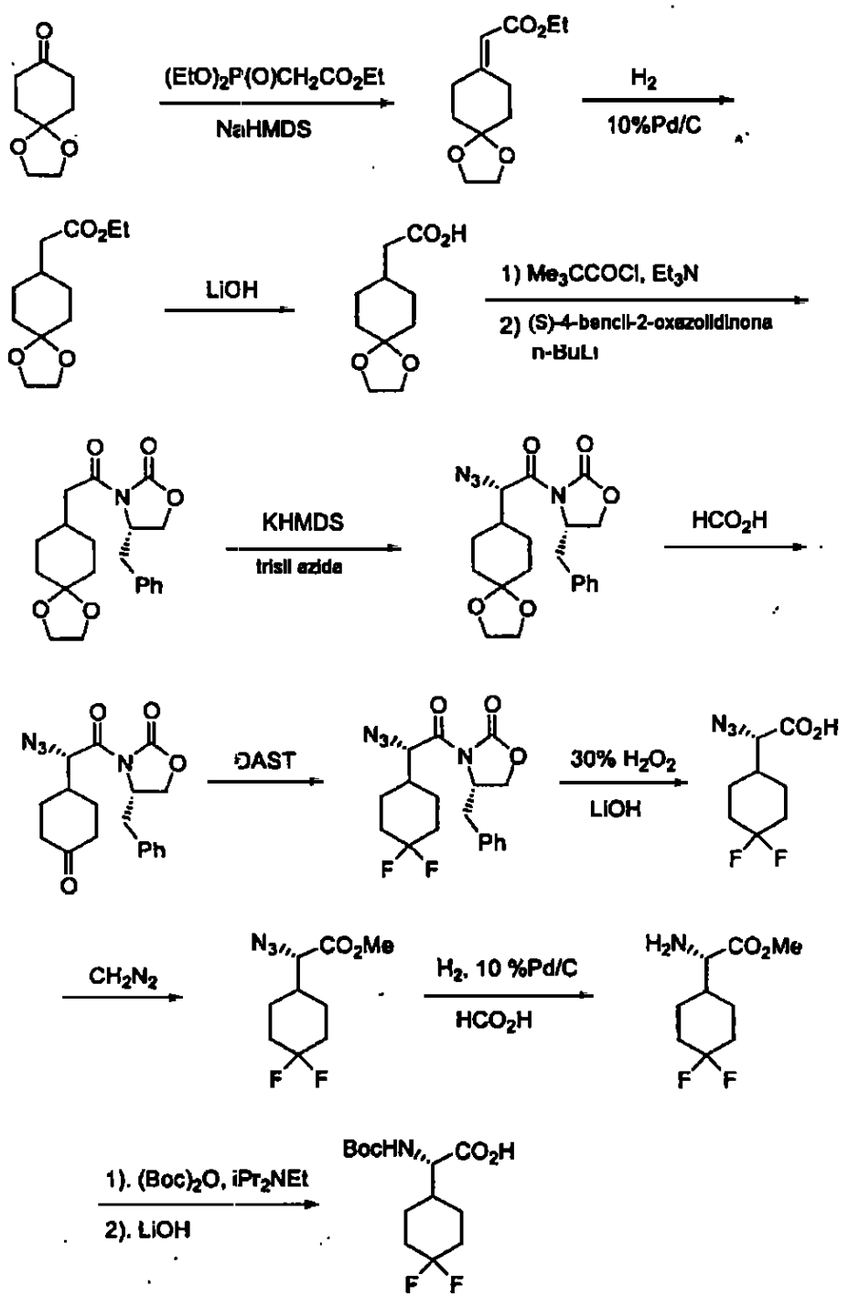
ESQUEMA 15



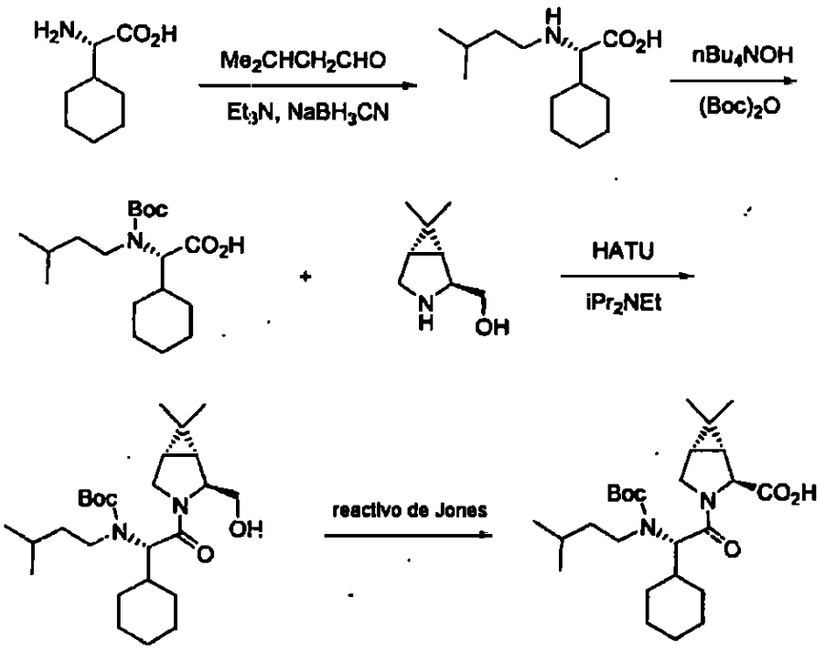
ESQUEMA 16


CNCH2CO2CH3
CH3CO2H, CH2Cl2
LiOH, THF
Rt
Ph
HCl.H2N
CONMe2
1. HOOBt, EDCI
NMM, DMF
2. HCl 4N, dioxano
HCl.H2N

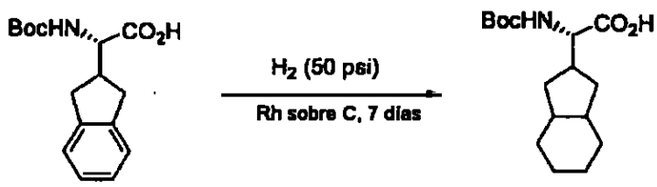
ESQUEMA 17


(EtO)2P(O)CH2CO2Et
NaHMDS
CO2Et
H2
10%Pd/C
LiOH
CO2H
1) Me3CCOCl, Et3N
2) (S)-4-bencil-2-oxazolidinona
n-BuLi
KHMDS
trisil azida
N3
Ph
HCO2H
DAST
30% H2O2
LiOH
F F
CH2N2
CO2Me
H2, 10 %Pd/C
HCO2H
H2N
1). (Boc)2O, iPr2NEt
2). LiOH
BocHN

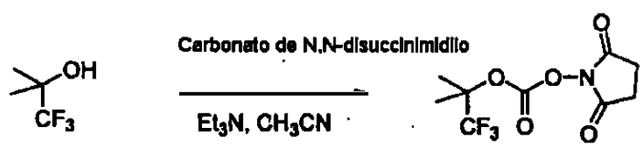
ESQUEMA 18



ESQUEMA 19



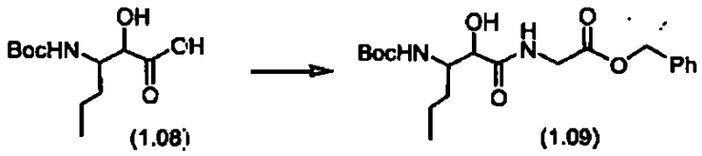
ESQUEMA 20



Preparación de los intermediarios:

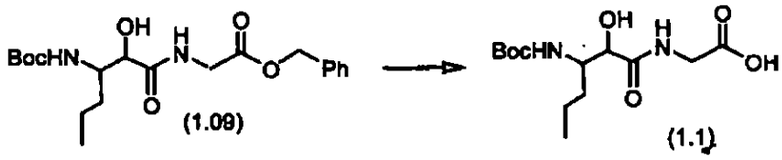
Ejemplo de Preparación 1

Paso A: Compuesto (1.1)



A una solución agitada del Compuesto (1.08) (3,00 g, 12,0 mmol (S. L. Harbeson *et al.* *J. Med. Chem.* 37 No. 18 (1994) 2918-2929) en DMF (15 mL) y CH_2Cl_2 (15 mL) a -20°C se agregó HOOBt (1,97 g, 12,0 mmol), N-metil morfolina (4,0 mL, 36,0 mmol) y EDCI (2,79 g, 14,5 mmol) y se agitó durante 10 minutos, seguido del agregado de HCl•H_2N-Gly-OBn (2,56 g, 13,0 mmol). La solución resultante se agitó a -20°C durante 2 hrs., se mantuvo refrigerada durante la noche y luego se concentró hasta secar, seguido de dilución con EtOAc (150 mL). La solución de EtOAc se lavó luego dos veces con $NaCHO_3$ saturado, H_2O, 5% de H_3PO_4, salmuera, se secó sobre Na_2SO_4, se filtró y se concentró hasta secar para dar el Compuesto (1.09) (4,5 g, 94%). LRMS m/z MH^+ = 395,1.

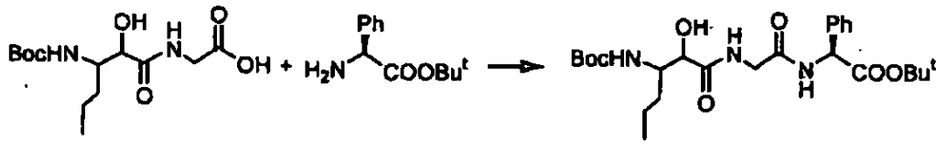
Paso B: Compuesto (1.1)



Una solución del Compuesto (1.09) (7,00 g, 17,8 mmol) en etanol absoluto (300 mL) se agitó a temperatura ambiente bajo atmósfera de hidrógeno en presencia de Pd-C (300 mg, 10%). El progreso de la reacción se monitoreó a través de tlc. Luego 2 h, la mezcla se filtró a través de un tapón de celite y la solución resultante se concentró al vacío para dar el Compuesto (1.1) (5,40 g, cuantitativo). LRMS m/z MH^+ = 305,1.

Ejemplo de Preparación 2

Paso A Compuesto (1.3)



(1.1) (1.2) (1.3)

Una mezcla del compuesto (1.1) del Ejemplo de Preparación 1, Paso B anterior (1 eq.), el Compuesto (1.2) (de Novabiochem, No. de Catálogo 04-12-5147) (1,03 eq.), HOOBt (1,03 eq.), N-metilmorfolina (2,2 eq.), y dimetilformamida (70 mL/g) se agitó a -20°C. Se agregó EDCI (1,04 eq.) y la reacción se agitó durante 48 hr. La mezcla de reacción se vertió en 5% de KH_2PO_4 acuoso y se extrajo con acetato de etilo (2 x). Los orgánicos combinados se lavaron con 5% de K_2CO_3 acuoso, frío, luego 5% de KH_2PO_4 acuoso, luego salmuera, y la fase orgánica se secó sobre $MgSO_4$ anhidro. La mezcla se filtró, luego se evaporó y el filtrado se secó al vacío, el residuo se trituró con Et_2O-hexano, y se filtró para dejar el compuesto del título (1.3) (86% de rendimiento), $C_{25}H_{39}N_3O_7$ (493,60), espectro de masa (FAB) M+1 = 494,3.

Paso B Compuesto (1.4)

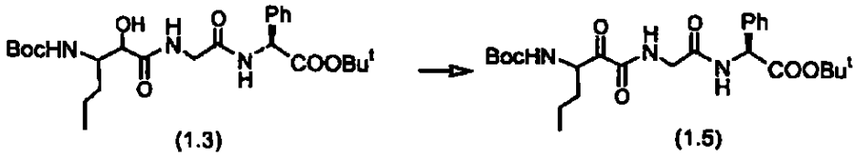


(1.3) (1.4)

El Compuesto (1.3) del Ejemplo de Preparación 2, Paso A (3,0 g) se trató con HCl 4N/dioxano (36 mL) y se agitó a temperatura ambiente durante 7 min. La mezcla se vertió en 1,5 L de hexano frío (5°C) y se agitó, luego se dejó fijar el frío durante 0,5 hr. La mezcla se filtró por succión en una atmósfera seca, y el sólido recolectado se secó en forma adicional para lograr el compuesto del título (1.4) (2,3 g, 88% de rendimiento), $C_{20}H_{31}N_3O_5$.HCl, H^1 RMN (DMSO-d_6/NaOD) δ 7,38 (m, 5H), 5,25 (m, 1 H), 4,3-4,1 (m, 1 H), 3,8 (m, 2H), 3,4-3,3 (m, oscurecido por D20), 1,7-1,1 (m, 4H), 1,35 (s, 9H), 0,83 (m, 3H).

Ejemplo de Preparación 3

Compuesto (1.5)

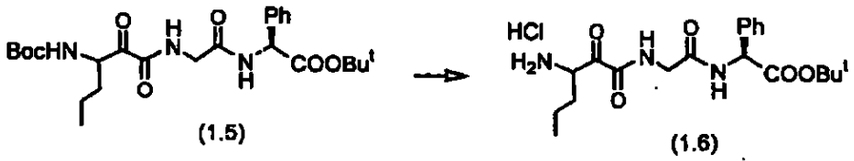


(1.3) (1.5)

El Compuesto (1.3) del Ejemplo de Preparación 2, Paso A, se trató en esencia del mismo modo que en el Ejemplo de Preparación 7, Paso A más adelante para lograr el Compuesto (1.5).

Ejemplo de Preparación 4

Compuesto (1.6)

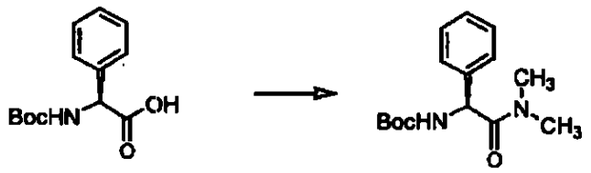


(1.5) (1.6)

El Compuesto (1.5) del Ejemplo de Preparación 3, se trató en esencia del mismo modo que en el Ejemplo de Preparación 2, Paso B, para lograr el Compuesto (1.6).

Ejemplo de Preparación 5

Paso A Compuesto (2.09)

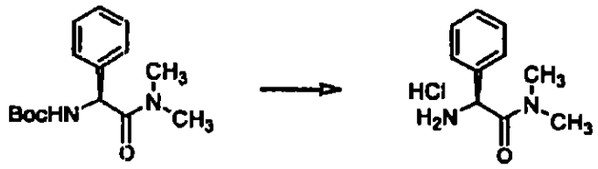


(2.08) (2.09)

A una solución de clorhidrato de dimetilamina (1,61 g, 19,7 mmol), N-Boc-fenilglicina, Compuesto (2.08) (4,50 g, 17,9 mmol, Bachem Co. # A-2225), HOOBt (3,07 g, 18,8 mmol) y EDCI (4,12 g, 21,5 mmol) en DMF anhidra (200 mL)

y CH_2Cl_2 (150 mL) a -20°C se agregó NMM (5,90 mL, 53,7 mmol). Luego de agitar a esta temperatura durante 30 min., la mezcla de reacción se mantuvo en un congelador durante la noche (18 h). Luego se dejó entibiar hasta la temperatura ambiente, y se agregaron EtOAc (450 mL), salmuera (100 mL) y 5% de H_3PO_4 (100 mL). Luego de que las fases se separaron, la fase orgánica se lavó con 5% de H_3PO_4 (100 mL), solución acuosa saturada de bicarbonato de sodio (2 X 150 mL), agua (150 mL), y salmuera (150 mL), se secó ($MgSO_4$), se filtró y se concentró al vacío para lograr el Compuesto (2.09) (4,86 g) como un sólido blanco, que se usó sin purificación adicional.

Paso B Compuesto (2.1)

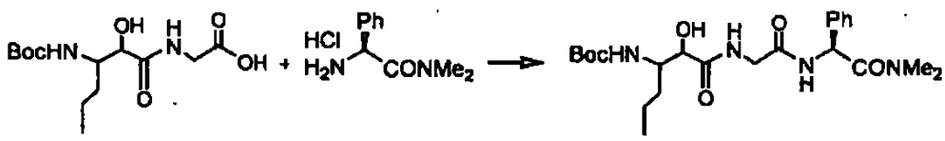


(2.09) (2.1)

El Compuesto (2.09) del Ejemplo de Preparación 5, Paso A (4,70 g, en bruto) se disolvió en HCl 4N (60 mL, 240 mmol) y la solución resultante se agitó a temperatura ambiente. El progreso de la reacción se monitoreó a través de TLC. Luego de 4 h, la solución se concentró al vacío para obtener como rendimiento el Compuesto (2.1) como un sólido blanco que se usó en la siguiente reacción sin purificación adicional. LRMS m/z MH^+ = 179,0.

Ejemplo de Preparación 6

Paso A Compuesto (2.2)

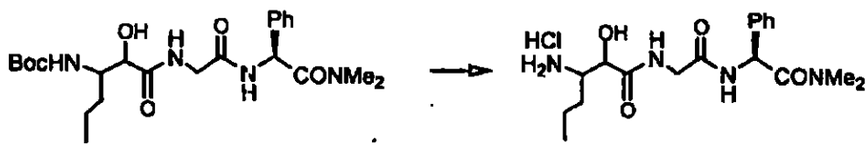


(1.1) (2.1) (2.2)

En esencia del mismo modo que en el Ejemplo de Preparación 2, Paso A.

sustituyendo la clorhidrato de la N,N-dimetilamida de la fenilglicina en lugar de clorhidrato del t-butil éster de la fenilglicina, se preparó el Compuesto (2.2), espectro de masa (FAB) M+1 = 465,3.

Paso B Compuesto (2.3).

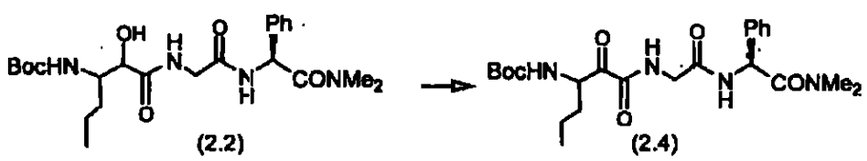


(2.2) (2.3)

El Compuesto (2,2) del Paso A (1,85 g) se reaccionó con HCl 4N/dioxano (50 mL) a temperatura ambiente durante 1 hr. La mezcla se evaporó al vacío en un baño de agua a 20°C, se trituró bajo éter isopropílico, se filtró, y se secó para lograr el Compuesto (2,3) (1,57 g, 98% de rendimiento), $C_{18}H_{28}N_4O_4$.HCl, espectro de masa (FAB) M+1 = 365,3

Ejemplo de Preparación 7

Paso A Compuesto (2.4)

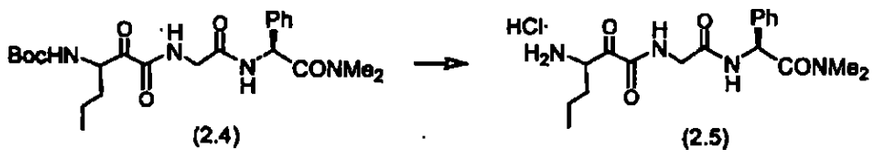


(2.2) (2.4)

Una solución del compuesto (2.2) del Ejemplo de Preparación 5, Paso A (2,0 g) en diclorometano (60 mL) se trató con dimetilsulfóxido (3,0 mL) y ácido 2,2-dicloroacético (0,70 mL). La mezcla agitada se enfrió hasta 5°C y luego se agregó solución 1M de diciclohexilcarbodiimida/ diclorometano (8,5 mL). El baño de frío se eliminó y la mezcla se agitó durante 22 hr. Luego se agregó 2-propanol (0,5 mL), y se agitó durante un adicional de 1 hr. La mezcla se filtró, luego se lavó con frío NaOH 0,1 N con hielo (50 mL), luego frío con hielo HCl 0,1 N (50 mL), luego 5% de KH_2PO_4 acuoso, luego salmuera saturada. La solución orgánica se secó sobre sulfato de magnesio anhidro, luego se filtró. El filtrado se evaporó, y

se cromatografió sobre gel de sílice, eluyendo con acetato de etilo para lograr el Compuesto (2.3) (1,87 g, 94% de rendimiento), $C_{23}H_{34}N_4O_6$, espectro de masa (FAB) M+1 = 463,3.

Paso B Compuesto (2.5)



(2.4) (2.5)

En esencia del mismo modo que en el Ejemplo de Preparación 2, Paso B, se preparó el Compuesto (2.5).

Ejemplo de Preparación 8

Paso A Compuesto (3.1)



(3.01) (3.1)

En un matraz se combinaron Metil éster de N-Cbz-hidroxiprolina (provisto por Bachem Biosciences, Incorporated, King of Prussia, Pennsylvania), Compuesto (3.01) (3,0 g), tolueno (30 mL), y acetato de etilo (30 mL). La mezcla se agitó vigorosamente, y luego se agregó una solución of NaBr/agua (1,28 g /5 mL). A ésta se agregó radical libre 2,2,6,6-tetrametil-1-piperidiniloxi (TEMPO, 17 mg, de Aldrich Chemicals, Milwaukee, Wisconsin). La mezcla agitada se enfrió hasta 5°C y luego se agregó una solución preparada de oxidante [blanqueador disponible en el mercado, Clorox® (18 mL), $NaCHO_3$ (2,75 g) y agua para formar 40 mL] gota a gota durante 0,5 hr. A esto se agregó 2-propanol (0,2 mL). La fase orgánica se separó, y la fase de agua se extrajo con acetato de etilo. Los extractos orgánicos se combinaron, se lavaron con 2% de tiosulfato de sodio, luego salmuera saturada. La solución orgánica se secó sobre $MgSO_4$ anhidro, se

filtró y se evaporó el filtrado al vacío para dejar una goma amarillo pálido apropiada para reacciones posteriores (2,9 g, 97% de rendimiento), $C_{14}H_{15}NO_5$ (277,28), espectro de masa (FAB) M+1 = 278,1.

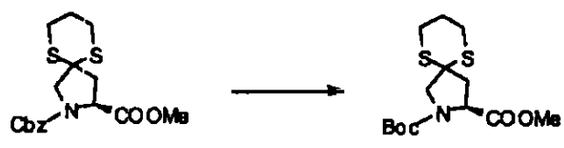
Paso B Compuesto (3.2).



(3.1) (3.2)

El Compuesto (3.1) del Paso A anterior (7,8 g) se disolvió en diclorometano (100 mL), y se enfrió hasta 15°C. A esta mezcla se agregó primero 1,3-propanditiol (3,1 mL), seguido de eterato de trifluoruro de boro recién destilado (3,7 mL). La mezcla se agitó a temperatura ambiente durante 18 h. Mientras se agitaba vigorosamente, una solución de K_2CO_3/agua (2 g / 30 mL) se agregó con cuidado, seguido de $NaCHO_3$ saturado (10 mL). La fase orgánica se separó de la fase de agua (pH -7,4), se lavó con agua (10 mL), luego salmuera. La solución orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se evaporó al vacío. El residuo se cromatografió sobre gel de sílice, eluyendo con tolueno, luego a con un gradiente de hexano-Et_2O (2:3 hasta 0:1) para lograr un aceite marrón (7,0 g, 68% de rendimiento), $C_{17}H_{21}NO_4S_2$ (367,48), espectro de masa (FAB) M+1 =368,1.

Paso C Compuesto (3.3)

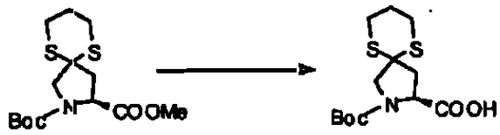


(3.2) (3.3)

Una solución del Compuesto (3.2) del Paso B anterior (45 g) en acetonitrilo (800 mL) a 20°C se trató con yodotrimetilsilano recién destilado (53 mL) de una

vez. La reacción se agitó durante 30 min., luego se vertió en una solución recién preparada de di-t-butildicarbonato (107 g), éter etílico (150 mL), y diisopropiletilamina (66,5 mL). La mezcla se agitó durante 30 min. más, luego se lavó con hexano (2 x 500 mL). Se agregó acetato de etilo (1000 mL) a la fase inferior de acetonitrilo, y luego la fase se lavó con 10% de KH_2PO_4 acuoso (2 x 700 mL), y salmuera. El filtrado se evaporó al vacío en un baño de agua a 25°C, se absorbió en acetato de etilo fresco (1000 mL), y se lavó sucesivamente con HCl 0,1 N, NaOH 0,1N, 10% de KH_2PO_4 acuoso, y salmuera. La solución orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se evaporó al vacío. El residuo (66 g) se cromatografió sobre gel de sílice (2 kg), eluyendo con hexano (2 L), luego Et_2O/hexano (55:45, 2 L), luego Et_2O (2 L) para lograr una goma naranja que se cristalizó lentamente en reposo (28 g, 69% de rendimiento), $C_{14}H_{23}NO_4S_2$ (333,46), espectro de masa (FAB) M+1 = 334,1.

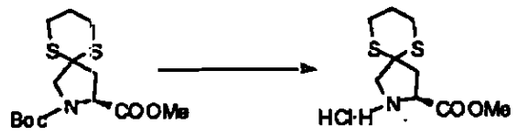
Paso D Compuesto (3.4)



(3.3) (3.4)

Una solución del Compuesto (3.3) del Paso C anterior (11 g) en dioxano (150 mL) a 20°C se trató con LiOH acuoso 1N (47 mL) y se agitó durante 30 h. La mezcla se concentró al vacío en un baño de agua a 30°C hasta la mitad del volumen. El resto se diluyó con agua (300 mL), se extrajo con Et_2O (2 x 200 mL). La fase de agua se acidificó hasta un pH ~4 con HCl 12 N (3-4 mL), se extrajo con acetato de etilo, y se lavó con salmuera. La solución orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se evaporó al vacío para dejar el Compuesto (3.4) (8,1 g, 78%), $C_{13}H_{21}NO_4S_2$ (319,44), espectro de masa (FAB) M+1 = 320,1.

Paso E Compuesto (3.5).

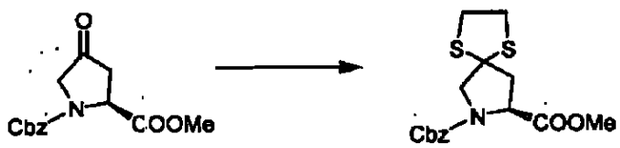


(3.3) (3.5)

A una solución del Compuesto (3.3) del Paso C anterior (1 g) en dioxano (5 mL), se agregó Solución de HCl 1N-dioxano (50 mL). La mezcla se agitó vigorosamente durante 1 hr. La mezcla se evaporó al vacío en un baño de agua a 25°C. El residuo se trituró con Et_2O, y se filtró para dejar el compuesto del título (0,76 g, 93% de rendimiento), $C_9H_{15}NO_2S_2.HCl$ (269,81), espectro de masa (FAB) M+1 = 234,0.

Ejemplo de Preparación 9

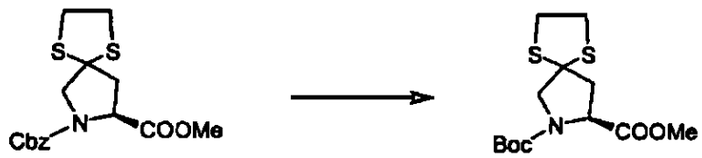
Paso A Compuesto (3.6)



(3.1) (3.6)

Siguiendo esencialmente el mismo procedimiento del Ejemplo de Preparación 8, Paso B, sustituyendo el etan ditiol por propan ditiol, se obtuvo el Compuesto (3.6).

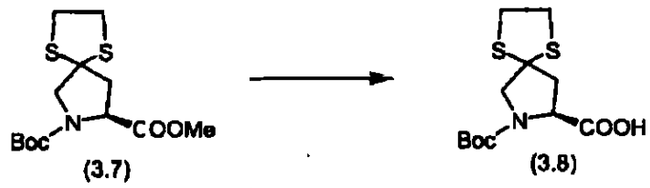
Paso B Compuesto (3.7).



(3.6) (3.7)

Siguiendo esencialmente el mismo procedimiento del Ejemplo de Preparación 8, Paso C, sustituyendo el Compuesto (3.6) por el Compuesto (3.2), se obtuvo el Compuesto producto (3.7).

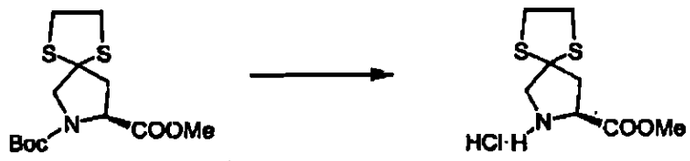
Paso C Compuesto (3.8)



(3.7) (3.8)

Siguiendo esencialmente el mismo procedimiento del Ejemplo de Preparación 8, Paso D, sustituyendo el Compuesto (3.7) por el Compuesto (3.3) se obtuvo el compuesto producto (3.8).

Paso D Compuesto (3.9)

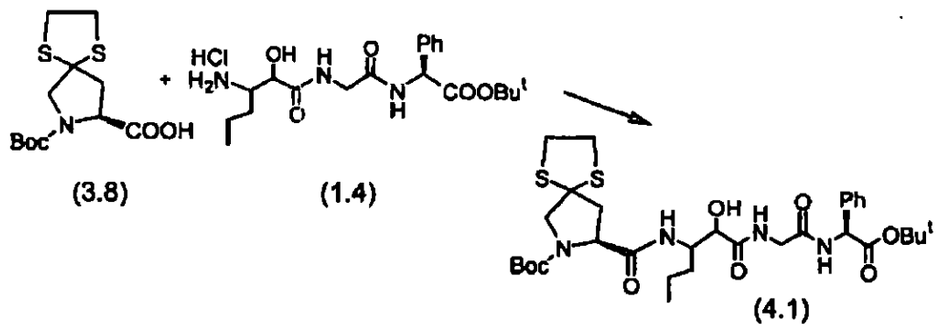


(3.7) (3.9)

Siguiendo esencialmente el mismo procedimiento del Ejemplo de Preparación 8, Paso E, sustituyendo el Compuesto (3.7) por el Compuesto (3.3) se obtuvo el compuesto producto (3.9).

Ejemplo de Preparación 10

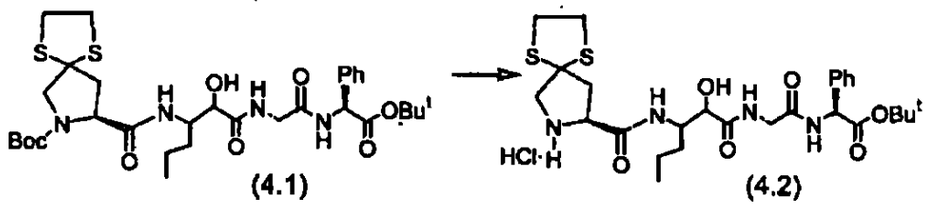
Paso A Compuesto (4.1)



(3.8) (1.4) (4.1)

En esencia del mismo modo que en el Ejemplo de Preparación 2, Paso A, se preparó el Compuesto (4.1) $C_{33}H_{48}N_4O_9S_2$ (708,89).

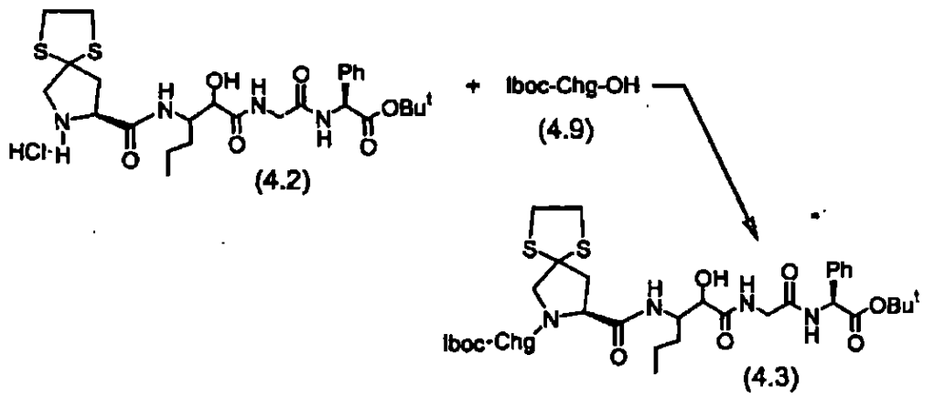
Paso B Compuesto (4.2)



(4.1) (4.2)

En esencia del mismo modo que en el Ejemplo de Preparación 2, Paso B, se preparó el Compuesto (4.2) espectro de masa (FAB) M+1 = 609,3.

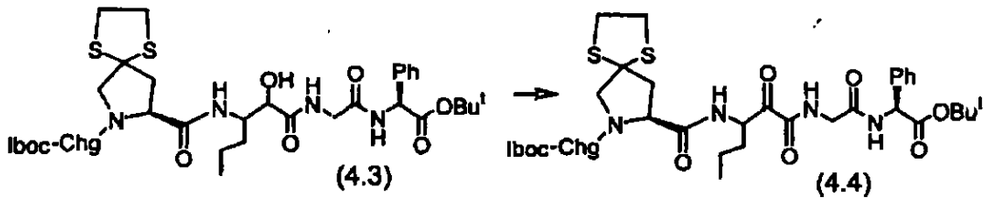
Paso C Compuesto (4.3)



(4.2) (4.9) (4.3)

En esencia del mismo modo que en el Ejemplo de Preparación 2, Paso A, se preparó el Compuesto (4.3), $C_{41}H_{61}N_5O_{10}S_2$ (708,89), espectro de masa (FAB) M+1 = 709,3.

Paso D Compuesto (4.4)

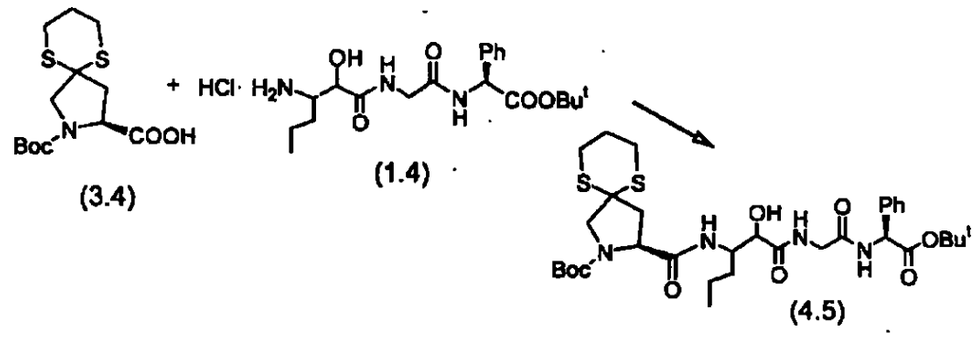


(4.3) (4.4)

En esencia del mismo modo que en el Ejemplo de Preparación 7, Paso A, se preparó el Compuesto (4.4).

Ejemplo de Preparación 11

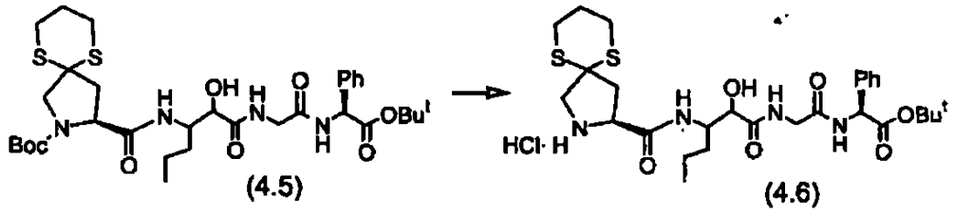
Paso A Compuesto (4.5)



(3.4) (1.4) (4.5)

En esencia del mismo modo que en el Ejemplo de Preparación 2, Paso A, se preparó el Compuesto (4.5).

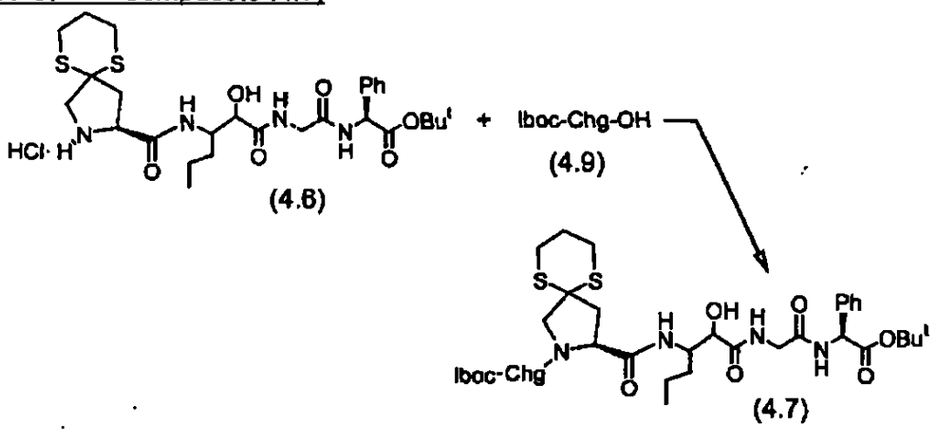
Paso B Compuesto (4.6)



(4.5) (4.6)

En esencia del mismo modo que en el Ejemplo de Preparación 2, Paso B, se preparó el Compuesto (4.6).

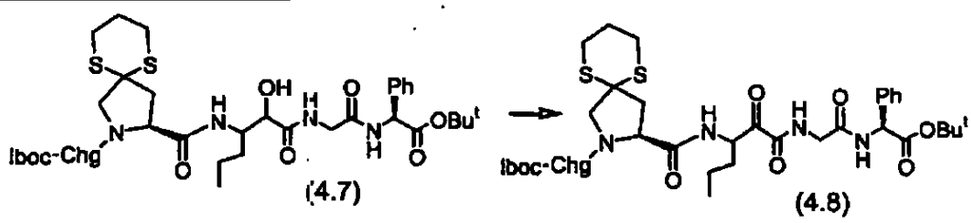
Paso C. Compuesto (4.7)



(4.6) (4.9) (4.7)

El Compuesto (4.9) del Ejemplo de Preparación 12, se reaccionó con el Compuesto (4.6) del Paso B anterior, en esencia del mismo modo que en el Ejemplo de Preparación 2, Paso A, para lograr el Compuesto (4.7).

Paso D. Compuesto (4.8)



(4.7) (4.8)

En esencia del mismo modo que en el Ejemplo de Preparación 7, Paso A, se preparó el Compuesto (4.8).

Ejemplo de Preparación 12

Compuesto (4.9)

i-BuOCOCl + H-Chg-OH ⟶ Iboc-Chg-OH

(4.01) (4.02) (4.9)

Una solución de L-ciclohexilglicina (4,02) (1,0 eq.), dimetilformamida (20 mL/g), y diisopropiletilamina (1,1 eq.) a 5°C se trata con cloroformiato de isobutilo (4,01) (1,1 eq.). El baño de frío se elimina y se agita durante 6 hr. La mezcla de reacción se vierte en 5% de KH_2PO_4 acuoso y se extrae con acetato de etilo (2 x). Los orgánicos combinados se lavan con 5% de K_2CO_3 acuoso frío, luego 5% de KH_2PO_4 acuoso, luego salmuera, y los orgánicos se secan sobre $MgSO_4$ anhidro. La mezcla se filtra, el filtrado se evapora al vacío, el residuo se cromatografía si es necesario o además el residuo se tritura con Et_2O-hexano, y filtra para dejar el compuesto del título (4,9), $C_{13}H_{23}NO_4$ (257,33).

Ejemplo de Preparación 13

Compuesto (13.1)

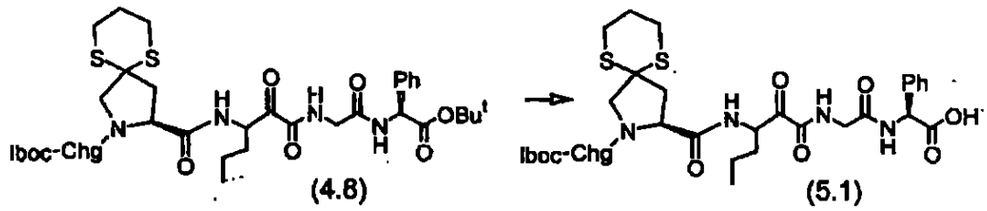
i-BuOCOCl + H-Thr(Bzl)-OH ⟶ Iboc-Thr(Bzl)-OH

(4.01) (13.02) (13.1)

En esencia del mismo modo que en el Ejemplo de Preparación 12, sustituyendo L-O-benciltreonina (13,02) (Wang et al, J. Chem. Soc., *Perkin Trans.* 1, (1997) No. 5, 621-624.) por L-ciclohexilglicina (4,02) se prepara el Compuesto

(13,1) $C_{16}H_{23}NO_5$ (309,36), espectro de masa (FAB) M+1 = 310,2.

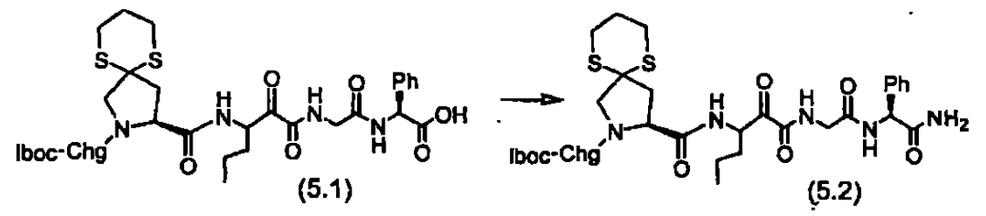
Ejemplo de Preparación 14



(4.8) (5.1)

El Compuesto (4.8) del Ejemplo de Preparación 11, Paso D (1,0 g) se reaccionó con una solución de ácido trifluoroacético anhidro-diclorometano (1:1, 50 mL) durante 2 hr. La solución se diluyó con xileno (100 mL) y se evaporó al vacío. El residuo se trituró con Et_2O, y se filtró para dejar el compuesto del título (5,1) (0,9 g), $C_{37}H_{53}N_5O_9S_2$ (775,98), espectro de masa (FAB) M+1 =776,5.

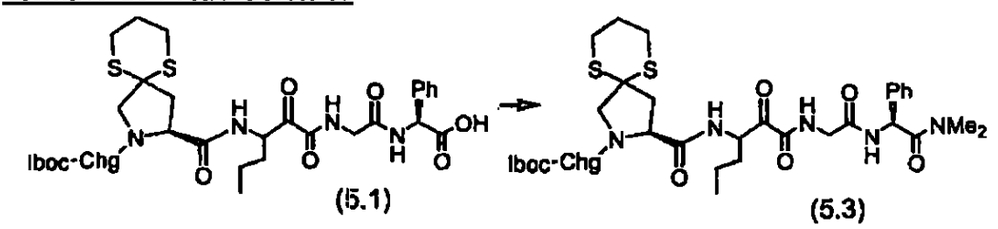
Paso B Compuesto (5.2)



(5.1) (5.2)

En esencia del mismo modo que en el Ejemplo de Preparación 2, Paso A, el Compuesto (5.1) se reaccionó con amoníaco (solución de 1,4-dioxano 0,5 M), para obtener el compuesto del título (5.2) $C_{37}H_{54}N_8O_8S_2$ (774,99), espectro de masa (FAB) M+1 = 775,4.

Ejemplo de Preparación 15



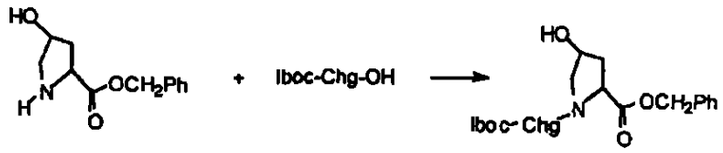
(5.1) (5.3)

Una mezcla del Compuesto (5.1) del Ejemplo de Preparación 14, Paso A (0,15 g), N,N-dimetilamina (0,12 mL de solución 2 M de THF), dimetilformamida

(10 mL), y Reactivo de acoplamiento PyBrOP (0,11 g) se enfrió hasta 5°C, luego se agregó diisopropiletilamina (DIEA o DIPEA, 0,12 mL). La mezcla se agitó fría durante 1 min., luego se agitó a temperatura ambiente durante 6 hr. La mezcla de reacción se vertió en 5% de H_3PO_4 acuoso, frío (50 mL) y se extrajo con acetato de etilo (2 x). Los orgánicos combinados se lavaron con 5% de K_2CO_3 acuoso frío, luego 5% de KH_2PO_4 acuoso, luego salmuera. La solución orgánica se secó sobre $MgSO_4$ anhidro, se filtró y se evaporó al vacío. El residuo se cromatografió sobre gel de sílice, eluyendo con MeOH-CH_2Cl_2 para lograr el compuesto del título (5.3), $C_{39}H_{58}N_6O_8S_2$ (303,05), espectro de masa (FAB) M+1 =803,5.

Ejemplo de Preparación 16

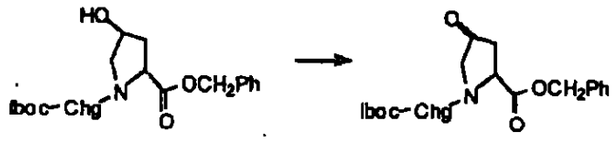
Paso A Compuesto (6.2)



(6.1) 4.9) (6.2)

En esencia del mismo modo que en el Ejemplo de Preparación 2, Paso A, el Compuesto (6.1), bencil éster de hidroxiprolina, clorhidrato se reaccionó con el Compuesto (4.9) del Ejemplo de Preparación 12, para obtener el compuesto del título (6.2), $C_{25}H_{36}N_2O_6$ (460,56), espectro de masa (FAB) M+1 = 461,2.

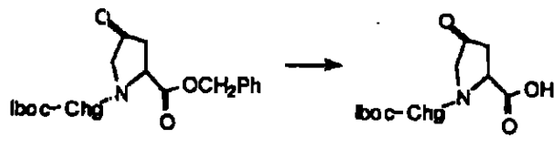
Paso B Compuesto (6.3)



(6.2) (6.3)

En esencia del mismo modo que en el Ejemplo de Preparación 8, se preparó el Compuesto (6.3), $C_{25}H_{34}N_2O_6$ (458,55), espectro de masa (FAB) M+1 = 459,2.

Paso C Compuesto (6.4)

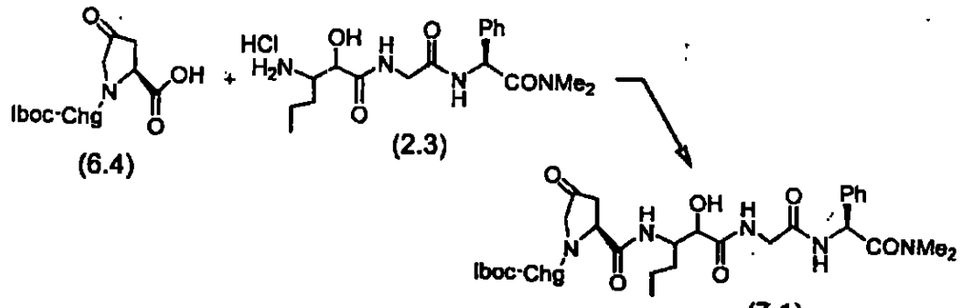


(6.3) (6.4)

Una mezcla del Compuesto (6.3) del Paso B (1 g), 10% de Pd/C (0,05 g), y EtOH (100 mL) se agitó bajo 1 atm. H_2 durante 6 hr. La mezcla se filtró, y se evaporó hasta secar al vacío para dejar el compuesto del título (6.4) (0,77 g), $C_{18}H_{28}N_2O_6$ (368,42) espectro de masa (FAB) M+1 = 369,2.

Ejemplo de Preparación 17

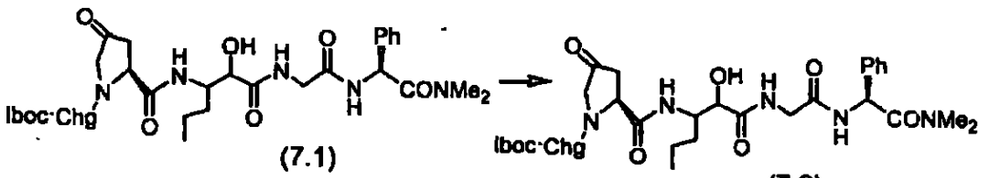
Paso A Compuesto (7.1)



(6.4) (2.3) (7.1)

El Compuesto (6.4) del Ejemplo de Preparación 16, Paso C, se reaccionó con el Compuesto (2.3) del Ejemplo de Preparación 6, Paso B, en esencia del mismo modo que en el Ejemplo de Preparación 2, Paso A, para lograr el Compuesto (7.1), $C_{36}H_{54}N_6O_9$ (714,85), espectro de masa (FAB) M+1 = 715,9.

Paso B Compuesto (7.2)

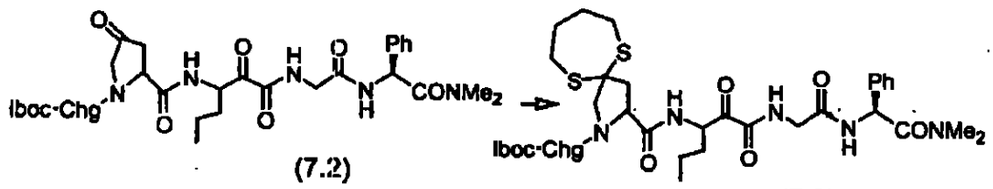


(7.1) (7.2)

El Compuesto (7.1) se reaccionó en esencia del mismo modo que en el Ejemplo de Preparación 7, Paso A, para lograr el Compuesto (7.2), $C_{36}H_{52}N_6O_9$

(712,83), espectro de masa (FAB) M+1 = 713,5.

Paso C Compuesto (7.3)



El Compuesto (7.2) del Paso B anterior, se reaccionó en esencia del mismo modo que en el Ejemplo de Preparación 8, Paso B, con 1,4-butanditiol, para obtener el compuesto del título (7.3), $C_{40}H_{60}N_6O_6S_2$ (817,07), espectro de masa (FAB) M+1 = 817,5.

Usando los procedimientos observados anteriormente y descritos aquí, se prepararon los compuestos de las Tablas 2 hasta 6 anexas. Como nota general para todas las Tablas (1 hasta 6) que se adjuntan como también para los Ejemplos y los Esquemas de esta memoria descriptiva, cualquier átomo de nitrógeno con extremo abierto con valencia no completa en las estructuras químicas de los Ejemplos y las Tablas se refiere a NH, o en el caso de un nitrógeno terminal, $-NH_2$. De modo similar, cualquier átomo de oxígeno con extremo abierto con valencia no completa en las estructuras químicas de los Ejemplos y las Tablas se refiere a -OH y cualquier átomo de carbono con extremo abierto con valencia no completa se llena apropiadamente con -H.

Síntesis en Fase Sólida:

Procedimiento General para reacciones de acoplamiento en fase sólida.

La síntesis se realizó en un recipiente de reacción que se construyó a partir de un cartucho de jeringa de polipropileno provisto de una frita de polipropileno en la parte inferior. Los aminoácidos F-moc-protegidos se acoplaron con técnicas estándar de fase sólida. Cada recipiente de reacción se cargó con 100 mg la resina inicial Fmoc-Sieber (aproximadamente 0,03 mmol). La resina se lavó con porciones de 2 mL de DMF (2 times). El grupo protector Fmoc se eliminó

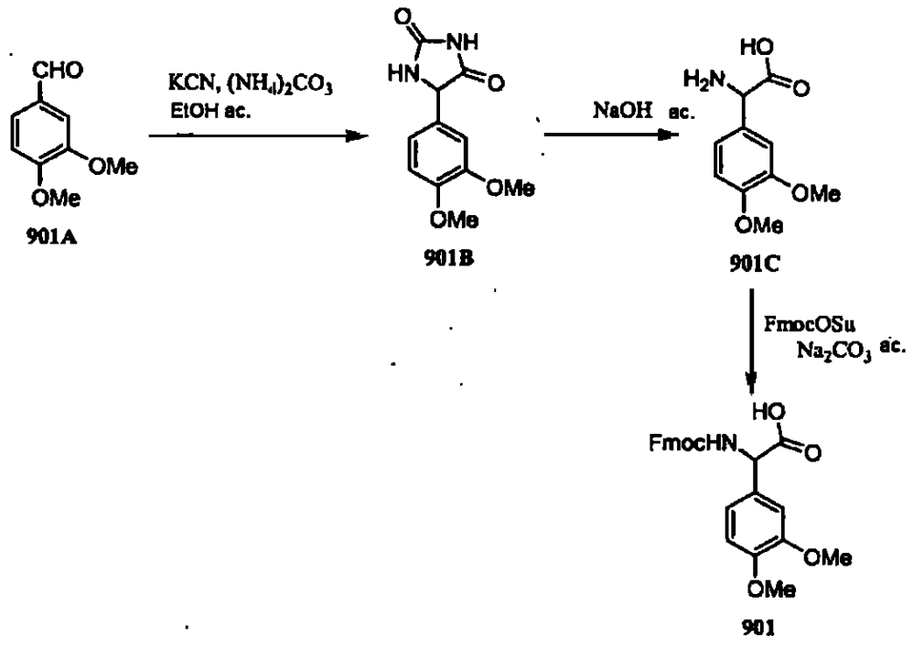
a través de tratamiento con 2 mL de una solución a 20 % v/v de piperidina en DMF durante 20 min. La resina se lavó con porciones de 2 mL de DMF (4 times). El acoplamiento se realizó en DMF (2 mL), usando 0,1 mmol de aminoácido Fmoc, 0,1 mmol de HATU hexafluorofosfato de [O-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio] y 0,2 mmol de DIPEA (N,N-diisopropiletilamina). Luego de agitar durante 2 h, el recipiente de reacción se drenó y la resina se lavó con porciones de 2 mL de DMF (4 veces). El ciclo de acoplamiento se repitió con el siguiente aminoácido Fmoc o grupo de extremo.

Procedimiento general para la oxidación de fase sólida de Dess-Martin.

La síntesis se condujo en un recipiente de reacción que se construyó a partir de un cartucho de jeringa de polipropileno provisto de una frita de polipropileno en la parte inferior. El compuesto hidroxi unido a la resina (aproximadamente 0,03 mmol) se trató con una solución de 0,12 mmol de periodinano de Dess-Martin y 0,12 mmol de t-BuOH en 2 mL de DCM durante 4 h. La resina se lavó con porciones de 2 mL de una solución a 20% v/v de iPrOH en DCM, THF, una solución a 50 % v/v de THF en agua (4 veces), THF (4 veces) y DCM (4 veces).

Ejemplo de Preparación 18

Preparación de N-Fmoc-2',3'-dimetoxifenilalicina Compuesto (901)

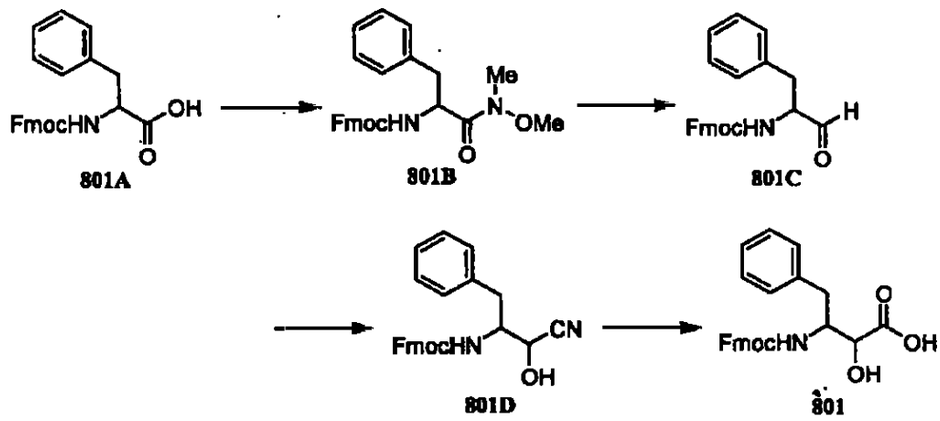


A una solución de cianuro de potasio (1,465 g, 22,5 mmol) y carbonato de amonio (5,045 g, 52,5 mmol) en agua (15 mL) se agregó una solución de 2,3-dimetoxibenzaldehído **901A** (2,5 g, 15 mmol) en etanol (15 mL). La mezcla de reacción se calentó a 40 °C durante 24 h. El volumen de la solución se redujo hasta 10 mL por sobre MgSO4 bajo presión reducida. Se agregó ácido clorhídrico concentrado (15 mL) y se obtuvo el compuesto **901 B** como un precipitado blanco. El Compuesto **901 B** se aisló por filtración (2,2 g, 9,3 mmol). El Compuesto **901 B** se disolvió en 10 % p/p de solución acuosa de hidróxido de sodio (15 mL) y la solución resultante se calentó a reflujo durante 24 h. Se agregó ácido clorhídrico concentrado y el pH se ajustó a neutro (pH 7). La solución resultante que contenía el compuesto **901 C** se evaporó bajo presión reducida. El residuo se disolvió en 5 % p/p de solución acuosa de bicarbonato de sodio (150 mL). La solución se enfrió hasta 0°C en un baño de hielo y 1,4-dioxano (30 mL) y una solución de 9-fluorenilmetil succinimidil carbonato (2,7 g, 8 mmol) en 1,4-dioxano (30 mL) se agregó a 0°C. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó a temperatura ambiente

durante 24 h. El 1,4-dioxano se evaporó bajo presión reducida. La solución acuosa se lavó con éter dietílico. Se agregó ácido clorhídrico concentrado y el pH se ajustó a ácido (pH 1). Se agregó acetato de etilo, la fase orgánica se lavó con agua y salmuera. La fase orgánica se secó sobre sulfato de sodio anhidro. El solvente se evaporó bajo presión reducida para lograr el compuesto deseado 901 como un sólido blanco con aspecto de espuma (3,44 g, 7,9 mmol). MS (LCMS-Electroaspersión) 434,1 MH+.

Ejemplo de Preparación 19

Compuesto (801)



A una solución de N-Fmoc-fenilalanina **801A** (5 g, 12,9 mmol) en DCM anhidro (22 mL) enfriada hasta -30°C en un baño de hielo seco-acetona se agregó N-metilpirrolidina (1,96 mL, 16,1 mmol) y cloroformiato de metilo (1,2 mL, 15,5 mmol) en forma secuencial. La mezcla de reacción se agitó a -30°C durante 1 h y una solución de se agregó Clorhidrato de N,O-dimetilhidroxilamina (1,51 g, 15,5 mol) y N-metilpirrolidina (1,96 mL, 16,1 mmol) en DCM anhidro (8 mL). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó a temperatura ambiente durante la noche. Se agregó tolueno y la fase orgánica se lavó con ácido clorhídrico diluido, solución acuosa de bicarbonato de sodio y salmuera. La fase orgánica se secó sobre sulfato de sodio anhidro. El solvente se evaporó bajo presión reducida para lograr el compuesto **801 B** (4 g,

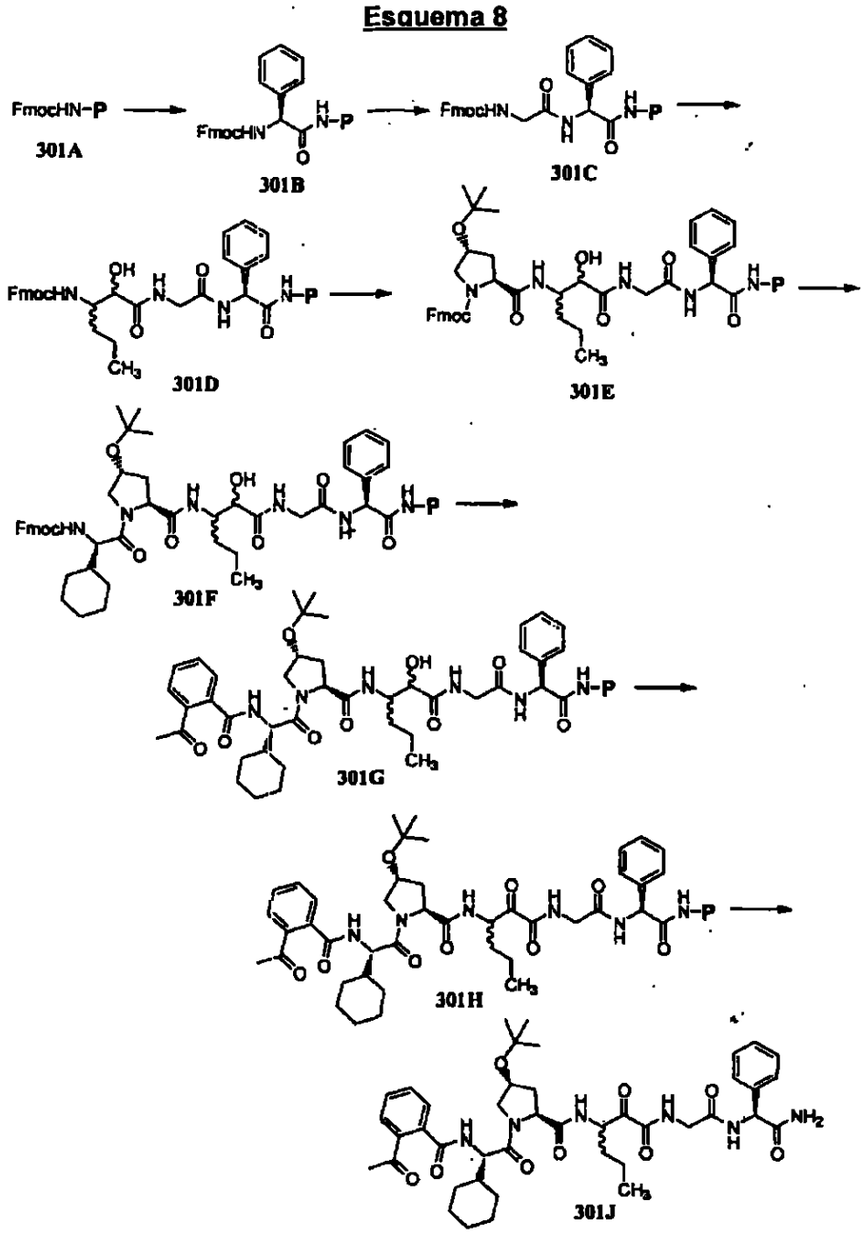
9,29 mmol).

A una solución de Red-Al (6,28 mL, 21,4 mmol) en tolueno anhidro (8 mL) enfriada hasta -20°C en un baño de hielo seco-acetona se agregó una solución del compuesto **801B** (4 g, 9,29 mmol) en tolueno anhidro (12 mL). La mezcla de reacción se agitó a -20 °C durante 1,5 h. La fase orgánica se lavó con ácido clorhídrico diluido, solución acuosa de bicarbonato de sodio y salmuera. La fase orgánica se secó sobre sulfato de sodio anhidro. El solvente se evaporó bajo presión reducida y el producto en bruto **801C** se usó en la siguiente reacción sin purificación adicional.

A una solución del compuesto **801C** (aprox. 9,29 mmol) en hexano (15 mL) se agregó una solución de cianuro de potasio (24 mg, 0,37 mmol) y yoduro de tetrabutilamonio (34 mg, 0,092 mmol) en agua (4 mL) y cianohidrina de acetona (1,27 mL, 13,9 mmol) en forma secuencial. La mezcla de reacción se agitó a temperatura ambiente durante 24 h. Se agregó acetato de etilo y la fase orgánica se lavó con agua y salmuera. La fase orgánica se secó sobre sulfato de sodio anhidro. El solvente se evaporó bajo presión reducida para lograr el Compuesto **801 D** (2,4 g, 6,03 mmol).

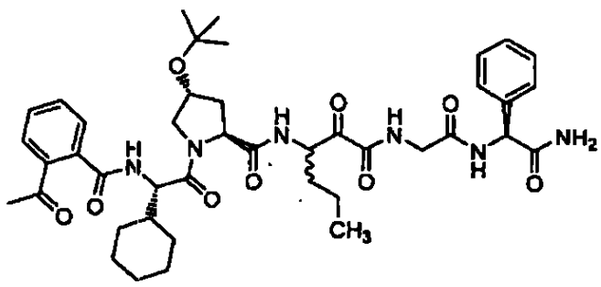
A una solución del compuesto **801 D** (2,4 g, 6,03 mmol) en 1,4-dioxano (11 mL) se agregó ácido clorhídrico concentrado (11 mL). La mezcla de reacción se calentó a 80 °C durante 3 h. Acetato de etilo (25 mL) y agua (25 mL) se agregó. La fase orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. El solvente se evaporó bajo presión reducida para lograr el compuesto deseado **801** como un sólido blanco con aspecto de espuma (2 g, 4,8 mmol). MS (LCMS-Electroaspersión) 418,1 MH^+.

Esquema 8



Ejemplo (301J):

Esquema 8 Compuesto (301J)



(301J)

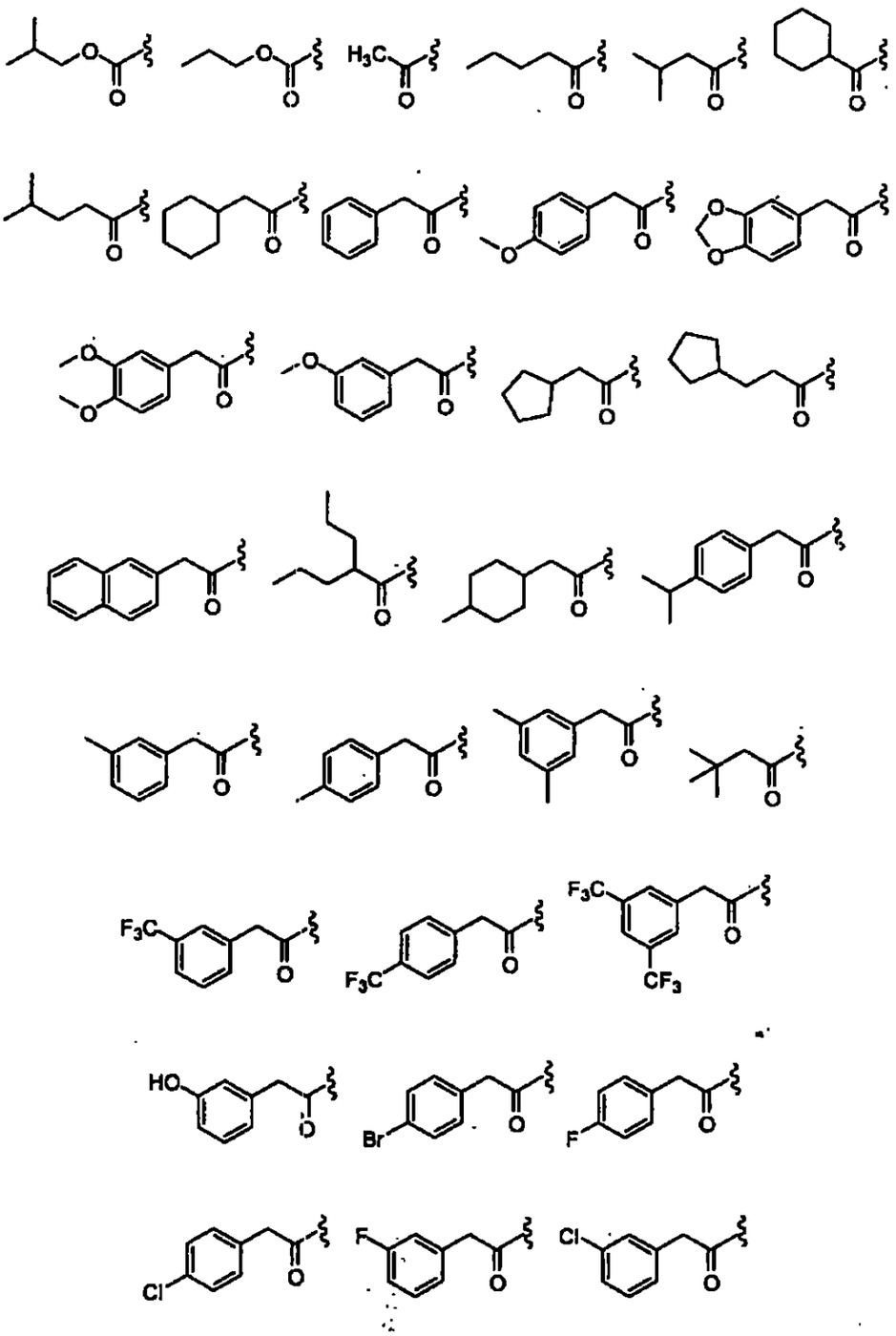
Los compuestos unidos a la resina **301 B, 301 C, 301 D, 301 E, 301 F** y **301 G** se prepararon de acuerdo con el procedimiento general para las reacciones de acoplamiento en fase sólida comenzando con 100 mg de resina de Fmoc-Sieber (0,03 mmol). El compuesto unido a la resina **301 G** se oxidó al compuesto unido a la resina **301H** de acuerdo con el procedimiento general para la oxidación de Dess-Martin en fase sólida. El compuesto unido a la resina **301 H** se trató con 4 mL de una solución a 2 % v/v de TFA en DCM durante 5 min. El filtrado se agregó a 1 mL de AcOH y la solución se concentró por centrifugado al vacío para dar el compuesto **301J** (0,0069 g, 29 % de rendimiento). MS (LCMS-Electroaspersión) 771,2 M H^+.

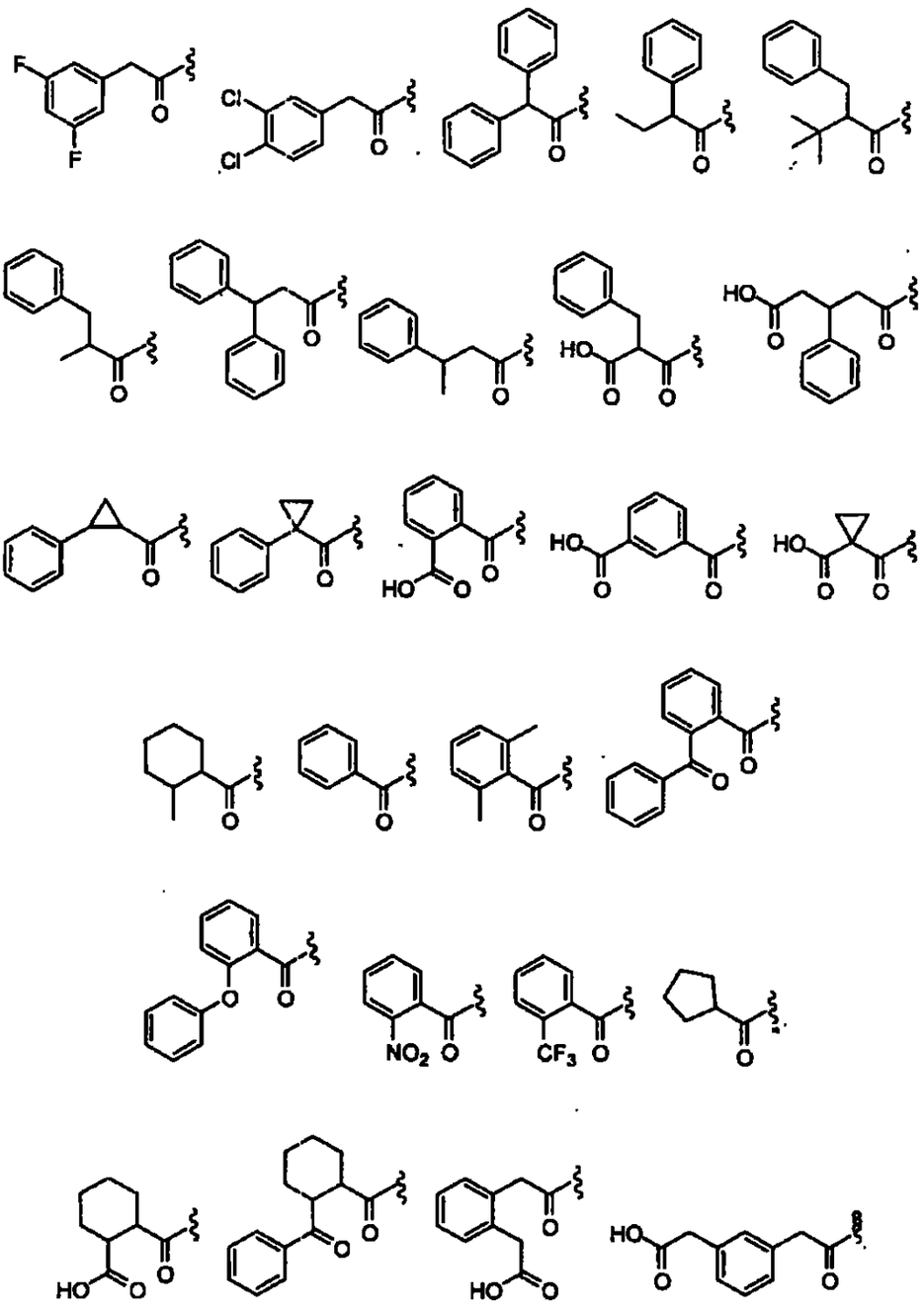
Usando las técnicas de síntesis en fase sólida detalladas anteriormente, y los siguientes restos para los diferentes grupos funcionales en el compuesto de Fórmula 1, se prepararon los compuestos de la **Tabla 3**:

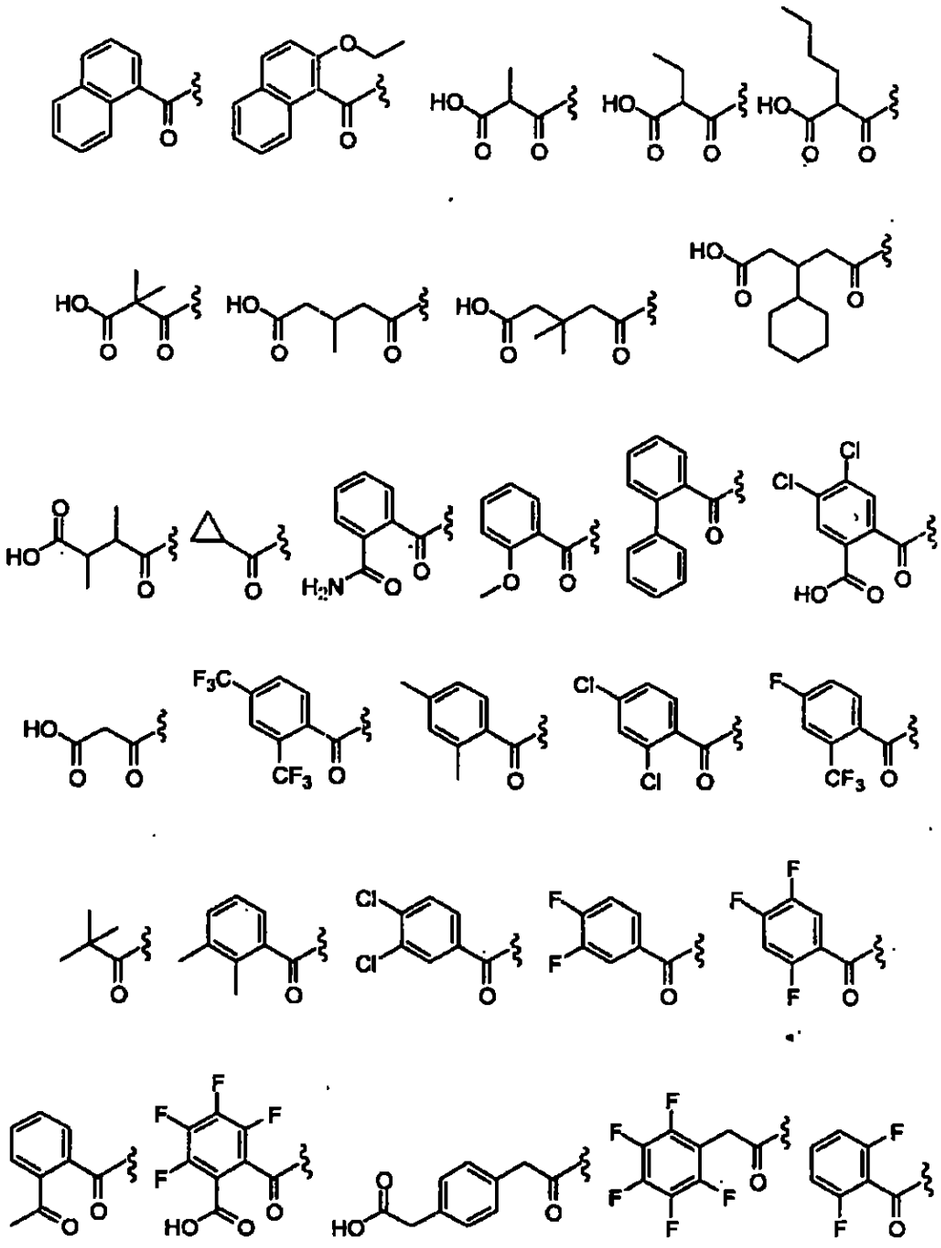
-W-:

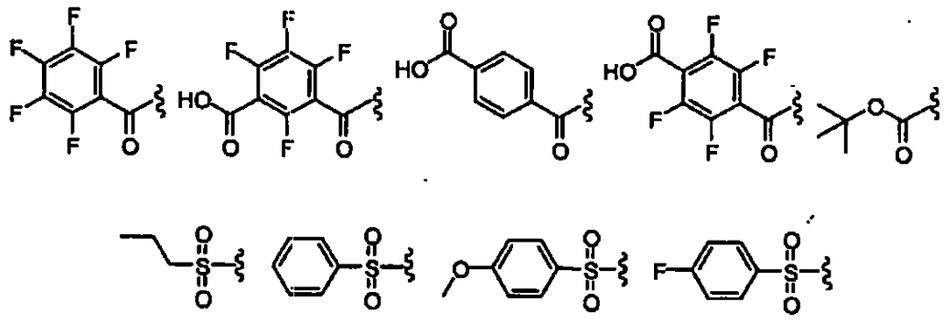


Y-W-:









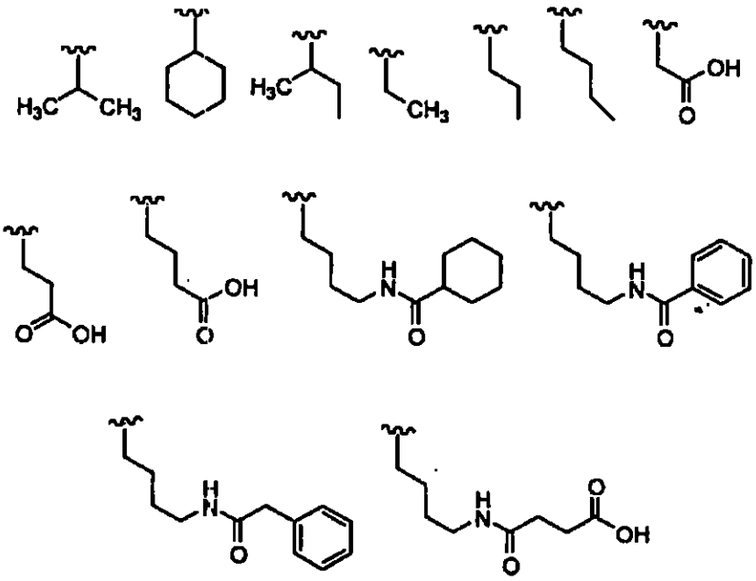
-R^4:

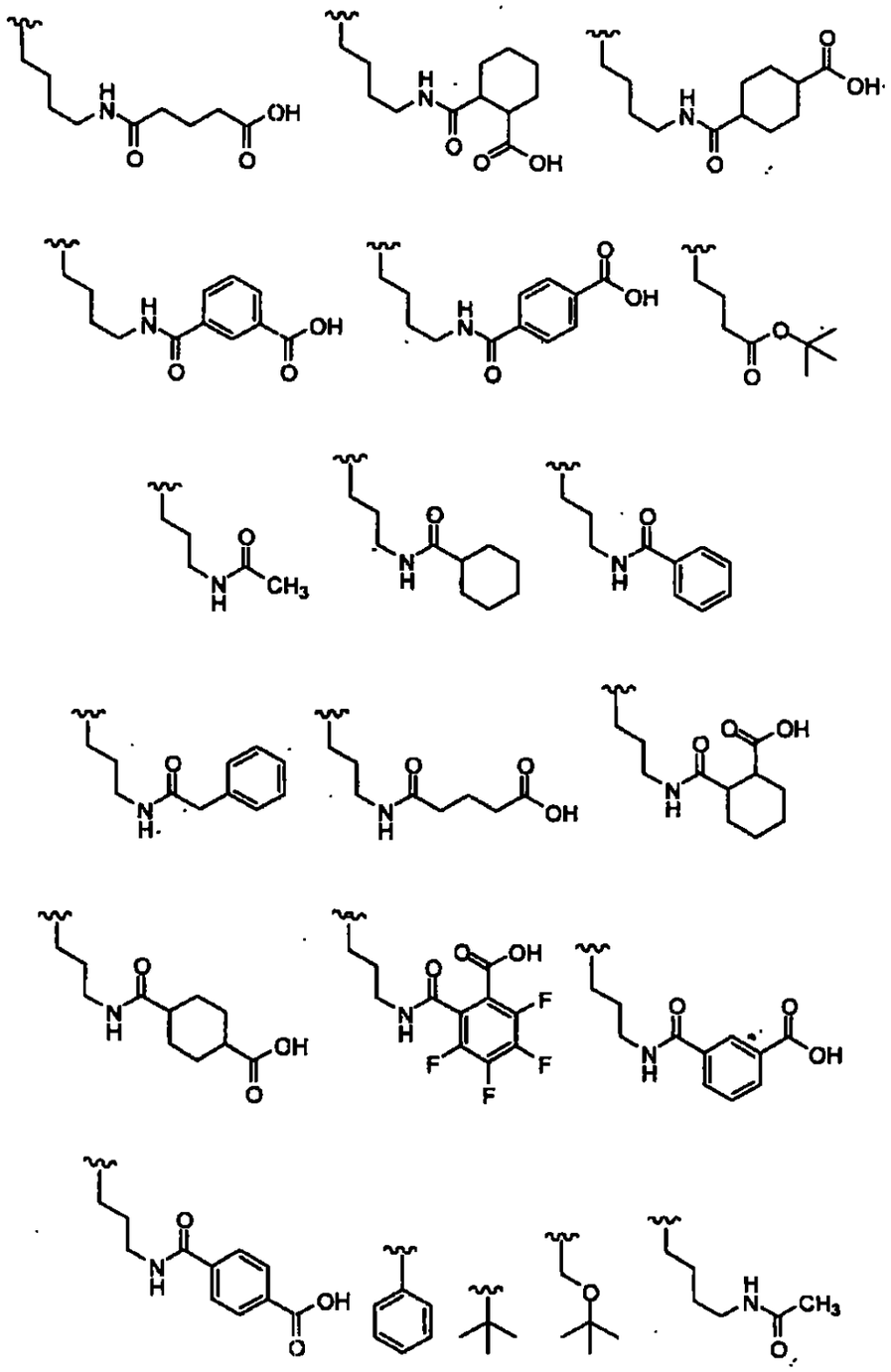


-Z-:

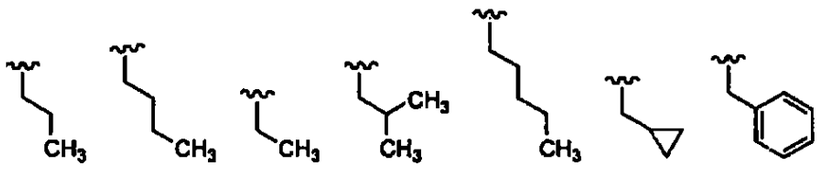


-R^3:





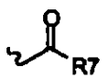
-R^2:



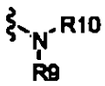
-R^1:



-R^5:



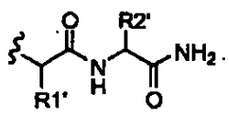
-R^7:



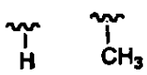
-R^9:



-R^{10}:



-$R^{1'}$:



-$R^{2'}$:

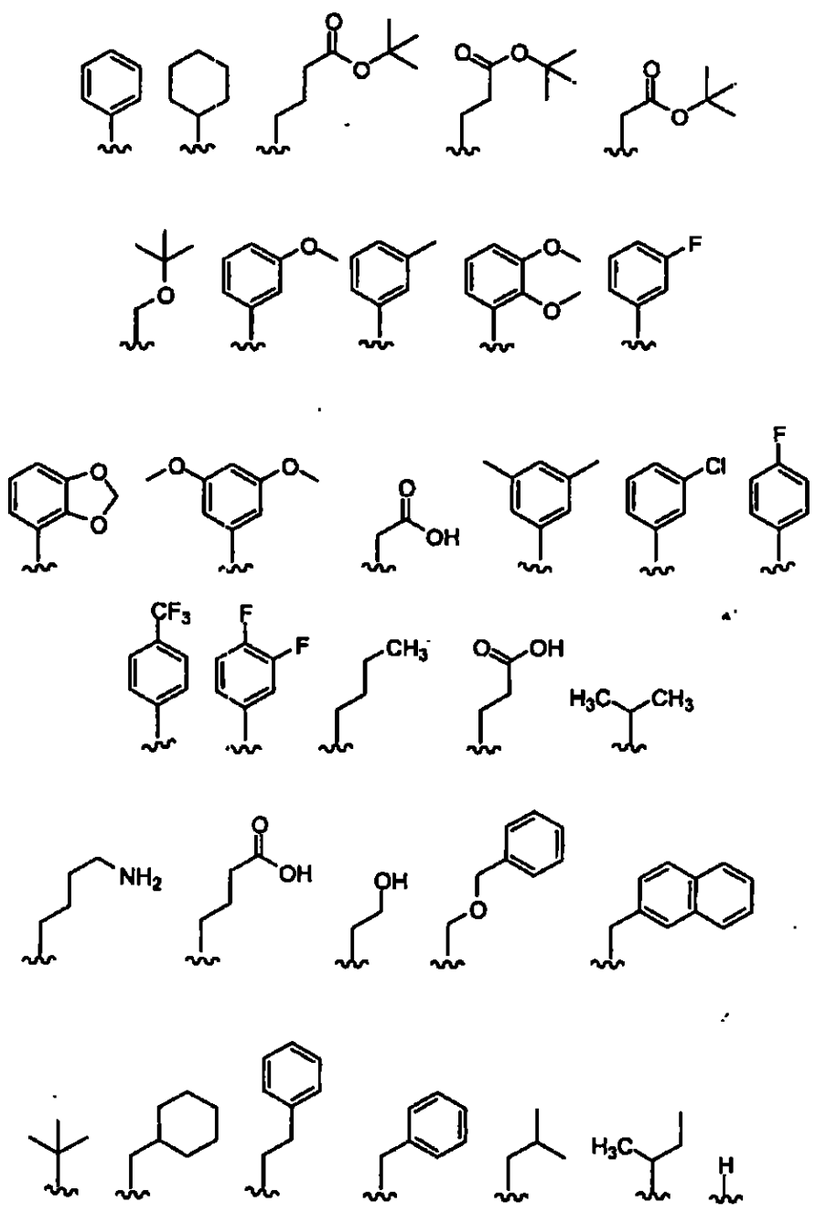
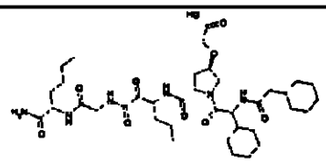
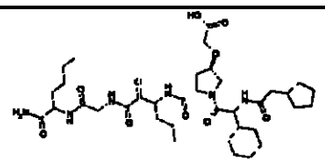
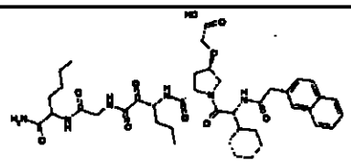
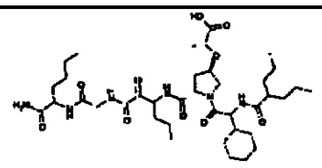
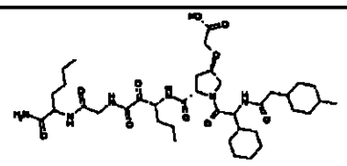
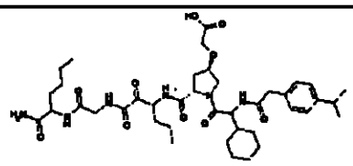
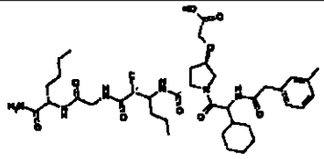
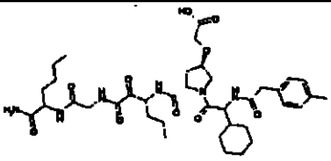
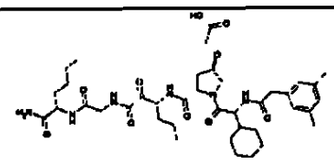
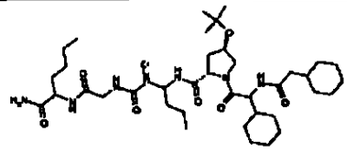
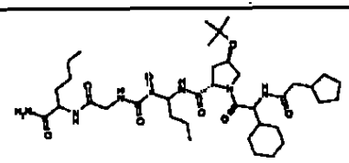
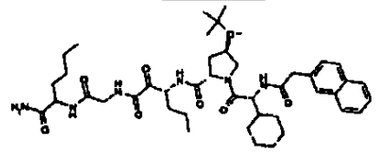
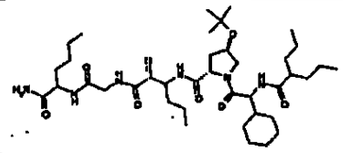
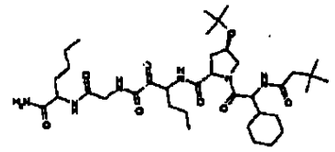
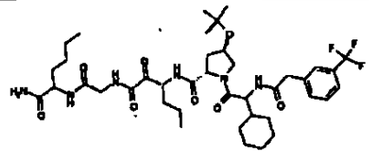
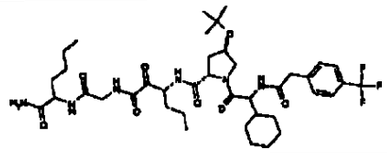
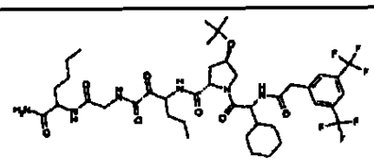
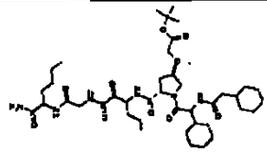
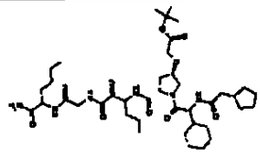
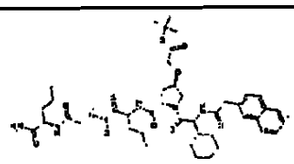
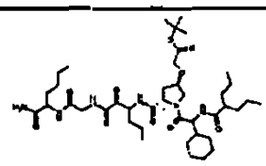
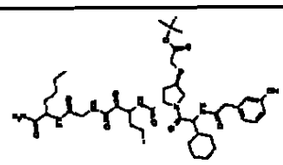
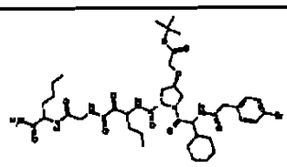
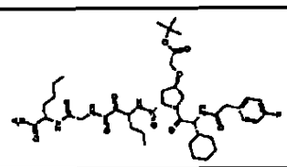


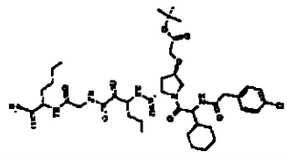
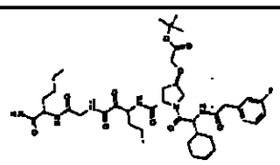
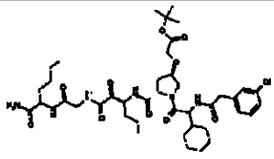
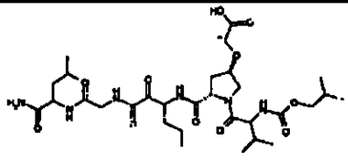
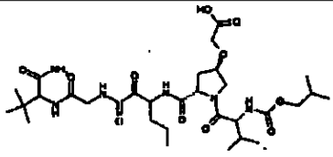
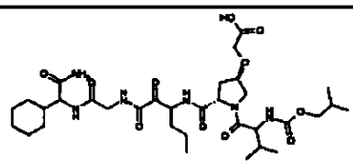
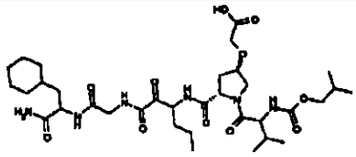
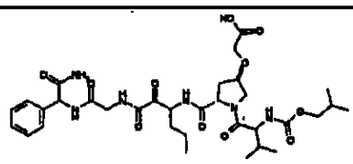
Tabla 3: Compuestos preparados a través de Síntesis en Fase Sólida

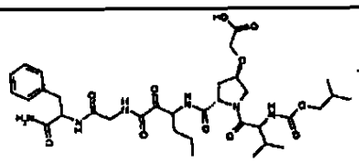
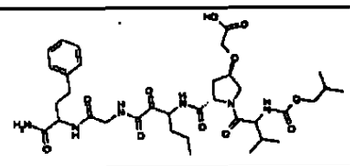
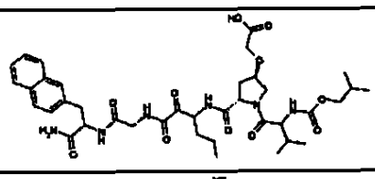
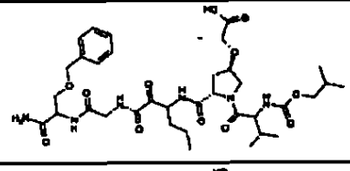
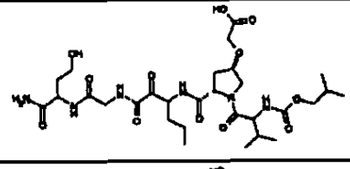
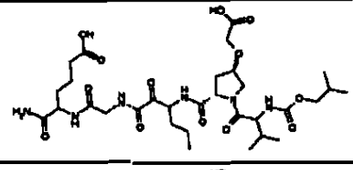
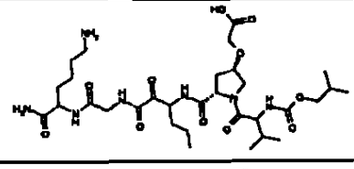
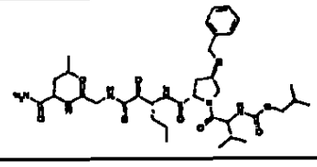
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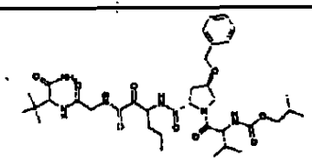
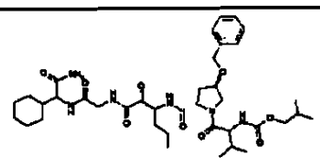
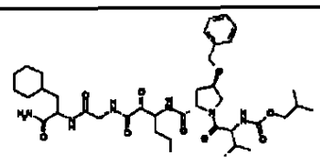
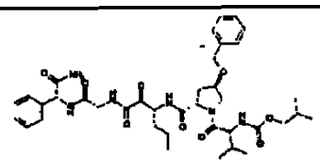
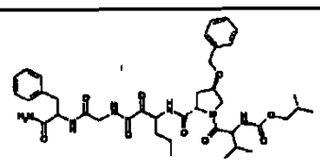
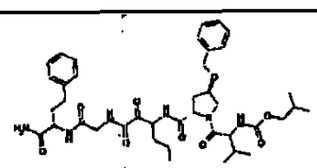
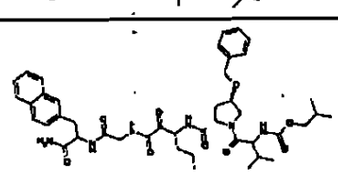
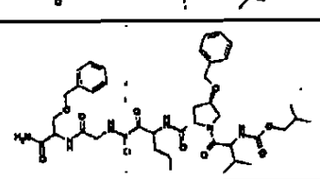
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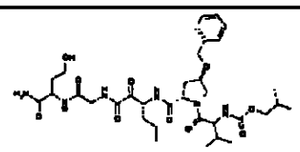
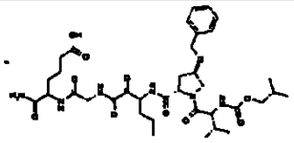
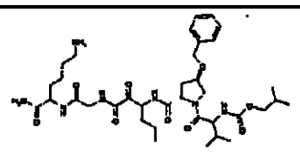
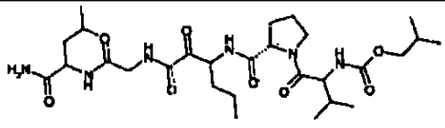
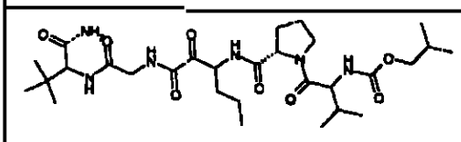
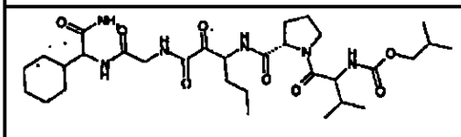
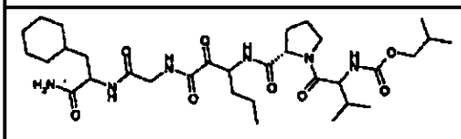
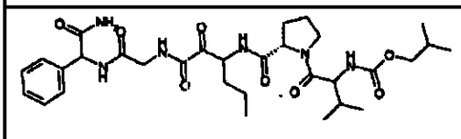
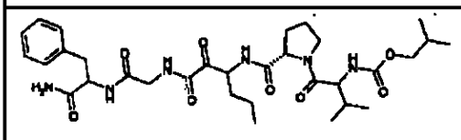
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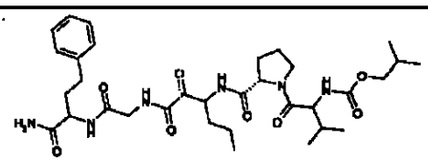
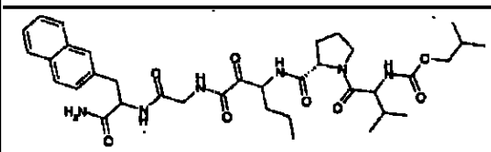
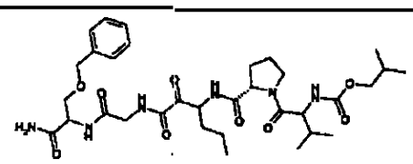
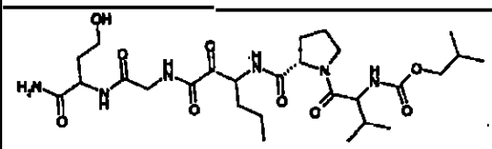
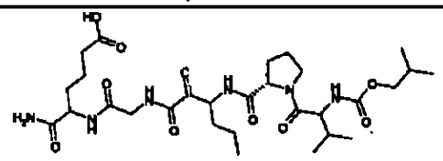
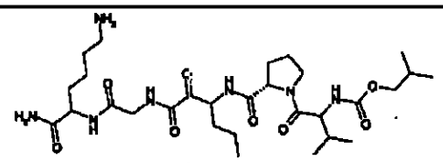
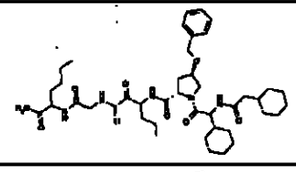
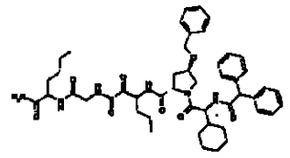
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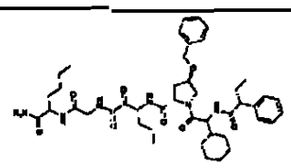
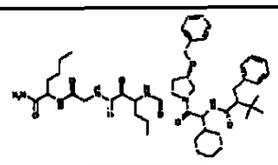
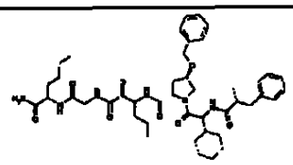
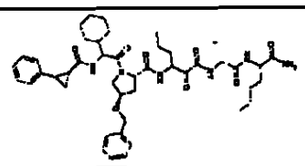
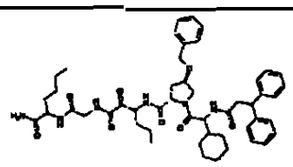
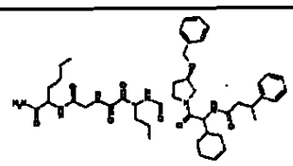
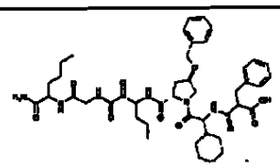
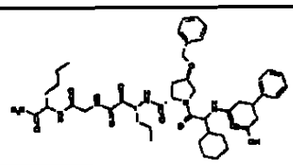
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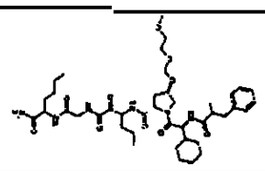
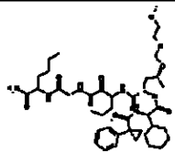
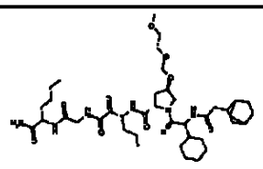
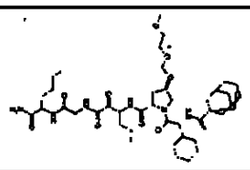
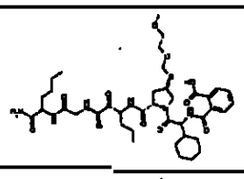
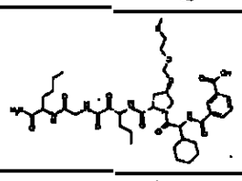
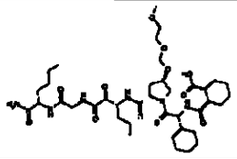
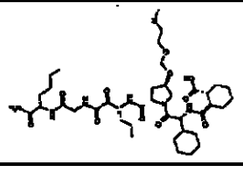
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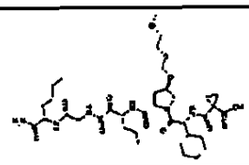
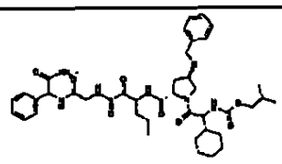
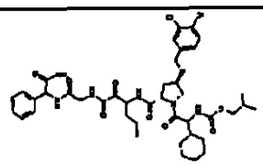
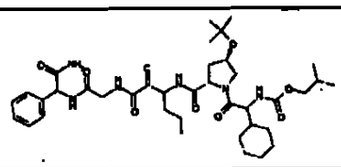
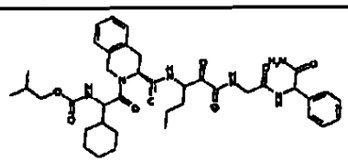
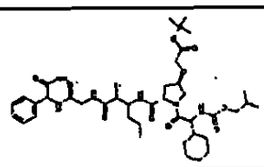
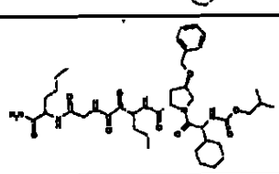
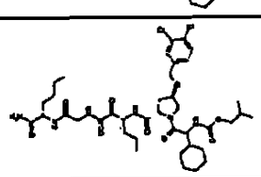
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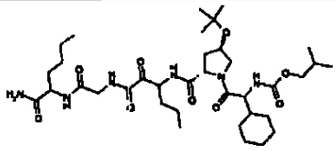
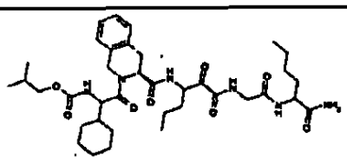
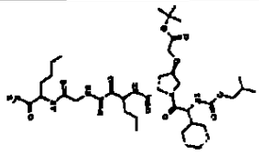
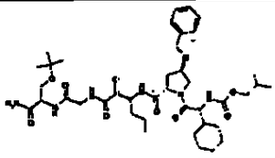
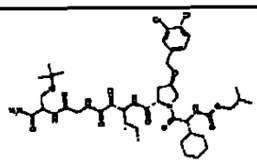
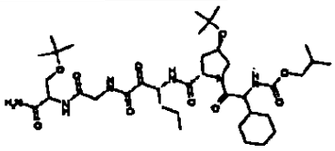
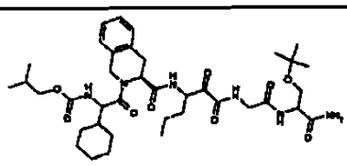
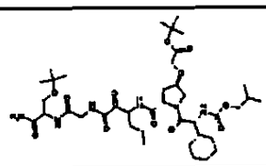
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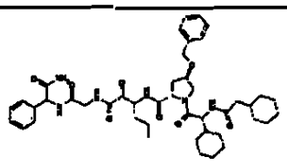
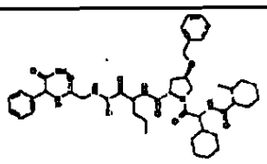
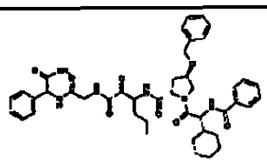
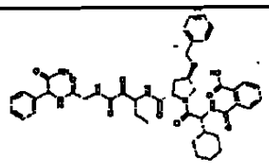
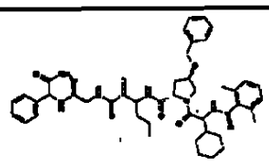
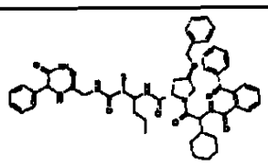
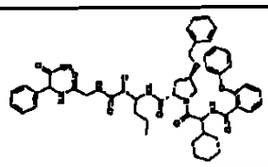
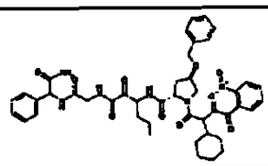
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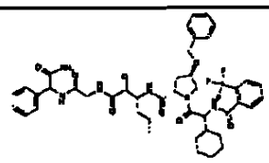
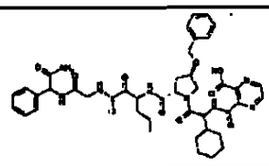
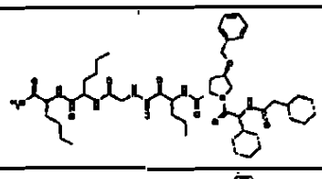
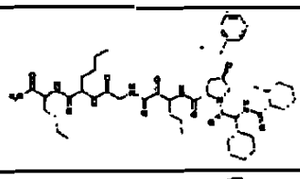
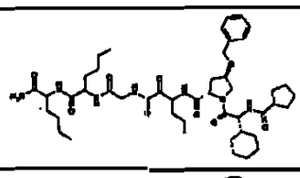
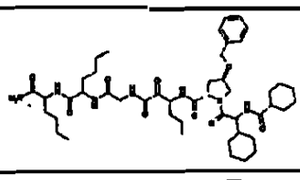
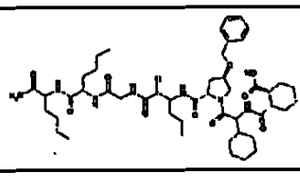
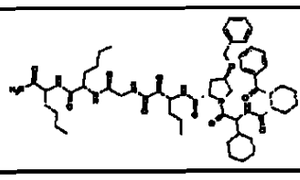
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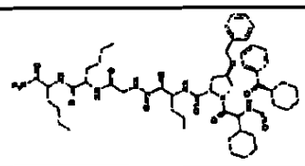
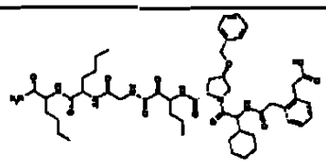
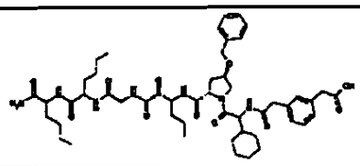
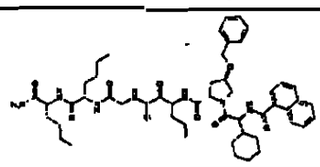
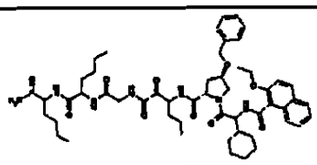
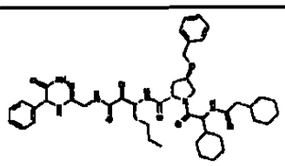
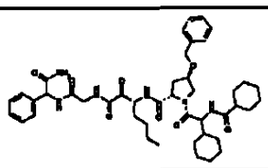
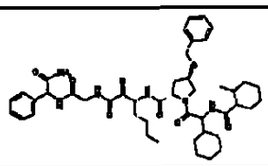
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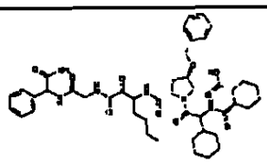
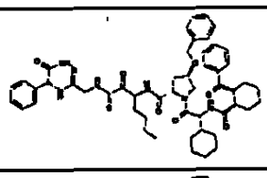
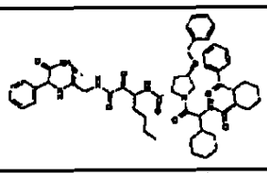
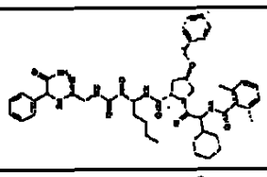
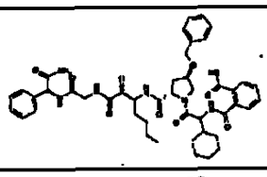
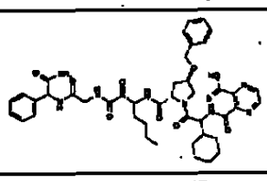
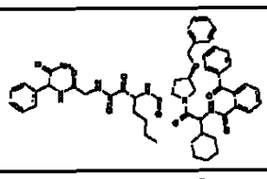
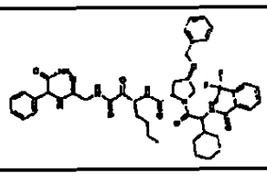
ESTRUCTURA	CLASE DE KI* ;
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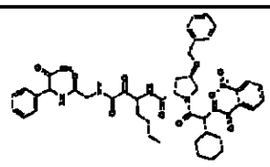
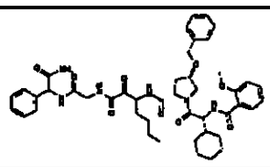
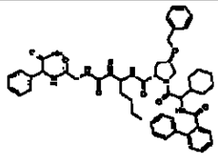
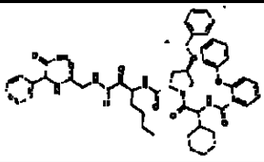
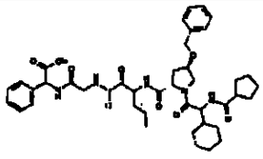
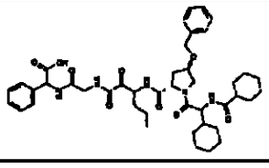
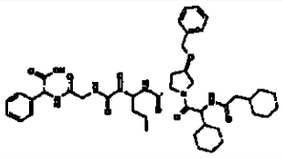
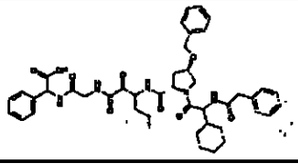
ESTRUCTURA	CLASE DE KI*
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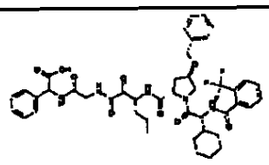
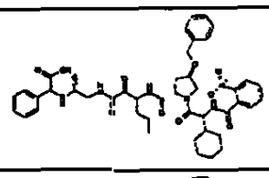
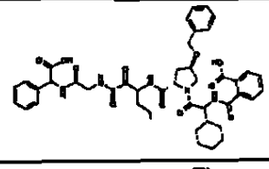
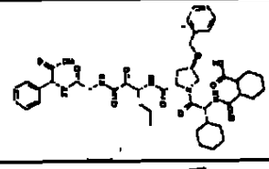
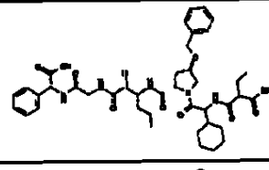
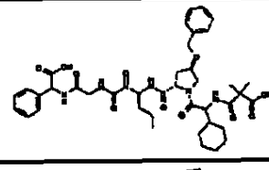
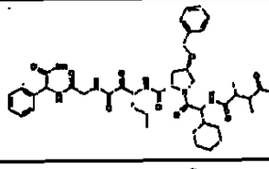
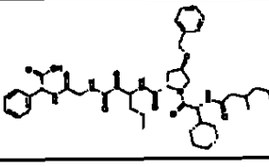
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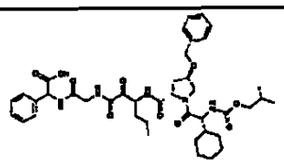
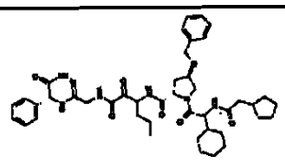
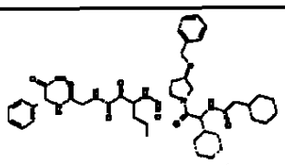
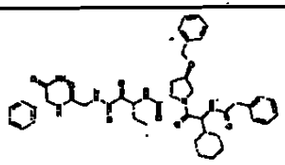
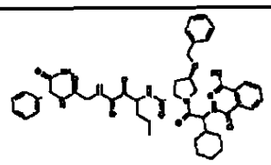
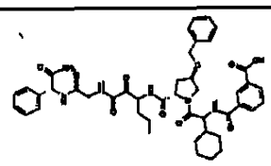
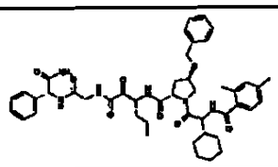
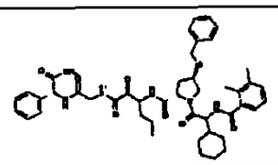
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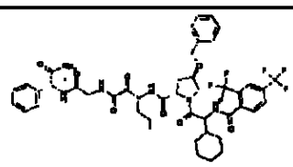
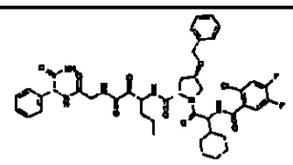
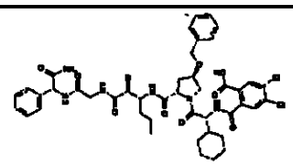
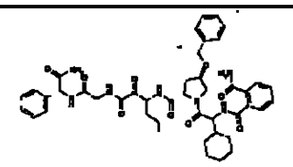
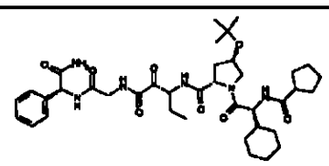
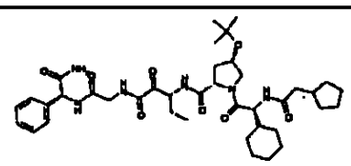
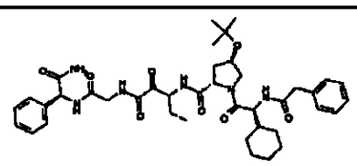
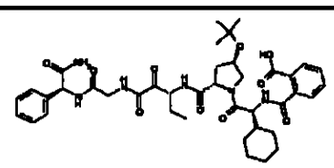
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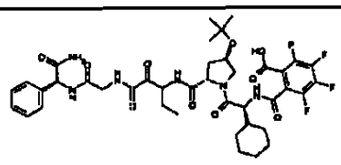
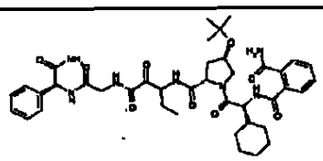
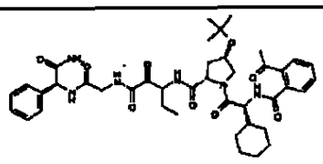
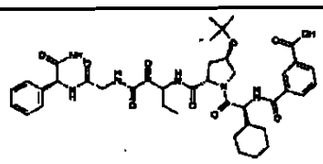
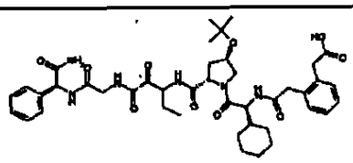
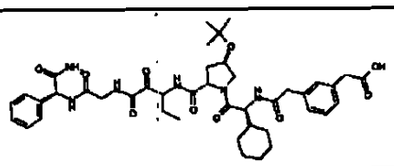
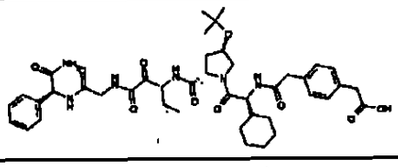
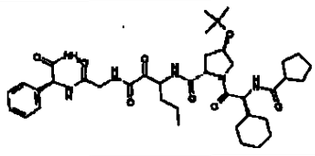
ESTRUCTURA	CLASE DE Ki*
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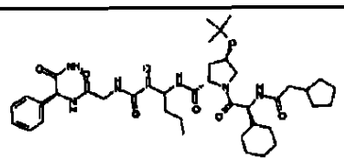
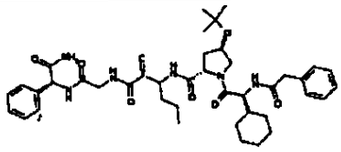
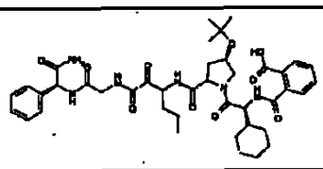
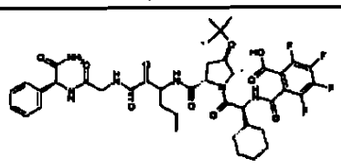
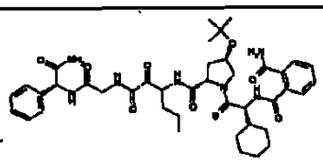
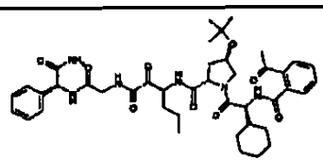
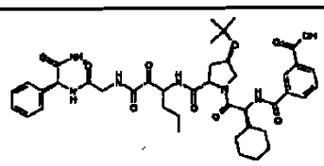
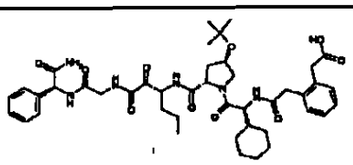
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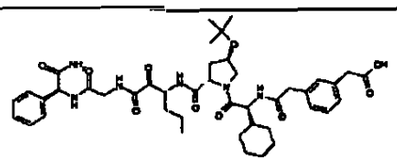
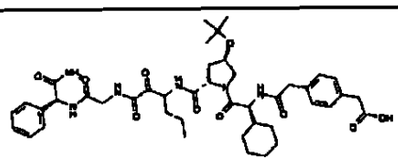
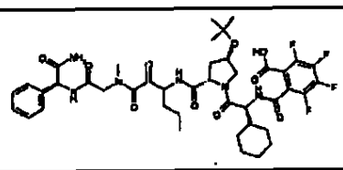
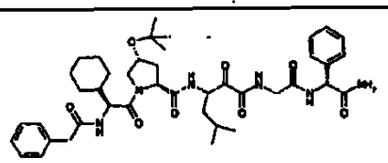
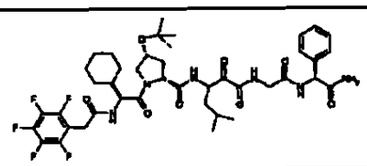
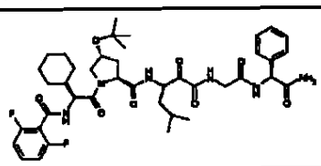
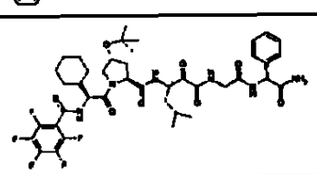
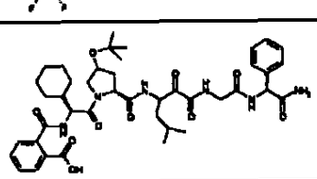
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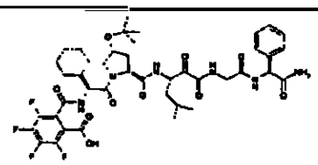
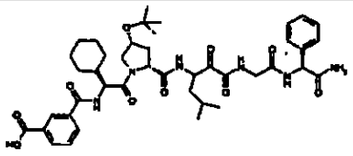
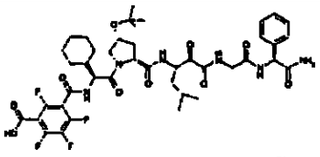
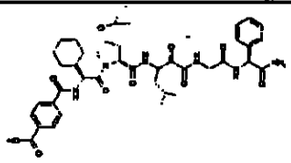
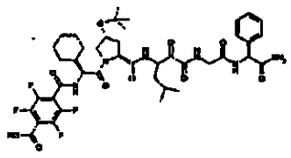
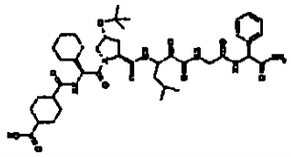
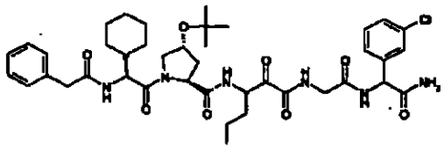
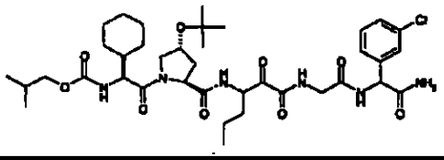
ESTRUCTURA	CLASE DE KI*
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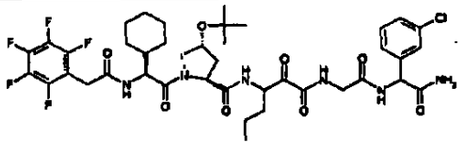
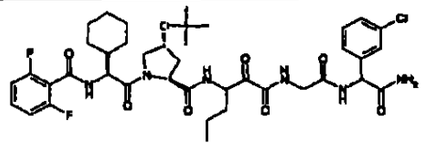
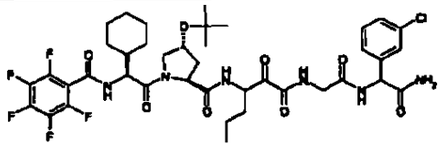
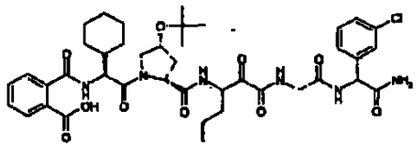
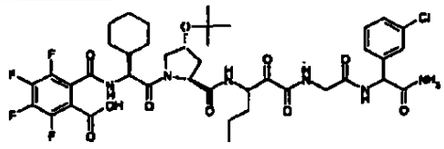
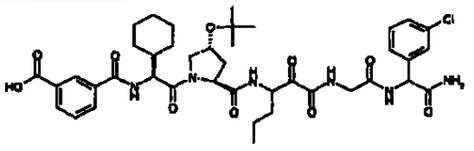
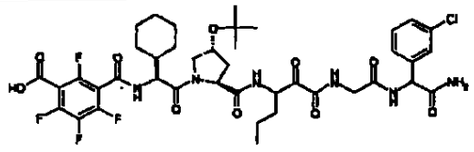
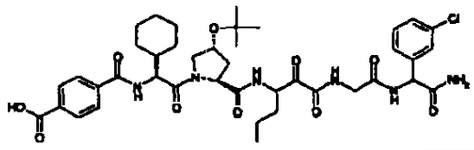
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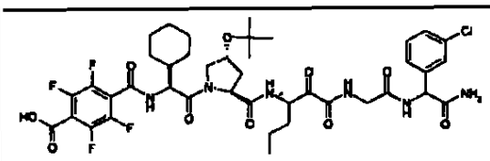
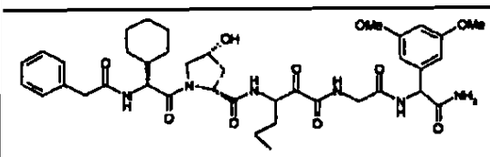
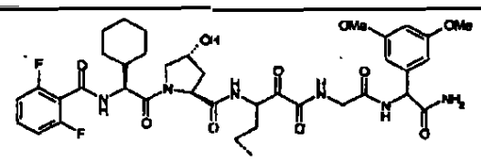
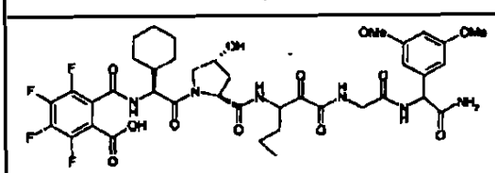
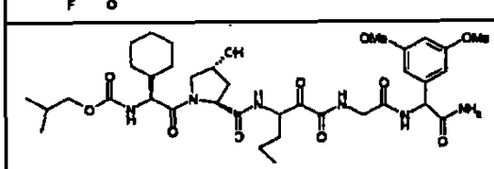
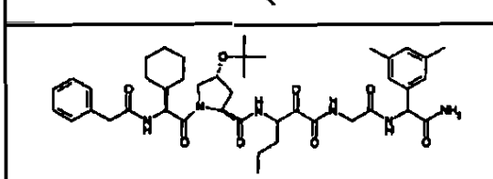
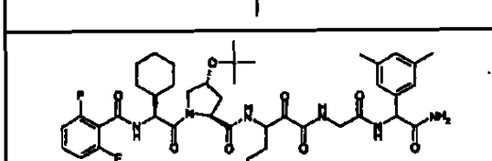
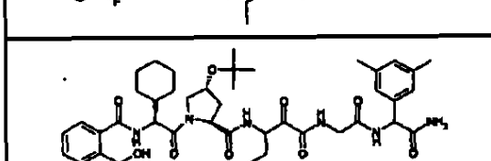
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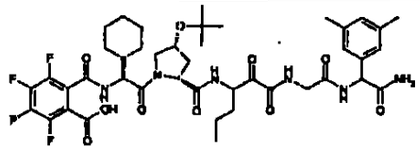
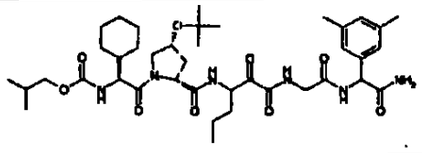
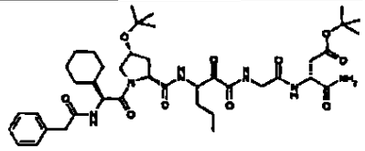
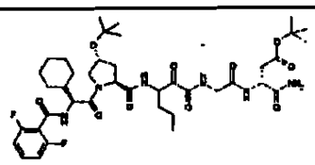
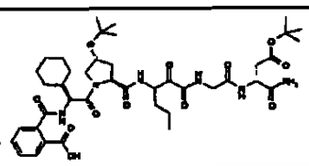
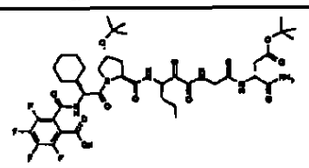
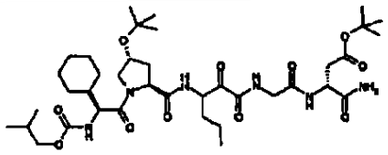
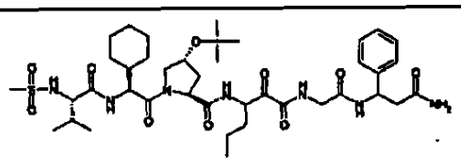
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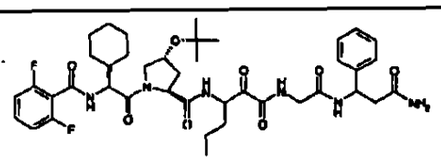
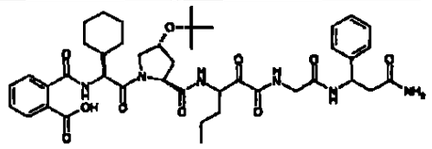
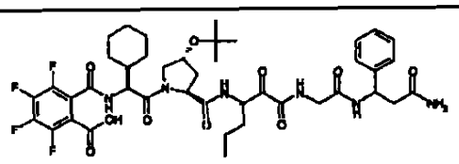
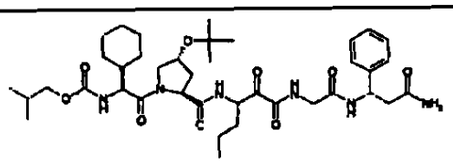
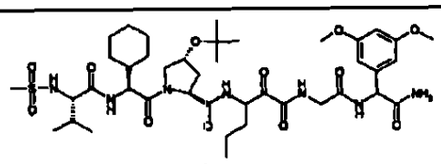
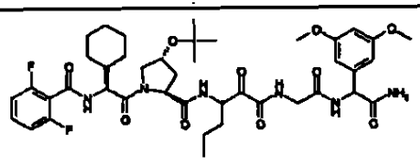
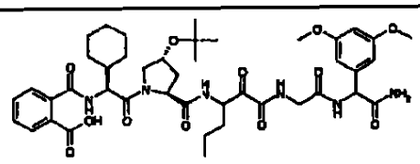
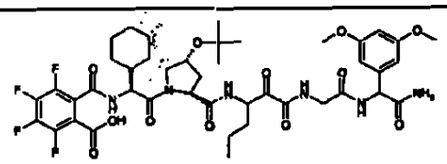
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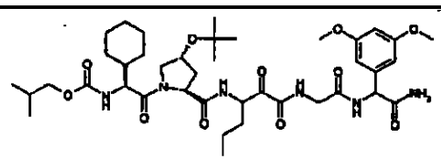
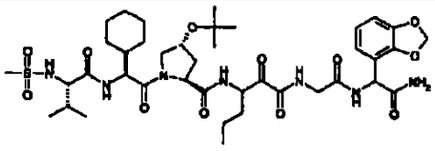
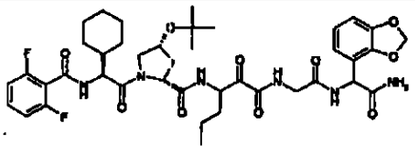
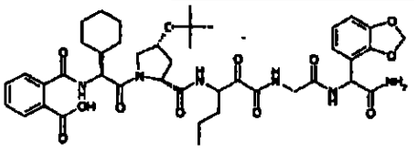
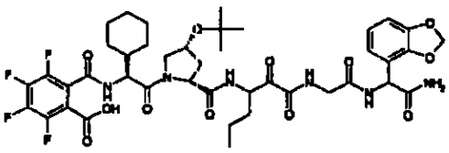
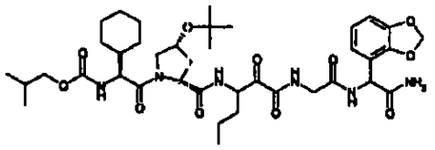
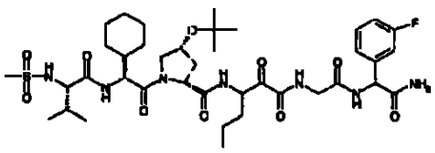
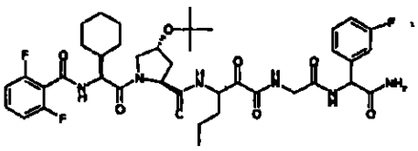
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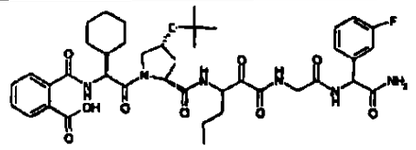
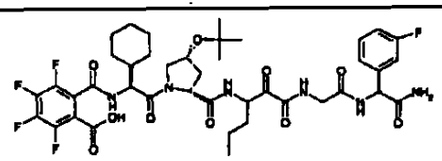
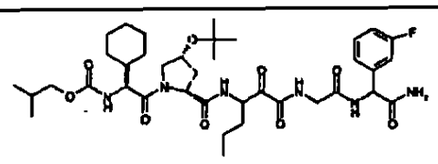
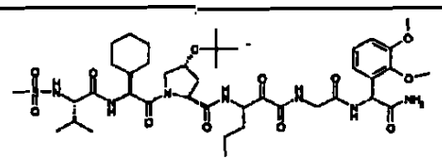
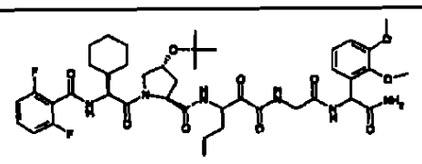
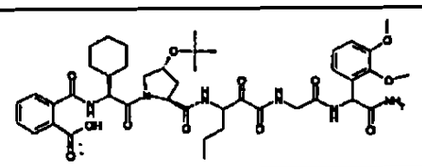
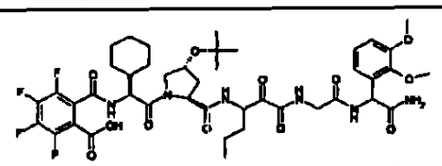
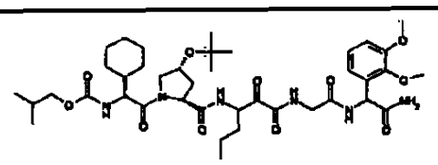
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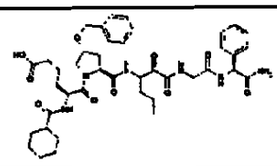
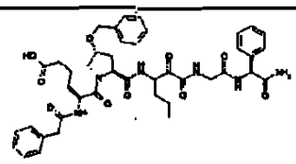
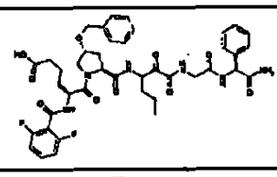
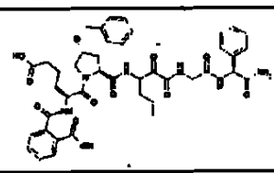
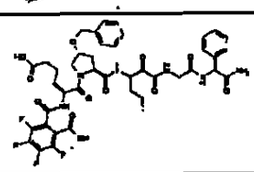
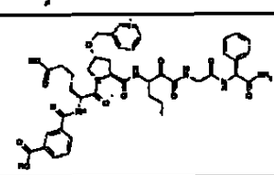
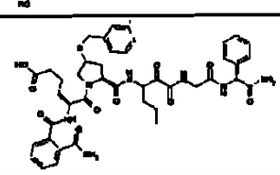
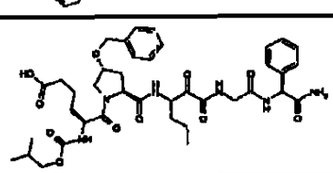
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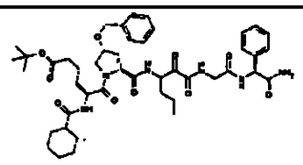
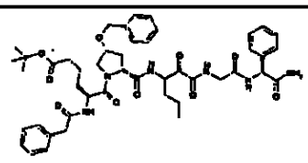
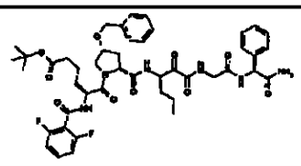
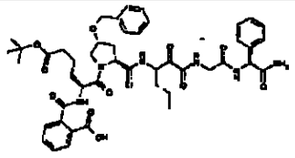
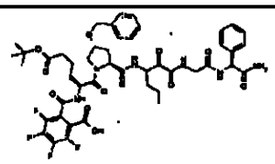
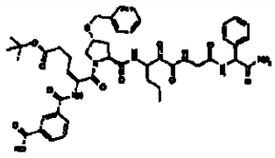
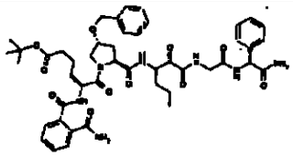
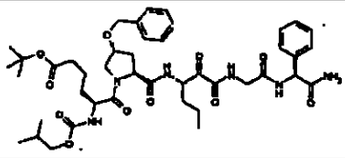
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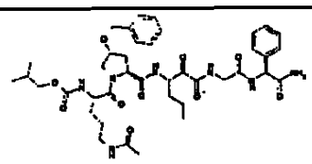
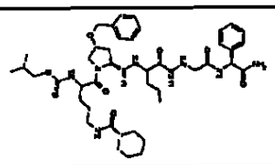
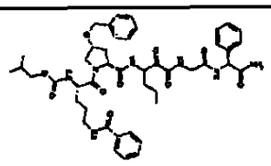
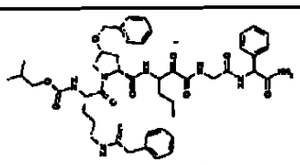
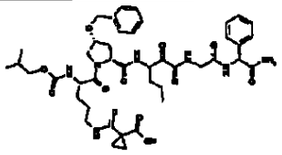
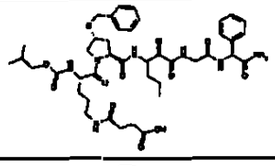
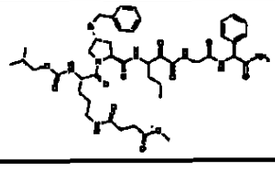
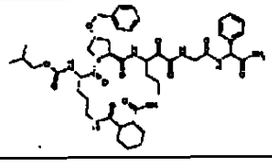
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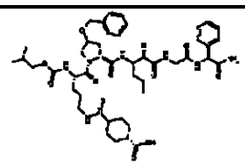
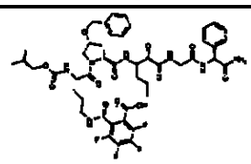
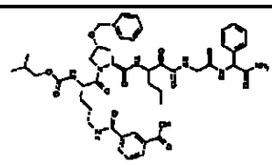
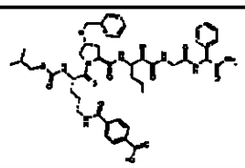
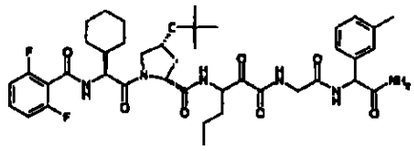
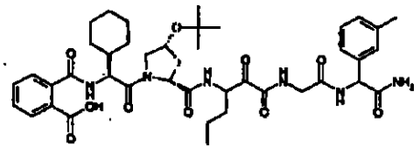
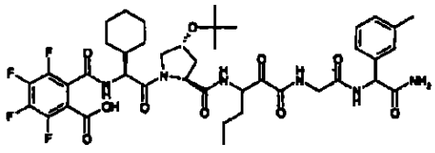
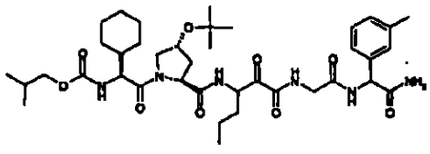
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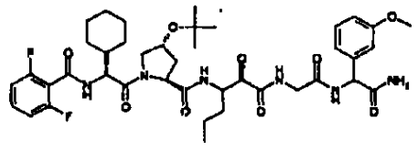
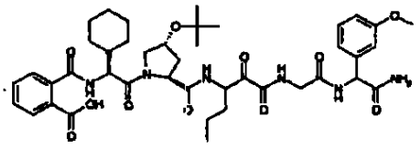
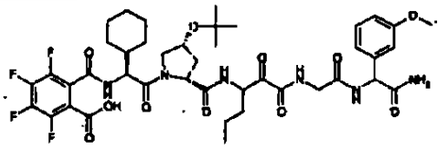
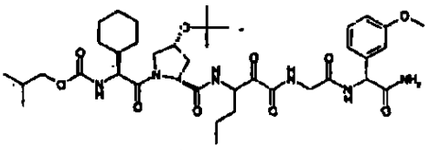
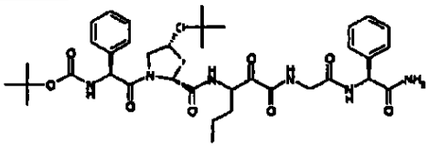
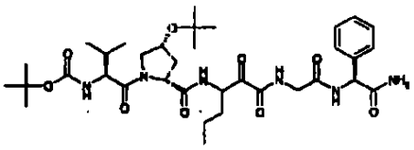
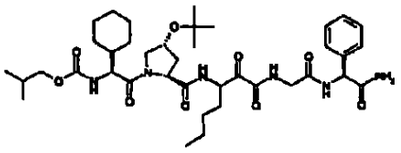
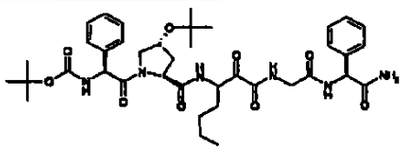
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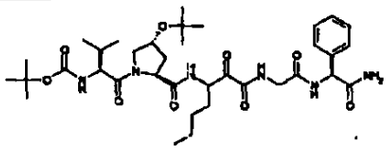
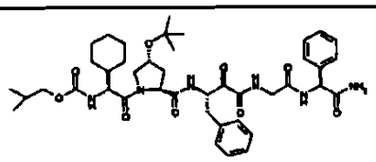
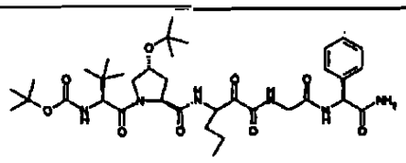
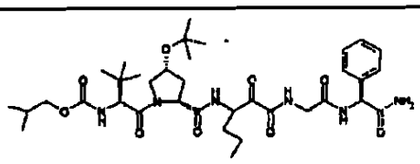
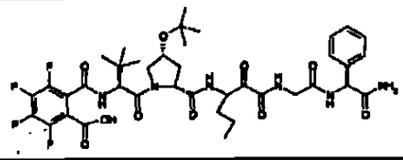
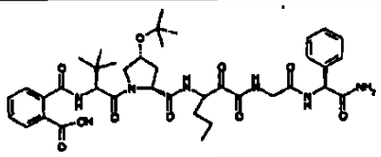
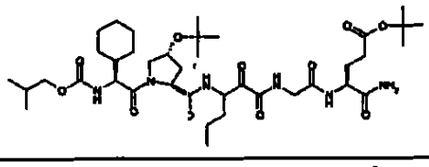
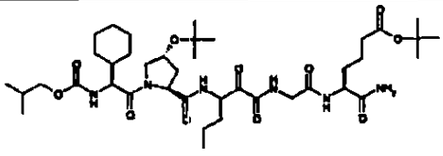
ESTRUCTURA	CLASE DE KI*
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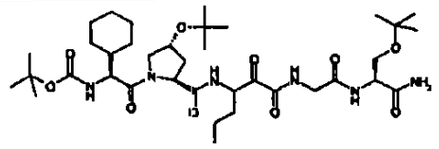
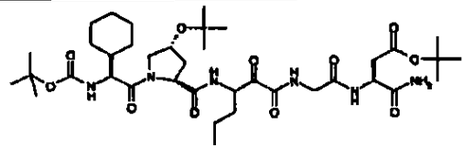
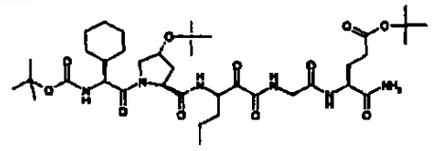
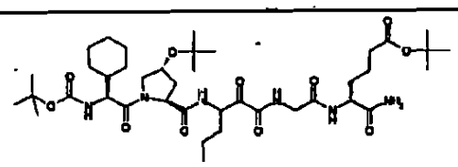
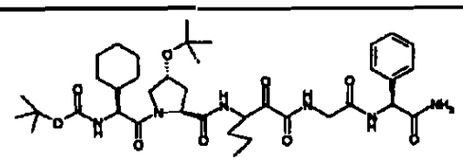
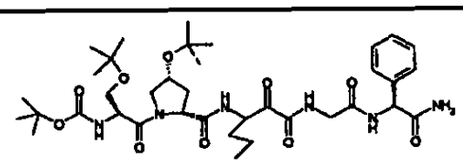
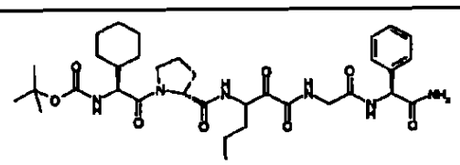
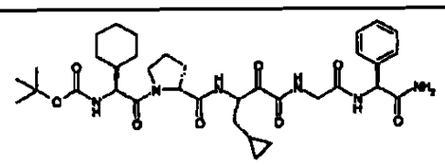
ESTRUCTURA	CLASE DE KI*
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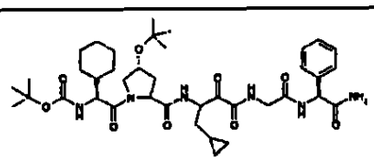
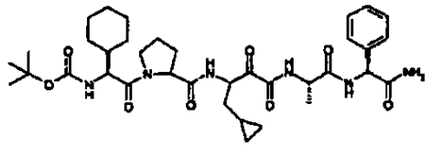
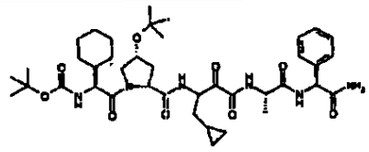
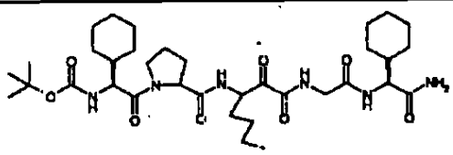
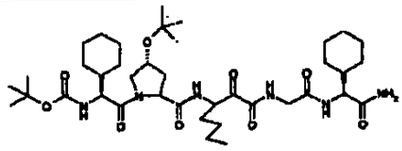
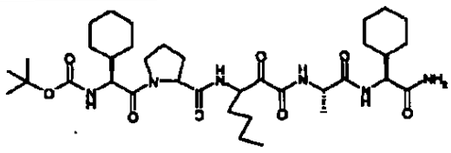
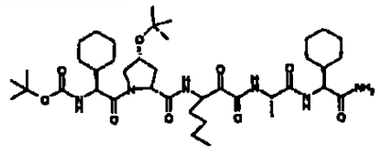
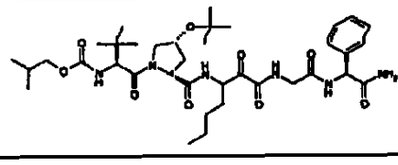
ESTRUCTURA	CLASE DE KI*
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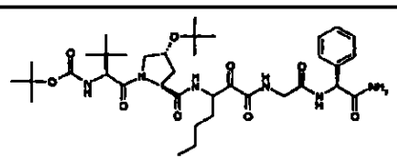
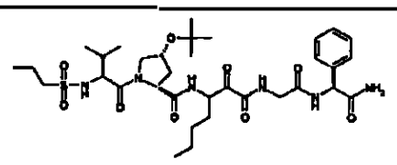
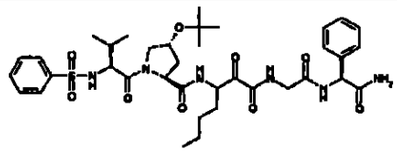
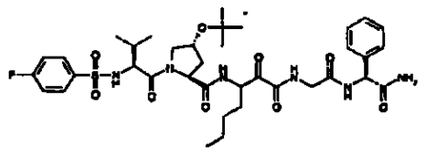
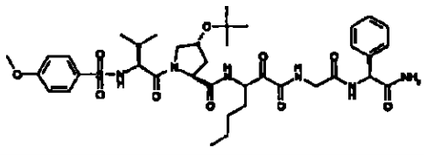
ESTRUCTURA	CLASE DE Ki*
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ESTRUCTURA	CLASE DE Ki*
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	B
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	C

ESTRUCTURA	CLASE DE KI*
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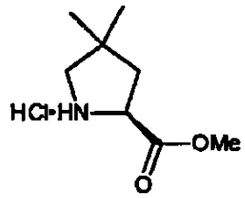
ESTRUCTURA	CLASE DE KI* ;
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ESTRUCTURA	CLASE DE KI*
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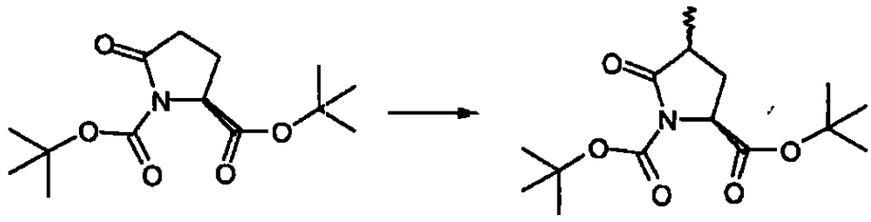
Los compuestos adicionales que se prepararon y sus rangos de actividad (Ki*) se proveen en las Tablas anexas 4, 5 y 6. El procedimiento usado para preparar los compuestos de las Tablas 4, 5 y 6 se define más adelante.

I) **Síntesis de los intermediarios para los compuestos de las Tablas 4. 5 y 6:**

Ejemplo I. Síntesis de metil éster de 4,4-dimetil prolina (H-Pro(4,4-diMe)-OMe)

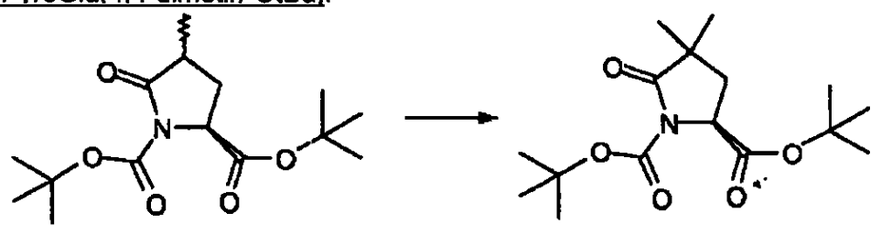


Paso 1. Síntesis de N-ter-butoxicarbonil-4-metil-L-piroglutamato de ter-Butilo (Boc-PyroGlu(4-metil)-OtBu):



A una solución de N-ter-butoxicarbonil-piroglutamato de ter-butilo (11,5 g, 40 mmol) en THF (200 mL) agitada a -78°C, se agregó una solución 1M de hexametildisilazida de litio en THF (42 mL, 42 mmol) gota a gota durante 5 minutos. Luego de 30 minutos, se agregó yoduro de metilo (3,11 mL, 50 mmol). Luego de un adicional de 2 horas a -78°C, el baño de frío se eliminó y se agregó 50% de cloruro de amonio acuoso saturado (200 mL). La solución se agitó durante 20 minutos, luego se extrajo con éter (3 x 200 mL). Las fases orgánicas combinadas se lavaron con salmuera (200 mL), se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se cromatografió con 1:1 acetato de etilo/hexanos para dar Boc-PyroGlu(4-metil)OtBu (10,6 gramos, 35,4 mmol, 88%) como una mezcla de isómeros (2:1 cis a trans).

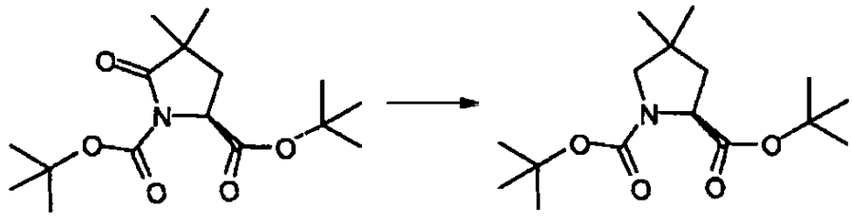
Paso 2. Síntesis de N-ter-butoxicarbonil-4,4-dimetil-L-piroglutamato de ter-Butilo (Boc-PyroGlu(4,4-dimetil)-OtBu):



A una solución de N-ter-butoxicarbonil-4-metil-L-piroglutamato de ter-butilo (1,2 g, 4,0 mmol) en tetrahidrofurano (20 mL) agitando a -78°C, se agregó una solución 1M de hexametildisilazida de litio en tetrahidrofurano (4,4 mL, 4,4 mmol) gota a gota durante 5 minutos. Luego de 30 minutos, se agregó yoduro de metilo (0,33 mL, 5,2 mmol). Luego de un adicional de 3 horas a -78°C, el baño de frío se eliminó y se agregó 50% de cloruro de amonio acuoso saturado (40 mL). La

solución se agitó durante 20 minutos, luego se extrajo con éter (2 x 50 mL). Las fases orgánicas combinadas se lavaron con agua (2 X 25 mL), bicarbonato de sodio saturado (2 x 25 mL), salmuera (50 mL), se secaron (Na_2SO_4), se filtraron y se concentraron para dar BocPyroGlu(4,4-dimetil)-OtBu (0,673 g, 54%).

Paso 3. Síntesis de ter-butil N-ter-butoxicarbonil-4,4-dimetilprolina (Boc-Pro(4,4-dimetil)-OtBu)

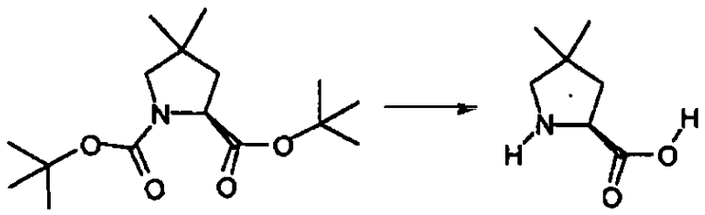


Modificación del procedimiento conocido: Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron Letters 1994,* 35(13), 20532056).

A una solución de N-ter-butoxicarbonil-4,4-dimetilpiroglutamato de ter-butilo (2,0 mmol) en tetrahidrofurano (5 mL) agitando a -78°C, se agregó una solución 1M de trietilborohidruro de litio en tetrahidrofurano (2,4 mL, 2,4 mmol) gota a gota durante 5 minutos. Luego de 30 minutos, el baño de frío se eliminó y se agregó bicarbonato de sodio acuoso saturado (5 mL). La mezcla de reacción se sumergió en un baño de agua/ hielo y se agregó 30% de peróxido de hidrógeno acuoso (10 gotas). La solución se agitó durante 20 minutos a 0°C, luego la mezcla de reacción se concentró al vacío para quitar el tetrahidrofurano. La solución acuosa se diluyó con agua (10 mL) y se extrajo con diclorometano (3 x 40 mL). Las fases orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se disolvió en diclorometano (20 mL) y trietilsilano (310 µL, 2,0 mmol), luego se enfrió hasta -78°C y trifluoruro dietileterato de boro (270 µL, 2,13 mmol) se agregó gota a gota. Se continuó la agitación durante 30 minutos, tiempo en el cual se agregaron trietilsilano adicional (310 µL, 2,0 mmol)

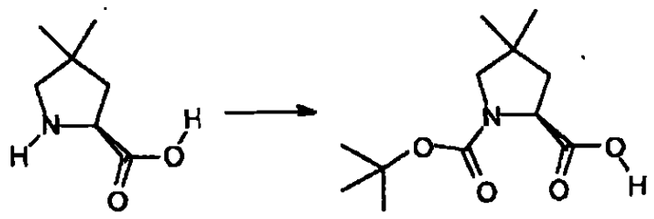
y trifluoruro dietileterato de boro (270 µL, 2,13 mmol). Luego de agitar a -78 °C durante un adicional de dos horas, el baño de frío se eliminó y se agregó bicarbonato de sodio acuoso saturado (4 mL). Luego de 5 minutos la mezcla se extrajo con diclorometano (3 x 40 mL). Las fases orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron para dar Boc-Pro(4,4-dimetil)-OtBu.

Paso 4. Síntesis de 4,4-dimetilprolina (H-Pro(4,4-dimetil)-OH):



Una solución de ter-butil N-ter-butoxicarbonil-4,4-dimetilprolina en diclorometano (5 mL) y trifluoroacético (5 mL) se agitó a temperatura ambiente durante cinco horas. La solución se concentró, se secó con vacío extremo y se llevó al paso siguiente sin purificación adicional.

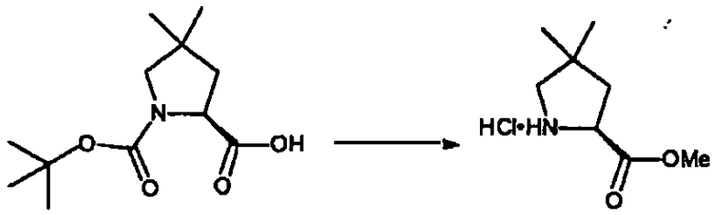
Paso 5. Síntesis de N-ter-butoxicarbonil 4,4-dimetilprolina (Boc-Pro(4,4-dimetil)-OH):



A una solución de sal trifluoroacética de 4,4-dimetilprolina (1,5 mmol) en dioxano (7 mL), acetonitrilo (12 mL) y diisopropiletilamina (700 µL, 4 mmol) se agregó una solución de di-ter-butil-dicarbonato (475 mg, 2,18 mmol) en acetonitrilo (5 mL). Luego de agitar durante 12 horas a temperatura ambiente la solución se concentró al vacío, se disolvió en bicarbonato de sodio acuoso saturado (50 mL) y se lavó con éter dietílico (3 x 40 mL). La fase de agua se acidificó hasta un pH=3 con ácido cítrico, luego se extrajo con diclorometano (3 x

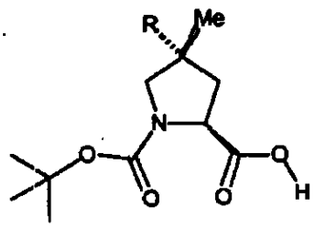
40 mL). Las fases orgánicas combinadas se secaron sobre sulfato de sodio, se filtraron y se concentraron.

Paso 6. Síntesis de metil éster de 4,4-dimetilprolina, sal de clorhidrato (HCl-H-Pro(4.4-dimetil)-OMe):



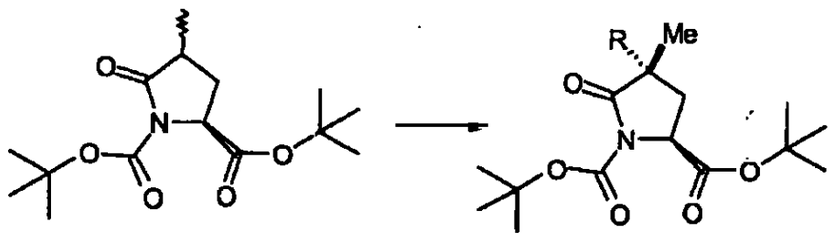
A una solución de Boc-Pro(4,4-diMe)-OH (0,5 g, 2,06 mmol) en metanol anhidro (8 ml) se agregó gota a gota cloruro de tionilo (448 µl, 6,18 mmol) y la reacción se agitó durante seis horas a temperatura ambiente. La mezcla de reacción se concentró hasta obtener un sólido amorfo (377 mg, 95%).

Ejemplo II. Procedimiento general para la síntesis de N-tertbutoxicarbonil-4-alquil-4-metil prolina:



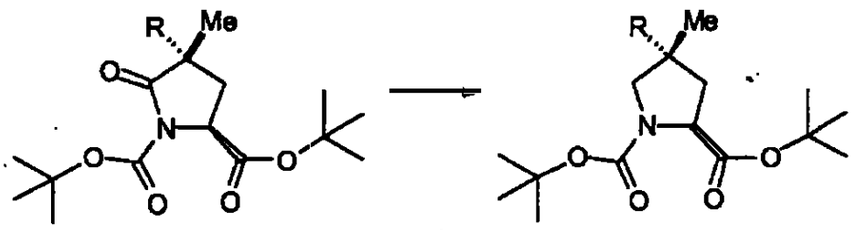
Los Compuestos en los cuales el grupo R es alilo y bencilo se sintetizaron siguiendo los pasos 1-4 más adelante:

Paso 1. Síntesis de N-ter-butoxicarbonil-4-alquil-4-metil-L-piroglutamato de ter-Butilo:



A una solución de N-ter-butoxicarbonil-4-metil-L-piroglutamato de ter-butilo (10,2 g, mmol) (ver Ejemplo I, paso 1) en tetrahidrofurano (170 mL) agitando a -78°C, se agregó una solución 1M de hexametildisilazida de litio en tetrahidrofurano (37,5 mL, 37,5 mmol) gota a gota durante 5 minutos. Luego de 40 minutos, se agregó halogenuro de alquilo (61,4 mmol). Luego de un adicional de 3 horas a -78°C, el baño de frío se eliminó y se agregó 50% de cloruro de amonio acuoso saturado (200 mL). La solución se agitó durante 20 minutos, luego se extrajo con éter (2 x 200 mL). Las fases orgánicas combinadas se diluyeron con hexanos (150 mL) y se lavaron con bicarbonato de sodio saturado (100 mL), agua (2 x 100 mL) y salmuera (100 mL), se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se sometió a cromatografía flash usando 20% acetato de etilo en hexanos para dar el N-ter-butoxicarbonil-4-alquil-4-metil-L-piroglutamato de ter-Butilo puro.

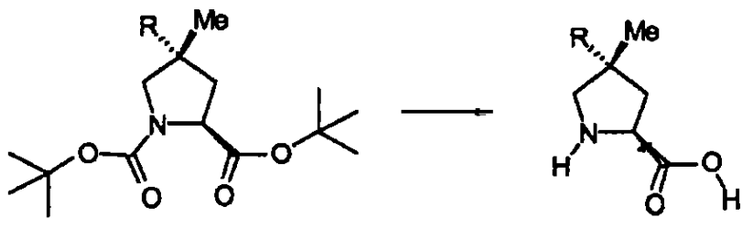
Paso 2. Síntesis de ter-butil N-ter-butoxicarbonil-4-alquil-4-metilprolina:



Modificación del procedimiento conocido: Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron Letters* (1994) 35(13), 20532056).

A una solución de ter-butilo N-ter-butoxicarbonil-4-alquil-4-metilpiroglutamato (16,6 mmol) en tetrahidrofurano (40 mL) agitando a -78°C, se agregó una solución 1M de trietilborohidruro de litio en tetrahidrofurano (20 mL, 20 mmol) gota a gota durante 10 minutos. Luego de 120 minutos, el baño de frío se dejó entibiar hasta -25°C momento en el cual se agregó bicarbonato de sodio acuoso saturado (40 mL). La mezcla de reacción se sumergió en un baño de agua/ hielo y se agregó 30% de peróxido de hidrógeno acuoso (4 mL). La solución se agitó durante 10 minutos a 0°C, luego la mezcla de reacción se concentró al vacío para quitar el tetrahidrofurano. La solución acuosa se diluyó con agua (300 mL) y se extrajo con diclorometano (3 x 200 mL). Las fases orgánicas se secaron (sulfato de sodio), se filtraron y se concentraron. El residuo se disolvió en diclorometano (100 mL) y trietilsilano (2,6 mL, mmol), luego se enfrió hasta -78°C y se agregó trifluoruro dietileterato de boro (2,2 mL, mmol) gota a gota. Se continuó la agitación durante 1 hora, tiempo en el cual se agregaron trietilsilano (2,6 mL, mmol) y trifluoruro dietileterato de boro adicional (2,2 mL, mmol). Luego de agitar a -78 °C durante un adicional de 4 horas, el baño de frío se eliminó y se agregaron bicarbonato de sodio acuoso saturado (30 mL) y agua (150 mL). Luego de 5 minutos la mezcla se extrajo con diclorometano (3 x 200 mL). Las fases orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron.

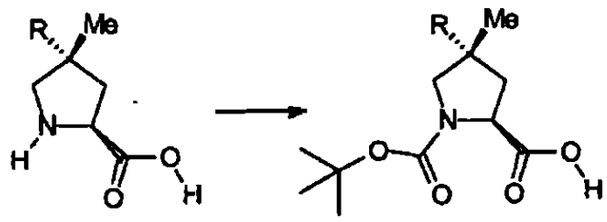
Paso 3. Síntesis de 4-alquil-4-metilprolina:



Una solución de ter-butil N-ter-butoxicarbonil-4-alquil-4-metilprolina en diclorometano (5 mL) y trifluoroacético (5 mL) se agitó a temperatura ambiente

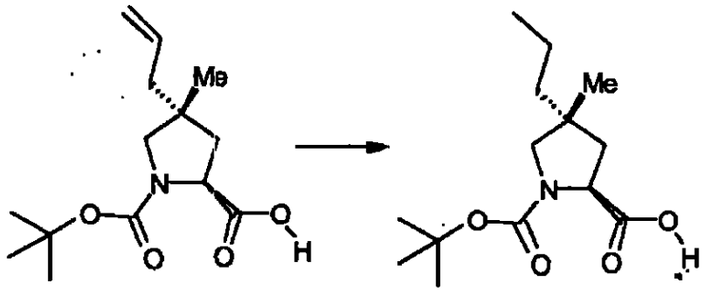
durante 5 horas. Se agregó tolueno y la solución se concentró y luego se secó con vacío extremo.

Paso 4. Síntesis de N-ter-butoxicarbonil 4-alquil-4-metilprolina:



A una solución de 4-alquil-4-metilprolina, sal trifluoroacética (1,5 mmol) en dioxano (7 mL), acetonitrilo (12 mL) y diisopropiletilamina (700 µL, 4 mmol) se agregó una solución de di-ter-butil-dicarbonato (475 mg, 2,18 mmol) en acetonitrilo (5 mL). Luego de agitar durante 12 horas a temperatura ambiente la solución se concentró al vacío, se disolvió en bicarbonato de sodio acuoso saturado (50 mL) y se lavó con éter dietílico (3 x 40 mL). La fase de agua se acidificó hasta un pH=3 con ácido clorhídrico 1N, luego se extrajo con diclorometano (3 x 40 mL). Las fases orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó a través de cromatografía flash usando 1:1 de acetato de etilo/hexanos con 1 % de ácido acético.

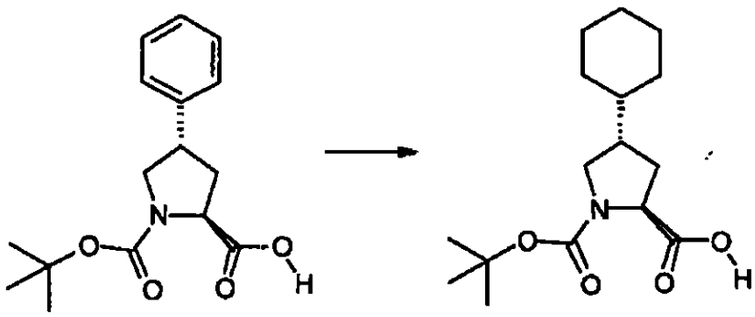
Ejemplo III. Síntesis de N-ter-butoxicarbonil 4-propil-4-metilprolina:



Una solución de N-tertbutoxicarbonil-4-alil-4-metilprolina (400 mg, 1,48 mmol) (ver Ejemplo 11 Paso 4) y 10% de Pd sobre carbón (400 mg) en metanol

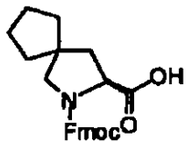
(20 mL) se hidrogenó a 50 psi durante 4 horas. La mezcla se filtró y se concentró.

Ejemplo IV. Síntesis de Boc-4-ciclohexilprolina:

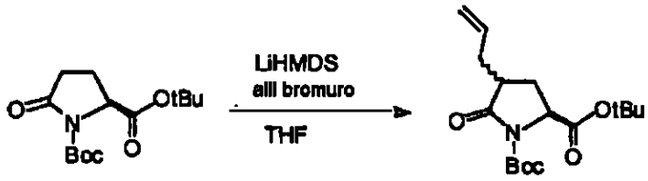


Una solución de la Boc-4-fenilprolina disponible en el mercado (750 mg) y 5% de Rh sobre carbón (750 mg) en metanol (15 mL) se hidrogenó a 50 psi durante 24 horas. La mezcla se filtró y se concentró para dar 730 mg de producto.

Ejemplo V: Preparación del ácido Fluorenilmetoxicarbonil-Pro(4-espirociclopentan) carboxílico



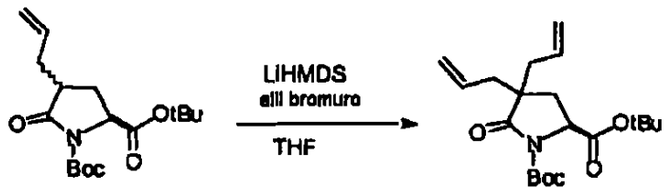
Paso 1. Síntesis de Boc-piroglutamic(4-alil)-ter-butiléster



A una solución enfriada (-78°C) del piroglutamato de N□-Boc-tertbutilo comercial (10 g, 35,1 mmol) en THF (175 ml) se agregó hexametildisilazida de litio (36,8 mL, 36,8 mmol) durante cinco minutos. Se continuó la agitación durante treinta minutos. Una solución de *bromuro de alilo* (6,1 ml, 70,2 mmol) en THF (39 mL) se agregó gota a gota a la primera solución. Luego de dos horas a -78°C, la reacción se inactivó a través del agregado lento de solución saturada de cloruro

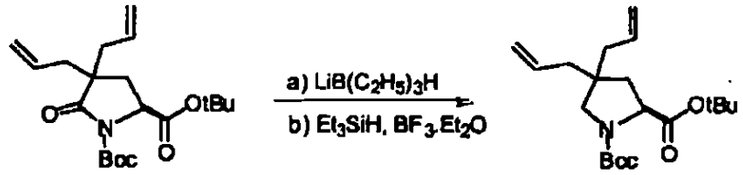
de amonio (50 mL). La mezcla de reacción se diluyó luego con acetato de etilo y las fases se separaron. La fase orgánica se secó sobre sulfato de sodio y se concentró. La cromatografía instantánea en columna llevada a cabo en 2:8 de acetato de etilo: hexanos logró el producto (6 g, 53%). RMN δ ppm ($CDCl_3$): 5,7 (m, 1 H), 5,1 (dd, 2H), 4,4 (m, 1 H), 2,6 (m, 2H), 2,4 (m, 1 H), 1,8-2,2 (m, 1 H), 1,45 (s, 9H), 1,4 (s, 9H).

Paso 2. Síntesis de N-Boc-piroglutamic(4,4-dialil)-ter-butiléster:



El N-Boc-piroglutamic(4-alil)-ter-butiléster obtenido en el Paso 1 anterior (2,68 g, 8,24 mmol) se sometió a una segunda alquilación con bromuro de alilo en condiciones similares. La cromatografía flash en 15:85 de acetato de etilo: hexanos dio 2,13 g de producto (71 %) como un aceite claro.

Paso 3. Síntesis de Boc-Pro(4,4-dialil)-ter-butiléster:

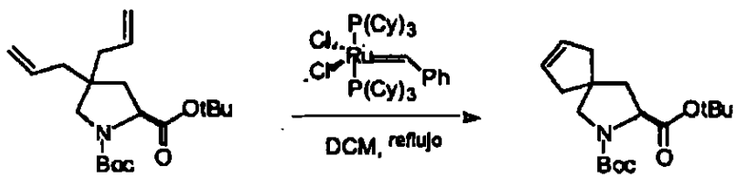


Parte a: A una solución enfriada (-78°C) de Boc-PyroGlu(4,4-dialil)-tertbutiléster (2,13 g, 5,83 mmol) en tetrahidrofurano (14 ml) se agregó trietilborohidruro de litio (1 M en tetrahidrofurano, 7,29 ml, 7,29 mmol) durante cinco minutos. Luego de dos horas a -78°C, la reacción se entibió hasta 0°C y se inactivó a través del agregado lento de solución saturada de bicarbonato de sodio (20 ml) y 30% de peróxido de hidrógeno (20 gotas). Se continuó la agitación durante 20 minutos. El tetrahidrofurano se eliminó bajo presión reducida y el residuo blanco espeso restante se diluyó con agua (80 ml) y se extrajo tres veces con diclorometano. La

fase orgánica se secó, se filtró y se concentró y se llevó al paso siguiente sin purificación adicional.

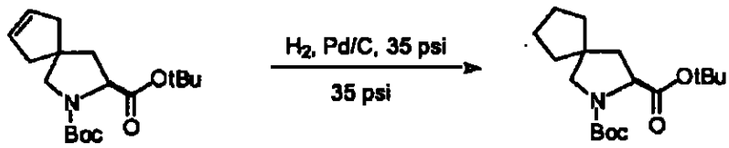
Parte b: Al producto obtenido en la parte (a) en diclorometano (14 ml) se agregó trietilsilano (931 pi, 5,83 mmol) seguido de trifluoruro de boro dietileterato (776 µl, 6,12 mmol). Luego de treinta minutos más se agregaron trietilsilano (931 µl, 5,83 mmol) y trifluoruro de boro dietileterato (776 Pl, 6,12 mmol) y la reacción se agitó a -78 °C durante tres horas tiempo en el cual la reacción se inactivó a través del agregado lento de solución saturada de bicarbonato de sodio y agua. La mezcla de reacción se extrajo con diclorometano y la fase orgánica se secó, se filtró y se concentró. La cromatografía instantánea en columna en 15% acetato de etilo en hexanos produjo 1,07 de aceite incoloro (57%). RMN δ ppm ($CDCl_3$): 5,7-5,8 (m, 2H), 5,1 (m, 4H), 4,1-4,2 (2 dd's, 1 H rotámeros), 3,5-3,3 (dd, 1 H) y 3,2 (dd, 1 H) rotámeros, 2,2-2,0 (m, 5H), 1,7(m, 1 H), 1,46 (s, 9H), 1,43 (s, 9H).

Paso 4. Síntesis de Boc-Pro(4-espirociclopenten)-ter-butiléster:



Al Boc-Pro(4,4-dialil)-ter-butiléster (1,07 g, 3,31 mmol) en diclorometano (66 ml) se agregó 5% de dicloruro de Bis(triciclohexilfosfin)bencilideno rutenio IV (Catalizador de Grubbs) y la mezcla se calentó a reflujo durante 1,5 horas. La mezcla de reacción se concentró y el residuo restante se purificó a través de cromatografía flash en 15% de acetato de etilo en hexanos. Se obtuvo un aceite amarillo (0,57 g, 53%). RMN δ ppm ($CDCl_3$): 5,56 (bs, 2H), 4,2 y 4,1 (t, 1 H, rotámeros), 3,2-3,5 (m, 2H), 2,2-2,5 (m, 5H), 1,9 (dd, 1 H) 1,47 y 1,46 (2 s's, 9H, rotámeros), 1,45 y 1,44 (2 s's, 9H, rotámeros).

Paso 5. Síntesis de Boc-Pro(4-espirociclopentan)-ter-butiléster:



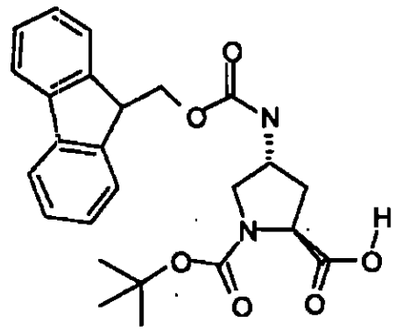
Una solución de Boc-Pro(4-espirociclopenten)-ter-butiléster (1,12 g) en metanol (18 ml), agua (4 ml) y ácido acético (4 ml) se colocó en el agitador de Parr y se hidrogenó durante tres horas a 35 psi en presencia de 10% de paladio sobre carbón (300 mg). El catalizador se eliminó por filtración y el filtrado se concentró hasta obtener un aceite incoloro (1,26 g). RMN δ ppm ($CDCl_3$): 4,1 y 4,2 (t, 1 H, rotámeros, 3,4 (d, 1 H), 3,2 (d, 1 H), 2,1 (m, 1 H), 1,9 (m, 1 H), 1,6-1,7 (m, 10H), 1,5 (3 s's, 18H, rotámeros).

Paso 6. Síntesis del ácido Fmoc-Pro(4-espirociclopentan)-carboxílico:

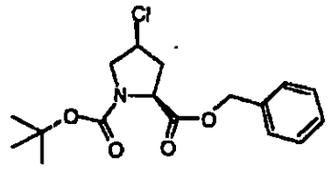


El Boc-Pro(4-espirociclopentan)-ter-butiléster (1,26, 3,9 mmol) se trató con diclorometano (10 ml) y ácido trifluoroacético (15 ml) durante tres horas. La mezcla de reacción se concentró y el aceite amarillo obtenido se disolvió en agua (6 ml). El fluorenilmetil succinil carbonato (1,45 g, 4,3 mmol) disuelto en dioxano (6 ml) se agregó en porciones seguido del agregado de carbonato de potasio (2,16 g, 15,6 mmol). La reacción se agitó durante 18 horas y se concentró. El residuo restante se diluyó con la solución saturada de bicarbonato de sodio (10 mL) y se lavó con éter dietílico (3 X 10 ml). La fase de agua se acidificó luego hasta un pH ~ 1 con solución 1N de bisufato de sodio y se extrajo con acetato de etilo. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró hasta obtener una espuma beige (1,3 g, 100%).

Ejemplo VI. Síntesis de Boc-Pro(4t-NH(Fmoc))-OH:



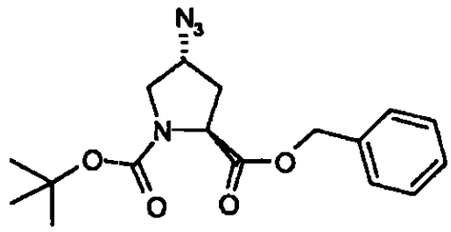
Paso 1. Síntesis de bencil éster de N^{α}-ter-butoxicarbonil-cis-4-cloro-L-prolina:



Una mezcla de la N^{α}-ter-butoxicarbonil-trans-4-hidroxi-prolina comercial (8,79 g, 38 mmol), carbonato de potasio (13,0 g, 94 mmol), bromuro de bencilo (4,5 ml, 38 mmol) y dimetilformamida (150 mL) se agitó durante 18 h. Al agregado del acetato de etilo (100 mL) le siguió la filtración. El filtrado turbio blanco se clarificó a través del agregado de HCl 1M (100 mL). Las fases se separaron y la fase de agua se extrajo con acetato de etilo adicional (2 x 100 mL). Las fases orgánicas combinadas se lavaron con agua (2 x 50 mL), se secaron (sulfato de sodio), se filtraron y se concentraron. Se agregó tolueno al éster benclílico en bruto, y la solución se filtró y se concentró nuevamente. Se agregó diclorometano (70 mL) y tetracloruro de carbono (70 mL), seguido de trifenilfosfina (21,11 g, 80 mmol). La mezcla de reacción se agitó durante 10 h, se inactivó con etanol (7 mL) y se agitó durante 5 hs más. La solución se concentró hasta aproximadamente 100 ml, luego se agregó diclorometano (40 mL), seguido del agregado de éter (200 mL) mientras se agitaba. La solución se enfrió durante 4 h, se filtró y se concentró para dar un aceite amarillo-marrón que se purificó a través de

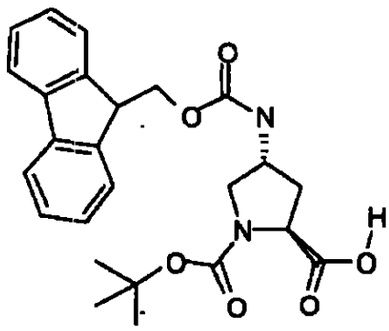
cromatografía flash usando éter/hexano/diclorometano a 2:2:1 para dar el compuesto del título (9,13 g, 26,9 mmol, 71 %) como un sólido blanco.

Paso 2. Síntesis de bencil éster de N^{α}-ter-butoxicarbonil-trans-4-azido-L-prolina:



Una solución de bencil éster de N^{α}-ter-butoxicarbonil-cis-4-cloro-L-prolina (9,0 g, 26,5 mmol) y azida de sodio (7,36 g, 113 mmol) en dimetilformamida (270 mL) se calentó a 75°C durante 2 días. Se agregó agua (100 mL) y la mezcla de reacción se extrajo con acetato de etilo (3 x 100 mL). Las fases orgánicas combinadas se lavaron con agua (3 x 50 mL), se secaron (sulfato de sodio), se filtraron y se concentraron. El aceite se purificó a través de cromatografía flash usando acetato de etilo/hexanos a 1:1 para dar el compuesto del título (8,59 g, 24,8 mmol, 94%).

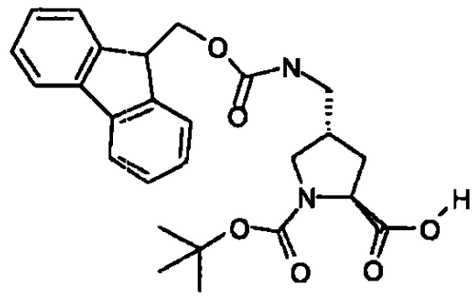
Paso 3. Síntesis de Boc-Pro(4t-NH(Fmoc))-OH:



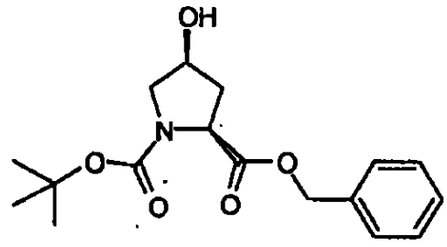
Una mezcla de bencil éster de N-α-t-butoxicarbonil-trans-4-azido-L-prolina (8,59 g, 24,8 mmol) y 10% de paladio sobre carbón (900 mg) en etanol (500 mL) se hidrogenó a 50 psi durante 14 h usando un aparato para hidrogenación de Parr. La mezcla se filtró, se concentró, se disolvió en metanol (60 mL), se filtró nuevamente y se concentró para dar un aceite incoloro. El aceite se disolvió en

agua (53 mL) que contenía carbonato de calcio (5,31 g, 50,1 mmol) y se agregó una solución de fluorenilmetil succinil carbonato (8,37 g, 29,8 mmol) en dioxano (60 mL) durante 40 min. La mezcla de reacción se agitó a temperatura ambiente durante 17 h, luego se concentró para quitar el dioxano y se diluyó con agua (200 mL). La solución se lavó con éter (3 x 100 mL). El pH de la solución acuosa se ajustó a 2 a través del agregado de ácido cítrico (precaución! formación de espuma!) y agua (100 mL). La mezcla se extrajo con diclorometano (400 mL, 100 mL, 100 mL) y las fases orgánicas combinadas se secaron (sulfato de sodio), se filtraron y se concentraron para dar el compuesto del título.

Ejemplo VII. Síntesis de N-t-butoxicarbonil-4-trans-(N-fluorenilmetiloxicarbonil aminometil)-L-prolina (Boc-Pro(4t-MeNHFmoc)-OHM



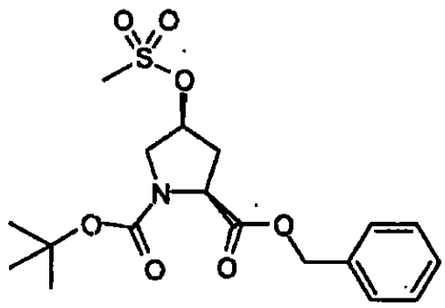
Paso 1. Síntesis del bencil éster de la ter-butoxicarbonil cis-4-hidroxi-L-prolina (BocPro(4-cis-OH)-OBn):



A una mezcla de cis-hidroxi-L-prolina (5 g, 38,1 mmol) en benceno (45 mL) y alcohol bencílico (45 mL) se agregó ácido p-toluensulfónico monohidrato (7,6 g, 40,0 mmol). La mezcla de reacción se calentó a 125°C durante 20 h mientras el agua (2 ml) se eliminó usando una trampa de Dean-Stark. La solución se filtró

mientras aún estaba caliente, y luego se agregó éter (150 ml). La solución se dejó enfriar durante tres h a temperatura ambiente, luego tres h a 4°C. El sólido resultante se recolectó, se lavó con éter (100 mL) y se secó al vacío durante 1 h para dar 13,5 gramos de sólido blanco. El sólido se disolvió en dioxano (40 mL) y diisopropiletilamina (7,6 mL), y luego se agregó di-ter-butil-dicarbonato (10 g, 45,8 mmol) durante 5 min. mientras se usaba un baño de hielo para mantener una temperatura de reacción constante. Luego de 10 h a temperatura ambiente la mezcla de reacción se vertió en agua fría (200 mL) y se extrajo con acetato de etilo (3 x 200 mL). Las fases orgánicas combinadas se lavaron con agua (3 x 100 mL) y cloruro de sodio acuoso saturado (50 mL), se secaron (sulfato de sodio), se filtraron y se concentraron. El producto en bruto se purificó a través de cromatografía flash usando 40-60% de acetato de etilo en hexanos para dar el compuesto del título (10,04 g, 31,24 mmol, 82%).

Paso 2. Síntesis del bencil éster de la N-t-butoxicarbonil cis-4-mesiloxi-L-prolina (Boc-Pro(4-cis-OMs)-OBn):

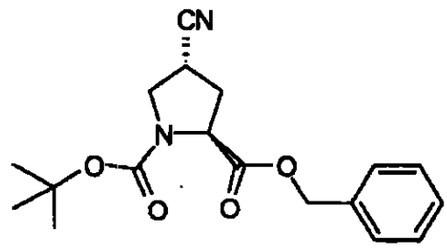


A una solución de Boc-Pro(4-cis-OH)-OBn (8,45 g, 26,3 mmol) en piridina (65 mL) a 0°C, se agregó cloruro de metansulfonilo (3,4 mL, 44 mmol) gota a gota durante 7 min. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente durante 2 h, luego se agitó durante la noche. Una solución de 10% de agua en piridina (20 mL) se agregó durante 15 min y la mezcla de reacción se concentró. El residuo se disolvió en agua y se extrajo con acetato de etilo (2 x 200 mL). Las fases orgánicas combinadas se lavaron con agua (2 x 50

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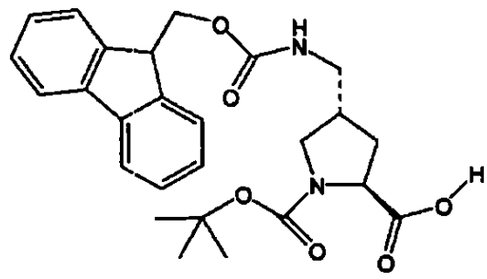
mL) bicarbonato de sodio acuoso saturado (50 mL) y cloruro de sodio acuoso saturado (50 mL), se secaron (sulfato de sodio), se filtraron y se concentraron. El residuo resultante se disolvió en tolueno (100 mL) y se concentró para eliminar los rastros de piridina. El residuo se secó al vacío durante 30 min para lograr el compuesto del título (10,7 g, 102%), luego se usó en el paso siguiente sin purificación.

Paso 3. bencil éster de la N-t-butoxicarbonil-trans-4R-ciano-L-prolina (Boc-Pro(4-trans-CN)-OBn):



Una solución de Boc-Pro(4-cis-OMs)-OBn (10,7 g, 26,3 mmol) y cianuro de tetrabutilamonio (15,0 g, 56 mmol) en dimetilformamida (100 mL) se calentó en un baño de aceite a 55°C durante 28 h. Luego de enfriar, se agregó agua (150 mL) y la mezcla se extrajo con acetato de etilo (3 x 200 mL). Las fases orgánicas combinadas se lavaron con agua (3 x 100 mL) y cloruro de sodio acuoso saturado (100 mL), se secaron (sulfato de sodio), se filtraron y se concentraron. El residuo resultante se purificó a través de cromatografía flash (1:1 éter/hexanos) y luego se recristalizó a partir de acetato de etilo/hexanos para dar el compuesto del título (2,40 g, 7,26 mmol, 28%).

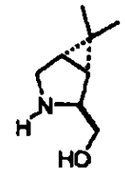
Paso 4. N-t-butoxicarbonil-4-trans-(N-fluorenilmetiloxicarbonil aminometil)-L-prolina (Boc-Pro(4t-MeNHFmoc)-OH)



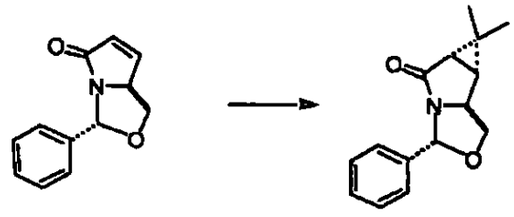
Una mezcla del compuesto del paso 3 anterior (2,31 g, 7 mmol), agua (10 mL), metanol (85 mL) y 10% de paladio sobre carbón (700 mg) se hidrogenó a 50 psi durante 11 h usando un aparato para hidrogenación de Parr. La mezcla se filtró y se concentró. Agua (15 mL) y carbonato de calcio (1,5 g, 14,2 mmol) se agregó al residuo. Una solución de fluorenilmetil succinil carbonato (2,36 g, 7,0 mmol) en dioxano (17 mL) se agregó durante 5 min y se continuó la agitación durante 28 h a temperatura ambiente. La reacción se concentró al vacío a un volumen de 15 mL, y se agregó agua (100 mL). La solución se lavó con éter (3 x 75 mL). El pH de la solución acuosa se ajustó a 2 a través del agregado de ácido cítrico (aprox. 20 g, precaución! formación de espuma!) y agua (100 mL). La mezcla se extrajo con diclorometano (4 x 100 mL), y las fases orgánicas combinadas se secaron (sulfato de sodio), se filtraron y se concentraron. El producto en bruto contenía una impureza mayor que necesitó una purificación de tres pasos. El producto en bruto se disolvió en diclorometano (50 mL) y ácido trifluoroacético (50 mL) y se agitó durante 5 h antes de concentrar. El residuo se purificó por HPLC preparatoria de fase inversa. La sal de trifluoroacetato de la 4-(N-fluorenilmetiloxicarbonil aminometil)prolina pura (1,887 g, 3,93 mmol) se disolvió en dioxano (10 mL), acetonitrilo (20 mL) y diisopropiletilamina (1,4 mL, 8 mmol). A la mezcla de reacción se agregó una solución de di-ter-butildicarbonato (1,1 g, 5 mmol) en dioxano (5 mL). Luego de agitar durante 18 h, el pH de la solución se ajustó a 2 a través del agregado de ácido cítrico (precaución: formación de espuma!) y agua (100 mL). La mezcla se extrajo con acetato de

etilo (3 x 150 mL) y las fases orgánicas combinadas se lavaron con cloruro de sodio acuoso saturado (100 mL), se secaron (sulfato de sodio), se filtraron y se concentraron. El producto en bruto se disolvió en bicarbonato de sodio acuoso saturado (100 mL) y se lavó con éter (3 x 75 mL). La fase de agua se ajustó a un pH = 3 a través del agregado de ácido cítrico, luego se extrajo con diclorometano (4 x 100 mL). Las fases orgánicas combinadas se secaron (sulfato de sodio), se filtraron y se concentraron to el compuesto del título (1,373 g, 2,94 mmol, 42%).

Ejemplo VIII. Síntesis del 3,4-isopropilidenprolinol:



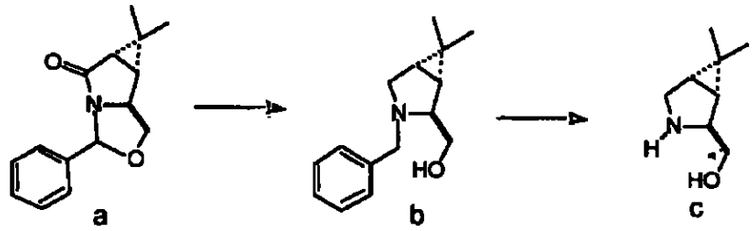
Paso I. Reacción de ciclopropanación *(Tetrahedron Lett.* 1993, 3416), 2691 y 2695



A una solución agitada de yoduro de isopropiltrifenil-fosfonio (4,14 g, 9,58 mmol) en tetrahidrofurano (60 mL) a 0°C, se agregó n-butil litio (1,6 M en hexanos, 5,64 mL, 9,02 mmol) durante 5 min. Luego de 30 min, una solución de enamida ((5R,7S)-5-fenil-5,6,7,7a-tetrahidro-6-oxapirrolizin-3-ona) (1,206 gramos, 6,0 mmol) (ver *J. Org. Chem.* 1999, 64(2), 547 para la síntesis de la enamida como material inicial) en tetrahidrofurano (40 mL) se agregó durante 10 min. Luego de un adicional de 10 min, el baño de frío se eliminó y la mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La reacción se vertió en agua (400 mL) y se extrajo con éter dietílico (400 mL) y acetato de etilo (2 x

400 mL). Los extractos orgánicos combinados se secaron con sulfato de sodio, se filtraron y se concentraron para dar el producto en bruto deseado. El residuo se purificó a través de cromatografía flash eluyendo con 3:5:2 acetato de etilo/hexanos/cloruro de metileno para dar el producto ciclopropanado puro (750 mg, 3,08 mmol, 51 %).

Paso 2. Síntesis de 3 4-isopropilidenprolinol P[3.4-(diMe-ciclopropil)]-alcohol *(J. Org. Chem.* (1999) 64(2), 330):

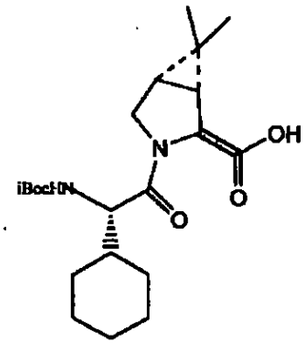


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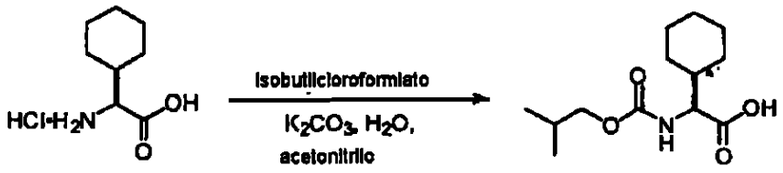
Una mezcla del producto obtenido en el paso 1 anterior (1,23 gramos, 5,06 mmol) e hidruro doble de litio y aluminio (1,0 M en THF, 15 mL, 15 mmol) se calentó a reflujo durante 5 horas. Luego de enfriar hasta 0°C, el hidruro de aluminio restante se inactivó cuidadosamente con el agregado gota a gota de sulfato de sodio acuoso saturado (1,5 mL) durante 15 min. La mezcla se diluyó con acetato de etilo (40 mL) y luego se filtró a través de celite. El filtrado se secó con sulfato de sodio, se filtró y se concentró para dar alcohol de N-bencilamino en bruto (1,25 gramos), que se llevó al paso siguiente sin purificación adicional. Una solución de alcohol N-aminobencílico en bruto (1,25 gramos, 5,06 mmol) en 1:1 de ácido acético/acetato de etilo (30 mL) con 10% de Pd/C (1 gram) se hidrogenó a 50 psi durante 16 horas usando un aparato para hidrogenación de Parr. La mezcla de reacción se filtró para quitar el catalizador con base de carbono y el filtrado se concentró. El residuo se disolvió en agua (30 mL) y el pH se ajustó a 13 con 50% de NaOH. La mezcla se extrajo con éter (3 x 60 mL). El extracto combinado se secó con sulfato de sodio, se filtraron y se concentraron para dar

aminoalcohol en bruto (485 mg, 3,43 mmol). Este material se llevó al paso siguiente sin purificación adicional.

Ejemplo IX. Síntesis del ácido iBoc-G(Chx)-Pro(3,4-isopropiliden)-carboxílico

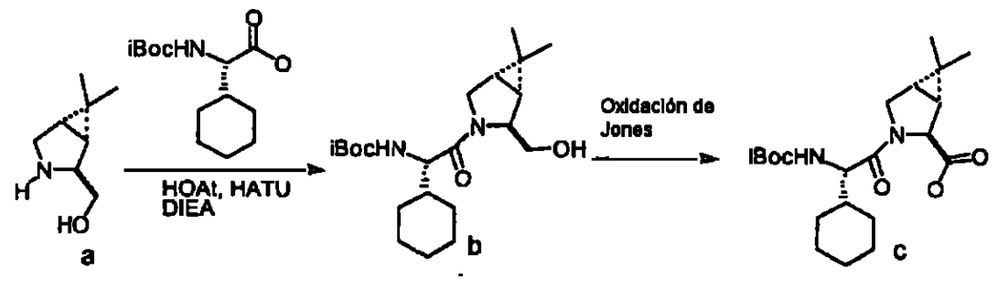


Paso 1. Síntesis de la isobutiloxicarbonil- ciclohexilglicina (iBoc-G(Chx)-OH):



A una solución del clorhidrato de ciclohexilglicina comercial (15 g, 77,4 mmol) en acetonitrilo (320 ml) y agua (320 ml) se agregó carbonato de potasio. Se agregó Isobutilcloroformiato (11,1 ml, 85,1 mmol) a la solución clara durante 15 minutos y la reacción se agitó durante 17 horas. El acetonitrilo se eliminó bajo presión reducida y la fase de agua remanente se extrajo dos veces con éter (100 ml). La fase de agua se acidificó luego hasta un pH 1 con ácido clorhídrico 6N y se extrajo con diclorometano (3 X 300 ml). La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró para dar como rendimiento 18,64 g (94%) de producto como un sólido blanco.

Paso 2. Síntesis de la isobutiloxicarbonil-ciclohexilglicil-3,4-isopropilidenprolina (iBoc-G(Chx)- P[3,4-(diMe-ciclopropil)]-OH):



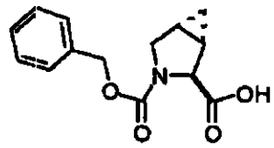
a) Paso de acoplamiento:

A una solución de iBoc-G(Chx)-OH (890 mg, 3,45 mmol) en acetonitrilo (20 mL) se agregó HATU (1,33 g, 3,5 mmol), HOAt (476 mg, 3,5 gramos) y luego diisopropiletilamina (2,5 mL, 14 mmol). Luego de a 2 minutos, se agregó 3,4-isopropilidenprolinol (485 mg, 3,43 mmol) y la mezcla de reacción se agitó durante la noche. Al agregado de bicarbonato de sodio acuoso saturado le siguió la extracción con éter y acetato de etilo. Las fases orgánicas combinadas se secaron, se filtraron y se concentraron. El residuo se purificó a través de cromatografía flash eluyendo con 1:1 acetato de etilo/hexanos para dar alcohol dipeptídico de iBoc-G(Chx)-3,4-isopropilidenprolinol puro (870 mg, 2,3 mmol, 67%)

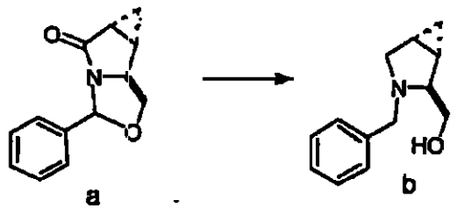
b) Paso de oxidación de Jones:

A una solución de alcohol dipeptídico de iBoc-G(Chx)-3,4-isopropilidenprolinol (100 mg, 0,26 mmol) en acetona (2 mL) agitando a 0°C se agregó Reactivo de Jones (300 µL) gota a gota durante 5 min. [Reactivo de Jones: Preparado a partir de trióxido de cromio (13,4 g) y ácido sulfúrico concentrado (11,5 mL) diluido con agua a un volumen total de 50 mL.] Luego de agitar a 0 °C durante 3 horas, se agregó isopropanol (500 µL) y se continuó la agitación durante un adicional de 10 minutos. La mezcla de reacción se diluyó con agua (20 mL) y se extrajo con acetato de etilo (3 x 70 mL). Las fases orgánicas combinadas se secaron, se filtraron y se concentraron para dar la iBoc-G(Chx)-3,4-isopropilidenprolina dipeptídica (100 mg, 0,25 mmol, 96%).

<u>Ejemplo X. Síntesis de N-Cbz-3,4-metanoprolina:</u>



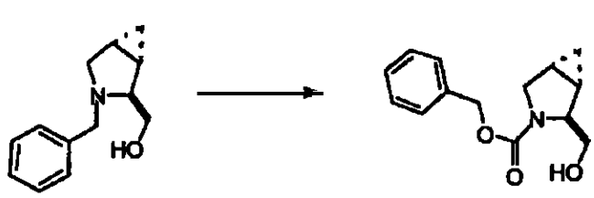
Paso 1. Síntesis del N-bencil-3,4-metanoprolinol:



a b

Una mezcla del material inicial bencilideno (J. Org. Chem. 1999, 64(2), 547) (4,6 gramos, 21,4 mmol) e hidruro doble de litio y aluminio (1,0 M en THF, 64 mL, 64 mmol) se calentó a reflujo durante 5 horas. Luego de enfriar hasta 0°C, el hidruro de aluminio restante se inactivó cuidadosamente con el agregado gota a gota de sulfato de sodio acuoso saturado (5 mL) durante 15 min. La mezcla se diluyó con acetato de etilo (200 mL) y luego se filtró a través de celite. El filtrado se secó con sulfato de sodio, se filtró y se concentró para dar alcohol de N-bencilamino en bruto (3,45 gramos), que se llevó al paso siguiente sin purificación adicional.

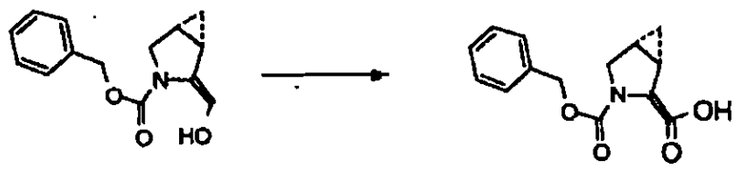
Paso 2. Síntesis de N-benciloxicarbonil-3.4-metanoprolinol (CBz-P(3 4-CH2)o



Una solución de alcohol de N-bencilamino en bruto (3 gramos, 14,76 mmol) en metanol (120 mL) y HCl concentrado (1,5 mL) con 10% de Pd/C (300 mg) se hidrogenó a 50 psi durante 16 horas. La mezcla de reacción se filtró para quitar el catalizador con base de carbono y el filtrado se concentró. El residuo se disolvió en agua/dioxano (100 mL) y se agregó diisopropiletilamina (3,2 mL). Se

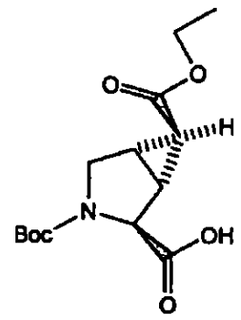
agregó cloroformiato de bencilo (2,76 mL, 16,2 mmol) y la reacción se agitó durante la noche. La mezcla de reacción se concentró, se disolvió en HCl 1M (100 mL) y se extrajo con acetato de etilo (3 x 200 mL). Las fases orgánicas combinadas se secaron con sulfato de magnesio, se filtraron y se concentraron. El residuo se purificó a través de cromatografía flash usando 1:3 acetato de etilo/hexanos para dar el N-Cbz-3,4-metanoprolinol (2,4 g)

Paso 3. Síntesis de N-benciloxicarbonil-3,4-metanoprolina (CBz-P(3,4-CH2)-OH):



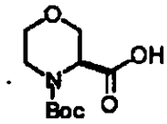
A una solución de N-Cbz-3,4-metanoprolinol (2,2 g, 8,90 mmol) en acetona (68 mL) agitando a 0°C, se agregó Reactivo de Jones (6,6 mL) gota a gota durante 5 min. [Reactivo de Jones: Preparado a partir de trióxido de cromio (13,4 g) y ácido sulfúrico concentrado (11,5 mL) diluido con agua a un volumen total de 50 mL.] Luego de agitar a 0 °C durante 3 horas, se agregó isopropanol (11 mL) y se continuó la agitación durante un adicional de 10 minutos. La mezcla de reacción se diluyó con agua (400 mL) y se extrajo con acetato de etilo (3 x 500 mL). Las fases orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se concentraron para dar N-Cbz-3,4-metanoprolina (2,25 g, 96%)

Ejemplo XI. Síntesis de Boc-(6S-carboetoximetan)prolina:



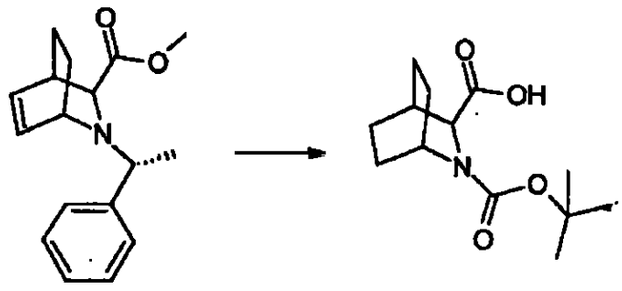
La síntesis del compuesto del título se llevó a cabo de acuerdo con el procedimiento publicado: Marinozzi, M.; Nataini, B.; Ni, M.H.; Costantino, G.; Pellicciari R. IL Farmaco (1995) 50 (5), 327-331.

Ejemplo XII. Síntesis del ácido Boc-3-morfolino carboxílico



La síntesis del compuesto del título se llevó a cabo de acuerdo con el procedimiento publicado: Kogami Y., Okawa, K. Bull. *Chem. Soc.* Jpn. (1987) 60, 2963-2965.

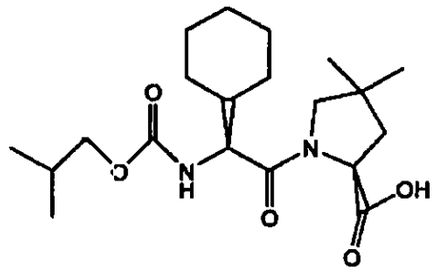
Ejemplo XIII. Síntesis del N-ter-butoxicarbonil 2-aza-3S-hidroxicarbonil-[2.2.2]-biciclooctano:



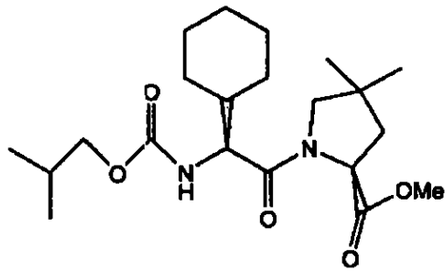
Una solución de 2-aza-2-(1-feniletil)-3S-metoxicarbonil-[2,2,2]-biciclooct-5-eno en bruto (10 mmol) (Tetrahedron (1992) 48(44) 9707-9718) y 10% de Pd sobre carbón (1 g) en metanol (30 mL) se acidificó con HCl 12N luego se hidrogenó a 50 psi durante 16 horas usando un aparato para hidrogenación de

Parr. La mezcla de reacción se filtró para quitar el catalizador con base de carbono y el filtrado se concentró. El residuo se disolvió en HCl concentrado y se agitó durante la noche. La solución se concentró y se disolvió nuevamente en acetonitrilo (50 mL). Se agregaron diisopropiletilamina (3,5 mL) y di-ter-butildicarbonato (1 g). La mezcla de reacción se agitó durante 24 horas y luego se concentró. El residuo se disolvió en CH_2Cl_2 y 5% de ácido sulfúrico acuoso. La mezcla de reacción se extrajo con CH2Cl2 y las fases orgánicas combinadas se concentraron. El residuo se disolvió en 10% bicarbonato de sodio saturado, se lavó con éter dietílico (2 x) y se acidificó con 5% de ácido sulfúrico acuoso. La fase de agua se extrajo con acetato de etilo (2 x). Las fases combinadas de acetato de etilo se secaron se filtraron y se concentraron para dar N-ter-butoxicarbonil 2-aza-3S-hidroxicarbonil[2,2,2]-biciclooctano (650 mg).

Ejemplo XIV. Síntesis de isobutiloxicarbonil-ciclohexilglicil-4,4-dimetilo prolina (iBoc-G(Chx)-P(4,4-dimetil)-OH):



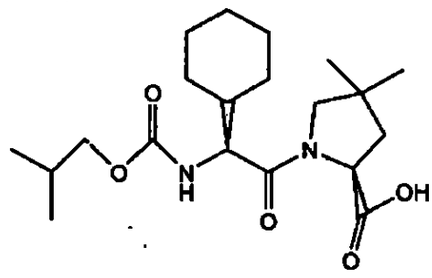
Paso I. Síntesis de iBoc-G(Chx)-P(4,4-dimetil)-OMe:



A una solución de iBoc-G(Chx)-OH (Ejemplo IX, Paso 1.) (377 mg, 1,95 mmol) en acetonitrilo (7 mL) se agregó sucesivamente HCl-HN-Pro(4,4-dimetil)-

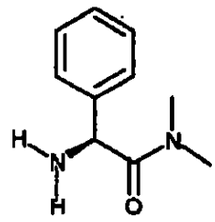
OMe (Ejemplo I, paso 6) (377 mg, 1,95 mmol), N-hidroxibenzotriazol (239 mg, 1,75 mmol), TBTU (845 mg, 2,63 mmol) y diisopropiletilamina (1,35 mL, 7,8 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se concentró y el residuo restante se disolvió en acetato de etilo. La fase orgánica se lavó dos veces con porciones de 10 ml de solución saturada de bicarbonato de sodio, solución clorhídrica 1N, y salmuera. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró hasta lograr un sólido blanco (612 mg, 79%).

Paso 2. Síntesis de iBoc-G(Chx)-P(4,4-dimetil)-OH:

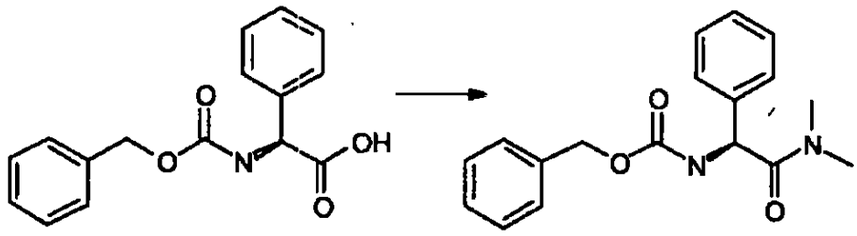


El metil éster obtenido en el Paso 1 anterior (612 mg, 1,54 mmol) en metanol (6 ml) se saponificó en presencia de hidróxido de litio 2M (1,16 ml) durante tres horas. El metanol se eliminó bajo presión reducida y el residuo restante se diluyó con acetato de etilo y se acidificó hasta un pH=2 con ácido clorhídrico 1N. Las fases se separaron y la fase orgánica se lavó con agua y salmuera, se secó sobre sulfato de sodio, se filtró y se concentró.

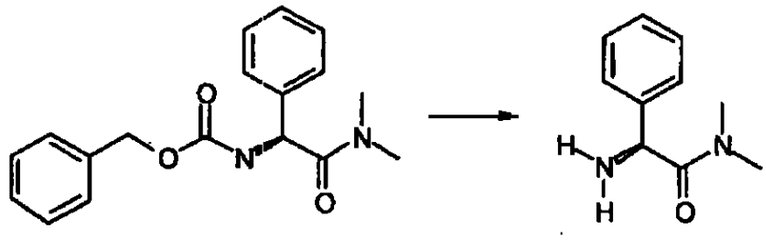
Ejemplo XV. Síntesis de dimetilamida de la L-fenilglicina



Paso 1. Síntesis de la dimetilamida de la N-benciloxicarbonil-L-fenilglicina (CBz-Phg-NMe2):



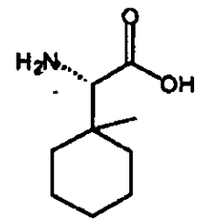
La N-benciloxicarbonil-L-fenilglicina (25 g, 88 mmols) se disolvió en THF (800 mL) y se enfrió hasta -10°C. Se agregaron N-metilmorfolina (9,7 mL, 88 mmols) y isobutilcloroformiato (11,4 mL, 88,0 mmols) y la mezcla se dejó agitar durante 1 minuto. Se agregó dimetilamina (100 mL, 2M en THF) y la reacción se dejó entibiar hasta alcanzar la temperatura ambiente. La mezcla se filtró y el filtrado se concentró al vacío para lograr dimetilamida de la N-benciloxicabonil-L-fenilglicina (32,5 g) como un aceite amarillo.



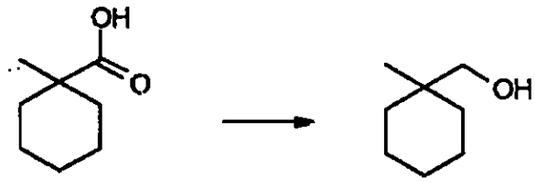
Paso 2. Síntesis de la dimetilamida de la L-fenilglicina (H-Phg-NMe2):

La dimetilamida de la N-benciloxicarbonil-L-fenilglicina (32,5 g) obtenida anteriormente se disolvió en metanol (750 ml) y se agregó 10% de paladio sobre carbón activado (3,3 g). Esta mezcla se hidrogenó en un aparato de Parr a 35 psi de hidrógeno durante 2 horas. La mezcla de reacción se filtró y el solvente se eliminó al vacío y el residuo se recristalizó a partir de metanol-hexanos para lograr dimetilamida de la fenilglicina (26 g) como un sólido blancuzco. El ee de este material se determinó en >99% a través del análisis por HPLC del derivado de 2,3,4,6-tetra-O-acetilglucopiranosiltioisocianato.

Ejemplo XVI. Síntesis de la (1-metilciclohexil)glicina:



Paso 1. 1-metil-1-hidroximetilciclohexano



A una solución de 1-metil-1-hidroxicarbonilciclohexano (10 g, 70 mmol) en tetrahidrofurano(300 mL) a 0°C se agregó diborano 1M en tetrahidrofurano (200 mL, 200 mmol) durante 90 minutos. El baño de frío se eliminó y la mezcla de reacción se agitó a temperatura ambiente durante dos días. El borano restante se inactivó a través del agregado lento de bisulfato de sodio saturado (10 mL) durante 90 min con frío. Se agregó bisulfato de sodio saturado adicional (200 mL) y luego de 20 min de agitación la fase de agua se eliminó. La fase orgánica se lavó con agua y cloruro de sodio saturado, se secó, se filtró y se concentró. El residuo se purificó a través de cromatografía flash usando 20% éter dietílico en hexanos para dar 1-metil-1-hidroximetilciclohexano (6,17 g, 48 mmol, 69%).

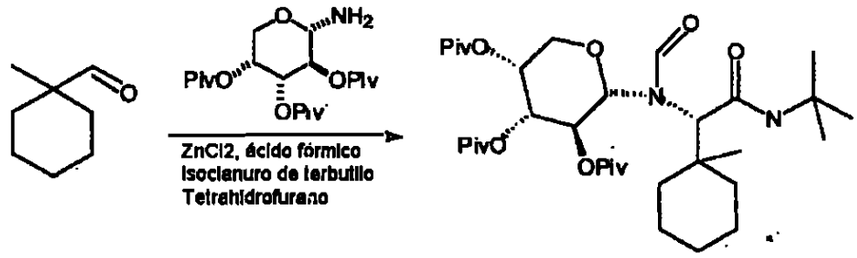
Paso 2. 1-metilciclohexilcarboxaldehído:



A una solución de 1-metil-1-hidroximetilciclohexano (6,17 g, 48 mmol) y trietilamina (20,1 mL, 144 mmol) en diclorometano (150 mL) a 0°C, se agregó una solución de complejo de trióxido de azufre y piridina (22,9 g, 144 mmol) en dimetilsulfóxido (150 mL) durante 15 min. El baño de frío se dejó entibiar hasta

alcanzar la temperatura ambiente durante dos horas, tiempo en el cual la mezcla de reacción se vertió en salmuera con hielo (400 mL). Las fases se separaron y la fase de agua se extrajo con diclorometano (200 mL). Las fases orgánicas combinadas se diluyeron con hexanos (600 mL) y se lavaron con HCl 1M (2 x 150 mL), cloruro de sodio saturado (2 x 100 mL), se secaron, se filtraron y se concentraron. El residuo se purificó a través de cromatografía flash para dar 1-metilciclohexilcarboxaldehído (1,77 g, 13,8 mmol, 29%).

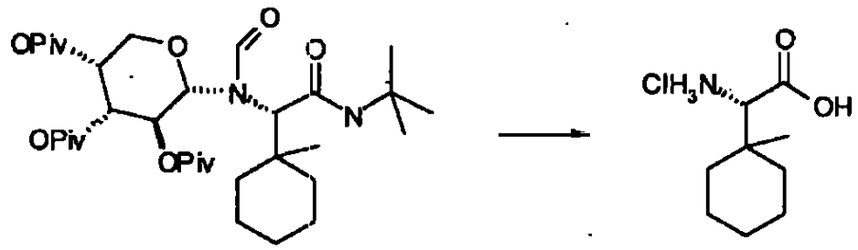
Paso 3. Síntesis de N-formil-N-glicosil-1-metilciclohexil- ter-butilamida



La síntesis de la 2,3,4-tri-O-pivaloil-O-D-arabinosilamina se llevó a cabo de acuerdo con el procedimiento publicado (Kunz. H.; Pfrengle, W.; Ruck, K.; Wilfried, S. *Síntesis de* (1991) 1039-1042).

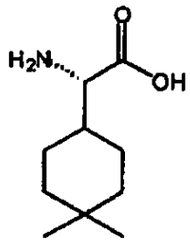
A una solución de 1-metilciclohexilcarboxaldehído (1,17 g, 8,34 mmol), 2,3,4-tri-O-pivaloil-□-D-arabinosilamina (8,3 g, 20,7 mmol), ácido fórmico (850 µL, 22,2 mmol) y ter-butilisocianuro (2,4 mL, 21,2 mmol) en tetrahidrofurano (170 mL) a -30°C se agregó cloruro de zinc 0,5M en tetrahidrofurano (41 mL, 20,57 mmol). La solución se agitó a -20 °C durante 3 días, luego se concentró. El residuo se diluyó con CH_2Cl_2 (500 mL), se lavó con bicarbonato de sodio saturado (2 x 500 mL), agua (500 mL). La fase orgánica se secó, se filtró y se concentró para dar un aceite claro. La cromatografía flash (20% acetato de etilo en hexanos) proveyó el producto puro (4,3 g, 6,6 mmol, 33%)

Paso 4. Síntesis de (1-metilciclohexil)glicina:

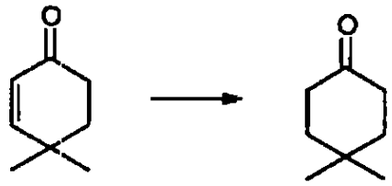


Una solución del producto obtenido en el paso 3 anterior (4,3 g, 6,6 mmol) en diclorometano (30 mL) y HCl de metanol anhidro saturado (30 mL) se agitó durante la noche. La solución se concentró y el residuo se disolvió en agua (100 mL) y se lavó con pentano (2 x 100 mL). La fase de agua se concentró y el residuo se disolvió en HCl 6N (50 mL) y se calentó a reflujo durante 30 horas. La solución se concentró para dar el clorhidrato de (1-metilciclohexil)glicina en bruto (790 mg, 3,82 mmol, 58%).

Ejemplo XVII. Síntesis de (4,4-dimetilciclohexil)glicina:



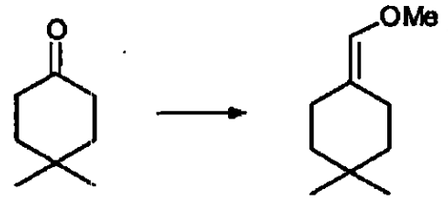
Paso 1. Síntesis de la 4,4-dimetilciclohexanona:



Una mezcla de 4,4-dimetilciclohex-2-en-1-ona (12 mL, 91,2 mmol) y 10% de Pd sobre carbón tipo Degussa (2 g) se hidrogenó a 40 psi durante 18 horas. La mezcla se filtró y se concentró (la ^{1}H RMN mostró una mezcla de cetona y alcohol en una relación 5:3). La mezcla se disolvió en acetona (400 mL) y se enfrió hasta 0°C. Se agregó reactivo de Jones (40 mL) durante 30 min y el baño

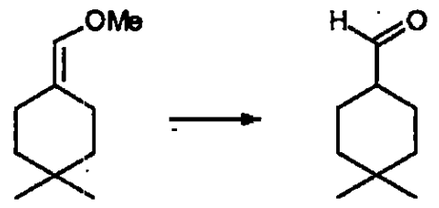
de frío se eliminó. Luego de 2 días el exceso de acetona se evaporó y el residuo resultante se disolvió en agua y éter dietílico. La fase de éter se lavó con agua hasta que resultó incolora, se secó, se filtró y se concentró para dar 4,4-dimetilciclohexanona (7,4 g, 58,6 mmol, 64%).

Paso 2. Síntesis del metil enol éter del 4,4-dimetilciclohexilcarboxaldehído:



A una solución de cloruro de metoximetil trifenilfosfonio (8,6 g) en tetrahidrofurano (125 mL) a 0°C se agregó n-butil litio (1,6M en hexanos, 14,3 mL) durante 10 min. Luego de 30 min la mezcla de reacción se enfrió hasta -78°C y una solución de 4,4-dimetilciclohexanona (2,45 g, 19,1 mmol) en tetrahidrofurano (50 mL) se agregó durante 20 min. Luego de 1 hora el baño de frío se eliminó y la reacción se entibió lentamente hasta 0°C. La reacción se diluyó con cloruro de amonio saturado (50 mL), acetato de etilo (100 mL) y hexanos (100 mL). La fase orgánica se lavó con agua y salmuera, se secó, se filtró y se concentró. El residuo se agitó con hexanos (70 mL) durante 10 min y se filtró. El filtrado se concentró y se cromatografió usando 25% de acetato de etilo en hexanos para dar el compuesto del título (1,925 g, 12,5 mmol, 65%).

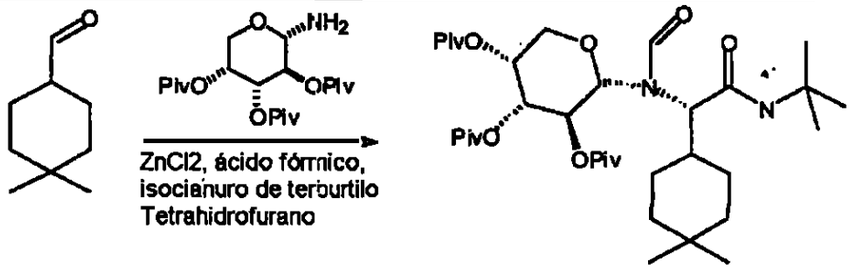
Paso 3: 4,4-dimetilciclohexilcarboxaldehído:



Una solución del metil enol éter del 4,4-dimetilciclohexilcarboxaldehído (1,925 g, 12,5 mmol) (Paso II anterior), tetrahidrofurano (100 mL) y HCl 6M (20

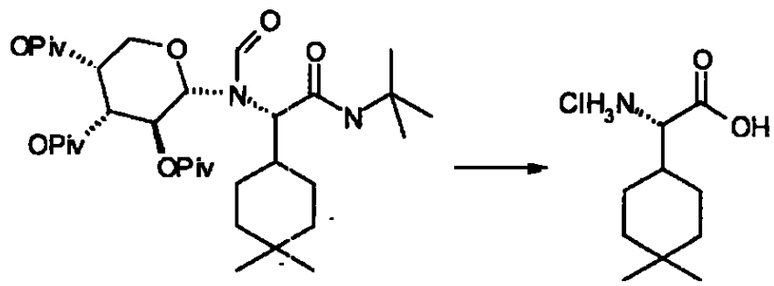
mL) se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se diluyó con hexanos, éter dietílico, salmuera y agua. La fase orgánica se secó, se filtró y se concentró para dar 4,4-dimetilciclohexilcarboxaldehído (1,0 g, 7,1 mmol, 57%).

Paso 4 Síntesis de N-formil-N-glicosil- 4,4-dimetilciclohexil- ter-butilamida



A una solución de 4,4-dimetilciclohexilcarboxaldehído (1,17 g, 8,34 mmol), 2,3,4-tri-O-pivaloil-α-D-arabinosilamina (3,43 g, 8,55 mmol), ácido fórmico (350 µL, 9,17 mmol) y ter-butilisocianuro (990 µL, 8,76 mmol) en THF (70 mL) a -30°C se agregó cloruro de zinc 0,5M en tetrahidrofurano (17 mL, 8,5 mmol). La solución se agitó a -20 °C durante 2 días, luego se concentró. El residuo se diluyó con diclorometano (200 mL), se lavó con bicarbonato de sodio saturado (2 x 200 mL), agua (200 mL). La fase orgánica se secó, se filtró y se concentró para dar un aceite claro. La cromatografía flash (20% acetato de etilo en hexanos) proveyó el producto puro (2,1 g, 3,3 mmol, 39%)

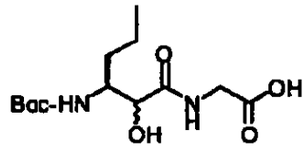
Paso 5. Síntesis de la (4,4-dimetilciclohexil)glicina:



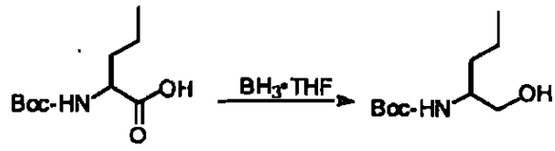
Una solución del producto de Ugi obtenido en el Paso 4 anterior (2,1 g, 3,3 mmol) en diclorometano (20 mL) y HCl de metanol anhidro saturado (20 mL) se

agitó durante la noche. La solución se concentró y el residuo se disolvió en agua (100 mL) y se lavó con pentano (2 x 100 mL). La fase de agua se concentró y el residuo se disolvió en HCl 6N (40 mL) y se calentó a reflujo durante 30 horas. La solución se concentró para dar el clorhidrato de (1-metilciclohexil)glicina en bruto (300 mg, 1,36 mmol, 41 %).

Ejemplo XVIII. Síntesis de Boc-nVal-(CHOH)-Gly-OH:

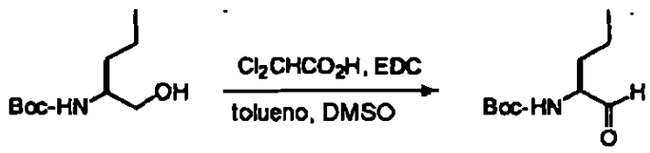


Paso 1. Preparación de Boc-norvalinol:



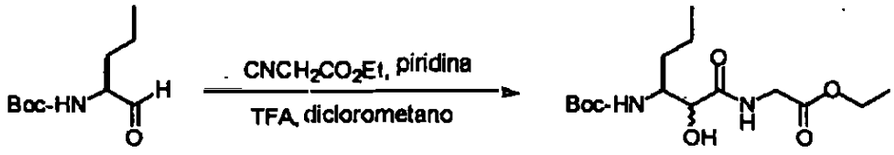
A una solución de Boc-norvalina (25,0 g, 0,115 mol) en tetrahidrofurano (461 mL), enfriada hasta 0°C, se agregó complejo de borano/ tetrahidrofurano (461 mL de una solución 1,0 M en tetrahidrofurano) gota a gota. Luego de 1 h a 0°C, la solución se entibió hasta alcanzar la temperatura ambiente durante un período de 1,5h. La TLC indicó que la reacción estaba completa. Se agregó metanol para inactivar la reacción. La solución se concentró para dar como rendimiento el compuesto del título (22,56 g, 96%) como un jarabe con aspecto espumoso. La TLC de los productos indicó pureza satisfactoria. Rf = 0,34 (40% de acetato de etilo/hexanos).

Paso 2. Preparación de Boc-norvalinal:



A Boc-norvalinol (7,77 g, 38 mmol), en dimetilsulfóxido anhidro (153 mL) y tolueno (153 mL) se agregó EDC (73,32 g, 382 mmol). Luego de que la solución se enfrió hasta 0°C, se agregó ácido dicloroacético (15,8 mL, 191 mmol) gota a gota. Después de completar la adición, la reacción se agitó durante 15 min. La solución se dejó entibiar hasta alcanzar la temperatura ambiente durante un período de 2h. La mezcla de reacción se concentró para quitar el tolueno, luego se disolvió en acetato de etilo. La solución se lavó sucesivamente con bisulfato de sodio 1N, bicarbonato de sodio saturado y salmuera, se secó sobre sulfato de sodio, se filtró y se concentró para lograr Boc-norvalinal en bruto que se usó directamente en el paso siguiente . Rf de TLC = 0,84 (40% de acetato de etilo/hexanos).

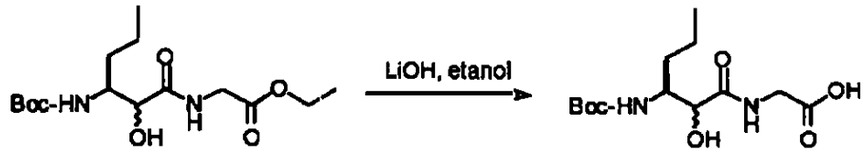
Paso 3. Síntesis de Boc-nVal-(CHOH)-Gly-OEt:



A una solución del Boc-norvalinal en bruto (4,18 g, 20,77 mmol) en diclorometano (83 mL) se agregó isocianoacetato de etilo (2,72 ml, 24,93 mmol) y piridina (6,72 ml, 83,09 mmol). Luego de que la solución se enfrió hasta 0°C, se agregó ácido trifluoroacético (4,15 ml, 41,54 mmol) gota a gota. Luego de agitar durante 1 h, la solución se agitó a temperatura ambiente durante 18 horas mientras se permitía que el solvente de la mezcla de reacción en un recipiente sin tapa se evapore en condiciones ambientales. La mezcla de reacción se concentró, luego se disolvió en acetato de etilo. La solución se lavó sucesivamente con bisulfato de sodio 1N, bicarbonato de sodio saturado y

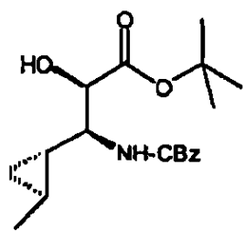
salmuera, se secó sobre sulfato de sodio, se filtró y luego se concentró. El residuo se purificó a través de cromatografía flash eluyendo con 20% hasta 40% de acetato de etilo/hexanos para lograr 2,8 g del compuesto del título como un jarabe amarillo. La espectroscopía de masa de baja resolución confirmó la presencia del producto deseado (MH+ 333).

Paso 4. Síntesis de Boc-nVal-(CHOH)-Gly-OH:

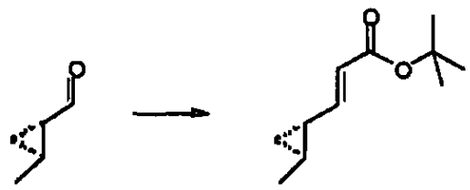


El producto obtenido (Boc-nVal-(CHOH)-Gly-OEt) (1,52 g, 4,70 mmol) disuelto en etanol (23 ml) se saponificó con hidróxido de litio 1N (18,81 ml) durante dos horas a temperatura ambiente. La mezcla de reacción se acidificó hasta un pH = 2 con resina de intercambio de iones Dowex© 50 WX8, se agitó durante 20 minutos y luego se filtró. La resina se lavó bien con etanol y agua y los filtrados combinados se concentraron hasta obtener una espuma blanca (0,48 g, 33%).

Ejemplo XVIV. Síntesis de N-CBz-3-amino-2-hidroxi-4,5-metilen-hexanoato de (2R,3S,4S,5S)-ter-Butilo:

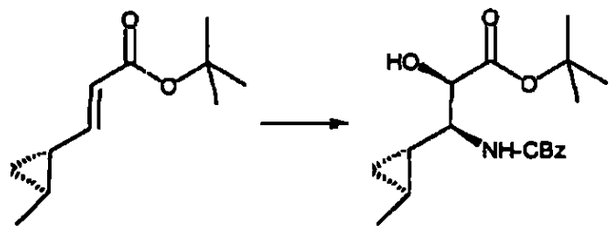


Paso 1:



A una solución de dietilfosfonoacetato de ter-butilo (4,7 mL, 20 mmol) disuelto en THF (50 mL) a -78° C se agregó n-butil litio 1,6M en hexanos (12,4 mL). Luego de 30 minutos se agregó (1S,2S)-2-metilciclopropilcarboxaldehído (1 g, 12 mmol) (Barrett, A. G. M.; Doubledía, W. W.; Kasdorf, K.; Tustin, G. J., J. Org. Chem. (1996) 61, 3280) en éter dietílico (100 mL) durante 10 min. La reacción se entibió to 0° C durante 2 horas y hasta 6°C durante 12 horas. La reacción se inactivó con cloruro de amonio saturado (20 mL) y la fase orgánica se separó, se lavó con 50 mL de salmuera y se secó sobre sulfato de sodio, se filtró y se concentró para lograr 3,5 g de un aceite claro. La cromatografía flash (20% acetato de etilo en hexanos) produjo ter-butiléster puro insaturado (1,4 g).

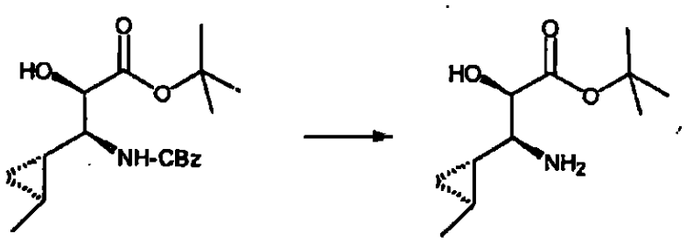
Paso 2:



A una solución de carbamato de bencilo (3,558, 23,5 mmols) en n-propanol (24 mL) se agregó una solución de hidróxido de sodio (900 mg, 22,7 mmol) en agua (48 mL), seguido de ter-butilhipoclorito (2,57 mL, 22,7 mmol). Luego de 15 minutos la reacción se enfrió hasta 0°C y se agregó $(DHQ)_2PHAL$ (350 mg, 0,45 mmol) en n-propanol (24 mL), seguido de éster terbutílico insaturado (1,4 g) del paso anterior en n-propanol (48 mL). Finalmente se agregó osmiato de potasio (110 mg, 0,30 mmol) en agua (2 mL) y la solución desarrolló muy rápidamente un

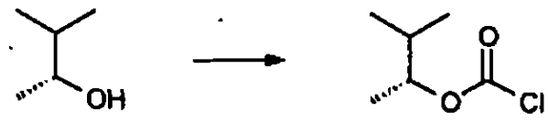
color verde oscuro que persistió durante 4 horas. Luego de 6 horas se agregó sulfato de sodio saturado (50 mL) y la mezcla se extrajo con acetato de etilo (2 x 50 mL). Las fases orgánicas combinadas se lavaron con salmuera (30 mL), se secaron sobre sulfato de sodio, se filtraron y se concentraron. La cromatografía flash con 20% de acetato de etilo en hexanos produjo el amino ter-butiléster protegido con cBz deseado como un sólido blanco (316 mg).

Paso 3:



Una mezcla de Amino terbutil éster protegido con CBz (316 mg, 0,9 mmol) y 32 mg de 10% de paladio sobre carbón en 9 mL metanol se hidrogenó durante 8 horas. La mezcla se filtró y se concentró para lograr la amina libre como un aceite claro (195 mg).

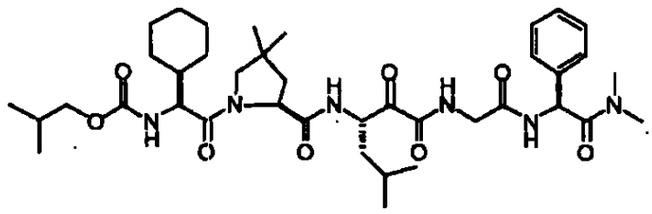
Ejemplo XX. Síntesis del cloroformiato de 1R,2-dimetilPropilo:



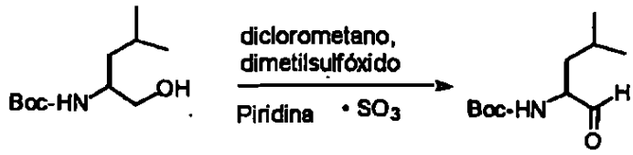
Al 2R-hidroxi-3-metilbutano comercial (410 mg, 4,65 mmol) se agregó una solución de 20% de fosgeno en tolueno (1 mL, 2 mmol). La solución se agitó durante 6 horas para generar el cloroformiato (2 mmol) que se reaccionó directamente e inmediatamente con la amina deseada. El S-isómero se sintetizó a través del mismo procedimiento.

II) Síntesis representativa en fase en solución de los inhibidores de HCV

Ejemplo XXI. Síntesis de fase en solución de iBoc-G(Chx)-Pro(4,4-dimetil)-Leu-(CO)-Gly-Phg-dimetilamida:

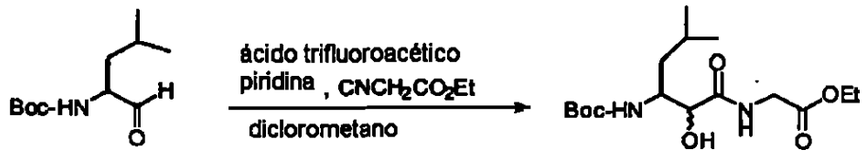


Paso 1. Síntesis de ter-butiloxicarbonil-leucinal (Boc-Leu-CHO):



A una solución del Boc-Leucinol comercial (Advanced Chem Tech) (0,78 g, 3,6 mmol) en diclorometano anhidro (17,5 ml) se agregó trietilamina (2 ml, 14,36 mmol) y la mezcla se enfrió hasta 0°C. Se agregó dimetil sulfóxido (17,5 ml) seguido de complejo de trióxido de azufre piridina (2,3 g, 14,36 mmol) y la reacción se agitó durante dos horas. La TLC en 1:1 de acetato de etilo: hexanos confirmó que la reacción estaba completa. La mezcla de reacción se concentró y el residuo restante se diluyó con acetato de etilo. La fase de acetato de etilo se lavó con ácido clorhídrico 1 M (2 x 75 ml) seguido de solución saturada de bicarbonato de sodio (2 x 75 ml) y salmuera (75 ml). La fase orgánica se secó (sulfato de sodio), se filtró y se concentró para dar como rendimiento 775 mg de producto.

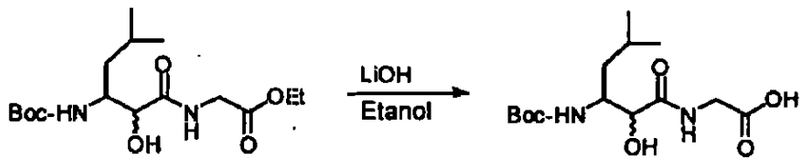
Paso 2. Síntesis del etil éster de la Boc-2-hidroxi-3-amino-5-metil hexanoil-glicina (Boc-Leu-(CHOH)-Gly-OEt):



A una solución de Aldehído de Boc-Leucina (0,77 g, 3,59 mmol) en diclorometano anhidro (24 ml) se agregó piridina anhidra (1,16 ml, 14,36 mmol) e isocianoacetato de etilo (0,4 ml, 4,66 mmol). La mezcla de reacción se enfrió

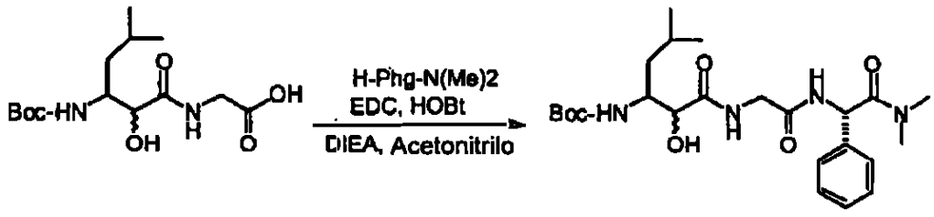
hasta 0°C y se agregó ácido trifluoroacético (0,55 ml, 7/18 mmol) durante dos minutos. La mezcla de reacción se tapó y se agitó a 4 °C durante cuatro días, y a temperatura ambiente durante un día. La mezcla de reacción se diluyó con diclorometano (350 ml) y se lavó dos veces cada una con porciones de 75 ml de ácido clorhídrico 1M, bicarbonato de sodio saturado y salmuera. La fase orgánica se secó, se filtró y se concentró. El residuo obtenido se sometió a cromatografía flash en una columna de gel de sílice de 2" X 6" (4,98 cm x 19,94 cm) usando 10% de acetato de etilo en hexanos (800 ml) seguido de 1:1 de acetato de etilo en hexanos (800 ml). Las fracciones correspondientes al producto se reunieron y se concentraron para dar como rendimiento 980 mg (79%) de producto.

Paso 3. Síntesis de Boc-Leu-(CHOH)-Gly-OH:



A una solución de Boc-Leu-(CHOH)-Gly-Oet (0,98 g, 2,83 mmol) en etanol (11,3 ml) se agregó hidróxido de litio 2M (4,25 ml) y la reacción se agitó durante cinco horas a temperatura ambiente. El etanol se eliminó bajo presión reducida y la fase de agua se diluyó con acetato de etilo. La fase orgánica se lavó con ácido clorhídrico 1M seguido de salmuera, se secó, se filtró y se concentró para dar como rendimiento 775 mg (86%) de producto como un sólido blanco.

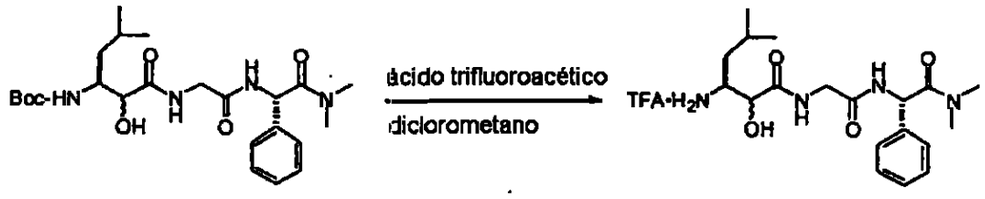
Paso 4. Síntesis de Boc-Leu-(CHOH)-Gly-Pha-dimetilamida:



A una solución de Boc-Leu-(CHOH)-Gly-OH (0,37 g, 1,18 mmol) en acetonitrilo (23 ml) se agregó sucesivamente dimetilamida de la fenilglicina

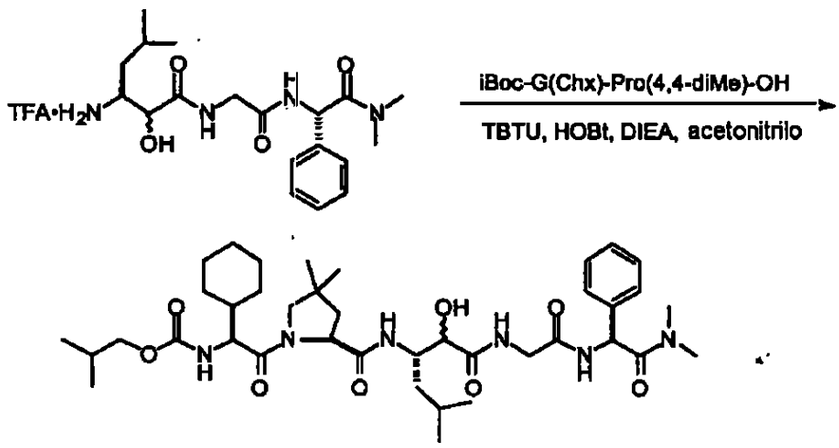
(obtenida en el Ejemplo XV, Paso 2), EDC (0,34 g, 1,76 mmol), N-hidroxibenzotriazol (HOBt) (0,18 g, 1,18 mmol) y diisopropiletilamina (DIEA) (0,82 ml, 4,7 mmol) y la reacción se agitó durante 18 horas a temperatura ambiente. La mezcla de reacción se concentró y el residuo restante se diluyó con acetato de etilo y se lavó sucesivamente con dos porciones de 75 ml de ácido clorhídrico 1M, bicarbonato de sodio saturado y salmuera. La fase orgánica se secó luego, se filtró y se concentró. El producto en bruto se sometió a cromatografía flash en una columna de gel de sílice de 2" x 6" (4,98 cm x 14,94 cm) usando 4:1 de acetato de etilo: hexanos (700 ml) seguido de acetato de etilo (1000 ml) y 10% de metanol en diclorometano (600 ml). Las fracciones correspondientes al producto se reunieron y se concentraron para dar como rendimiento 445 mg (80%) de sólido blanco.

Paso 5. Síntesis de H-Leu-(CHOH)-Gly-Phg-dimetilamida, sal de trifluoroacetato:



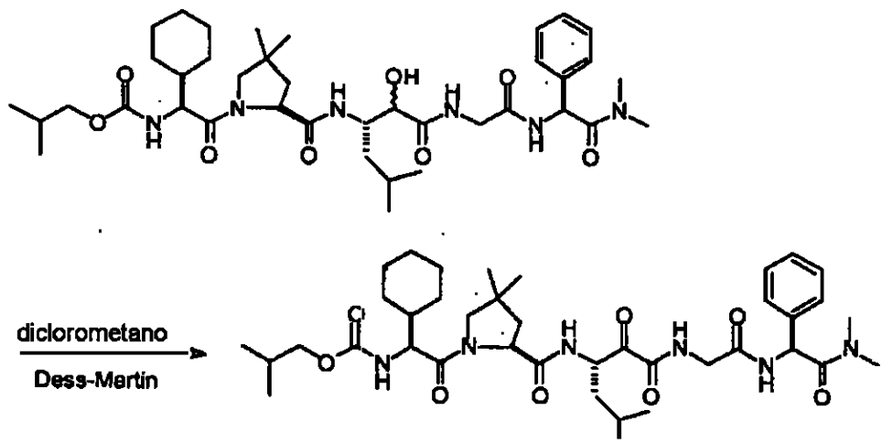
A una solución de Boc-Leu-(CHOH)-Gly-Phg-dimetilamida (70 mg, 0,146 mmol) en diclorometano (1 ml) se agregó ácido trifluoroacético (1 ml) y la reacción se agitó a temperatura ambiente durante 1 hora. La mezcla de reacción se concentró y se llevó al paso siguiente sin purificación adicional.

Paso 6 Síntesis de la iBoc-G(Chx)-Pro(4,4-dimetil)-Leu-(CHOH)-Gly-Phg-dimetilamida:



A una solución de iBoc-G(Chx)-P(4,4-diMe)-OH (Ejemplo XIV, paso 2) (53 mg, 0,148 mmol) en acetonitrilo (3 ml) se agregó sucesivamente TFA•2HN-Leu(CHOH) Gly-Phg-NMe2 (61 mg, 0,148 mmol), N-Hidroxibenzotriazol (HOBt) (23 mg, 0,148 mmol), TBTU (71,5 mg, 0,222 mmol y diisopropiletilamina (103 111, 0,593 mmol). La reacción se agitó a temperatura ambiente durante 18 horas y se concentró. El residuo restante se disolvió en acetato de etilo y se lavó con ácido clorhídrico 1M (2 x 5 ml), solución saturada de bicarbonato de sodio (2 x 5 ml), y salmuera (2 x 5 ml). La fase orgánica se secó, se filtró y se concentró. El producto (100 mg) se llevó al paso siguiente sin purificación adicional.

Paso 7. Síntesis de iBoc-G(Chx)-Pro(4,4-dimetil)-Leu-(CO)-Gly-Phg-dimetilamida:



A una solución de iBoc-G(Chx)-Pro(4,4-dimetil)-Leu-(CHOH)-Gly-Phg-dimetilamida (30 mg, 0,04 mmol) en diclorometano (1 ml) se agregó el reactivo de Dess-Martin comercial (Omega Chemical Company Inc.) (67,8 mg, 0,16 mmol) y la reacción se agitó a temperatura ambiente durante 90 minutos. La mezcla de reacción se concentró y el residuo restante se agitó en 5% de tiosulfato de sodio. Se diluyó luego con diclorometano y las fases se separaron. La fase orgánica se lavó con tiosulfato de sodio (4 x 3 ml), seguido de agua y salmuera. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró. El producto en bruto se disolvió en hexanos y alcohol isopropílico y se sometió a purificación por HPLC usando una columna de silice Kromasil 5 de fase normal (Phenomenex, 250 x 21,20 mm, tamaño de poros de 100 angstrom, partículas de gel de 5 pm) eluyendo con un gradiente a 30 minutos formado por 0 hasta 25% de alcohol isopropílico en hexanos (25 ml/minutos). Las fracciones correspondientes al producto se reunieron y se concentraron. La liofilización a partir de agua dio como rendimiento 6,7 mg de polvo blanco. Los espectros de masa de baja resolución confirmaron la masa deseada (MH^+ = 741,4).

III) Síntesis en Fase Sólida:

La Síntesis en fase sólida es útil para la producción de pequeñas cantidades de ciertos compuestos de la presente invención. Como con la síntesis convencional en fase sólida de los péptidos, los reactores para la síntesis de fase

sólida de las peptidil cetoamidas están formados por un recipiente de reactor con por lo menos una superficie permeable al solvente y los reactivos disueltos, pero no permeable a la resina de la síntesis de un tamaño de malla seleccionado. Dichos reactores incluyen recipientes de reacción de fase sólida de vidrio con una frita de vidrio sinterizado, tubos de polipropileno o columnas con fritas, o el reactor KansTM fabricado por Irori Inc., San Diego CA. El tipo de reactor elegido depende del volumen de resina de fase sólida que se necesite, y pueden usarse diferentes tipos de reactor en las diferentes etapas de una síntesis. Los siguientes procedimientos se mencionarán en los ejemplos posteriores:

Procedimiento A: *Reacción de acoplamiento:* A la resina suspendida en N-metilpirrolidina (NMP) (10-15 mL/ gramo de resina) se agregó Aminoácido Fmoc (2 eq), HOAt (2 eq), HATU (2 eq) y diisopropiletilamina (4 eq). La mezcla se dejó reaccionar durante 448 horas. Los reactivos se drenaron y la resina se lavó sucesivamente con dimetilformamida, diclorometano, metanol, diclorometano y éter dietílico (usar 10-15 mL de solvente/ gramo de resina). La resina se secó luego al vacío.

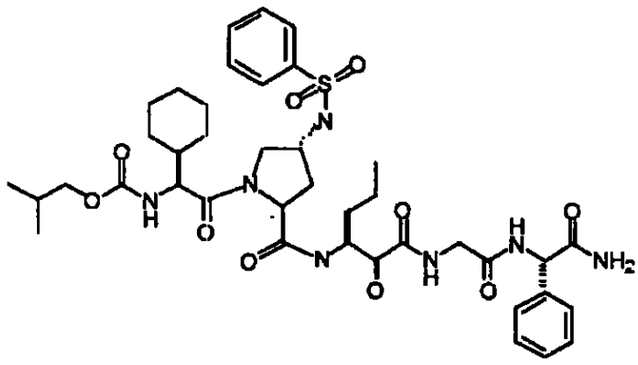
Procedimiento B: *Desprotección de Fmoc:* La resina protegida por Fmoc se trató con 20% de piperidina en dimetilformamida (10 mL de reactivo/ gramo de resina) durante 30 minutos. Los reactivos se drenaron y la resina se lavó sucesivamente con dimetilformamida, diclorometano, metanol, diclorometano y éter dietílico (10 mL de solvente/ gramo de resina).

Procedimiento C: *Desprotección de Boc:* La resina protegida por Boc se trató con una mezcla a 1:1 de diclorometano y ácido trifluoroacético durante 20-60 minutos (10 mL de solvente/ gramo de resina). Los reactivos se drenaron y la resina se lavó sucesivamente con diclorometano, dimetilformamida, 5% de diisopropiletilamina en dimetilformamida, dimetilformamida, diclorometano y dimetilformamida (10 mL de solvente/ gramo de resina).

Procedimiento D: *Hidrólisis de semicarbazona*: La resina se suspendió en el coctail de disociación (10 mL/ gramo de resina) formado por ácido trifluoroacético: ácido pirúvico: diclorometano: agua 9:2:2:1 durante 2 horas. Los reactivos se drenaron y el procedimiento se repitió tres veces más. La resina se lavó sucesivamente con diclorometano, agua y diclorometano y se secó al vacío.

Procedimiento E: *Disociación de HF*: La resina peptídica-nVal(CO)-G-O-PAM seca (50 mg) se colocó en un recipiente de HF que contiene una pequeña barra de agitación. Se agregó anisol (10% del volumen total) como depurador. En presencia de ácido glutámico y aminoácidos de cisteína, se agregaron también tioanisol (10%) y 1,2-etanditiol (0,2%). El recipiente de HF al aparato de HF (Immuno Dynamics) y el sistema se enjuagó con nitrógeno durante cinco minutos. Luego se descendió la temperatura hasta -70°C con un baño de hielo seco/ isopropanol. Luego de 20 minutos, el HF se destiló al volumen deseado (10 mL de HF/ gramo de resina). La reacción se dejó evolucionar durante una hora y media a 0°C. El procesamiento consistió en la eliminación de la totalidad de HF usando nitrógeno. Luego se agregó diclorometano a la resina y la mezcla se agitó durante cinco minutos. A esto le siguió el agregado de 20% de ácido acético en agua (4 mL). Luego de agitar durante 20 minutos, la resina se filtró usando un embudo fritado y el diclorometano se eliminó bajo presión reducida. El residuo restante y la mezcla se lavó con hexanos (2 x) para quitar los depuradores. Mientras tanto, la resina se remojó en 1 mL de metanol. La fase de agua (20% de HOAc) se agregó nuevamente a la resina y la mezcla se agitó durante cinco minutos y luego se filtró. El metanol se eliminó bajo presión reducida y la fase de agua se liofilizó. El péptido se disolvió luego en 10-25% de metanol (que contenía 0,1 % de ácido trifluoroacético) y se purificó a través de HPLC de fase inversa.

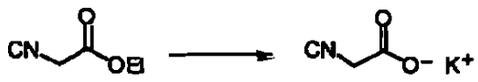
Ejemplo XXII: Síntesis en Fase Sólida Representativa de los inhibidores de Hep C: (iBoc-G(Chx)-P(4t-NHSO2Ph)-nV-(CO)-G-G(Ph)-NH2)



Paso 1. Síntesis de Fmoc-nV-(dpsc)-Glv-OH:

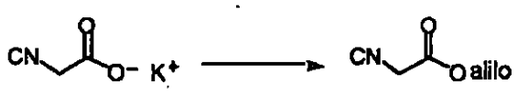
A) Síntesis del isocianoacetato de alilo (pasos a-b más adelante):

a) Síntesis de la sal de potasio del ácido isocianoacético:



Se agregó isocianoacetato de etilo (96,6 ml, 0,88 mol) gota a gota a una solución congelada de etanol (1,5 L) y hidróxido de potasio (59,52 g, 1,0 mol). La reacción se entibió lentamente hasta alcanzar la temperatura ambiente. Luego de dos horas el producto precipitado se filtró en un embudo de vidrio y se lavó con varias porciones de etanol congelado. La sal de potasio del ácido isocianoacético así obtenida se secó al vacío hasta obtener un sólido marrón-dorado (99,92 g, 91,8%).

b) Síntesis del isocianoacetato de alilo:

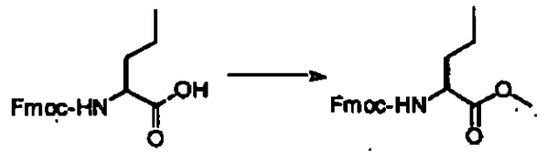


Al producto de la parte a (99,92 g, 0,81 mol) disuelto en acetonitrilo (810 ml) se agregó bromuro de alilo (92 ml, 1,05 mol). Luego de calentar a reflujo durante cuatro horas se obtuvo una solución marrón oscuro. La mezcla de reacción se concentró y el residuo restante se disolvió en éter (1,5 L) y se lavó tres veces con agua (500 ml). La fase orgánica se secó, se filtró y se concentró

hasta obtener un jarabe marrón oscuro. El producto en bruto se purificó por destilación al vacío a 7 mm Hg (98°C) hasta obtener un aceite claro (78,92 g, 78%). RMN δ ppm ($CDCl_3$): 5,9 (m, 1 H), 5,3 (m, 2H), 4,7 (d, 2H), 4,25 (s, 2H).

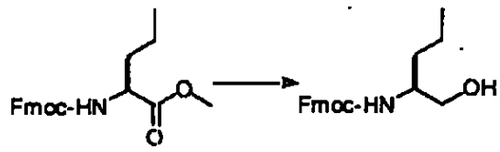
B) Síntesis del 9-fluorenilmetoxicarbonil-norvalinal (pasos a-c más adelante):

a) Síntesis del metil éster de la 9-fluorenilmetoxicarbonil-L-norvalina (Fmoc-nVal-OMe):



A una solución congelada de la Fmoc-norvalina comercial (25 g, 73,75 mmol) en metanol anhidro (469 ml) se agregó cloruro de tionilo (53,76 ml, 737,5 mmol) durante una hora. La TLC en acetato de etilo tomada una hora después confirmó que la reacción estaba completa (Rf = 0,85). La mezcla de reacción se concentró y el residuo restante se disolvió en acetato de etilo. La fase orgánica se lavó con varias porciones de 200 ml de bicarbonato de sodio saturado seguido de salmuera. La fase orgánica se secó, se filtró y se concentró para lograr Fmoc-norVal-OMe) como un sólido blanco (26,03 g) en rendimiento cuantitativo. RMN δ ppm (CD_3OD): 7,7 (m, 2H), 7,6 (m, 2H), 7,4 (m, 2H), 7,3 (m, 2H), 4,3 (m, 2H), 4,1 (m, 2H), 3,7 (s, 3H), 1,7 (m, 1 H), 1,6 (m, 1 H), 1,4 (m, 2H), 0,95 (t, 3H).

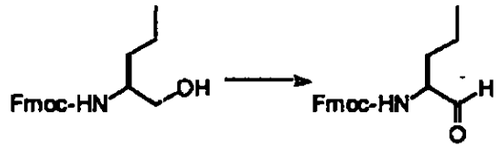
b) Síntesis del 9-fluorenilmetoxicarbonil-norvalinol (Fmoc-nValinol):



A Fmoc-nVal-OMe (26,03 g, 73,75 mmol) en tetrahidrofurano (123 ml) y metanol (246 ml) se agregó cloruro de calcio (16,37 g, 147,49 mmol). La mezcla de reacción se enfrió hasta 0°C y se agregó borohidruro de sodio (11,16 g, 294,98 mmol) en varios lotes. A la pasta espesa obtenida, se agregó metanol

(500 ml) y la reacción se dejó agitar a temperatura ambiente durante 90 minutos. La TLC en 2:3 de acetato de etilo: hexanos confirmó que la reacción estaba completa (Rf = 0,25). La reacción se inactivó con el agregado lento de agua (100 ml) a 0°C. El metanol se eliminó bajo presión reducida y la fase de agua restante se diluyó con acetato de etilo. La fase orgánica se lavó con agua (3 X 500 ml), bicarbonato de sodio saturado (3 x 500 ml) y salmuera (500 ml). La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró hasta lograr un sólido blanco (21,70 g, 90,5%). RMN δ ppm (CD_3OD): 7,8 (m, 2H), 7,7 (m, 2H), 7,4 (m, 2H), 7,3 (m, 2H), 4,3-4,5 (m, 2H), 4,2 (m, 1 H), 3,6 (s, 1 H), 3,5 (s, 2H), 1,5 (m, 1 H), 1,3-1,4 (m, 3H), 0,99 (m, 3H).

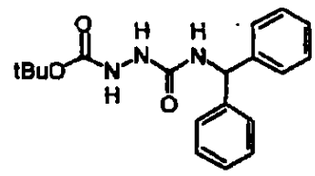
c) Síntesis del 9-fluorenilmetoxicarbonil-norvalinal (Fmoc-nVal-CHO):



A una solución de Fmoc-norValinol (21,70 g, 66,77 mmol) en diclorometano (668 ml) se agregó trietilamina (37,23 ml, 267 mmol) y la solución se enfrió hasta 0°C. Una suspensión del complejo de trióxido de azufre y piridina (42,51 g, 267 mmol) en dimetilsulfóxido (96 ml) se agregó a la solución congelada. Luego de una hora, la TLC en 2:3 de acetato de etilo: hexanos confirmó que la reacción estaba completa. El diclorometano se eliminó bajo presión reducida y el residuo restante se disolvió en acetato de etilo y se lavó con agua (2 X 50 ml), bisulfato de sodio 1N saturado (2 X 50 ml), bicarbonato de sodio saturado (2 x 50 ml) y salmuera (50 ml). La fase orgánica se concentró para dar como rendimiento lograr un sólido blanco. El rendimiento teórico (21,57 g) se supuso y la reacción se llevó al paso siguiente sin purificación adicional.

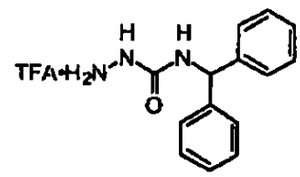
C) Síntesis de la sal de trifluoroacetao de la semicarbazida de difenilmetilo (dpsc) (pasos a-b más adelante):

a) Síntesis de Boc-semicarbazid-4-il difenilmetano



A una solución de carbonildiimidazol (16,2 g, 0,10 mole) en dimetilformamida (225 ml) se agregó una solución de carbazato de t-butilo (13,2 g, 0,100 mol) en dimetilformamida (225 ml) gota a gota durante 30 minutos. Se agregó difenilmetilamina (18,3 g, 0,10 mol) luego durante 30 minutos. La reacción se dejó agitar a temperatura ambiente durante una hora. Se agregó agua (10 mL) y la mezcla se concentró hasta aproximadamente 150 mL bajo presión reducida. Esta solución se vertió en agua (500 mL) y se extrajo con acetato de etilo (400 mL). La fase de acetato de etilo se lavó dos veces cada una con 75 mL de HCl 1N, agua, solución saturada de bicarbonato de sodio y cloruro de sodio, y se secó con sulfato de magnesio. La mezcla se filtró y la solución se concentró para dar 29,5 g (85% de rendimiento) de una espuma blanca. Este material pudo purificarse a través de recristalización a partir de acetato de etilo/hexano, pero fue lo suficientemente puro para usar directamente en el paso siguiente: punto de fusión 142-143°C. ^{1}H RMN ($CDCl_3$) δ 1,45 (s, 9H), 6,10 (dd, 2H), 6,42 (s, 1 H), 6,67 (bs, 1 H), 7,21-7,31 (m, 10H). Analítico calculado para $C_{19}H_{23}N_3O_3$: C, 66,84; H, 6,79; N, 12,31. Encontrado: C, 66,46; H, 6,75; N; 12,90.

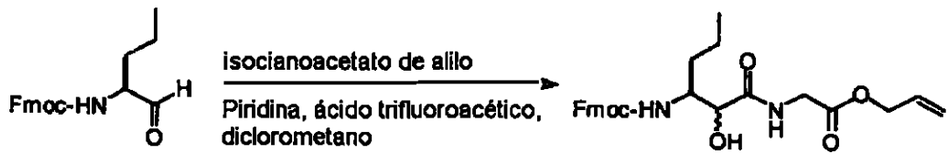
b) Síntesis de la sal de trifluoroacetato de la semicarbazida de difenilmetilo (dpsc)



Una solución de Boc-semicarbazid-4-ilo difenilmetano (3,43 g, 10 mmol) en diclorometano (12,5 mL) se trató con 12,5 mL de ácido trifluoroacético a temperatura ambiente y se agitó durante 30 min. La solución se agregó gota a

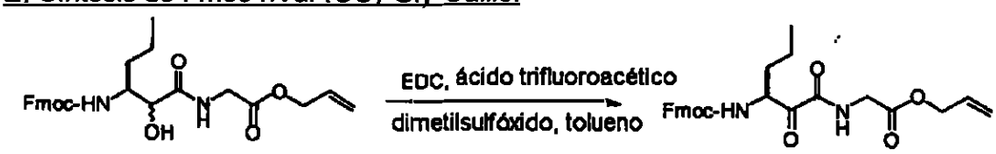
gota a 75 mL de éter y el sólido resultante (2,7 g, 80%) se recolectó por filtración. Punto de fusión 182-184°C. ^{1}H RMN (CD_3OD) δ 6,05 (s, 1 H), 7,21-7,35 (m, 10H). ^{13}C RMN (CD_3OD) δ 57,6, 118,3 (q, CF3), 126,7, 127,9, 141,6, 156,9, 160,9 (q, $CF_3\underline{C}O_2H$).

D) Síntesis del Fmoc-nVal-(CHOH)-Gly-Oalilo:



A una solución de Fmoc-nVal-CHO (Paso IB) (5,47 g, 16,90 mmol) en diclorometano (170 ml) se agregó isocianoacetato de alilo (Paso IA) (2,46 ml, 20,28 mmol) y piridina (5,47 ml, 67,61 mmol). La mezcla de reacción se enfrió hasta 0°C y se agregó ácido trifluoroacético (3,38 ml, 33,80 mmol) gota a gota. La reacción se agitó a 0°C durante 1 h, y luego a temperatura ambiente durante 48 horas. La TLC tomada en acetato de etilo confirmó que la reacción estaba completa. La mezcla de reacción se concentró y se sometió a cromatografía flash usando 20% hasta 70% de acetato de etilo en hexanos. Las fracciones que contenían el producto deseado se reunieron y se concentraron hasta obtener una espuma blanca (6,88 g, 87,3%). La TLC en 50:50 de acetato de etilo muestra una mancha (Rf = 0,37). RMN δ ppm (CD_3OD): 7,8 (m, 2H), 7,65 (m, 2H), 7,4 (m, 2H), 7,3 (m, 2H), 5,9 (m, 1 H), 5,1-5,4 (m, 2H), 4,55-4,65 (m, 2H), 4,3-4,4 (m, 2H), 4,15-4,25 (m, 1 H), 4,01 (s, 1 H), 3,9-4,0 (m, 3H), 1,5-1,6 (m, 2H), 1,35-1,45 (m, 3H), 0,9 (m, 3H).

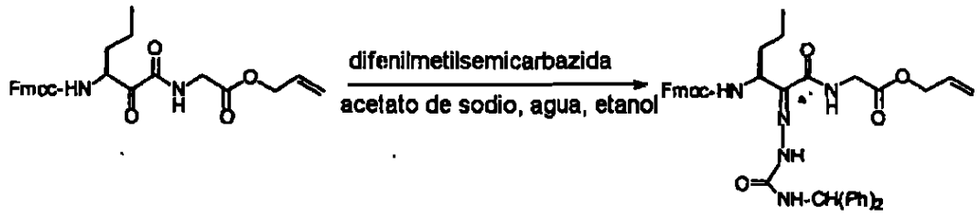
E) Síntesis de Fmoc-nVal-(CO)-Gly-Oalilo:



A una solución de Fmoc-nVal-(CHOH)-Gly-Oalilo (Paso D) (5,01 g, 10,77

mmol) en dimetilsulfóxido (100 ml) y tolueno (100 ml) se agregó EDC (20,6 g, 107,7 mmol). La mezcla de reacción se enfrió hasta 0°C y se agregó ácido dicloroacético (4,44 ml, 53,83 mmol) gota a gota. La reacción se agitó durante 15 minutos a 0°C y 1 h a temperatura ambiente. Luego de enfriar nuevamente hasta 0°C, se agregó agua (70 ml) y el tolueno se eliminó bajo presión reducida. El residuo restante se diluyó con acetato de etilo y se lavó varias veces con una solución saturada de bicarbonato de sodio seguido de bisulfato de sodio 1N y salmuera. La fase orgánica se secó sobre sulfato de sodio, se filtró y se concentró. El rendimiento teórico de 4,99 g se supuso y la reacción se llevó al paso siguiente sin purificación adicional. La TLC en 50:50 de acetato de etilo muestra una mancha (Rf = 0,73).

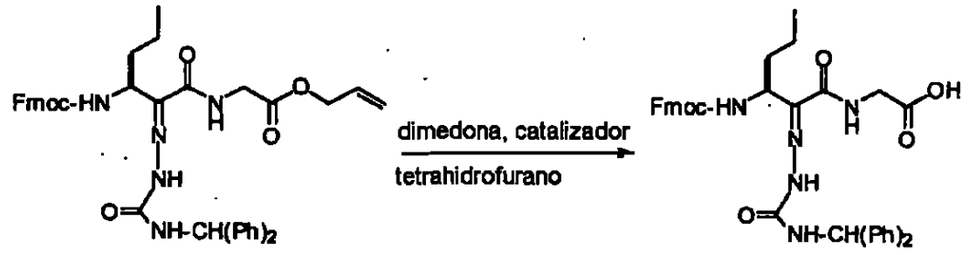
F) Síntesis de Fmoc-nVal-(dpsc)-Gly-Oalilo:



A una solución de Fmoc-nVal-(CO)-Gly-Oalilo (Paso E) (4,99 g, 10,75 mmol) en etanol (130 ml) y agua (42 ml) se agregó sal de trifluoroacetato de la semicarbazida de difenilmetilo (dpsc) (Paso IC) (7,6 g, 21,5 mmol) y acetato de sodio•$3H_2O$ (1,76 g, 12,9 mmol), sucesivamente. La mezcla de reacción se calentó a reflujo durante 90 minutos. La finalización de la reacción se confirmó a través de TLC tomada en 1:1 de acetato de etilo: hexano. El etanol se eliminó bajo presión reducida y el residuo restante se disolvió en acetato de etilo y se lavó con bisulfato de sodio 1N (2 X 10 ml), bicarbonato de sodio saturado (2 x 10 ml), seguido de salmuera (10 ml). La fase orgánica se secó, se filtró y se concentró. El residuo resultante se purificó a través de cromatografía flash en 20% hasta 50% de acetato de etilo en hexanos para dar un sólido blanco (5,76 g, 78%). La TLC en 50:50 de acetato de etilo: hexanos mostró dos manchas

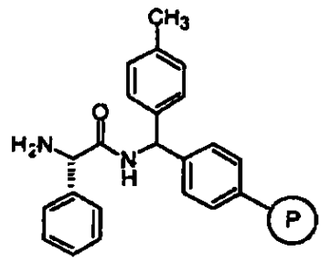
(isómeros cis y trans) con Rf = 0,42 y 0,5.

G) Síntesis de Fmoc-nVal-(dpsc)-Gly-OH:



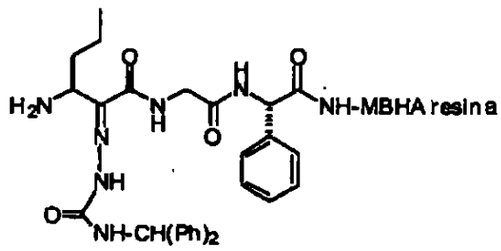
A una solución de Fmoc-nVal-(dpsc)-Gly-Oalilo (Paso IG) (4,53 g, 6,59 mmol) en tetrahidrofurano (300 ml) se agregó dimedona (4,62 g, 32,97 mmol) seguido de catalizador de tetrakis(trifenilfosfin) paladio(0) (0,76 g, 0,66 mmol). La finalización de la reacción se confirmó a través de TLC luego de 90 minutos usando 9:1 de diclorometano: metanol. La mezcla de reacción se concentró y el residuo restante se disolvió en acetato de etilo y se lavó tres veces con porciones de 50 ml de bifosfato de potasio 0,1 M. La fase orgánica se trató luego con 50 ml de bisulfito de sodio y el sistema de dos fases se agitó durante 15 minutos. Las fases se separaron y el procedimiento se repitió dos veces más. La fase orgánica se secó y se concentró y se sometió a cromatografía flash con 20% hasta 100% de acetato de etilo en hexanos. A esto le siguió una solución a 9:1 de diclorometano: metanol. Las fracciones correspondientes al producto puro se reunieron y se concentraron para obtener un sólido blanco (3,99 g, 94%). La TLC en 9:1 de diclorometano: metanol mostró dos manchas (isómeros cis y trans). RMN δ ppm (CD_3OD): 7,75 (m, 2H), 7,6 (m, 3H), 7,2-7,4 (m, 14H), 6,1-6,2 (m, 1 H), 4,25-4,4 (m, 2H), 4,1-4,2 (m, 2H), 3,85 (s, 2H), 1,6-1,8 (m, 2H), 1,3-1,5 (m, 2H), 0,95 (t, 3 H).

Paso 2. Síntesis de la resina H-Pha-MBHA:



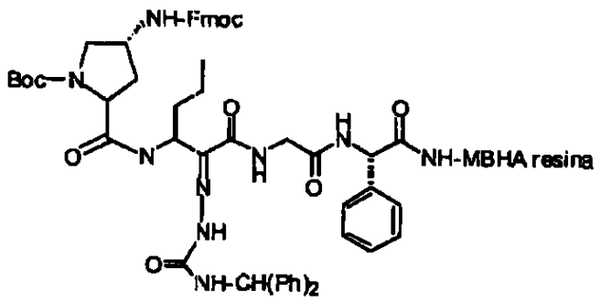
La resina comercial MBHA (2,6 g, 1,12 mmol/g, 2,91 mmol) se transfirió a un recipiente de reacción en fase sólida frito de 250 mL equipado con una entrada de nitrógeno. Luego se lavó minuciosamente con porciones de 30 ml de diclorometano, metanol, dimetilformamida y diclorometano y se acopló durante 18 horas al Fmoc-Phg-OH comercial (2,17 g, 5,82 mmol) de acuerdo con el Procedimiento A con 99,82% de eficiencia. La resina luego se sometió a Desprotección de Fmoc de acuerdo con el Procedimiento B. Un ensayo cualitativo de ninhidrina en una alícuota pequeña dio solución y resina azul oscura, lo que indicó una reacción exitosa.

Paso 3. Síntesis de la resina H-nVal(dpsc)-Gly-Phg-MBHA:



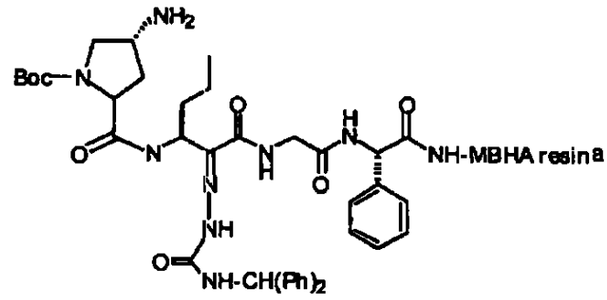
La resina obtenida en el Paso II (2,6 g, 0,8 mmol/g, 2,91 mmol) se reaccionó con Fmoc-nVal-(dpsc)-Gly-Oalilo (Paso IG) (5,82 mmol, 3,77 g) de acuerdo con el Procedimiento A. Luego de 18 horas, el análisis cuantitativo de ninhidrina indicó una eficacia de acoplamiento de 99,91. La resina se sometió a Desprotección de Fmoc de acuerdo con el Procedimiento B. Un ensayo cualitativo de ninhidrina en una alícuota pequeña dio solución y resina azul oscura, lo que indicó una reacción exitosa.

Paso 4. Síntesis de la resina Boc-Pro(4t-NHFmoc)-nVal(dpsc)-Gly-Phg-MBHA:



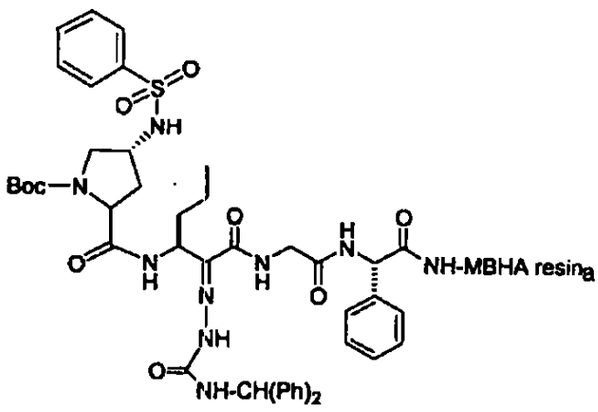
La resina compuesta H-nVal(dpsc)-Gly-Phg-MBHA (Paso 3 anterior) (600 mg, 0,8 mmol/g, 0,67 mmol) se transfirió a un tubo de polipropileno frito y se acopló a Boc-Pro(4t-NHFmoc)-OH (Ejemplo VI, Paso 3) (610 mg, 1,34 mmol) de acuerdo con el Procedimiento A. Luego de 18 horas, el análisis cuantitativo de ninhidrina indicó un 99,96% de eficiencia de acoplamiento.

Paso 5. Síntesis de la resina Boc-Pro(4t-NHz)-nVal(dpsc)-Gly-Phg-MBHA:



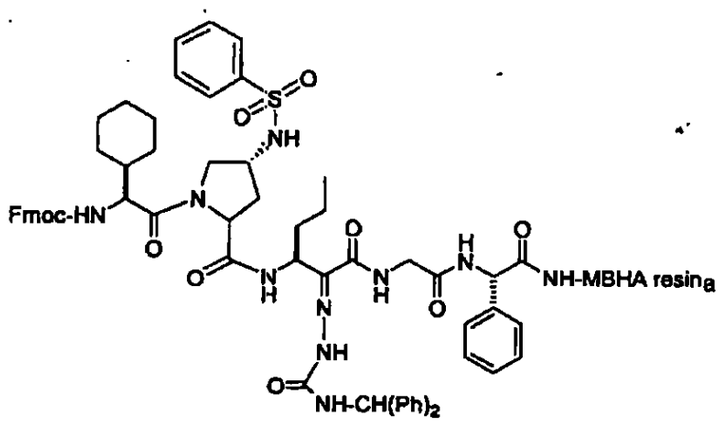
La resina del paso anterior (resina Boc-Pro(4t-NHFmoc)-nVal(dpsc)-Gly-PhgMBHA) se sometió a Desprotección de Fmoc de acuerdo con el Procedimiento B. Un ensayo cualitativo de ninhidrina en una alícuota pequeña dio solución y resina azul oscura, lo que indicó una reacción exitosa.

Paso 6. Síntesis de la resina Boc-Pro(4t-NHSO$_2$Bn)-nVal(dpsc)-Gly-Phg-MBHA:



A la resina obtenida del paso anterior (resina Boc-Pro(4t-NH2)-nVal(dpsc)-Gly-Phg-MBHA) (0,2 g, 0,22 mmol) suspendida en NMP (2 ml) se agregó 2,4,6-colidina (0,24 ml, 1,79 mmol) y cloruro de bencensulfonilo y la reacción se agitó durante 18 horas. El solvente se drenó y la resina se lavó minuciosamente con porciones de 2 mL de diclorometano, metanol, dimetilformamida y diclorometano. El análisis cualitativo de ninhidrina mostró perlas y solución incoloras lo que indicó una reacción exitosa.

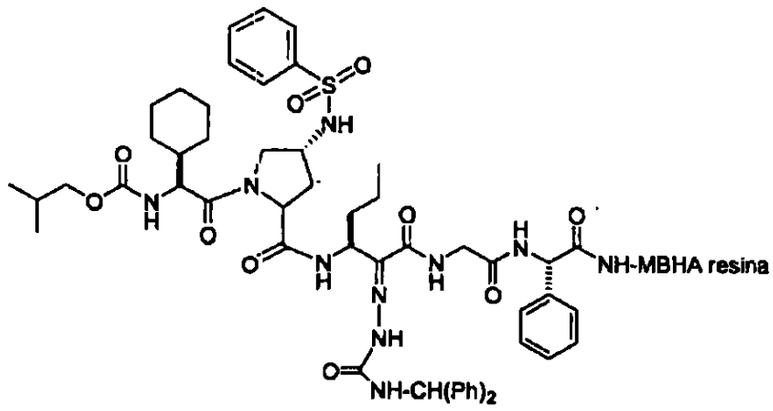
Paso 7. Síntesis de la resina Fmoc-G(Chx)-Pro(4t-NHSO$_2$Bn)-nVal(dpsc)-Gly-Phg-MBHA:



La resina obtenida en el paso anterior (resina Boc-Pro(4t-NHSO$_2$Bn)-nVal(dpsc)Gly-Phg-MBHA) se sometió al procedimiento de desprotección de Boc de acuerdo con el Procedimiento C. La Fmoc-G(Chx) (0,17

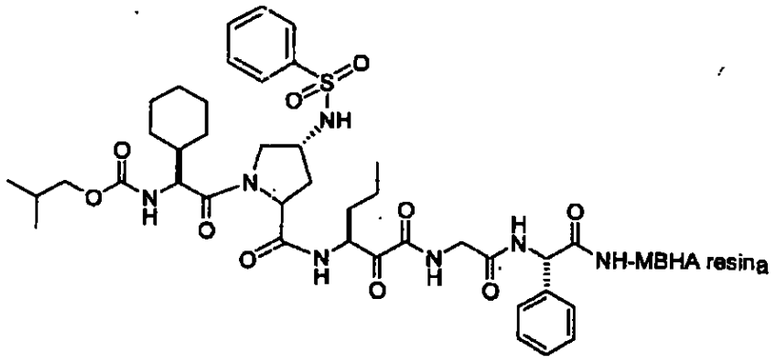
g, 0,45 mmol) se acopló luego de acuerdo con el Procedimiento A. Luego de 18 horas el análisis cualitativo de ninhidrina mostró perlas incoloras y el análisis cuantitativo de ninhidrina indicó un 99,79% de eficiencia de acoplamiento.

Paso 8. Síntesis de la resina iBoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal(dpsc)-Gly-Phg-MBHA:



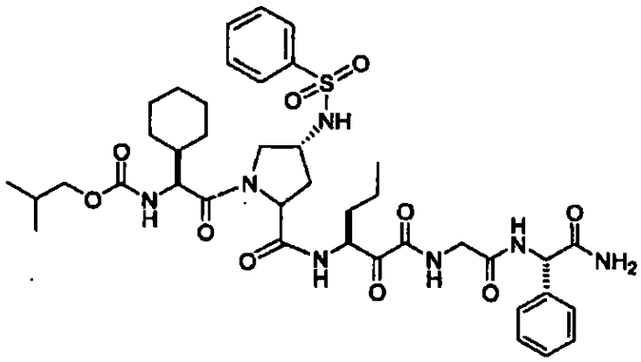
La resina obtenida en el paso anterior (resina Fmoc-G(Chx)-Pro(4t-$NHSO_2Bn$)nVal(dpsc)-Gly-Phg-MBHA) se sometió a Desprotección de Fmoc de acuerdo con el Procedimiento B. Un ensayo de ninhidrina en una alícuota pequeña dio solución y resina azul oscura, lo que indicó una reacción exitosa. A la resina (0,2 g, 0,22 mmol) suspendida en 2 ml NMP se agregó isobutilcloroformiato (0,12 ml, 0,90 mmol) seguido de diisopropiletilamina (0,31 ml, 1,79 mmol), y la mezcla de reacción se agitó durante 18 horas a temperatura ambiente. El análisis cualitativo de ninhidrina mostró perlas y solución incoloras lo que indicó una reacción exitosa.

Paso 9. Síntesis de la resina iBoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal(CO)-Gly-Phg-MBHA:



El compuesto del paso anterior (la resina iBoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal(dpsc)-Gly-Phg-MBHA) (200 mg) se sometió a hidrólisis de semicarbazona Procedimiento D.

Paso 10. Síntesis de iBoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal(CO)-GlyPhg-NH_2:



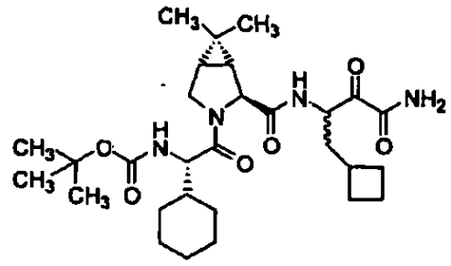
La resina del paso anterior (resina iBoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal(CO)Gly-Phg-MBHA) (100 mg) se sometió a condición de disociación de HF (Procedimiento E) para dar como rendimiento el producto en bruto deseado. El material se purificó a través de HPLC usando una columna de fase inversa de 2,2 x 25 cm, que contenía una resina C-18 formada con partículas de gel de un tamaño de 10 micrones con un tamaño de poros de 300 angstrom, eluyendo con un gradiente usando 20-50% de acetonitrilo en agua. La HPLC analítica usando una columna de fase inversa de 4,6 X 250 mm, que contenía una resina C-18 formada con partículas de gel de un tamaño de 5 micrones con un tamaño de poros de 300 angstrom, eluyendo con 25-75% de

acetonitrilo (que contenía 0,1 % de ácido trifluoroacético) mostró un pico a los 13,5 minutos. El espectro de masa de baja resolución confirmó la masa deseada (MH^+ 826,4).

IV. Compuestos adicionales preparados por medio de Síntesis de fase en Solución:

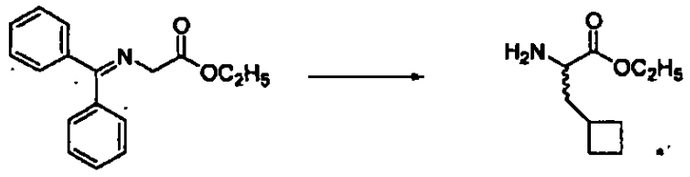
Los procedimientos representativos para preparar los compuestos adicionales de la invenció se muestran a continuación, y los compuestos preparados a través de dichos procedimientos se enumeran en las **Tablas 5 y 6.**

Ejemplo XXIII : Preparación de un Compuesto de Fórmula XXIII:



XXIII

Paso 1.

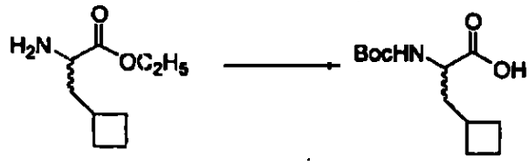


XXIIIa **XXXIIIb**

Una solución agitada de cetimina **XXIIIa** (50 g, 187,1 mmol) bajo N_2 en THF anhidro (400 mL) se enfrió hasta -78°C y se trató con solución 1M de K-tBuO (220 mL, 1,15 equiv.) en THF. La mezcla de reacción se entibió hasta 0°C y se agitó durante 1 h y se trató con ciclobutano de bromometilo (28 mL, 249 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 48 h y se concentró al vacío. El residuo se disolvió en Et_2O (300 mL) y se trató con HCl

acuoso (2 M, 300 mL). La solución resultante se agitó a temperatura ambiente durante 5 h y se extrajo con Et_2O (1 L). La fase de agua se hizo básica hasta un pH ~12-14 con NaOH (50 acuoso) y se extrajo con CH_2Cl_2 (3 x 300 mL). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron para dar la amina pura (**XXIIIb,** 18 g) como un aceite incoloro.

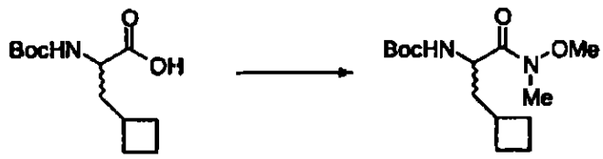
Paso 2.



XXIIIb XXIIIc

Una solución de la amina **XXIIIb** (18 g, 105,2 mmol) a 0°C en CH_2Cl_2 (350 mL) se trató con di-ter-butildicarbonato (23 g, 105,4 mmol) y se agitó a temperatura ambiente durante 12 h. Luego de la finalización de la reacción (TLC), la mezcla de reacción se concentró al vacío y el residuo se disolvió en THF/H_2O (200 ml, 1:1) y se trató con LiOH•H2O (6,5 g, 158,5 mmol) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró y la fase de agua básica se extrajo con Et_2O. La fase de agua se acidificó con HCl conc. hasta un pH ~1-2 y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron al vacío para dar como rendimiento **XXIIIc** como un aceite viscoso sin color que se usó para el paso siguiente sin ninguna purificación adicional.

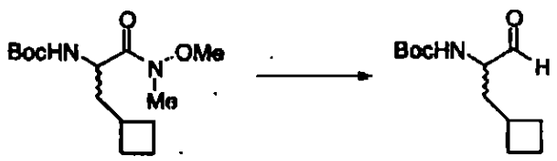
Paso 3.



XXIIIc XXIIId

Una solución del ácido **XXIIIc** (15,0 g, 62 mmol) en CH_2Cl_2 (250 mL) se trató con reactivo de BOP (41,1 g, 93 mmol), N-metil morfolina (27 mL), Clorhidrato de N,O-dimetil hidroxilamina (9,07 g, 93 mmol) y se agitó durante la noche a temperatura ambiente. La mezcla de reacción se diluyó con HCl 1N acuoso (250 mL), y las fases se separaron y la fase de agua se extrajo con CH_2Cl_2 (3 x 300 ml). Las fases orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron al vacío y se purificaron a través de cromatografía (SiO_2, EtOAc/Hex a 2:3) para dar como rendimiento la amida **XXIIId** (15,0 g) como un sólido incoloro.

Paso 4.

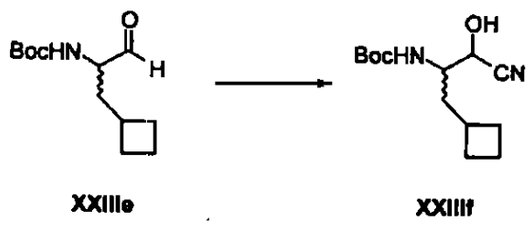


XXIIId XXIIIe

Una solución de la amida **XXIIId** (15 g, 52,1 mmol) en THF anhidro (200 mL) se trató gota a gota con una solución de $LiAlH_4$ (1 M, 93 mL, 93 mmol) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 1 h y se inactivó cuidadosamente a 0°C con una solución de $KHSO_4$ (10% acuoso) y se agitó durante 0,5 h. La mezcla de reacción se diluyó con HCl acuoso (1 M, 150 mL) y se extrajo con CH_2Cl_2 (3 x 200 mL). Las fases orgánicas combinadas se lavaron con HCl acuoso (1 M), $NaCHO_3$ saturado, salmuera, y se secaron ($MgSO_4$). La

mezcla se filtró y se concentró al vacío para dar como rendimiento **XXIIIe** como un aceite viscoso incoloro (14 g).

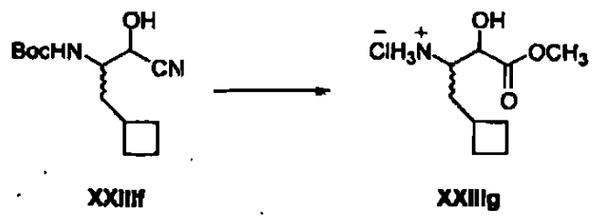
Paso 5.



XXIIIe **XXIIIf**

Una solución del aldehído **XXIIIe** (14 g, 61,6 mmol) en CH_2Cl_2 (50 mL), se trató con Et_3N (10,73 mL, 74,4 mmol), y cianohidrina de acetona (10,86 g, 127,57 mmol) y se agitó a temperatura ambiente durante 24 hrs. La mezcla de reacción se concentró al vacío y se diluyó con HCl acuoso (1 M, 200 mL) y se extrajo en CH_2Cl_2 (3 x 200 mL). La fase orgánica combinada se lavó con H_2O, salmuera, se secó ($MgSO_4$), se filtró, se concentró al vacío y se purificó a través de cromatografía (SiO_2, EtOAc/Hex a 1:4) para dar como rendimiento **XXIIIf** (10,3 g) como un líquido sin color.

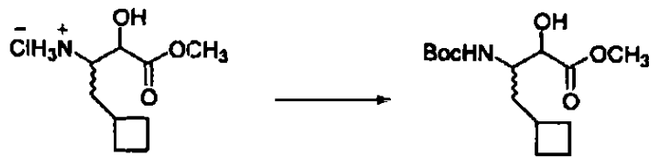
Paso 6.



XXIIIf **XXIIIg**

Se trató metanol saturado con HCl*, preparado a través del burbujeo de HCl gaseoso a CH_3OH (700 ml) a 0°C, con la cianohidrina **XXIIIf** y se calentó hasta el reflujo durante 24 h. La reacción se concentró al vacío para dar como rendimiento **XXIIIg,** que se usó en el paso siguiente sin purificación. * Alternativamente, puede usarse HCl 6M preparado a través del agregado de AcCl a metanol anhidro.

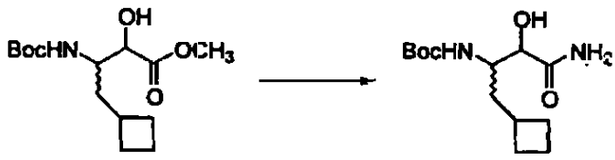
Paso 7.



XXIIIg XXIIIh

Una solución del clorhidrato de amina **XXIIIg** en CH_2Cl_2 (200 mL) se trató con Et_3N (45,0 mL, 315 mmol) y BOC_2O (45,7 g, 209 mmol) a -78°C. La mezcla de reacción se agitó luego a temperatura ambiente durante la noche y se diluyó con HCl (2 M, 200 mL) y se extrajo en CH_2Cl_2. La fase orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío y se purificó a través de cromatografía (EtOAc/Hex a 1:4) para dar como rendimiento el hidroxi éster **XXIIIh.**

Paso 8.



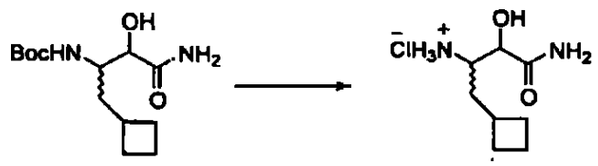
XXIIIh XXIII

Una solución del metil éster **XXIIIh** (3 g, 10,5 mmol) en THF/H_2O (1:1) se trató con $LiOH•H_2O$ (645 mg, 15,75 mmol) y se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se acidificó con HCl acuoso (1 M, 15 mL) y se concentró al vacío. El residuo se secó al vacío.

Una solución del ácido en CH_2Cl_2 (50 mL) y DMF (25 mL) se trató con NH_4Cl (2,94 g, 55,5 mmol), EDCI (3,15 g, 16,5 mmol), HOOBt (2,69 g, 16,5 mmol), y NMM (4,4 g, 44 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 d. Los solventes se eliminaron al vacío y el residuo se diluyó con HCl acuoso (250 mL) y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se lavaron con $NaCHO_3$ acuoso saturado, se secaron ($MgSO_4$), se

filtraron, se concentraron al vacío para obtener **XXIIIi**, que se usó como es en los pasos siguientes. (Alternativamente **XXIIIi** puede obtenerse también directamente a través de la reacción de **XXIIIf** (4,5 g, 17,7 mmol) con H_2O_2 acuoso (10 mL), $LiOH{\cdot}H_2O$ (820 mg, 20,8 mmol) a 0°C en 50 mL de CH_3OH durante 0,5 h.)

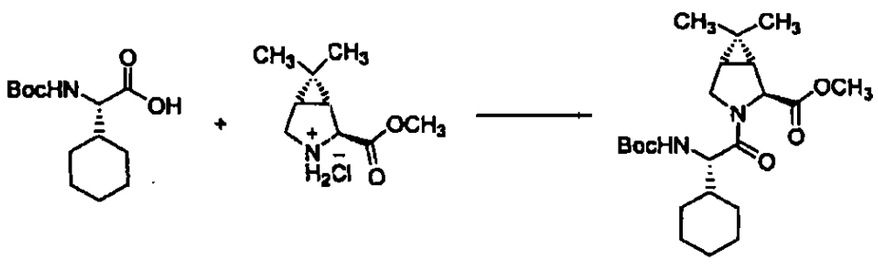
Paso 9.



XXIIIi **XXIIIj**

Una solución de **XXIIIi** obtenida en el paso anterior se disolvió en HCl 4N en dioxano y se agitó a temperatura ambiente durante 2 h. La mezcla de reacción se concentró al vacío para dar **XXIIIj** como un sólido, que se usó sin purificación adicional.

Paso 10.



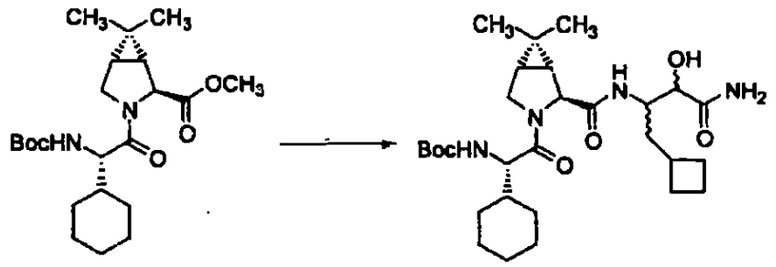
XXIIIk **XXIIIl** **XXIIIm**

El amino éster XXIIIl se preparó siguiendo el método de R. Zhang y J. S. Madalengoitia (J. Org. *Chem. 1999, 64, 330)*, con la excepción de que el grupo Boc se disoció a través de la reacción del aminoácido protegido con Boc con HCl metanólico.

Una solución del aminoácido comercial Boc-Chg-OH, XXIIIk (Senn chemicals, 6,64 g, 24,1 mmol) y clorhidrato de amina **XXIIIl** (4,5 g, 22 mmol) en

CH_2Cl_2 (100 mL) a 0°C se trató con reactivo de BOP y se agitó a temperatura ambiente durante 15 h. La mezcla de reacción se concentró al vacío, luego se diluyó con HCl acuoso 1M y se extrajo en EtOAc (3 x 200 mL). Las fases orgánicas combinadas se lavaron con $NaCHO_3$ saturado (200 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío, y se cromatografiaron (SiO_2, EtOAc/Hex a 3:7) para obtener **XXIIIm** (6,0 g) como un sólido incoloro.

Paso 11.

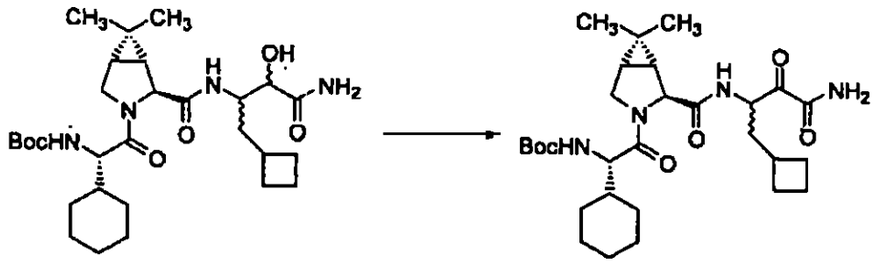


XXIIIm **XXIIIn**

Una solución del metil éster **XXIIIm** (4,0 g, 9,79 mmol) en THF/H_2O (1:1) se trató con LiOH•H_2O (401 mg, 9,79 mmol) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se acidificó con HCl acuoso y se concentró al vacío para obtener el ácido libre.

Una solución del ácido (1,5 g, 3,74 mmol) en DMF/CH_2Cl_2 (1:1 50 mL) se trató con la amina **XXIIIj** (772 mg, 3,74 mmol), EDCI (1,07 g, 5,61 mmol), HOOBt (959 mg, 5,61 mmol) y NMM (2,15 mL, 14,96 mmol) a -10°C. La mezcla de reacción se agitó a 0 °C durante 48 h y se concentró al vacío. El residuo se diluyó con HCl acuoso 1M y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se extrajeron con $NaCHO_3$ acuoso, HCl acuoso, salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron al vacio para obtener **XXIIIn** (2,08 g) como un aceite de color tostado.

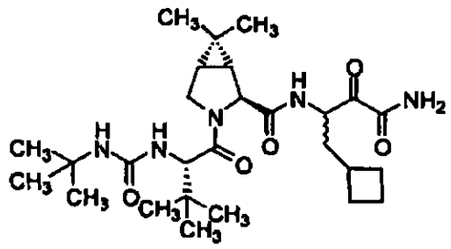
Paso 12.



XXIIIn XXIII

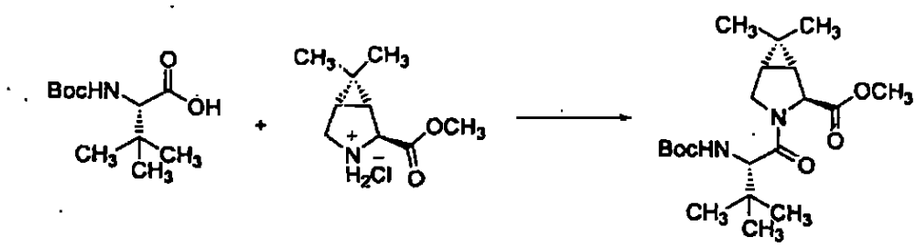
Una solución de la amida **XXIIIn** (2,08 g, 3,79 mmol) en tolueno y DMSO (1:1, 20 mL) a 0°C se trató con EDCI (7,24 g, 37,9 mmol) y ácido dicloroacético (2,42 g, 19,9 mmol) y se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se diluyó con CH_2Cl_2, se lavó con $NaCHO_3$ saturado, y salmuera. La fase orgánica se secó ($MgSO_4$), se filtró, se concentró al vacío y se purificó a través de cromatografía (SiO_2, Acetona/Hexanos a 3:7) para dar como rendimiento **XXIII** como un sólido incoloro.

Ejemplo XXIV Preparación de un Compuesto de Fórmula XXIV:



XXIV

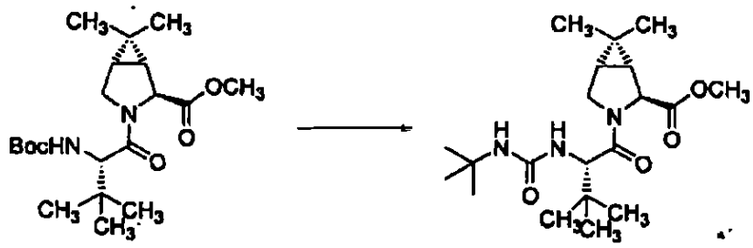
Paso 1.



XXIVa XXIIII XXIVb

Una solución de Boc-ter-Lue **XXIVa** (Fluka, 5,0 g 21,6 mmol) en CH_2I_2 anhidro/DMF (50 mL, 1:1) se enfrió hasta 0°C y se trató con la amina XXIIII (5,3 g, 25,7 mmol), NMM (6,5 g, 64,8 mmol) y reactivo de BOP (11,6 g, 25,7 mmol). La reacción se agitó a temperatura ambiente durante 24H, se diluyó con HCl acuoso (1 M) y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se lavaron con HCl (acuoso, 1 M), $NaCHO_3$ saturado, salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron al vacío y se purificaron a través de cromatografía (SiO_2, Acetona/Hexano 1:5) para dar como rendimiento **XXIVb** como un sólido incoloro.

Paso 2.



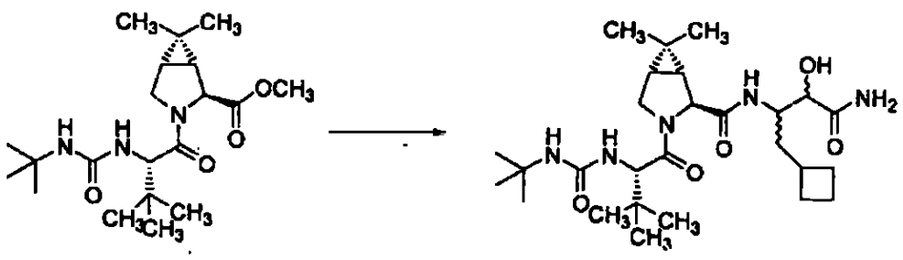
XXIVb **XXIVc**

Una solución del metil éster **XXIVb** (4,0 g, 10,46 mmol) se disolvió en HCl (solución 4M dioxano) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró al vacío para obtener la sal de clorhidrato de la amina usada en el paso siguiente .

Una solución de la sal de clorhidrato de la amina (397 mg, 1,24 mmol) en CH_2Cl_2 (10 mL) se enfrió hasta -78°C y se trató con isocianato de ter-butilo (250

mg, 2,5 mmol) y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró al vacío y el residuo se diluyó con HCl acuoso (1 M) y se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se lavaron con HCl acuoso (1 M), $NaCHO_3$ saturado y salmuera. Las fases orgánicas se secaron, se filtraron y se concentraron al vacío y el residuo se purificó a través de cromatografía (SiO_2, acetona/Hex a 1:4) para dar como rendimiento **XXIVc** como un sólido incoloro.

Paso 3.

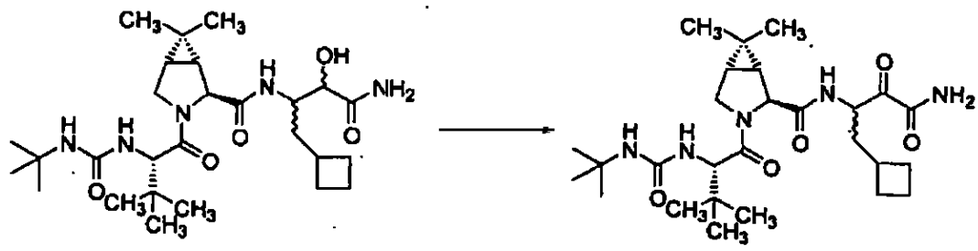


XXIVc **XXIVd**

Una solución del metil éster **XXIVc** (381 mg, 1,0 mmol) en THF/H_2O (1:1, 5 mL) se trató con LiOH•H_2O (62 mg, 1,5 mmol) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se acidificó con HCl acuoso y se concentró al vacío para obtener el ácido libre.

Una solución del ácido (254,9 mg, 0,69 mmol) en DMF/CH_2Cl_2 (1:1, 5,0 mL) se trató con la amina **XXIIIj** (159 mg, 0,763 mmol), EDCI (199 mg, 1,04 mmol), HOOBt (169,5 mg , 1,04 mmol) y NMM (280 mg, 2,77 mmol) a -20°C. La mezcla de reacción se agitó a -20 °C durante 48 h y se concentró al vacío. El residuo se diluyó con HCl acuoso 1M y se extrajo con EtOAc. Las fases orgánicas combinadas se extrajeron con $NaCHO_3$ acuoso, HCl acuoso, salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron al vacío para obtener **XXIVd** (470 mg) como un aceite de color tostado.

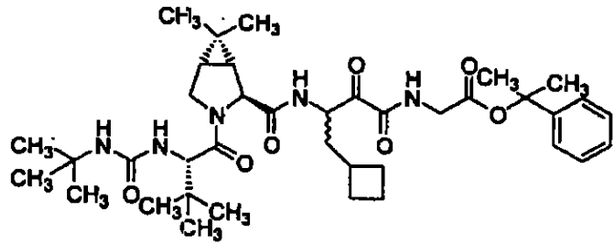
Paso 4.



XXIVd XXIV

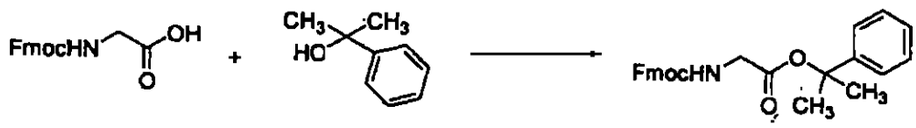
Una solución de la amida **XXIVd** (470 mg, 0,9 mmol) en tolueno y DMSO (1:1 20 mL) a 0°C se trató con EDCI (1,72 g, 9,0 mmol) y ácido dicloroacético (0,37 mL, 4,5 mmol) y se agitó a 0 °C durante 4h. La mezcla de reacción se diluyó con CH_2Cl_2, y se lavó con $NaCHO_3$ saturado, y salmuera. La fase orgánica se secó ($MgSO_4$), se filtró y se concentró, al vacío y se purificó a través de cromatografía (SiO_2, Acetona/Hexanos a 3:7) para dar como rendimiento XXIV como un sólido incoloro.

Ejemplo XXV Preparación de un Compuesto de Fórmula XXV:



XXV

Paso 1.

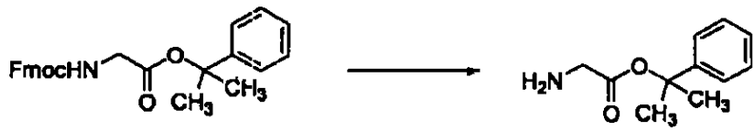


XXVa XXVb XXVc

Una solución de Fmoc-glicina (Bachem, 2,0 g, 6,87 mmol) en CH_2Cl_2 (20 mL) se trató con 2-fenil-2-propanol (Aldrich, 3,36 g, 24,7 mmol), DCC (solución

1M de CH_2Cl_2, 8,24 mL), DMAP (167 mg, 1,37 mmol) y se agitó a temperatura ambiente durante 24 h. La mezcla de reacción se concentró al vacío y se diluyó con Et_2O (100 mL). El sólido que se separó se filtró y el filtrado se lavó con $NaCHO_3$ saturado. La fase orgánica se secó ($MgSO_4$), se filtró y se concentró al vacío, y se purificó a través de cromatografía (SiO_2, EtOAc/Hex a 1:5) para dar como rendimiento éster **XXVI** (1,1 g) como un líquido viscoso incoloro.

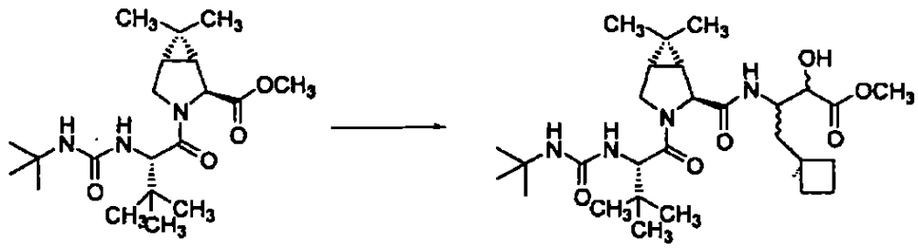
Paso 2.



XXVc **XXVd**

Una solución de **XXVc** en CH_2Cl_2 (16,0 mL) se trató con piperidina (4,0 mL) y se agitó a temperatura ambiente durante 0,5 h. La mezcla de reacción se concentró al vacío y se purificó a través de cromatografía (SiO_2, Acetona/Hexanos a 1:10 hasta 1:1) para dar como rendimiento la amina **XXVd** (420 mg) como un líquido sin color.

Paso 3.

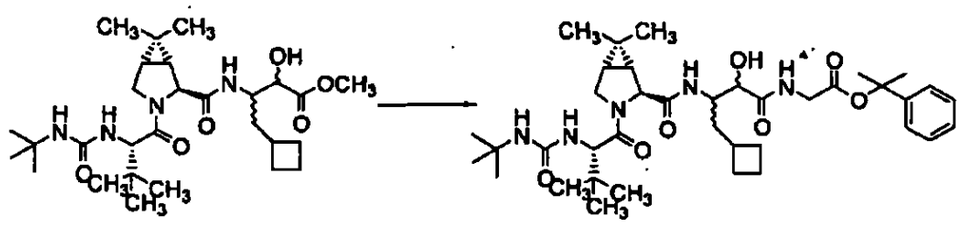


XXIVc **XXVe**

Una solución del metil éster **XXIVc** (381 mg, 1,0 mmol) en THF/H_2O (1:1, 5 mL) se trató con $LiOH \cdot H_2O$ (62 mg, 1,5 mmol) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se acidificó con HCl acuoso y se concentró al vacío para obtener el ácido libre.

Una solución del ácido (2,0 g, 5,5 mmol) en DMF/CH_2Cl_2 (1:1, 40,0 mL) a -10°C se trató con la amina **XXIIIg** (1,51 g, 6,8 mmol), EDCI (1,57 g, 8,25 mmol), HOOBt (1,41 g, 8,25 mmol) y NMM (2,5 g, 24,7 mmol). La mezcla de reacción se agitó a 0 °C durante 48 h y se concentró al vacío. El residuo se diluyó con HCl acuoso 1M (100 mL) y se extrajo con CH_2Cl_2 (3 x 100 mL). Las fases orgánicas combinadas se extrajeron con $NaCHO_3$ acuoso, HCl acuoso, salmuera, se secaron ($MgSO_4$), se filtraron, se concentraron al vacío para obtener **XXVe** (3,17 g) como un aceite de color tostado usado sin ninguna purificación adicional.

Paso 4.

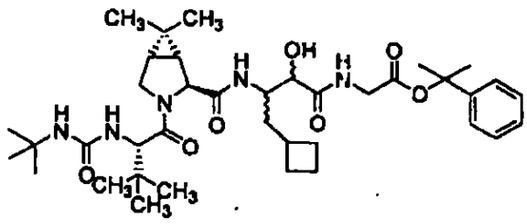


XXVe **XXVf**

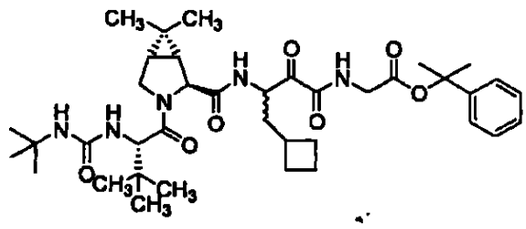
Una solución del metil éster **XXVe** (2,5 g, 4,66 mmol) en THF/H_2O/CH_3OH (1:1:1, 60 mL) se trató con LiOH•H_2O (200 mg, 4,87 mmol) y se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se acidificó con HCl acuoso y se concentró al vacío para obtener el ácido libre.

Una solución del ácido (200,0 mg, 0,38 mmol) en DMF/CH_2Cl_2 (1:1, 6,0 mL) a -10°C se trató con la amina **XXVd** (78 mg, 0,4 mmol), EDCI (105 mg, 0,55 mmol), HOOBt (95 mg, 0,55 mmol) y NMM (150 mg, 1,48 mmol). La mezcla de reacción se agitó a 0 °C durante 48 h y se concentró al vacío. El residuo se diluyó con HCl acuoso 1M (30 mL) y se extrajo con CH_2Cl_2 (3 x 30 mL). Las fases orgánicas combinadas se extrajeron con $NaCHO_3$ acuoso (2 x 30 mL), HCl acuoso, salmuera (30 mL), se secaron ($MgSO_4$), se filtraron y se concentraron al vacío para obtener **XXVf** (240 mg) como un aceite de color tostado.

Paso 5.



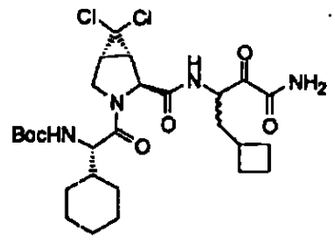
XXVf



XXV

Una solución de **XXVf** (240 mg, 0,28 mmol) en CH_2Cl_2 (10 mL) se trató con reactivo de Dess-Martin (Omega, 242 mg, 0,56 mmol) y se agitó a temperatura ambiente durante 2 h. Luego de completar la oxidación (TLC, Acetona/Hex a 1:4) la mezcla de reacción se diluyó con $NaCHO_3$ saturado (20 mL) y $Na_2S_2O_3$ (solución acuosa al 10%, 20 mL). La mezcla de reacción se agitó durante 30 min y se extrajo con CH_2Cl_2 (3 x 30 mL). Las fases orgánicas combinadas se extrajeron con $NaCHO_3$ saturado, salmuera, se secaron ($MgSO_4$), se filtraron, se concentraron al vacío y se purificaron a través de cromatografía (SiO_2, acetona/Hexanos a 1:5) para dar como rendimiento **XXV** (122 mg) como un sólido incoloro.

Ejemplo XXVI Preparación de un Compuesto de Fórmula XXVI:



XXVI

Paso 1:



XXVIa XXVIb

A una solución agitada de N-Boc-3,4-deshidroprolina **XXVIa** (5,0 g, 23,5 mmol), dicarbonato de di-ter-butilo (7,5 g, 34,4 mmol), y 4-N,N-dimetilaminopiridina (0,40 g, 3,33 mmol) en acetonitrilo (100 mL) a temperatura ambiente se agregó trietilamina (5,0 mL, 35,6 mmol). La solución resultante se agitó a esta temperatura durante 18 h antes de concentrarse al vacío. El residuo marrón oscuro se purificó a través de cromatografía flash eluyendo con 10-25% de EtOAc/hexano para dar el producto **XXVIb** como un aceite amarillo pálido (5,29 g, 84%).

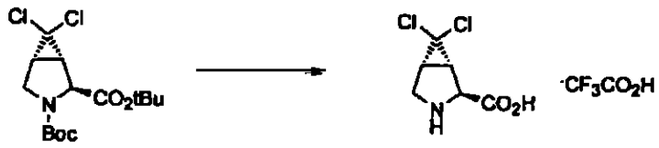
Paso 2:



XXVIb XXVIc

A una solución agitada de deshidroprolina **XXVIb** (10,1 g, 37,4 mmol), cloruro de benciltrietilamonio (1,60 g, 7,02 mmol) en cloroformo (120 mL) a temperatura ambiente se agregó 50% de hidróxido de sodio acuoso (120 g). Luego de agitar vigorosamente a esta temperatura durante 24 h, la mezcla negra se diluyó con CH_2Cl_2 (200 mL) y éter dietílico (600 mL). Luego de que las fases se separaron, la solución acuosa se extrajo con CH_2Cl_2/Et_2O (1:2, 3 x 600 mL). La solución orgánica se secó ($MgSO_4$) y se concentró. El residuo se purificó a través de cromatografía flash usando 5-20% de EtOAc/hexano para lograr 9,34 g (71 %) de **XXVII** como un sólido blancuzco.

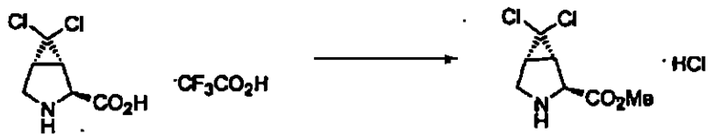
Paso 3:



XXVIc XXVId

La solución de **XXVII** (9,34 g, 26,5 mmol) en CH_2Cl_2 (25 mL) y CF_3CO_2H (50 mL) se agitó a temperatura ambiente durante 4,5 h antes de concentrarse al vacío para dar un residuo marrón que se usó en el Paso 4 sin purificación adicional.

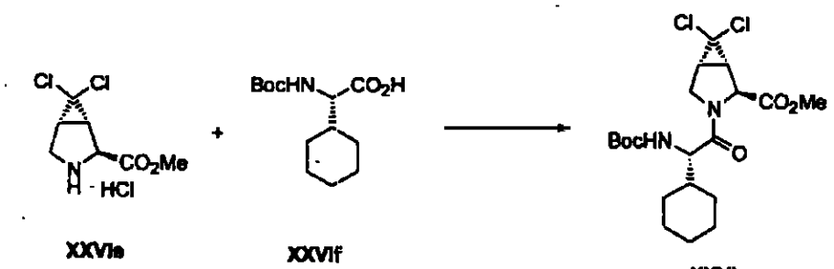
Paso 4



XXIIId XXIIIe

El ácido clorhídrico concentrado comercial (4,5 mL) se agregó a una solución del residuo del Paso 3 en metanol (70 mL) y la mezcla resultante se entibió hasta 65°C en un baño de aceite. Luego de 18 h, la mezcla se concentró al vacío para dar un aceite marrón **XXVIe,** que se usó en el Paso 5 sin purificación adicional.

Paso 5:

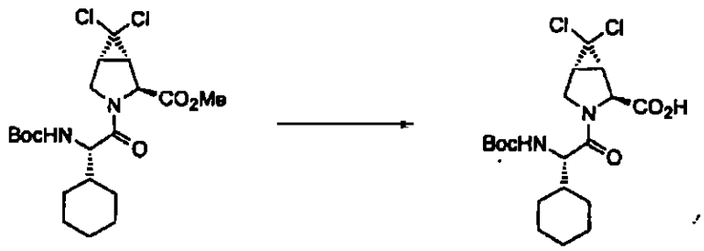


XXVIe XXVIf XXVIg

A una solución agitada de metil éster de prolina **XXVIe** del Paso 4, N-Boc-ciclohexilglicina comercial **XXVIf** (10,2 g, 40,0 mmol) y [hexafluorofosfato

de O-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio] (HATU) (16,0 g, 42,1 mmol) en DMF (200 mL) a 0°C se agregó diisopropiletilamina (18,0 mL, 104 mmol) . Luego de dejar entibiar hasta alcanzar la temperatura ambiente junto con el baño de hielo durante la noche (18 h), la mezcla de reacción se diluyó con EtOAc (600 mL), 5% de H_3PO_4 (150 mL) y salmuera (150 mL). La solución orgánica se lavó con 5% de H_3PO_4 (150 mL), $NaCHO_3$ saturado (2 x 200 mL) antes de secar ($MgSO_4$), filtrar y concentrar al vacío. El residuo se purificó a través de cromatografía flash usando 5-20% de EtOAc/hexano para lograr 3,84 g (32%, tres paso s) de **XXVIg** como un sólido blancuzco.

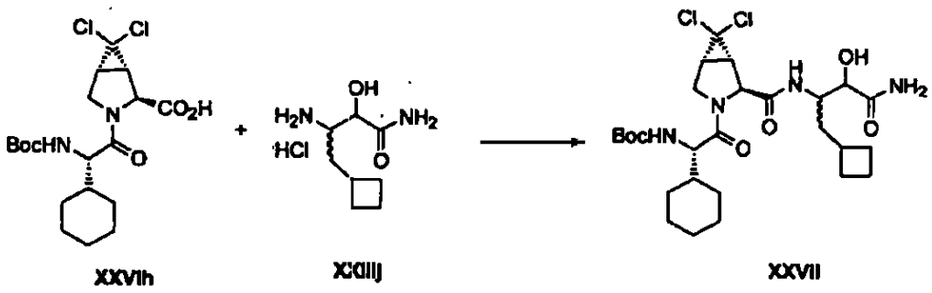
Paso 6:



XXVIg **XXVIh**

La solución del metil éster **XXVIg** (5,87 g, 13,1 mmol) y LiOH (1,65 g, 39,3 mmol) en THF/MeOH/H_2O (1:1:1, 90 mL) se agitó a temperatura ambiente durante 4 h. El metanol y el THF se eliminaron bajo presión reducida. La solución acuosa se acidificó hasta un pH ~2 usando solución 1N acuosa de HCl (50 mL) y saturada con cloruro de sodio sólido antes de extraer con EtOAc (3 x 150 mL). Las soluciones orgánicas se combinaron, se secaron ($MgSO_4$), se filtraron y se concentraron al vacío para dar un sólido blanco **XXVIh** (5,8 g, cuantitativo).

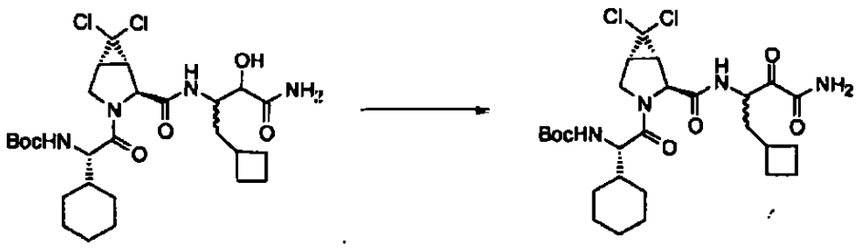
Paso 7:



XXVIh XXIIIj XXVII

El producto deseado XXIIIi se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIII, Paso 11.

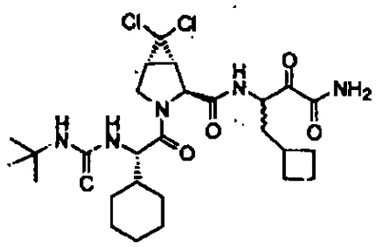
Paso 8:



XXVII XXVI

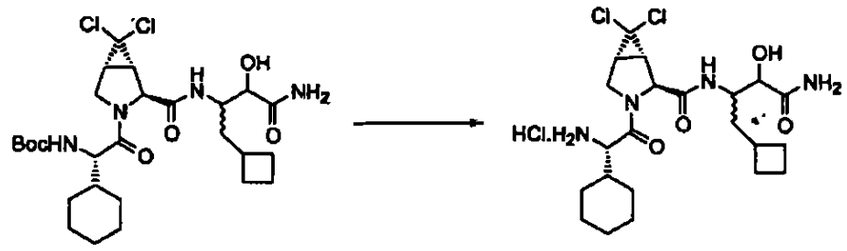
El producto deseado XXVI se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIII, Paso 12.

Ejemplo XXVII: Preparación del compuesto de fórmula XXVII:



XXVII

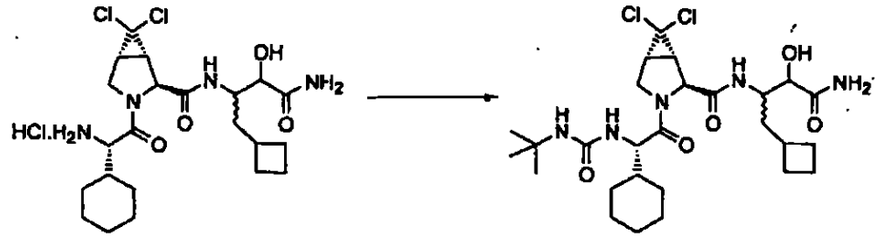
Paso 1



XXVII XXVIIa

El producto deseado XXVIIa se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIII, Paso 9.

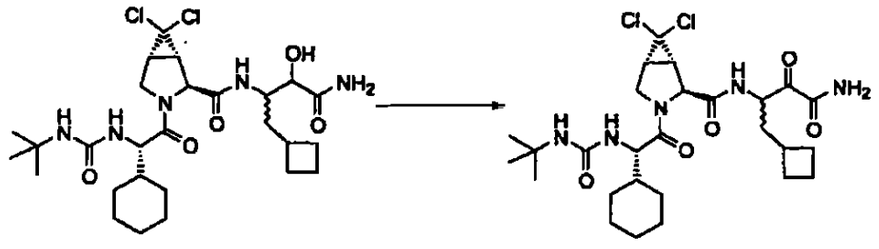
Paso 2



XXVIIa XXVIIb

El producto deseado XXVIIb se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIV, Paso 2.

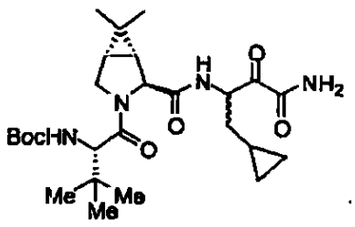
Paso 3



XXVIIb XXVII

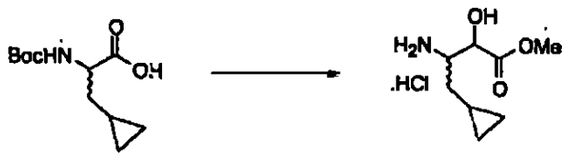
El producto deseado XXVII se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIII, Paso 12.

Ejemplo XXVIII: Preparación de un Compuesto de fórmula XXVIII:



XXVIII

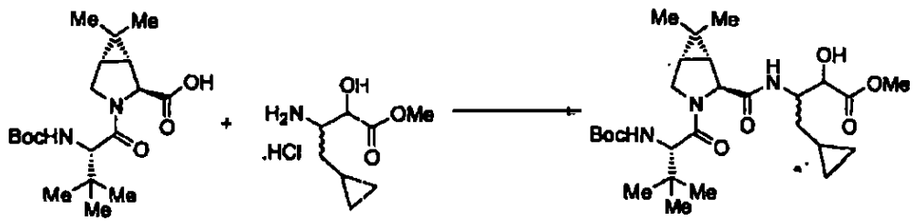
Paso 1



XXVIIIa XXVIIIb

El intermediario XXVIIIb se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIII, Pasos 3-6.

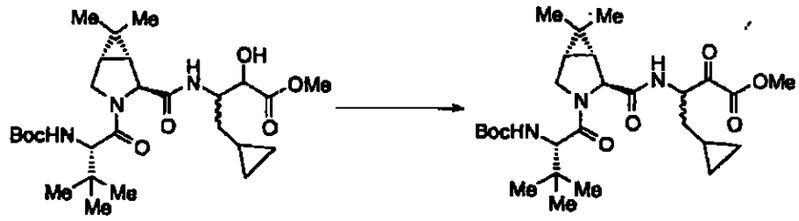
Paso 2:



XXVIIIc XXVIIIb XXVIIId

El ácido del Ejemplo XXIV, Paso 2 (XXVIIIc) (0,7 g) se reaccionó con el producto del Paso 1 anterior (0,436 g), HATU (0,934 g) y DIPEA (1,64 mL) del modo previamente descrito en el Ejemplo IX, Paso 2a para lograr 0,66 g del producto deseado **XXVIIId.**

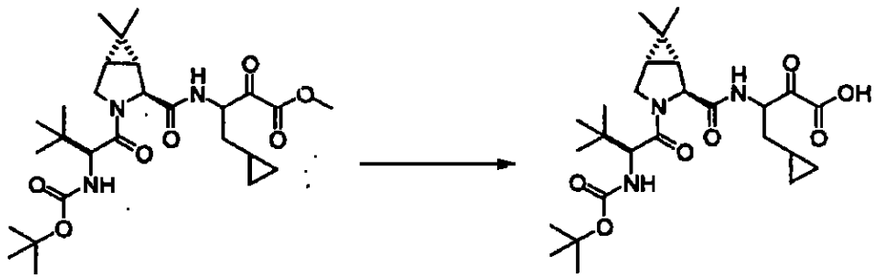
Paso 3:



XXVIIId XXVIIIe

El producto del paso 2 (0,5 g) se reaccionó con Reactivo de Dess-Martin (1 g) del modo previamente descrito en el Ejemplo XX, Paso 7. La purificación a través de cromatografía flash (40% EtOAc, Hexano, sílice) logró 0,358 de producto **XXVIIIe.** Espectro de masa (LCMS) 522 ($M+H^+$).

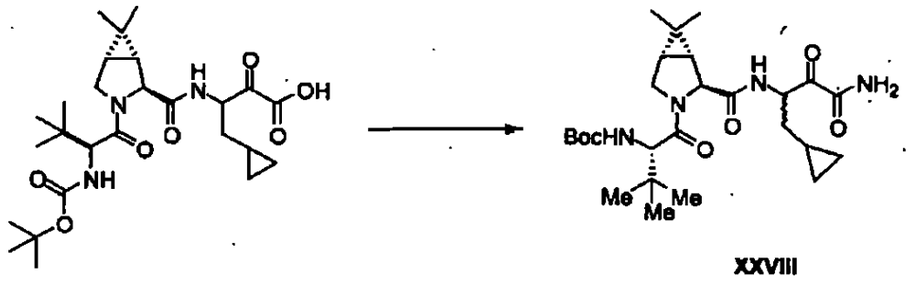
Paso 4:



XXVIIIe XXVIIIf

El producto del paso 4 (0,3 g) se agregó a una solución a 1/1 de H_2O/MeOH (20 mL) y $NaCHO_3$ sólido (242 mg, 5 equiv.). Luego de agitar durante 18 horas a temperatura ambiente, la reacción se diluyó con EtOAc y las fases se separaron. La fase de agua se acidificó hasta un pH 2 con HCl 1,0 N y se extrajo con EtOAc. La fase de EtOAc se lavó con salmuera, luego se secó sobre $MgSO_4$, se filtró y se concentró al vacío para lograr el producto **XXVIIIf** como un polvo blanco (0,26 g). Espectro de masa (LCMS) 508 ($M+H^+$).

Paso 5:

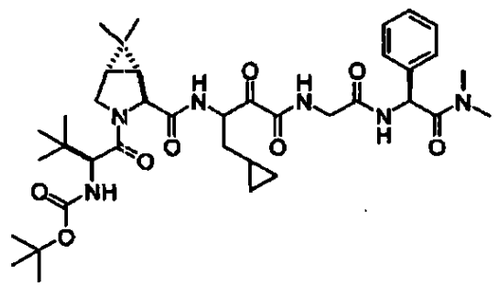


XXVIII'

XXVIII

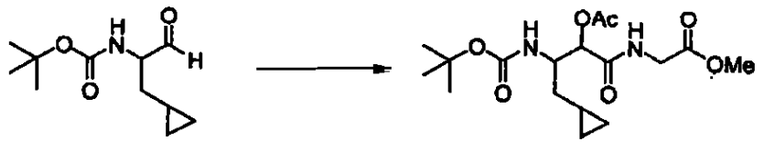
El producto del paso 5 (0,15 g) se disolvió en CH_2Cl_2 y se reaccionó con HATO (0,137 g), NH_4Cl (0,08 g, 5 equiv.) y DIPEA (0,53 mL). Luego de 2 horas a temperatura ambiente, la reacción se diluyó con EtOAc, se lavó con una solución al 10% de ácido cítrico, luego una solución de $NaCHO_3$ saturado. La fase de EtOAc se lavó con salmuera, luego se secó sobre $MgSO_4$, se filtró y se concentró al vacío para lograr una mezcla en bruto. La purificación a través de cromatografía flash (30% de Acetona, Hexano, sílice) logró el producto deseado **XXVIII** (0,096 g). Espectro de masa (LCMS) 507 ($M+H^+$).

Ejemplo XXIX: Preparación de un Compuesto de fórmula XXIX:



XXIX

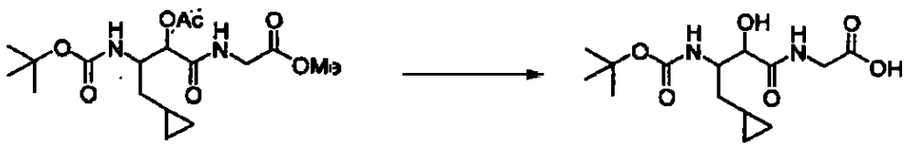
Paso 1:



XXIXa

A una solución a 0°C del aldehído inicial (4,0 g) en CH_2Cl_2 (75 mL) se agregó ácido acético (2,0 equiv., 2,15 mL) seguido de isocianoacetato de metilo (1,1 equiv., 1,9 mL). La reacción se entibió luego en forma gradual hasta alcanzar la temperatura ambiente. Luego de 18 horas (toda la noche), la reacción se diluyó con EtOAc y se lavó con una solución de $NaCHO_3$ saturado. La fase de EtOAc se lavó con salmuera, luego se secó sobre MgSO4, se filtró y se concentró al vacío para lograr una mezcla en bruto. La purificación a través de cromatografía flash (30 hasta 40% de EtOAc, Hexano, sílice) logró el producto **XXIXa** (4,5 g).

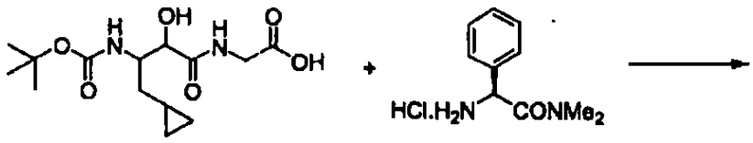
Paso 2:



XXIXa **XXIXb**

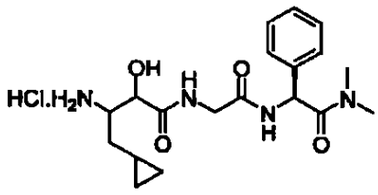
A una solución a 0°C de **XXIXa** (4,4 g) en THF (100 mL) se agregó 26 mL (2,2 equiv.) de una solución 1,0N de LiOH. La reacción se agitó a esta temperatura durante 2 horas luego se entibió hasta alcanzar la temperatura ambiente. Luego de 2 horas, la mezcla de reacción se acidificó hasta un pH 2 con una solución 1,0 N de HCl. Se agregó EtOAc y las fases se separaron. La fase de EtOAc se lavó con salmuera luego se secó sobre MgSO4, se filtró y se concentró al vacío para lograr el producto **XXIXb** (3,7 g).

Paso 3:



XXIXb

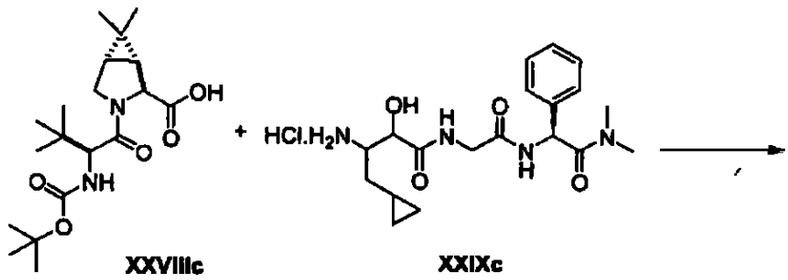
XV



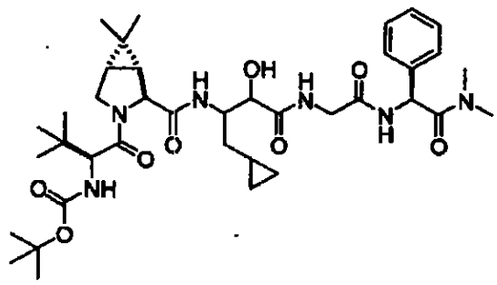
XXIXc

El ácido **XXIXb** se reaccionó con la amina del Ejemplo XV del modo previamente descrito en el Ejemplo XXI, Paso 4. El intermediario resultante se trató luego con HCl del modo previamente descrito en el Ejemplo XXIII, Paso 9 para lograr el producto XXIXc.

Paso 4:



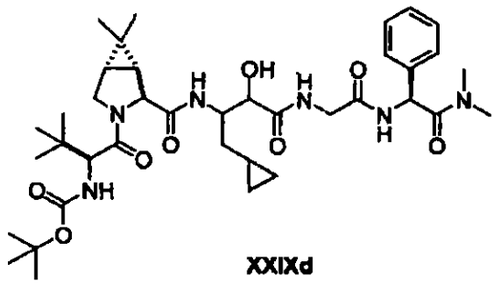
XXVIIIc XXIXc



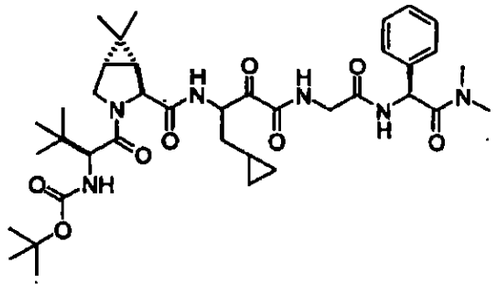
XXIXd

El ácido XXVIIIc (2,43 g) se disolvió en CH_2Cl_2 y se reaccionó con la amina **XXIXc** (2,47 g), HATU (2,5 g) y DIPEA (5,8 mL) del modo previamente descrito en el Ejemplo IX, Paso 2a para lograr, luego de la purificación a través de cromatografía flash (4% de MeOH, CH_2Cl_2, sílice), el producto deseado **XXIXd** (4,35 g). Espectro de masa (LCMS) 727 ($M+H^+$).

Paso 5:



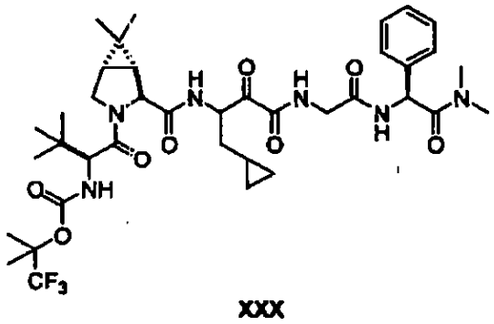
XXIXd



XXIX

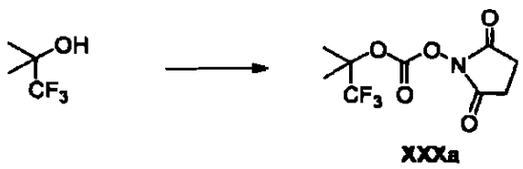
El producto del Paso 4 (4,2 g) se reaccionó con Reactivo de Dess-Martin (6,4 g) del modo previamente descrito en el Ejemplo de Preparación XX, Paso 7. La purificación a través de cromatografía flash (100% de EtOAc, sílice) logró 3 g del producto final **XXIX**. Espectro de masa (LCMS) 725 ($M+H^+$).

Ejemplo XXX: Preparación de un Compuesto de fórmula XXX:



XXX

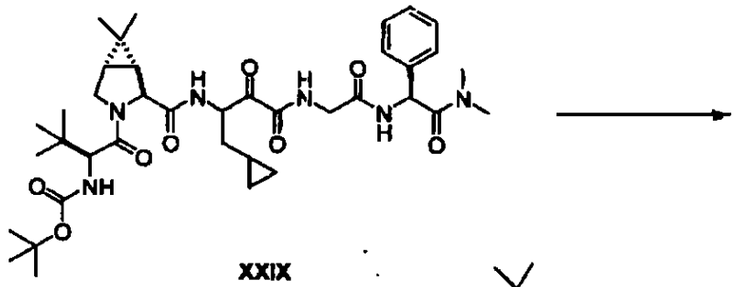
Paso 1:



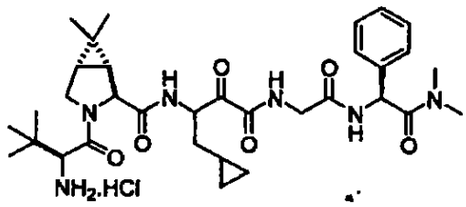
XXXa

El alcohol 2-(trifluorometil)propan-2-ol (1,28 g) se reaccionó con carbonato de N,N-disuccíminidilo (3,84 g) y Et_3N (4,2 mL) en CH_3CN anhidro (50 mL) durante 18 horas. La mezcla se diluyó con EtOAc (200 mL) y se filtró. El filtrado se lavó con $NaCHO_3$, salmuera, luego se secó sobre $MgSO_4$, se filtró y se concentró al vacío para lograr una mezcla en bruto. La purificación a través de cromatografía flash (50% de EtOAc, Hexano, sílice) logró el producto deseado XXXa (0,3 g).

Paso 2:



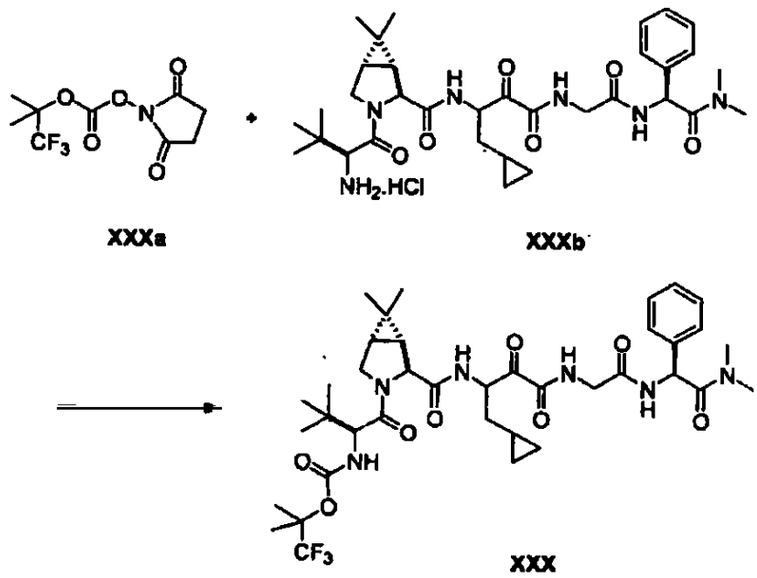
XXIX



XXXb

El producto del Ejemplo **XXIX** (0,3 g) se trató con 100 mL de HCl 4,0 N en dioxano. Luego de 1 h, se agregaron 200 mL de Et_2O y el precipitado resultante se eliminó por filtración y se secó al vacío para lograr el producto **XXXb** (0,27 g) como un polvo blanco. Espectro de masa (LCMS) 625 (M - HCl $+H^+$).

Paso 3:

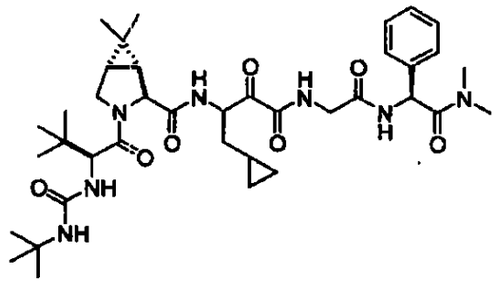


XXXa XXXb

XXX

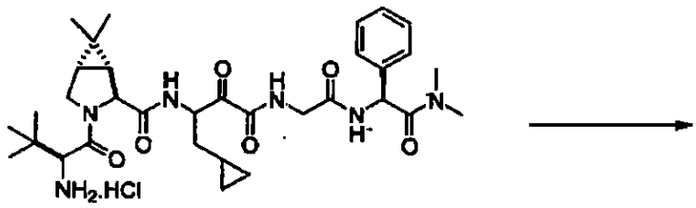
A una solución a temperatura ambiente de **XXXb** (0,05 g) en CH_2Cl_2 (5 mL) se agregó DIPEA (0,040 mL) **XXXa** (1,5 equiv., 0,030 g), seguido de 1 cristal de DMAP. Luego de 30 minutos, la reacción se diluyó con EtOAc (20 mL) y se lavó con HCl 1,5 N luego $NaCHO_3$ luego salmuera. La fase de EtOAc se secó sobre $MgSO_4$, se filtró y se concentró al vacío para lograr una mezcla en bruto. La purificación a través de cromatografía preparativa (40% de Acetona, Hexano, sílice) logró el producto deseado **XXX** (0,044 g). Espectro de masa (LCMS) 779 ($M+H^+$).

Ejemplo XXXI: Preparación de un Compuesto de fórmula XXXI:

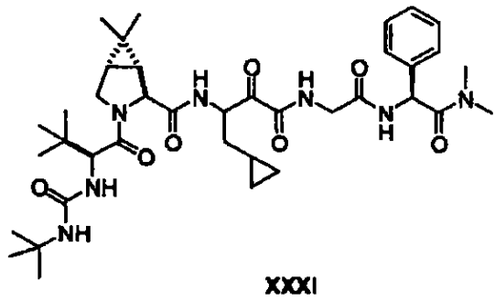


XXXI

Paso 1:



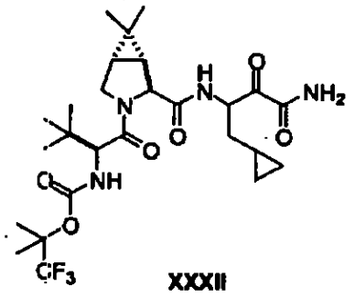
XXXb



XXXI

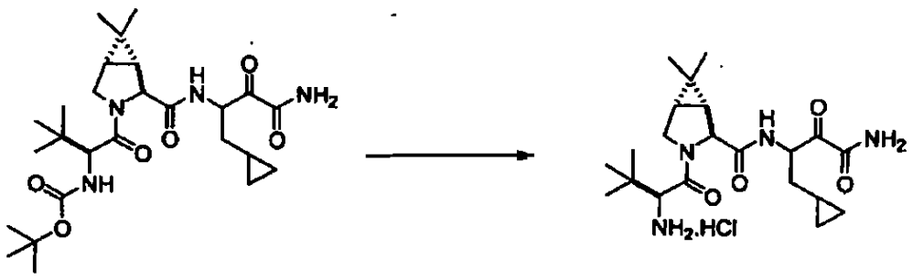
A una solución de **XXXb** (0,05 g) en CH_2Cl_2 (5 mL) a temperatura ambiente se agregó DIPEA (0,040 mL) y ter-butilisocianato (1,2 equiv., 0,01 mL). Luego de 18 horas, la reacción se diluyó con EtOAc (20 mL) y se lavó con HCl 1,5 N, $NaCHO_3$ y salmuera. La fase de EtOAc se secó sobre MgSO4, se filtró y se concentró al vacío para lograr una mezcla en bruto. La purificación a través de cromatografía preparativa (100% de EtOAc, sílice) logró el producto final **XXXI** (0,021 g). Espectro de masa (LCMS) 724 ($M+H^+$).

Ejemplo XXXII: Preparación de un Compuesto de fórmula XXXII:



XXXII

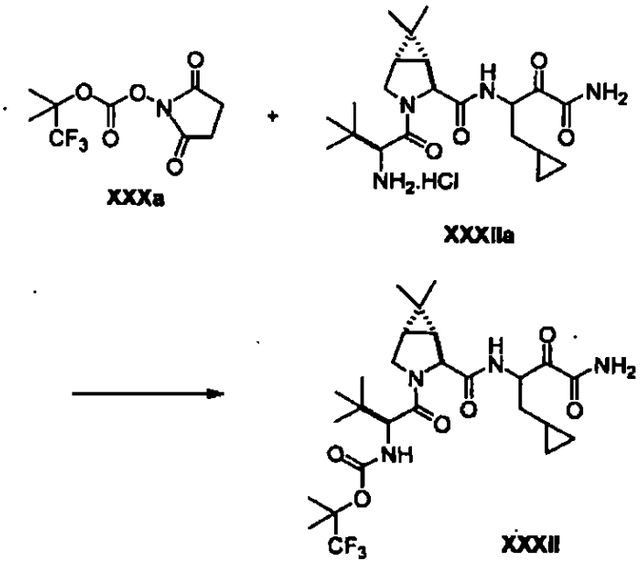
Paso 1:



XXVIII **XXXIIa**

El producto del Ejemplo XXVI II se trató del modo previamente descrito en el Ejemplo de Preparación XXX, Paso 2 para lograr el producto XXXIIa. Espectro de masa (LCMS) 407 (M - HCl +H$^+$).

Paso 2:

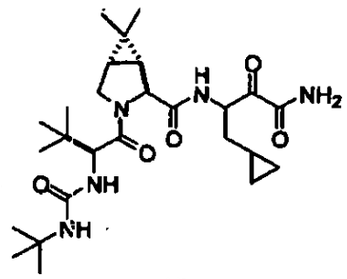


XXXa **XXXIIa**

XXXII

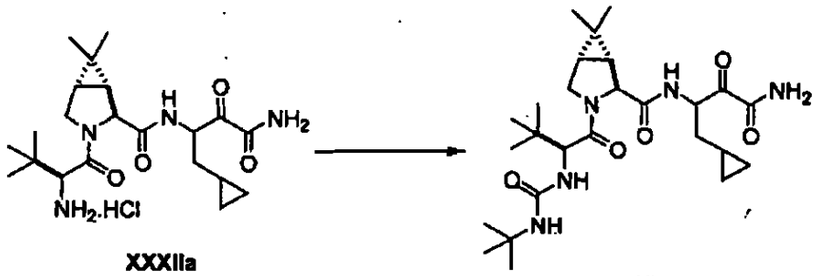
La amina **XXXIIa** se reaccionó con **XXXa** del modo previamente descrito en el Ejemplo de Preparación XXX, Paso 3 para lograr el producto deseado XXXII. Espectro de masa (LCMS) 508 (M+H$^+$).

Ejemplo XXXIII: Preparación de un Compuesto de fórmula XXXIII:



XXXIII

Paso 1:

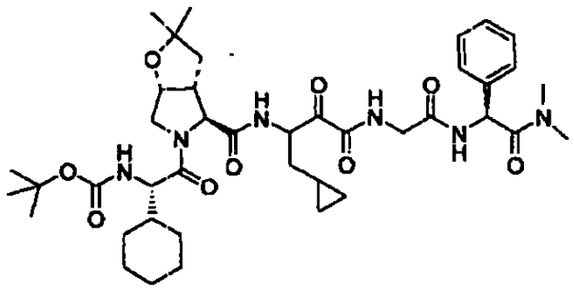


XXXIIa

XXXIII

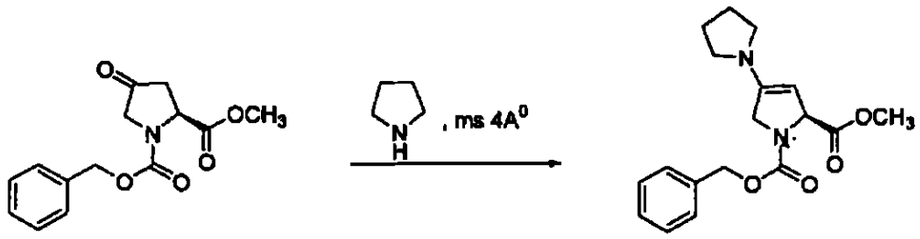
La amina **XXXIIa** se reaccionó con ter-butilisocianato del modo previamente descrito en el Ejemplo XXXI, Paso 1, para lograr el producto XXXIII. Espectro de masa (LCMS) 561 ($M+H^+$).

Ejemplo XXXIV: Preparación de un Compuesto de fórmula XXXIV:



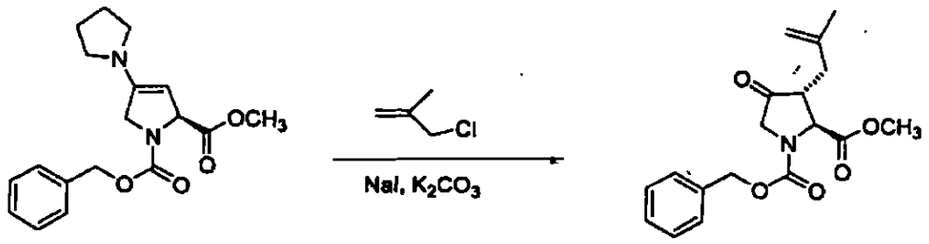
XXXIV

Paso 1:



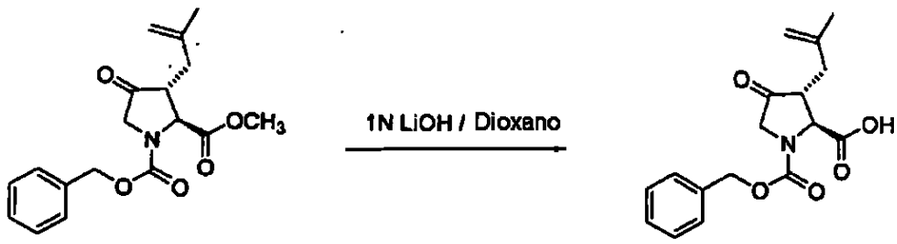
A la mezcla de éster (5,0 g) y tamiz molecular (5,2 g) en cloruro de metileno anhidro (35 mL) se agregó pirrolidina (5,7 mL, 66,36 mmoL). La emulsión marrón resultante se agitó a temperatura ambiente bajo N2 durante 24 h, se filtró y se concentró con CH_3CN anhidro. El filtrado combinado se concentró para dar como rendimiento el producto deseado.

Paso 2:



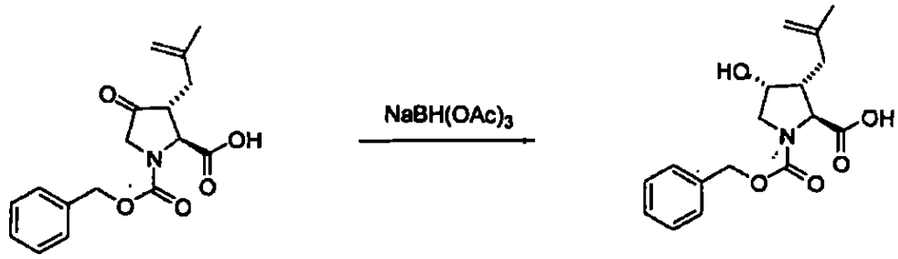
A una solución del producto del Paso anterior en CH_3CN (35 mL) se agregó K_2CO_3 anhidro, cloruro de metalilo (2,77 g, 30,5 mmoL), NaI (1,07 g, 6,7 mmoL). La emulsión resultante se agitó a temperatura ambiente bajo N_2 durante 24 h. Se agregó 50 mL de agua enfriada con hielo seguido de solución 2N de $KHSO_4$ hasta que el pH fue 1. Se agregó EtOAc (100 mL) y la mezcla se agitó durante 0,75 h. La fase orgánica combinada se recolectó y se lavó con salmuera, se secó sobre $MgSO_4$, y se evaporó para dar como rendimiento el producto deseado.

Paso 3:



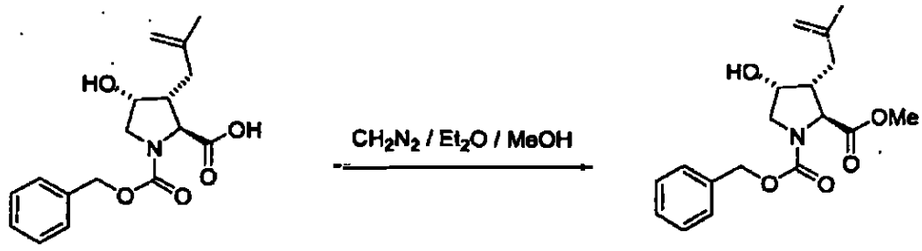
El producto del Paso anterior (2,7 g, 8,16 mmoL) se disolvió en dioxano (20 mL) y se trató con LiOH 1N recién preparado (9 mL). La mezcla de reacción se agitó a temperatura ambiente bajo N_2 durante 20 h. La mezcla de reacción se llevó en EtOAc y se lavó con H_2O. La fase de agua combinada se enfrió hasta 0°C y se acidificó hasta un pH 1,65 usando HCl 1N. La mezcla turbia se extrajo con EtOAc (2 x 100 mL). La fase orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, se concentró para dar el ácido deseado (3,40 g).

Paso 4:



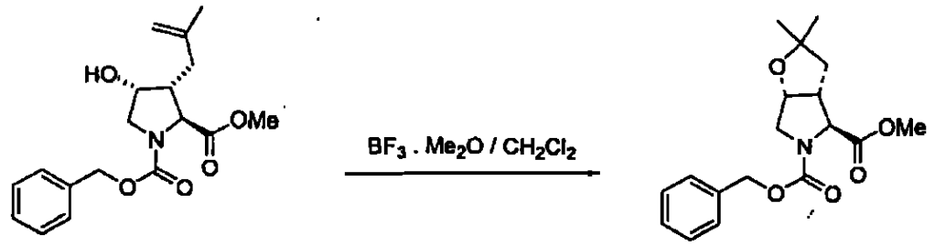
A una suspensión de $NaBH(OAc)_3$ (3,93 g, 18,5 mmoL) en CH_2Cl_2 (55 mL) se agregó una solución de producto del Paso anterior en CH_2Cl_2 anhidro (20 mL) y ácido acético (2 mL). La emulsión se agitó a temperatura ambiente durante 20 h. Se agregó agua fría con hielo (100 mL) a la emulsión y se agitó durante 1/2 hr. La fase orgánica se separó, se filtró, se secó y se evaporó para dar como rendimiento el producto deseado.

Paso 5:



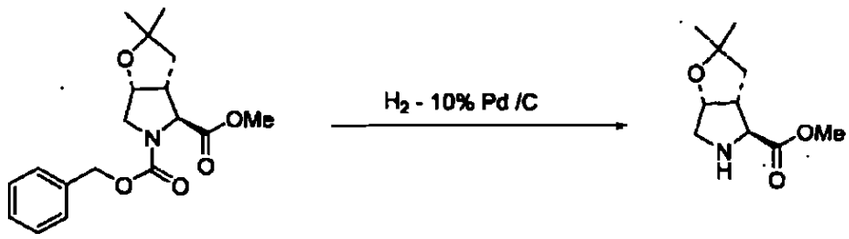
A una solución del producto del Paso anterior (1,9 g) en MeOH (40 mL) se trató con exceso de solución de CH_2N_2 / Et_2O y se agitó durante la noche. La mezcla de reacción se concentró hasta secar para dar como rendimiento un residuo en bruto. El residuo se cromatografió sobre gel de sílice, eluyendo con un gradiente de EtOAc / hexano para lograr 1,07 g del producto deseado en bruto.

Paso 6:



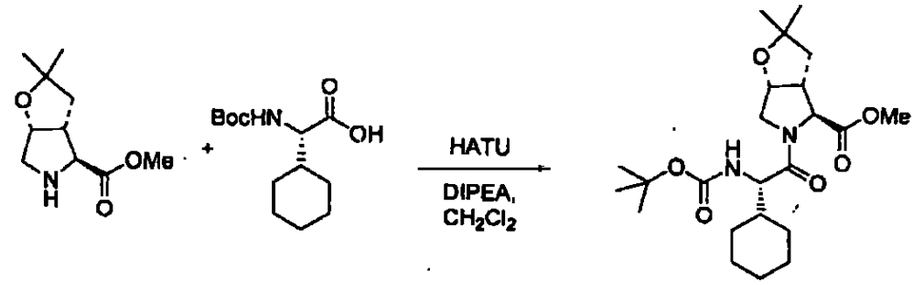
A una solución de producto del Paso anterior (1,36 g) en CH_2Cl_2 anhidro (40 mL) se trató con BF_3• Me_2O (0,7 mL). La mezcla de reacción se agitó a temperatura ambiente durante 20 h y se inactivó con $NaCHO_3$ saturado (30 mL) y se agitó durante 1/2 hr. La fase orgánica se separó y la fase orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, se concentró para dar el residuo en bruto. El residuo se cromatografió sobre gel de sílice eluyendo con un gradiente de EtOAc / hexano para lograr 0,88 g del compuesto deseado.

Paso 7:



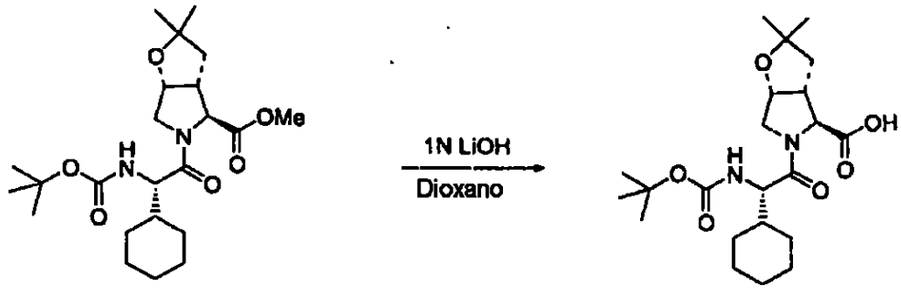
A una solución del producto (0,92 g) del Paso anterior en MeOH (30 mL) se agregó 10 % de Pd/C (0,16 g) a temperatura ambiente y se hidrogenó a temperatura ambiente bajo presión a 1 atm. La mezcla de reacción se agitó durante 4 h y se concentró hasta secar para lograr el compuesto deseado.

Paso 8:



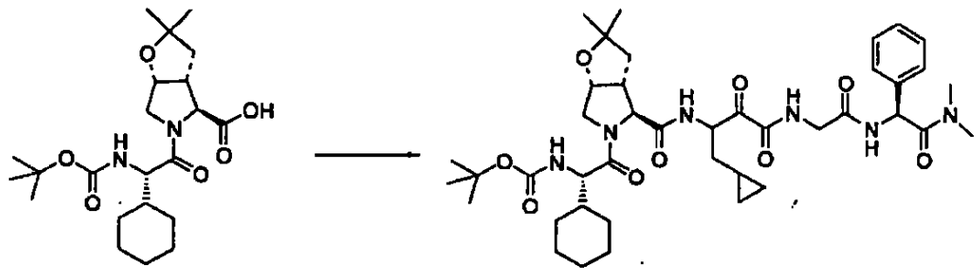
El producto deseado se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIII, Paso 10.

Paso 9:



El producto ácido deseado se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIV, Paso 3.

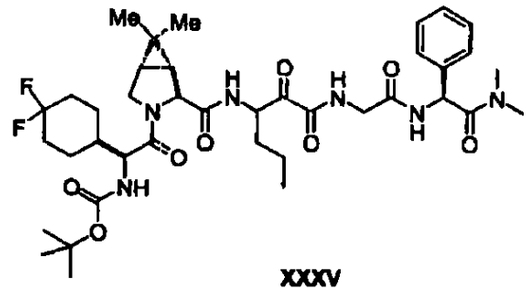
Paso 10:



XXXIV

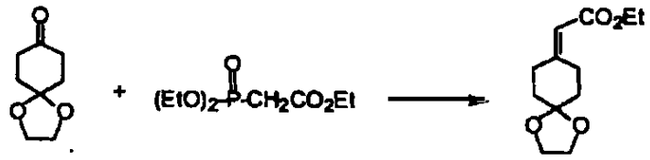
El producto deseado XXXIV se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIX, Pasos 4-5.

Ejemplo XXXV: Preparación de un Compuesto de fórmula XXXV



XXXV

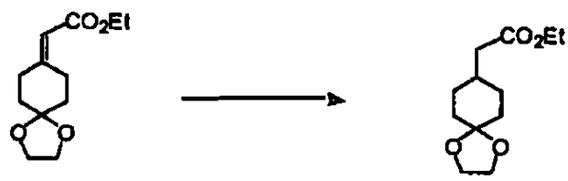
Paso 1:



Una solución de fosfonato de trietilo (44,8 g) en THF (30 mL) a 0°C se trató con una solución 1M (200 mL) de bis(trimetilsililamida) de sodio en THF. La mezcla resultante se agitó a temperatura ambiente durante 0,5 hora, y luego se enfrió hasta 0°C. Una solución de 1,4-ciclohexanodiona etileno cetal (15,6 g) en THF (50 mL) se agregó gota a gota, y la solución resultante se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se enfrió luego hasta 0°C, se trató con ácido cítrico frío acuoso, y la mezcla se extrajo con

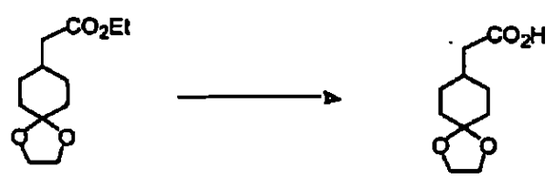
EtOAc. El extracto se lavó con $NaCHO_3$ acuoso saturado, luego salmuera; luego se secó sobre Na_2SO_4 anhidro, se filtró, y el filtrado se evaporó. El residuo se cromatografió sobre gel de sílice, eluyendo con un gradiente de CH_2Cl_2/EtOAc para lograr el compuesto del título (21 g), 92% de rendimiento. Espectro de masa (FAB) 227,3 ($M+H^+$).

Paso 2:



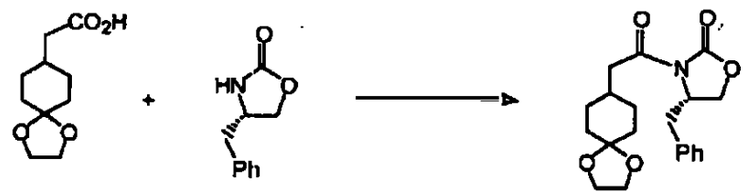
El producto del Paso precedente (20 g) se disolvió en EtOH (150 mL) y se trató con 10% de Pd/C bajo 1 atm de hidrógeno durante 3 días. La mezcla se filtró y el filtrado se evapora para lograr el compuesto del título (20,3 g), 100 de rendimiento. Espectro de masa (FAB) 229,2 ($M+H^+$).

Paso 3:



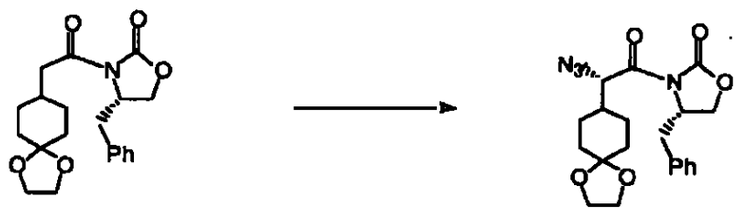
El producto del Paso precedente (20 g) se disolvió en MeOH (150 mL) y se trató con una solución de LiOH (3,6 g) en agua (50 mL). La mezcla se agitó durante 18 horas, y se concentró al vacío. El residuo se disolvió en agua fría (100 mL), la solución se acidificó hasta un pH 2-3 con HCl 5N, y la mezcla resultante se extrajo con EtOAc. El extracto se secó sobre Na_2SO_4 anhidro, se filtró, y el filtrado se evapora para lograr el compuesto del título (17,1 g), 97% de rendimiento. Espectro de masa (FAB) 201,2 ($M+H^+$).

Paso 4:



1. El producto del Paso precedente (3,0 g) se disolvió en Et_2O (150 mL), se trató con Et_3N (2,1 mL), y la solución se enfrió hasta -78°C. Se agregó cloruro de pivaloilo (1,85 mL) gota a gota, y luego de 0,25 hora de agitación adicional, la reacción se dejó entibiar hasta 0°C durante 0,75 hora, y luego se enfrió nuevamente hasta -78°C para lograr una solución de anhídrido mixto para la reacción de la parte 2. 2. Una solución de (S)-4-bencil-2-oxazolidinona (2,66 g) en THF (22 mL) se enfrió hasta -78°C, y una solución 1,6 M (9,38 mL) de n-butil litio en hexano se agregó gota a gota. Luego de un adicional de 0,33 hora agitando a esta temperatura, la solución se transfirió a través de una cánula a la solución fría de la parte 1. La mezcla se agitó a -78°C , luego se entibió hasta 0°C, y se agitó a esta temperatura durante 0,5 hora. La fase orgánica se separó, la fase de agua se extrajo con Et_2O, los orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4 anhidro, se filtraron, y el filtrado se evaporó. El residuo se cromatografió sobre gel de sílice, eluyendo con un gradiente de hexano/EtOAc (9:1) para lograr el compuesto del título (5,0 g), 93% de rendimiento. Espectro de masa (FAB) 360,4 ($M+H^+$).

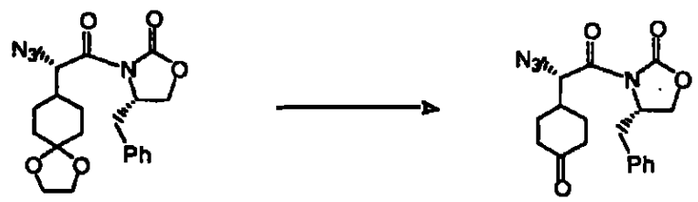
Paso 5:



El producto del Paso precedente (2,7 g) se disolvió en THF (25 mL), enfriada hasta -78°C, se transfirió a través de una cánula a una solución 0,5 M de

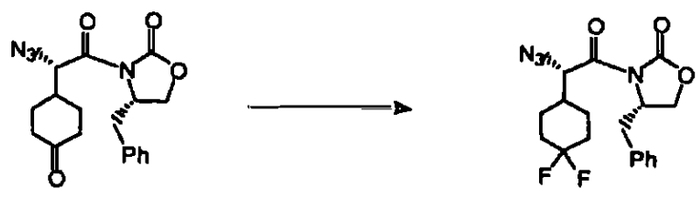
bis(trimetilsilil)amida de potasio/tolueno (16,5 mL) en THF (25 mL) a -78°C, y la solución resultante se agitó a -78°C durante 0,75 hora. A esta solución se agregó a través de una cánula una solución de azida de trisilo (3,01 g) en THF (25 mL) pre-enfriada hasta -78°C. Luego de 1,5 minutos, la reacción se inactivó con ácido acético (1,99 mL), la reacción se entibió hasta la temperatura ambiente, y luego se agitó durante 16 horas. La reacción se diluyó con EtOAc (300 mL), y se lavó con 5% de NaCl acuoso. La fase de agua se extrajo con EtOAc, las fases orgánicas combinadas se lavaron con $NaCHO_3$ acuoso saturado, luego salmuera; luego se secaron sobre Na_2SO_4 anhidro, se filtraron, y el filtrado se evapora. El residuo se cromatografió sobre gel de sílice, eluyendo con EtOAc/hexano (1:3) para lograr el compuesto del título (2,65 g), 88% de rendimiento.

Paso 6:



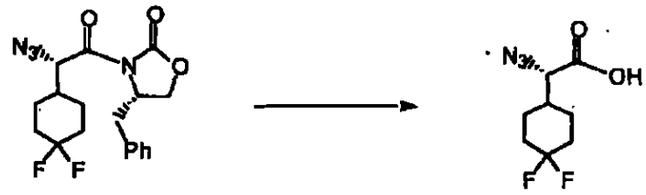
El producto del Paso precedente (11,4 g) se disolvió en 95% de ácido fórmico (70 mL) y se calentó a 70°C durante 0,5 hora mientras se agitaba. La solución se evaporó al vacío, y el residuo se absorbió en EtOAc. La solución se lavó con $NaCHO_3$ acuoso saturado, luego salmuera; luego se secó sobre Na_2SO_4 anhidro, se filtró, y el filtrado se evaporó. El residuo se cromatografió sobre gel de sílice para lograr el compuesto del título (8,2 g).

Paso 7:



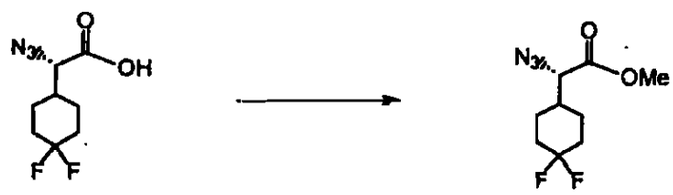
El producto del Paso precedente (8,2 g) se disolvió en CH_2Cl_2 (16 mL) y se trató con trifluoruro e dietilaminoazufre (DAST, 7,00 mL) a temperatura ambiente durante 3 horas. La reacción se vertió sobre hielo/ agua (200 cc), y se extrajo con CH_2Cl_2. El extracto se lavó con $NaCHO_3$ acuoso saturado, luego salmuera; luego se secó sobre Na_2SO_4 anhidro, se filtró, y el filtrado se evapora. El residuo se cromatografió sobre gel de sílice, eluyendo con EtOAc/hexano (15:85) para lograr el compuesto del título (4,5 g), 52% de rendimiento.

Paso 8:



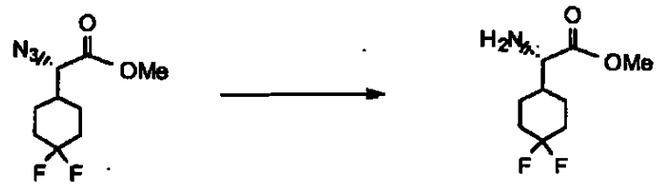
El producto del Paso precedente (3,7 g) se disolvió en una mezcla de THF (150 mL) y agua (48 mL), se enfrió hasta 0°C, se trató con 30% de H_2O_2 (3,95 mL), y luego con $LiOH \cdot H_2O$ (0,86 g). La mezcla se agitó durante 1 hora a 0°C, luego se inactivó con una solución de Na_2SO_3 (5,6 g) en agua (30 mL), seguido de una solución de $NaCHO_3$ 0,5N (100 mL). La mezcla se concentró al vacío hasta la mitad del volumen, se diluyó con agua (hasta 500 mL), y se extrajo con CH_2Cl_2 (4 x 200 mL). La fase de agua se acidificó hasta un pH 1-2 con HCl 5N, y se extrajo con EtOAc (4 x 200 mL). El extracto se lavó salmuera; luego se secó sobre Na_2SO_4 anhidro, se filtró, y el filtrado se evapora para lograr el compuesto del título (1,95 g), 91% de rendimiento, que se usó directamente en el paso siguiente.

Paso 9:



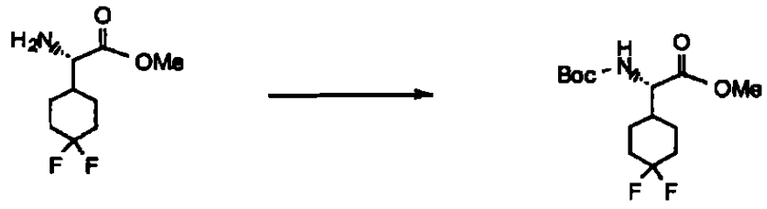
El producto del ejemplo anterior (2,6 g) se disolvió en Et_2O (50 mL) y se trató gota a gota con una solución de CH_2N_2 en Et_2O hasta que la solución permaneció amarilla. La solución se agitó durante 18 horas, luego se evaporó al vacío para lograr el compuesto del título (2.8), que se usó directamente en el paso siguiente.

Paso 10:



El producto del Paso precedente (1,95 g) se disolvió en MeOH (150 mL), se trató con ácido fórmico (1,7 mL), luego se trató con 10% de Pd/C (3,3 g, tipo Degussa E101) bajo 1 atm de hidrógeno durante 1,5 horas. La mezcla se filtró y el filtrado se evapora para lograr el compuesto del título (2,1 g) como la sal del ácido fórmico, que se usó directamente en el paso siguiente.

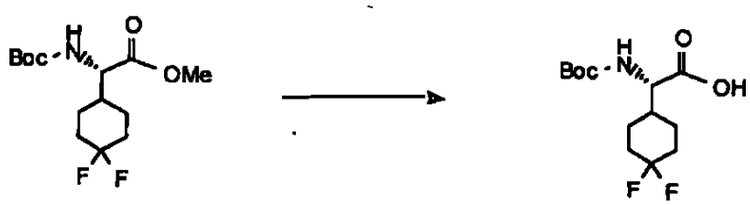
Paso 11:



El producto del Paso precedente (2,1 g) se disolvió en 1,4-dioxano (100 mL) y se agregó dicarbonato de · di-ter-butilo (1,9 g), seguido de diisopropiletilamina (2,9 mL). La solución se agitó durante 18 horas, y se concentró al vacío. El residuo se trató con 5% de KH_2PO_4 acuoso y la mezcla se extrajo con EtOAc. El extracto se lavó con salmuera; luego se secó sobre $MgSO_4$ anhidro, se filtró, y el filtrado se evapora. El residuo se cromatografió sobre gel de

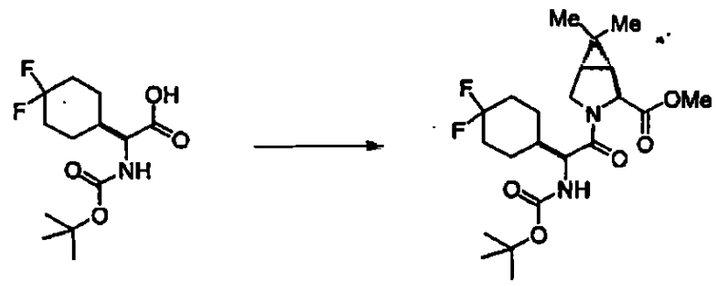
sílice, eluyendo con un gradiente de CH_2Cl_2/Et_2O para lograr el compuesto del título (2,5 g), 99% de rendimiento. Espectro de masa (FAB) 307,9 ($M+H^+$).

Paso 12:



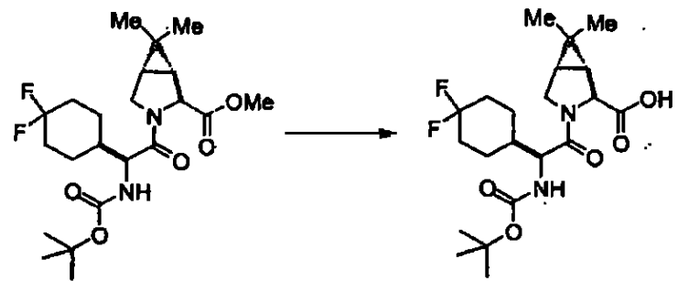
El producto del Paso precedente (2,5 g) se disolvió en 1,4-dioxano (35 mL), se trató con LiOH 1M acuoso (17 mL), y se agitó durante 2 horas. La mezcla se inactivó con hielo/agua (125 cc), la mezcla se acidificó hasta un pH 3-4 con HCl 3N, y se extrajo con EtOAc. El extracto se secó sobre $MgSO_4$ anhidro, se filtró, y el filtrado se evaporó para lograr el compuesto del título (2,3 g), 96% de rendimiento. Espectro de masa (FAB) 294,0 ($M+H^+$).

Paso 13:



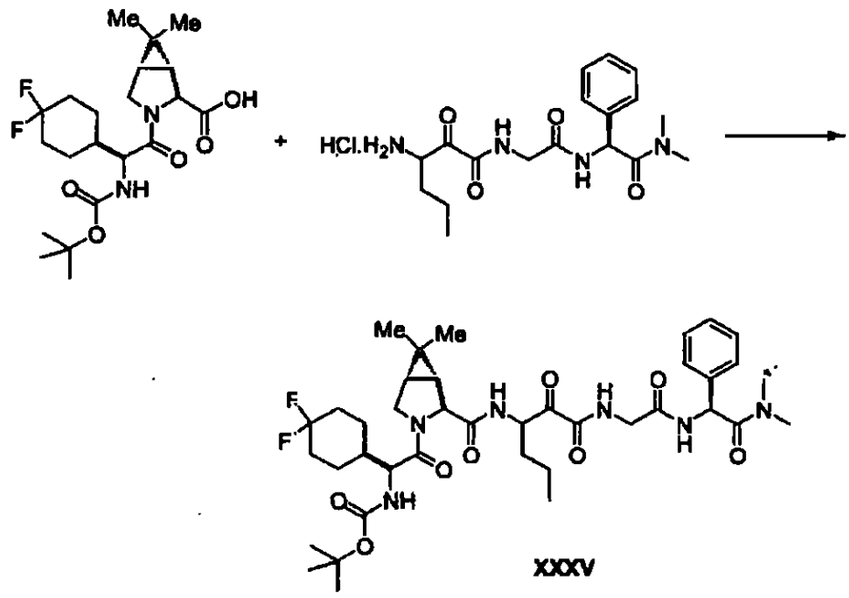
El producto deseado se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIII, Paso 10.

Paso 14:



El producto ácido deseado se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIV, Paso 3.

Paso 15:

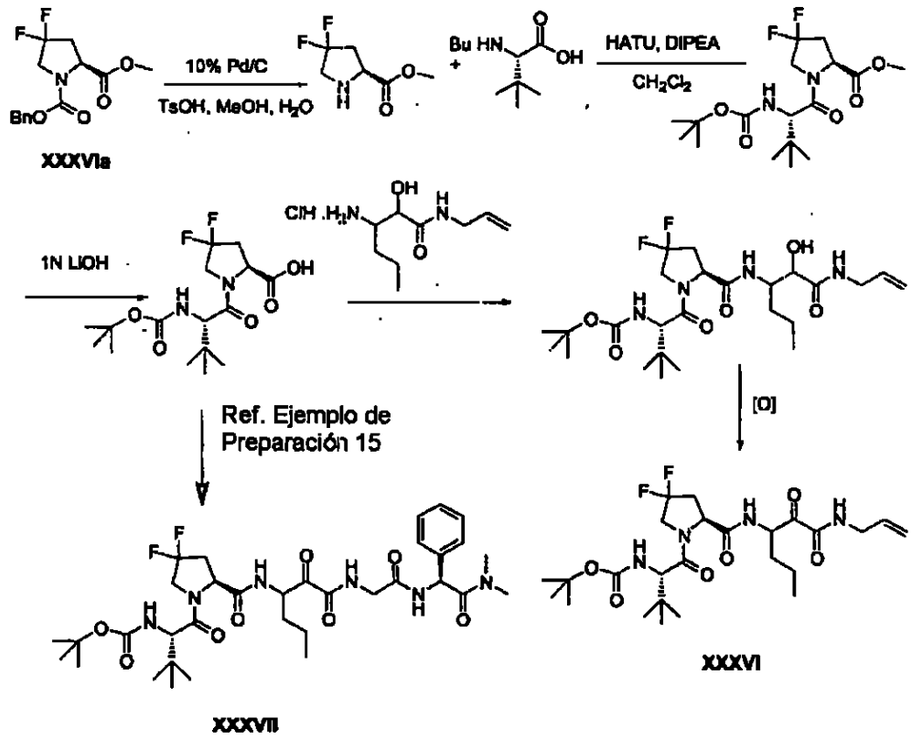


XXXV

El producto ácido deseado se preparó de acuerdo con el procedimiento descrito en el Ejemplo XXIX, Paso 4.

Ejemplo XXXVI. Preparación del compuestos de Fórmulas XXXVI y XXXVIII

Los Compuestos de fórmulas XXXVI y XXXVIII se prepararon de acuerdo con el esquema siguiente y usando los Ejemplos de Preparación 11 hasta 15 descritos anteriormente.

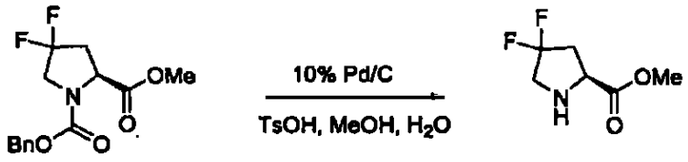


XXXVIa

XXXVII

XXXVI

El compuesto de fórmula XXXVIb se preparó a partir de un compuesto de fórmula XXXVIa como sigue a partir de procedimientos conocidos:



XXXVIa

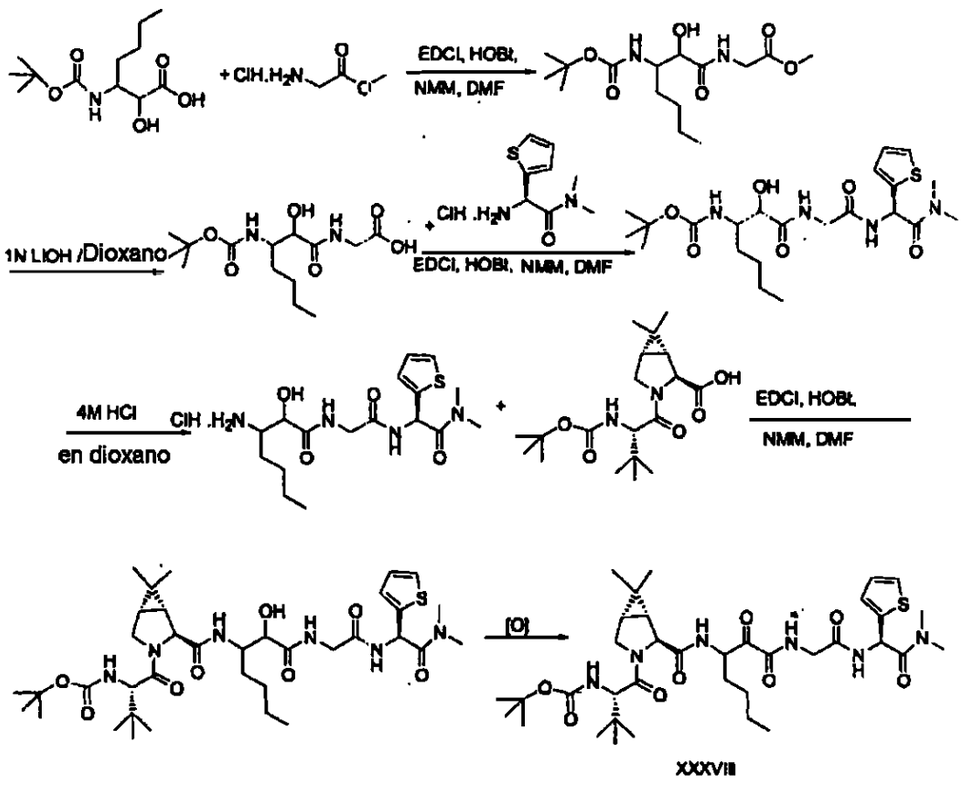
XXXVIb

A una solución del compuesto XXXVIa (6,58 g, 22 mmol) en 100 mL de MeOH se agregó 10% de Pd/C (0,8 g) y ácido p-toluen sulfónico (4,2 g). La mezcla de reacción se sometió a hidrogenación a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite y se lavó con exceso de MeOH. El filtrado combinado se concentró al vacío para dar el compuesto del título XXXVIb como una goma. La conversión de XXXVIb a XXXVI y XXXVII

siguió la ruta que se muestra en el esquema anterior y de acuerdo con los Ejemplos de Preparación 11-15.

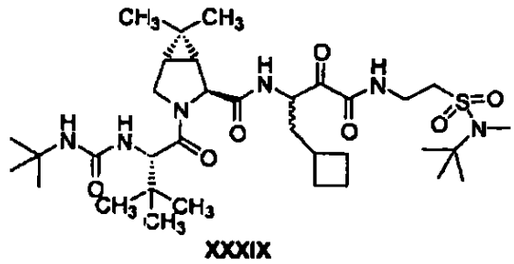
Ejemplo XXXVIII. Preparación de un Compuesto de fórmula XXXVIII:

Un Compuesto de fórmula XXXVIII se preparó usando el siguiente esquema y siguiendo los Ejemplos de Preparación 11 hasta 15 descritos con anterioridad.



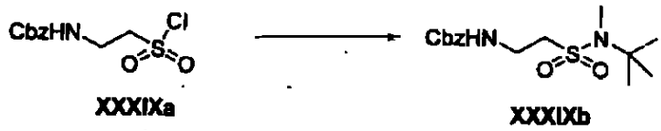
XXXVIII

Ejemplo XXXIX. Síntesis de el compuesto de Fórmula XXXIX



XXXIX

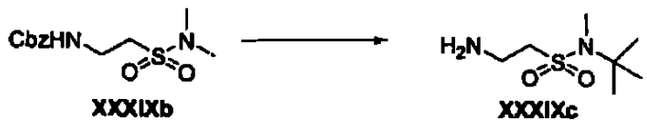
Paso 1:



XXXIXa XXXIXb

Una solución del cloruro de sulfonilo XXXIXa preparado a través del procedimiento de H. Mcklwain (J. Chem. Soc 1941, 75) se agregó gota a gota a una mezcla de 1,1. equiv de t-butilmetilamina y trietilamina a -78°C y se agitó a temperatura ambiente durante 2h. La mezcla de reacción se concentró al vacío y se purificó a través de cromatografía (SiO_2, Hex/Acetona a 4:1) para dar como rendimiento sulfonamida XXXIXb como un aceite incoloro.

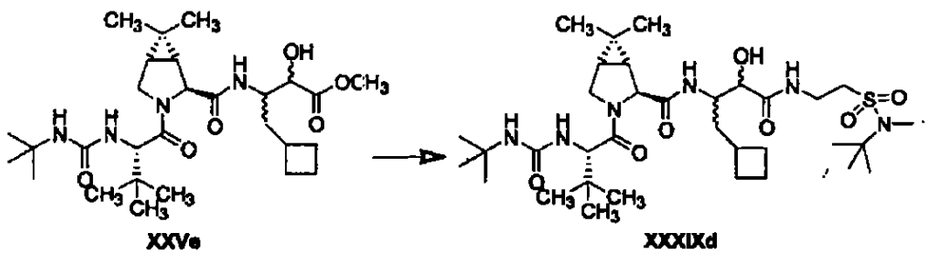
Paso 2:



XXXIXb XXXIXc

Una solución de la amina protegida con Cbz XXXIXb se disolvió en metanol y se trató con 5 % molar de Pd /C (5% p/p) y se hidrogenó a 60 psi. La mezcla de reacción se filtró a través de un tapón de y se concentró al vacío para obtener la amina libre XXXIXc que se solidificó en reposo.

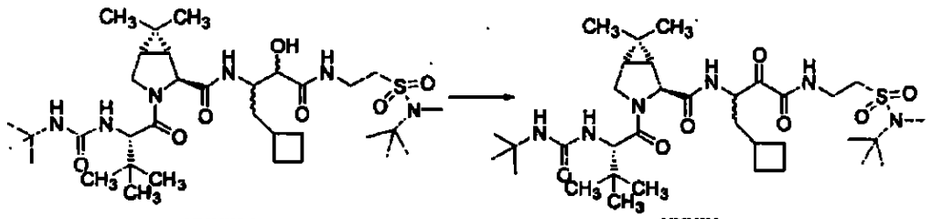
Paso 3:



XXVe XXXIXd

La hidroxi sulfonamida **XXXIXd** se sintetizó similar al procedimiento para la síntesis de **XXVf** excepto que se reemplazó la amina **XXVd** con **XXXIXc**. La mezcla de reacción en bruto se usó directamente para la reacción siguiente.

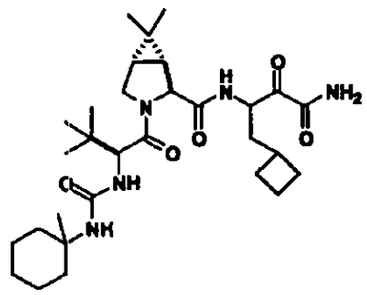
Paso 4:



XXXIXd XXXIX

La hidroxi amida **XXXIXd** se oxidó al compuesto **XXXIX** usando el reactivo de Dess Martin siguiendo el procedimiento para la síntesis de **XXV** (paso 5). La mezcla en bruto se purificó a través de cromatografía (SiO_2, Acetona/Hexano a 3:7) para obtener **XXXIX** como un sólido incoloro.

Ejemplo XXCX Preparación del compuesto de Fórmula XXXX



XXXX

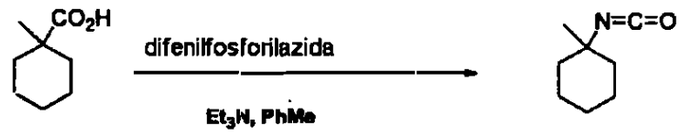
Paso 1



XXXXa XXXXb

XXXXa se reaccionó del modo previamente descrito para XXXII paso 1 para lograr el producto **XXXXb** del paso 1. Espectro de masa (LCMS) 421 (M - HCl $+H^+$).

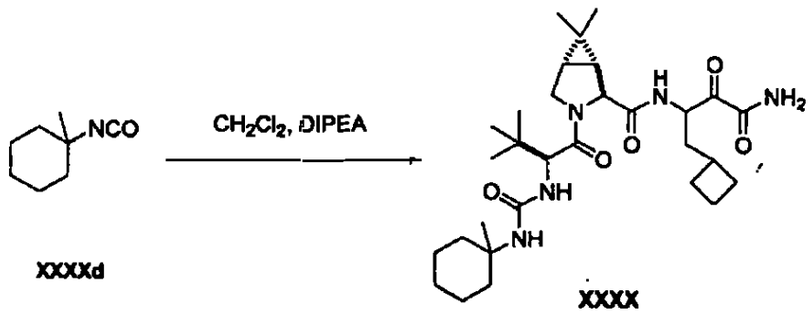
Paso 2



XXXXc **XXXXd**

Et_3N (1,4 mL) y difenilfosforilazida (2,2 mL) se agregaron a una solución de ácido carboxílico **XXXXc** en tolueno (13 mL). La reacción se agitó a temperatura ambiente durante 30 min luego se reflujó durante la noche. Luego de 18 h, la reacción se enfría hasta la temperatura ambiente y el producto **XXXXd** del paso 2, que se usó directamente como una solución 0,7 M en Tolueno.

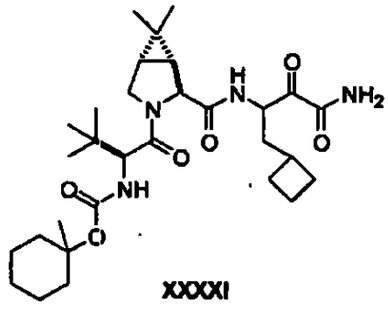
Paso 3



XXXXd **XXXX**

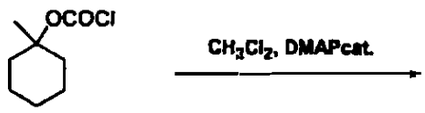
XXXXb, Producto del paso 1 del Ejemplo de Preparación XXXX se reaccionó con **XXXXd**, producto del paso 2 del Ejemplo de Preparación XXXX del modo previamente descrito en el Ejemplo VIII para lograr XXXX. Espectro de masa (LCMS) 560 ($M+H^+$).

Ejemplo XXXXI Preparación del compuesto de Fórmula XXXXI



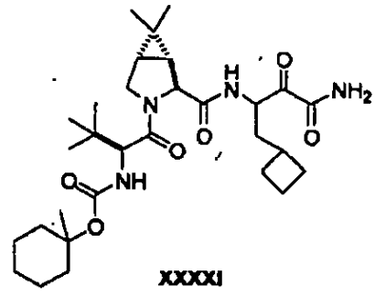
XXXXI

Paso 4



Preparado según J. Org. Chem. 1977, 42, 143

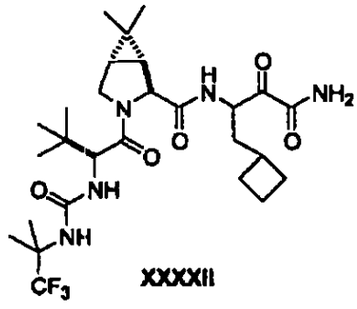
XXXXIa



XXXXI

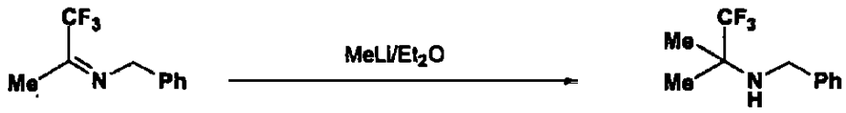
XXXXb, producto del paso 1 del Ejemplo de Preparación XXXX se reaccionó con el cloroformiato **XXXXIa** preparado como indica J. Org. Chem.,1977,42, 143 del modo previamente descrito en el Ejemplo de Preparación 12 compuesto 4.1 descrito para lograr XXXXI. Espectro de masa (LCMS) 561 ($M+H^+$).

Ejemplo XXXXII Preparación del compuesto de Fórmula XXXXIi



XXXXII

Paso 1



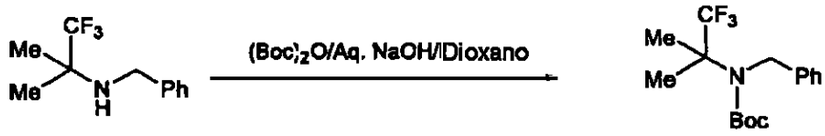
Preparado según J. Org. Chem., 1996 p 6567

XXXXIIa

XXXXIIb

A una solución agitada y enfriada (baño de hielo seco/ acetona) de la imina inicial **XXXXII a** (3,679 g) en éter dietílico (50 ml) se agregó metil litio 1,6M en éter dietílico (12,6 ml). La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente durante 2 hrs. Se agregó $NaCHO_3$ saturado y luego de agitar durante -30 min la fase orgánica se separó. Se lavó luego con salmuera, se secó sobre Na_2SO_4 anhidro y se concentró hasta secar al vacío. El producto en bruto se sometió a cromatografía sobre gel de sílice (2% de acetato de etilo en n-hexano) para dar el producto deseado **XXXXIIb** (0,3 g).

Paso 2

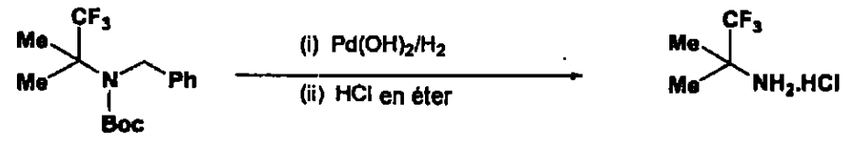


XXXXIIb

XXXXIIc

A una solución agitada y enfriada (baño de hielo) de **XXXXIIb**, el producto del Paso 1 (0,3 g) se agregó NaOH 1,0N (1,38 ml) seguido de $(Boc)_2O$. La mezcla de reacción se agitó a temperatura ambiente durante -20 hrs. luego de lo cual se distribuyó entre acetato de etilo (50 ml) y agua (10 ml). La fase de acetato de etilo se separó, se lavó con salmuera y se secó sobre Na_2SO_4 anhidro. La evaporación al vacío hasta secar proveyó el derivado Nboc deseado **XXXXIIc** (0,660 g), que se usó sin purificación adicional en el paso siguiente.

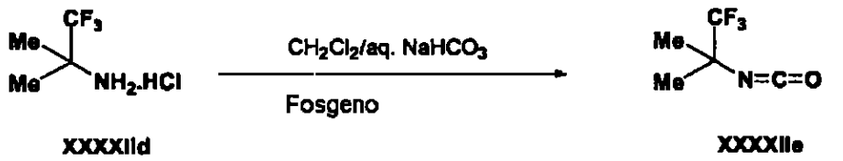
Paso 3



XXXXIIc **XXXXIId**

Una solución de **XXXXIIc**, producto del paso 2 en metanol (10 ml) se hidrogenó en presencia de $Pd(CH)_2$ hasta que la cromatografía en capa delgada mostró la ausencia del material inicial. El $Pd(OH)_2$ se eliminó por filtración y se lavó con metanol. El filtrado combinado y los lavados se concentraron hasta secar al vacío para dar un sólido que se disolvió en metanol y se trató con HCl 1,0N en éter dietílico. Luego de ~2 hr. la mezcla de reacción se evaporó hasta secar al vacío para dar **XXXXIId** el clorhidrato de amina deseado como un sólido blanco (0,2 g).

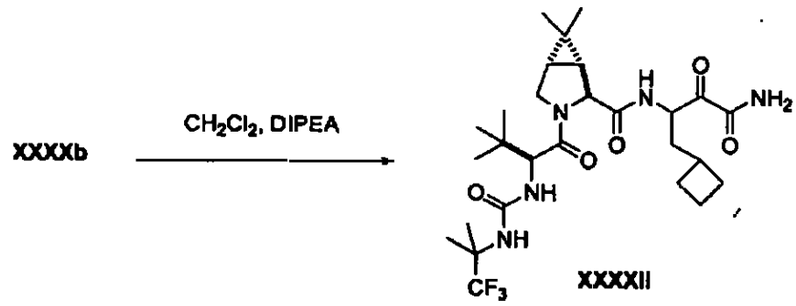
Paso 4



XXXXIId **XXXXIIe**

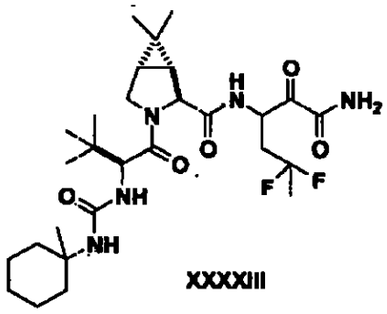
A una solución agitada y enfriada (baño de hielo) de **XXXXIId** el producto del Paso C (0,1 g) en CH_2Cl_2 (6 ml) se agregó solución saturada de $NaCHO_3$ (4 ml) seguido de fosgeno (0,64 ml). La mezcla de reacción se agitó a 0°C durante 30 min y a temperatura ambiente durante 1 hr. La fase orgánica se separó, se secó sobre $MgSO_4$ anhidro y se concentró hasta secar al vacío para dar el isocianato deseado **XXXXIIe** (0,0611 g).

Paso 5

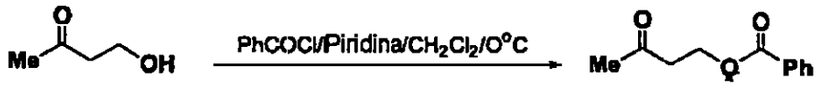


XXXXIIe, producto del paso 5 se reaccionó con XXXXb del Ejemplo de Preparación XXXX del modo previamente descrito en el Ejemplo XXXIII, descrito para lograr XXXXII. Espectro de masa (LCMS) 574 ($M+H^+$).

Ejemplo XXXXIII Preparación del compuesto de Fórmula XXXXIII



Paso 1

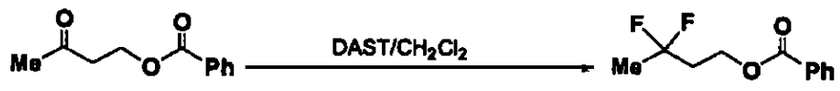


XXXXIIIa **XXXXIIIb**

A una solución enfriada (baño de hielo) de 4-hidroxi-2-butanona (8,81 g) **XXXXIIIa** en CH_2Cl_2 (100 ml) se agregó con agitación, cloruro de benzoilo (14,76 g) seguido de piridina (16,15 ml) y DMAP (0,01 g). La mezcla de reacción se agitó a temperatura ambiente durante la noche, luego se diluyó con acetato de etilo (~200 ml). La solución se lavó con $CuSO_4$ acuoso, NH_4Cl acuoso y salmuera. La fase orgánica se secó luego sobre $MgSO_4$ anhidro y se evaporó hasta secar. El

producto se purificó a través de cromatografía en columna sobre gel de sílice (5%-15% de acetato de etilo en n-hexano) para dar **XXXXIIIb** (16,3 g; 84,9%).

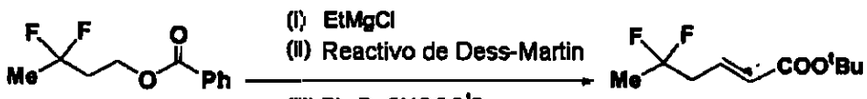
Paso 2



XXXXIIIb **XXXXIIIc**

A una solución de **XXXXIIIb**, el producto del Paso 1 (16,3 g) en CH_2Cl_2 (150 ml), se agregó DAST (26,1 ml) y la mezcla de reacción se agitó a temperatura ambiente durante ~72 hrs. La mezcla luego se agregó gota a gota a una solución saturada, fría de Na_2CO_3 (150 ml). La mezcla se diluyó con acetato de etilo (~200 ml) y luego de agitar durante ~30 min la fase orgánica se separó; se lavó con salmuera y se secó sobre $MgSO_4$ anhidro. La concentración al vacío y la purificación a través de cromatografía sobre gel de sílice (4% de acetato de etilo en n-hexano) proveyó **XXXXIIIc** (14,6 g; 80,4%).

Paso 3

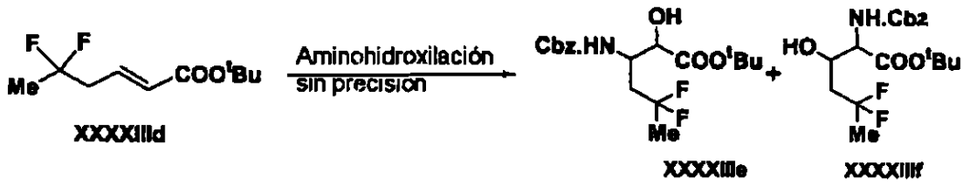


XXXXIIIc **XXXXIIId**

A una solución de **XXXXIIIc** el producto del Paso 2 (4 g) en éter dietílico anhidro (150 ml) se agregó con frío (baño de hielo) EtMgCl (28 ml). La mezcla de reacción se agitó en el baño de frío durante ~6 hrs. luego de lo cual se vertió en NH_4Cl acuoso saturado con frío de hielo. La fase orgánica se separó, se lavó con salmuera, se secó sobre $MgSO_4$ anhidro y se concentró hasta secar al vacío. El residuo se disolvió en CH_2Cl_2 (100 ml) y se trató con Reactivo de Dess-Martin (15,8 g). Luego de agitar a temperatura ambiente durante 1 hr. se agregó Ph_3P=CHCOOtBu (10,54 g). Se continuó la agitación durante ~20 hrs. Se agregó acetato de etilo (~200 ml) seguido de una mezcla de $Na_2S_2O_3$ saturado y

$NaCHO_3$ saturado (200 ml; 1/1) y se agitó durante ~10 min. La fase orgánica se separó y se lavó sucesivamente con $NaCHO_3$ saturado y salmuera. La fase orgánica lavada se secó sobre $MgSO_4$ anhidro y se evaporó hasta secar al vacío para dar el producto en bruto deseado. La reacción anterior se repitió usando el producto del Paso 2 (10,6 g). Los productos finales en bruto de las dos reacciones se combinaron y se sometieron a purificación a través de cromatografía sobre gel de sílice (10% CH_2Cl_2 en n-hexano) para dar **XXXXIIId** (7,93 g; 57%).

Paso 4

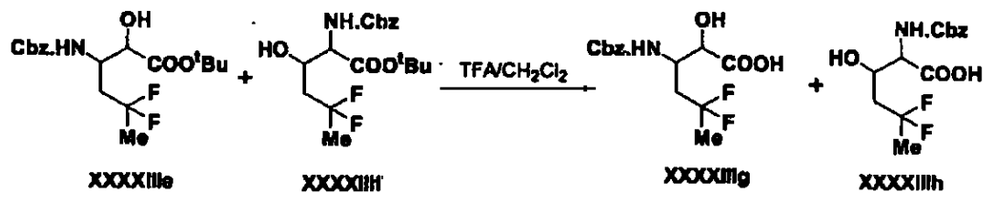


XXXXIIId XXXXIIIe XXXXIIIf

Se disolvió carbamato de bencilo (8,92 g) en alcohol n-propílico (79 ml). A la solución resultante se agregó con agitación una solución recién preparada de NaOH (2,33 g) en agua (145 ml), seguido de ter-butilhipoclorito (6,57 ml). A la mezcla resultante se agregó $(DHQ)_2PHAL$ (0,742 g) disuelta en alcohol n-propílico (66 ml) seguido de **XXXXIIId** (19,05 mmol). El catalizador de osmio, $K_2OsO_2(OH)_2$ se agregó luego y la mezcla de reacción se agitó a temperatura ambiente durante 1 hr.

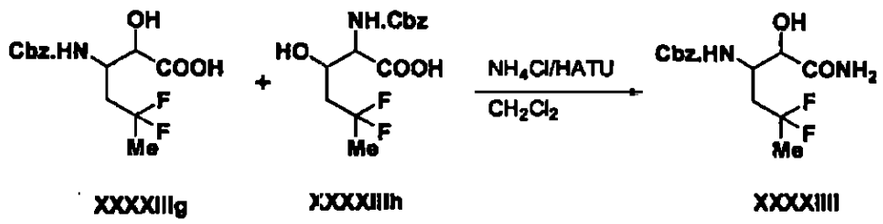
La reacción anterior se repitió usando **XXXXIIId** (19,36 mmol). Las dos reacciones se combinaron seguido de dilución con acetato de etilo (500 ml). La mezcla se sacudió con agua (100 ml), la fase orgánica se separó y se lavó con agua, salmuera y finalmente se secó sobre $MgSO_4$ anhidro. La evaporación al vacío proveyó el producto en bruto que se cromatografió sobre gel de sílice (10%-20% de acetato de etilo en n-hexano) para dar el producto puro deseado (3 g) como una mezcla de **XXXXIIIe** y **XXXXIIIf**

Paso 5



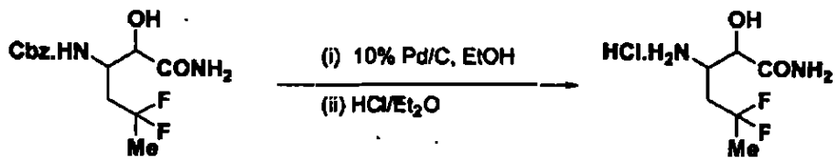
Una solución agitada de **XXXXIIIf** y **XXXXIIIe** el producto del Paso 4 en CH_2Cl_2 (50 ml) se trató con ácido trifluoroacético (50 ml). Luego de 4 hrs. la mezcla de reacción se concentró hasta secar al vacío. El residuo se disolvió en 10% de Na_2CO_3 acuoso, la solución se lavó con éter dietílico y la fase de agua se acidificó con H_2SO_4 2M hasta un pH ~1,5. La extracción de la solución ácida con acetato de etilo seguido de secado sobre $MgSO_4$ anhidro y evaporación al vacío proveyó el producto deseado como una mezcla de **XXXXIIIg** y **XXXXIIIh** (2,6 g).

Paso 6



A una solución del producto del Paso 5 (1 g) en CH_2Cl_2 (50 ml) se agregó HATO (1,43 g), NH_4Cl (0,842 g) y DMSO (5,59 ml). La mezcla de reacción se agitó a temperatura ambiente durante ~20 hrs., se diluyó con acetato de etilo y se lavó con $NaCHO_3$ saturado y salmuera. La fase orgánica se secó luego sobre $MgSO_4$ anhidro y se concentró hasta secar al vacío para dar el producto en bruto. La cromatografía sobre gel de sílice (10% de n-hexano en acetato de etilo) proveyó en una de las fracciones el producto puro deseado XXXXIIIi (0,205 g).

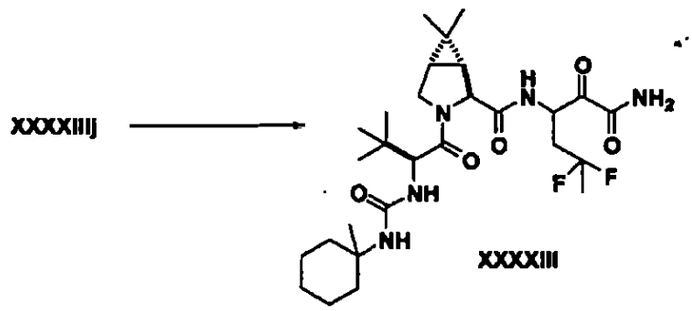
Paso 7



XXXXIIIi **XXXXIIIj**

A una solución de **XXXXIIIi** el producto del Paso 6 (0,205 g) en etanol (15 ml) se agregó 10% de Catalizador de Pd/C. La suspensión resultante se hidrogenó hasta que la cromatografía en capa delgada indicó el consumo completo del material inicial (~3 hrs.). El catalizador se eliminó por filtración y se lavó con etanol. El filtrado combinado y los lavados se evaporaron al vacío hasta secar para dar el producto deseado **XXXXIIIj** (0,164 g).

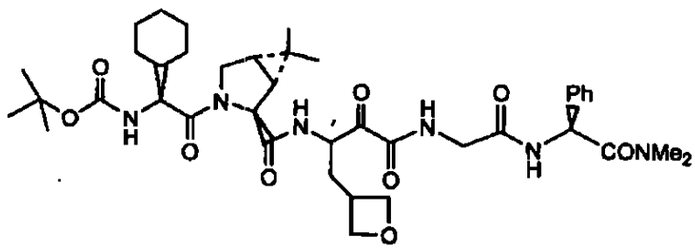
Paso 8



XXXXIII

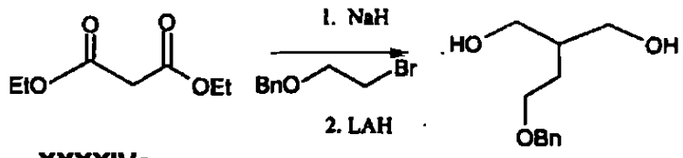
XXXXIIIj se convirtió en **XXXIII** siguiendo el procedimiento similar al Ejemplo **XXVIII** y **XXXIII**

Ejemplo XXXXIV Preparación del compuesto de Fórmula XXXXIV



XXXXIV

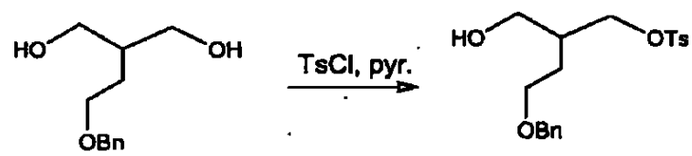
Paso 1



XXXXIVa **XXXXIVb**

El malonato de etilo **XXXXIVa** (5,4 ml; 36 mmol) se agregó a una suspensión de NaH (1,44 g de una dispersión al 60% en aceite mineral; 0,9 eq.) en tetrahidrofurano anhidro (THF; 60 ml) a 0°C, bajo una atmósfera de nitrógeno y la mezcla se agitó a temperatura ambiente durante 30 min. Se agregó 2-bromoetiléter de bencilo (8,5 ml; 40 mmol) antes de reflujar la reacción durante un período de 24H. Luego de enfriar, la reacción se repartió entre EtOAc y HCl diluido (aprox. 1 M). La fase orgánica se separó, se secó ($MgSO_4$) y se concentró para dar como rendimiento un residuo. El residuo mencionado anteriormente se disolvió en THF anhidro (100 ml) y una solución de hidruro doble de litio y aluminio (LAH; 66 ml de una solución 1,0M) se agregó bajo una atmósfera de nitrógeno y la mezcla resultante se agitó a temperatura ambiente durante un período de 4h. y se agregó EtOAc seguido de HCl diluido. La fase orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró. El producto de reacción en bruto se purificó a través de cromatografía en columna sobre gel de sílice usando EtOAc:Hexano (70:30) como eluyente para dar el diol deseado **XXXXIVb** (3,59 g) como un aceite incoloro.

Paso 2

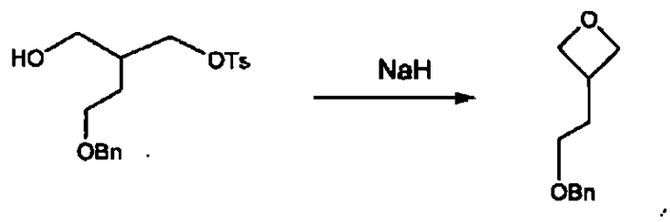


XXXXIVb **XXXXIVc**

Se agregó sulfonilcloruro de p-tolueno (1,12 g; 5,9 mmol) al diol **XXXXIVb**

(1,00 g; 4,9 mmol) en una mezcla de diclorometano (15 ml) y piridina (1,18 ml; 14,6 mmol) y la mezcla resultante se agitó a temperatura ambiente durante la noche (aprox. 16h.). La mezcla de reacción se repartió entre EtOAc y HCl acuoso diluido. La fase orgánica se separó, se lavó con bicarbonato de sodio acuoso saturado, se secó (MgSO4) y se concentró bajo presión reducida. El residuo se purificó a través de cromatografía en columna sobre gel de sílice usando EtOAc: hexano (30:70) como eluyente para dar I) el ditosilato (0,291 g), seguido de ii) el mono-tosilato deseado **XXXXIVc** (1,02 g) y iii) el diol recuperado (0,27 g).

Paso 3

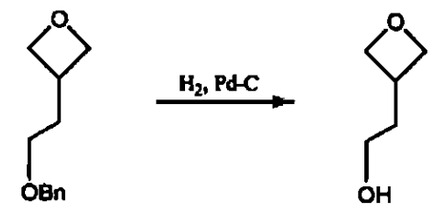


XXXXIVc **XXXXIVd**

El mono-tosilato **XXXXIVc** (1,0 g; 2,8 mmol) dimetilformamida anhidra (DMF; 3 ml) se agregó a una suspensión de NaH (0,333 g de una dispersión al 60% en aceite mineral; 8,3 mmol) en DMF (13 ml) y la mezcla resultante se agitó a temperatura ambiente durante un período de 3 h. La mezcla de reacción se repartió entre EtOAc y agua. La fase orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$) y se concentró para dar un residuo que se purificó a través de cromatografía en columna sobre gel de sílice usando EtOAc: hexano (1:5) como eluyente para dar el oxetano deseado **XXXXIVd** (0,37 g) como un aceite incoloro.

930

Paso 4



XXXXIVd **XXXXIVe**

Una suspensión de 10% de Pd-C (0,10 g) y el éter bencílico **XXXXIVd** (0,33 g) en metanol (10 ml) se colocó bajo una atmósfera de hidrógeno (globo) durante un período de 1 h. La mezcla de reacción se filtró a través de un tapón de celite y el sólido se lavó minuciosamente con metanol. El filtrado combinado se concentró bajo presión reducida para dar el alcohol **XXXXIVe** (0,17 g) como un aceite incoloro usado en procedimientos posteriores sin purificación.

Paso 5

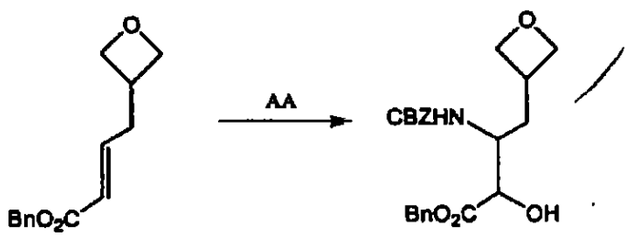


XXXXIVe **XXXXIVf**

El periodonano de Dess-Martin (0,658 g; 0,16 mmol) se agregó a una solución del alcohol **XXXXIVe** (0,144 g; 1,4 mmol) en diclorometano (5 ml) y se agitó a temperatura ambiente durante un período de 1 h., antes de agregar el fosforano (0,637 g; 0,16 mmol). La mezcla de reacción resultante se agitó durante un período de aprox. 16 h., luego se repartió entre EtOAc y agua. La fase orgánica se separó, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó a través de cromatografía en columna sobre gel de sílice

usando EtOAc:hexano; 1:5 para dar el éster **XXXXIVf** (0,131 g) como un aceite incoloro.

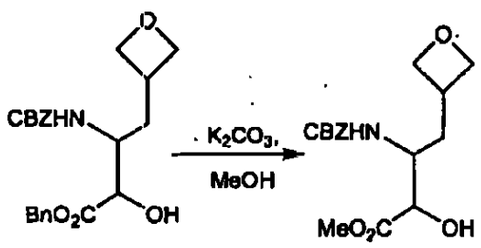
Paso 6



XXXXIVf **XXXXIVg**

El carbamato de bencilo (0,657 g; 4,3 mmol) se disolvió en n-propanol (6 ml). Se agregó hidróxido de sodio acuoso (0,171 g; 4,3 mmol, en 11 ml de agua) seguido de hipoclorito de ter-butilo (0,49 ml; aprox. 4,3 mmol) y una solución de $(DHQ)_2PHAL$ (0,056 g) en n-propanol (5 ml). La mezcla resultante se colocó en a baño de agua y se agitó durante 5 min. antes de agregar la olefina **XXXXIVf** (0,326 g; 1,4 mmol) seguido de osmiato de potasio dihidrato (0,021 g). La mezcla de reacción resultante se agitó durante 3 h., y se agregó a EtOAc. La fase de agua se separó y se lavó con EtOAc. Las fases orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron bajo presión reducida. El residuo se purificó a través de cromatografía en columna sobre gel de sílice usando EtOAc; hexano (7:3) como eluyente para dar el alfa-hidroxi éster **XXXXIVg** (0,367 g), que contenía aprox. 20% del beta-hidroxi éter no deseado.

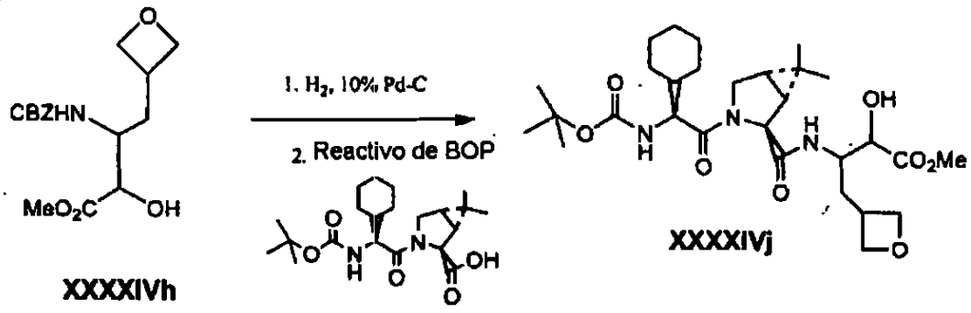
Paso 7



XXXXIVg **XXXXIVh**

El carbonato de potasio (0,100 g) se agregó a una solución en metanol (30 ml) de aprox. 2 g del éster bencílico **XXXXIVg** (contaminado con una pequeña cantidad de carbamato de bencilo). La mezcla resultante se agitó a temperatura ambiente durante 2h., luego se repartió entre EtOAc y agua. La fase orgánica se separó, se lavó con salmuera, se secó y se concentró bajo presión reducida. El residuo se purificó a través de cromatografía en columna sobre gel de sílice usando EtOAc:hexanos (7:3) para dar el éster **XXXXIVh** (1,02 g).

Paso 8

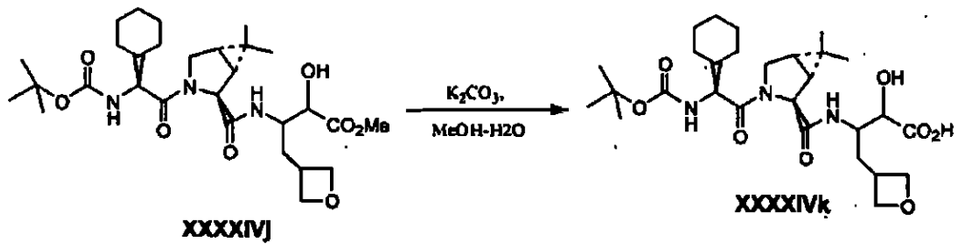


XXXXIVh **XXXXIVi** **XXXXIVj**

Una suspensión de 10% de Pd-C (0,030 g) y el carbamato de bencilo **XXXXIVh** (0,090 g) en metanol (5 ml) se colocó bajo una atmósfera de hidrógeno (globo) durante un período de 1 h. La reacción se filtró a través de un tapón de celite y el sólido se lavó minuciosamente con metanol. El filtrado combinado se concentró bajo presión reducida para dar como rendimiento el intermediario

amina (0,050 g) que se usó inmediatamente. Se agregaron reactivo de BOP (0,131 g; 0,31 mmol) seguido de trietilamina (0,130 ml;0,93 mmol) a una mezcla de la amina (0,050 g; 0,28 mmol) y el ácido carboxílico **XXXXIVi** (0,121 g; 0,31 mmol) en diclorometano (3 ml) y la mezcla resultante se agitó durante un período de 4h. y se repartió entre HCl acuoso diluido (aprox. 1 M) y EtOAc. La fase orgánica se separó, se lavó con bicarbonato de sodio acuoso saturado, se secó ($MgSO_4$) y se concentró bajo presión reducida. El residuo se purificó a través de cromatografía en columna sobre gel de sílice usando EtOAc como eluyente para dar el metil éster **XXXXIVj** (0,107 g) como un sólido blanco.

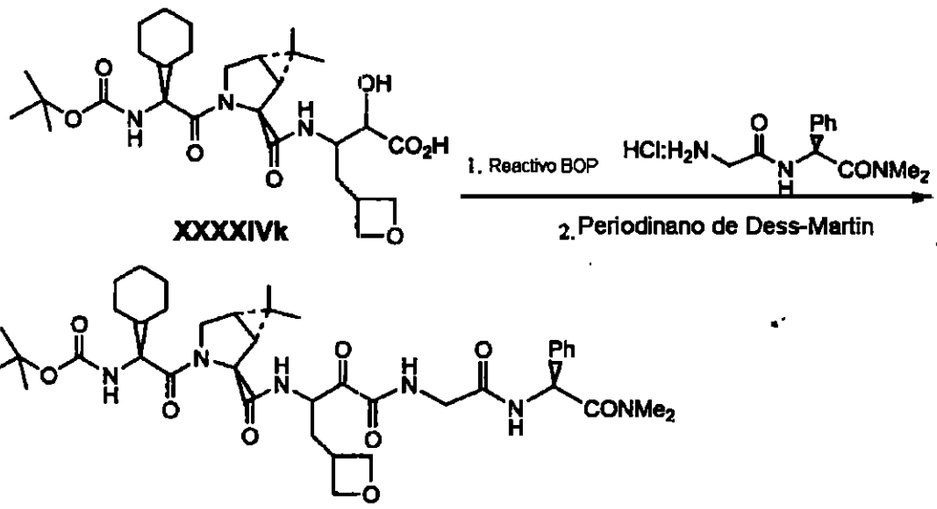
Paso 9



XXXXIVj **XXXXIVk**

El carbonato de potasio (0,054 g; 0,39 mmol) se agregó al éster **XXXXIVj** (0,107 g; 0,19 mmol) en una mezcla de metanol (3 ml) y agua (1 ml) y la reacción resultante se agitó durante un período de 16h. y se repartió entre EtOAc y agua. La fase orgánica se separó, se lavó con salmuera, se secó y se concentró para dar como rendimiento el ácido **XXXXIVk** (0,099 g).

Paso 10

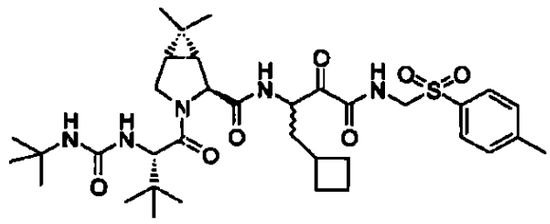


XXXXIVk

XXXXIV

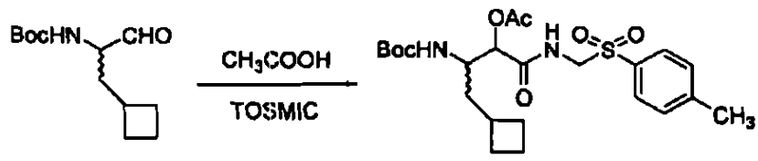
Se agregó trietilamina (0,035 ml; 0,25 mmol) a una mezcla del ácido carboxílico **XXXXIVk** (0,041 g; 0,08 mmol), la sal de clorhidrato (0,023 g; 0,08 mmol) y reactivo de BOP (0,037 g; 0,08 mmol) en diclorometano (3 ml) y la mezcla resultante se agitó a temperatura ambiente durante un período de 4h. La reacción se repartió entre EtOAc y HCl acuoso diluido (1 M). La fase orgánica se separó, se lavó con bicarbonato de sodio acuoso saturado, agua, se secó y se concentró bajo presión reducida. El residuo del procedimiento anterior se disolvió en diclorometano (3 ml) y se agregó periodinano de Dess-Martin (0,065 g; 0,15 mmol) y la mezcla se agitó a temperatura ambiente durante 2h. La reacción se repartió entre 5% de sulfito de sodio acuoso, bicarbonato de sodio acuoso saturado, agua, se secó y se concentró bajo presión reducida. El residuo se purificó a través de cromatografía en columna sobre gel de sílice usando CH_2Cl_2;MeOH; 20:1 como eluyente para dar la alfa-ceto amida **XXXXIV** (0,021 g). FABMS: MH+, 767,4.

Ejemplo XXXXVI Preparación del compuesto de Fórmula XXXXVI



XXXXVI

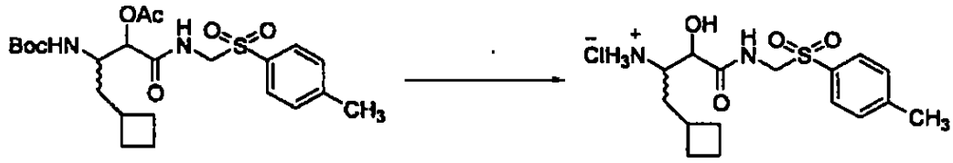
Paso 1



XXIIIe **XXXXVIa**

Una solución del aldehído **XXIIIe** (0,626 g, 2,75 mmol), TOSMIC (1,63 g, 8,27 mmol) y CH_3COOH (0,48 mL, 8,27 mmol) en CH_2Cl_2 anhidro (15 mL) se agitó a temperatura ambiente durante 36 h. La mezcla de reacción se concentró al vacío y se purificó a través de cromatografía (SiO_2, EtOAc/Hex 2:3) para dar como rendimiento 0,90 g (68%) de **XXXXVIa** como un sólido incoloro MS (ES) m/z, intensidad relativa 965 [$(2M+1)^+$, 30], 483 [$(M+1)^+$, 53], 427 (60), 383 (100), 365 (71), 272 (64).

Paso 2

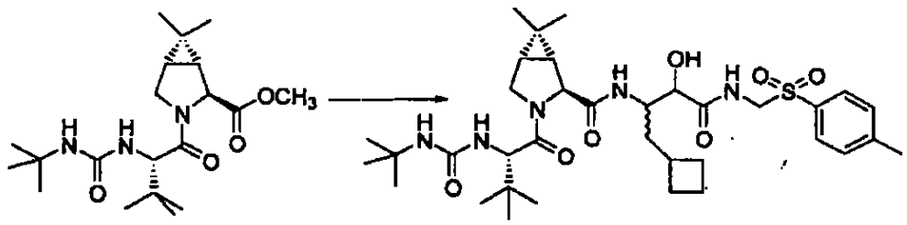


XXXXVIa **XXXXVIb**

Una solución de **XXXXVIa** (0,9 g, 1,86 mmol) en HCl (30 mL, 6 M en CH_3OH, preparada a través del agregado de cloruro de acetilo a CH_3OH a 0°C)

se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró al vacío y se usó como es en el paso siguiente MS (ES) m/z, intensidad relativa 681 [$(2M+1)^+$, 26], 341 [$(M+1)^+$, 100], 180 (40)

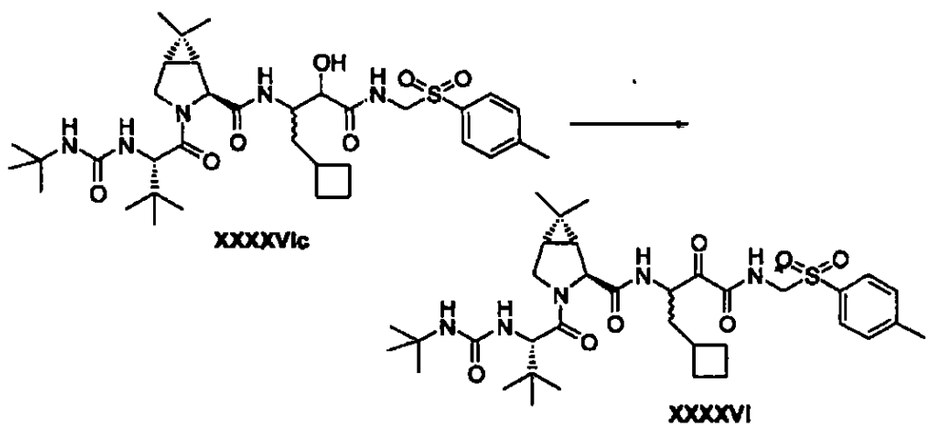
Paso 3



XXIVc **XXXXVIc**

La síntesis de **XXXXVIc** se logró usando **XXIVc** (134 mg, 0,36 mmol), y la amina **XXXXVIb** (120 mg, 0,32 mmol) siguiendo el procedimiento indicado para el Ejemplo XXIV del Paso **3** para dar como rendimiento el producto **XXXXVIc** que se usó para oxidación adicional sin purificación por MS (ES) m/z, intensidad relativa 690 [$(M+1)^+$, 100], 591 (27)., 537 (18), 513 (27), 478 (63), 438 (18), 414 (60), 268 (27)

Paso 4



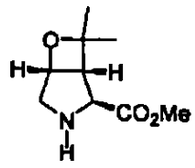
XXXXVIc **XXXXVI**

La síntesis de **XXXXVI** se logró a través de la oxidación del alcohol **XXXXVIc** (219 mg, 0,32 mmol), EDCI (609 mg, 3,2 mmol), y $Cl_2CHCOOH$ (131 µL, 1,59 mmol) siguiendo el procedimiento reportado en el Ejemplo XXIV, paso 4

que se purificó a través de cromatografía (SiO_2, Acetona/Hexanos 3:7) para dar como rendimiento el producto XXXXVI (117 mg, 53% en 2 pasos) como un sólido incoloro. MS (ES) m/z, intensidad relativa 688 [$(M+1)^+$, 32], 589 (81), 476 (100)

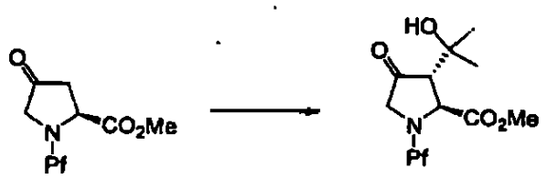
Síntesis de los intermediarios

Ejemplo XXXXVII Preparación del intermediario de Fórmula XXXXVII



XXXXVII

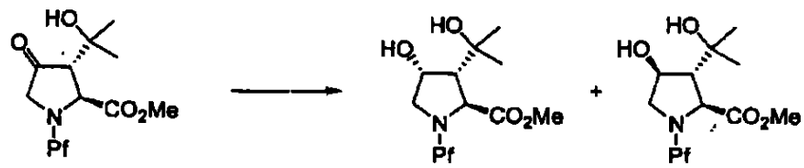
Paso 1



XXXXVIIa **XXXXVIIb**

A la solución de la cetona **XXXXVIIa** (4,93 g, 12,8 mmol) en THF anhidro (100 mL) a -78°C se agregó una solución de hexametildisiliazida de litio (LiHMDS) (17,0 mL, 17,0 mmol). La solución resultante se agitó a esa temperatura durante 1 h antes de agregar una solución de acetona (1,51 mL, 20,5 mmol) y BF_3•Et_2O (2,60 mL, 20,5 mmol) en THF (15 mL). Luego de agitar durante otras 4 h, se agregó 5% de H_3PO_4 (20 mL) seguido de solución de cloruro de amonio saturado (200 mL) y éter dietílico (200 mL). Las fases se separaron y la fase de agua se extrajo con éter dietílico (2 X 200 mL). La solución orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El producto en bruto se purificó a través de cromatografía flash con 20-50% de EtOAc/hexano para dar 1,84 g de **XXXXVIIb** (33%) y 3,26 g de material inicial **XXXXVIIa.**

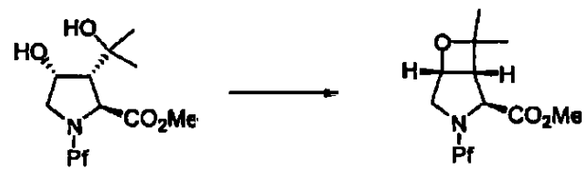
Paso 2



XXXXVIIb **XXXXVIIc** **XXXXVIId**

A la solución de la cetona **XXXXVIIb** (0,94 g, 2,13 mmol) en THF anhidro (20 mL) a -78°C se agregó una solución de LiAlH4 en THF (2,6 mL, 2,6 mmol) y la mezcla de reacción se agitó durante 40 min antes de agregar la solución de $KHSO_4$ (1,0 M, 16 mL). La mezcla se dejó entibiar hasta la temperatura ambiente y a ésta se agregó EtOAc (100 mL) y agua (50 mL). Luego las fases se separaron y la fase de agua se extrajo con EtOAc (2 X 50 mL). La solución orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El producto en bruto se purificó a través de cromatografía flash con 30-100% de EtOAc/ hexano para dar 0,49 g de **XXXXVIIc** (52%) y 0,18 g (19%) **XXXXVIId.**

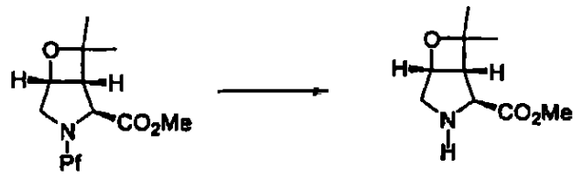
Paso 3



XXXXVIIc **XXXXVIIe**

La solución de **XXXXVIIc** (103 mg, 0,232 mmol), trifenilfosfina (120 mg, 0,456 mmol) y azodicarboxilato de dietilo (0,055 mL, 0,349 mmol) en CH_2Cl_2 anhidro (5 mL) se agitó a temperatura ambiente durante 18 h. Luego de concentrar al vacío, la mezcla se purificó a través de cromatografía flash usando 10-30% de EtOAc/hexano para dar 24 mg (24 %) de **XXXXVIIe**.

Paso 4

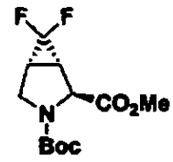


XXXXVIIe **XXXXVII**

La solución de **XXXXVIIe** en EtOH se hidrogenó a temperatura ambiente en el catalizador al 10% de Pd-C a **XXXXVII**.

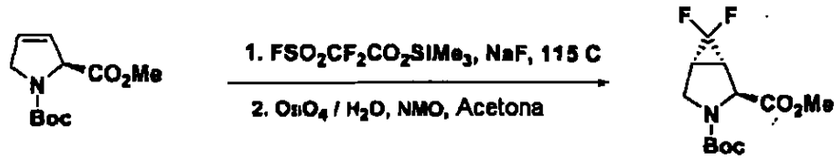
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios **XXXXVII** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación XXIII, XXIV, XXVIII, XXIX, y XXXX

Ejemplo XXXXVIII Preparación del intermediario de Fórmula XXXXVIII



XXXXVIII

Paso 1



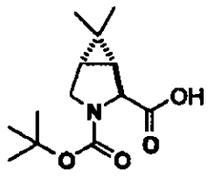
XXXXVIIIa **XXXXVIII**

A 5 g (22 mmol) del N-Boc-deshidroprolinmetil éster **XXXXVIIIa** se agregó 25 mg de NaF y 2 g de Tolueno. A 110°C, se agregó a través de un bombeador de jeringa 1,6 equiv (35 mmol, 8,75 g) de TMSfluorosulfonildifluoroacetato (TFDA) en 1 h. Luego de 2h, la reacción se enfría hasta la temperatura ambiente. A la mezcla se agrega NMO (6,8 g, 50 mmol), acetona (50 mL), H_2O (25 mL) y $OsSO_4$ (0,015 M en H_2O, 1 % molar, 0,44 mmol, 28 mL). La reacción se agita durante la

noche a temperatura ambiente luego se diluye con EtOAc y se lava con H_2O y salmuera. La fase orgánica se secó sobre $MgSO_4$, se filtró y se concentró hasta secar. La purificación a través de cromatografía flash (10 EtOAc, Hexano, sílice) logró el Producto **XXXXVIII** (0,76 g).

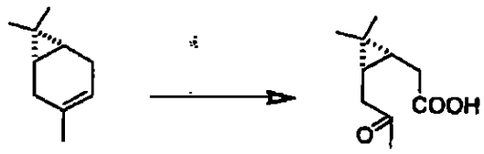
Un número de inhibidores descritos en la Tabla 6 usando el intermediario XXXXVIII se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo IL Preparación del intermediario de Fórmula IL



IL

Paso 1. ÁCIDO (1R,3S)-2,2-DIMETIL-3-(2-OXOPROPIL)CICLOPROPAN ACÉTICO .



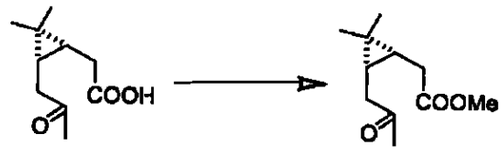
3-careno
ILa

ILb

Una mezcla de 0,55 L de ter-butanol, 1,1 L de agua, 100 mL de 3-careno **ILa** (Aldrich Chemical Co.), y 490 g de $NaIO_4$, se trató con 2,2 g de cloruro de ruterio hidrato. La mezcla vigorosamente agitada se calentó y se enfrió en forma alternada durante 2 hr. para mantener una temperatura de 35-40°C. La mezcla vigorosamente agitada se calentó y se enfrió en forma alternada durante otra hora para mantener una temperatura de 40-50°C. La mezcla vigorosamente agitada se calentó luego durante otra 1/2 hr. para mantener una temperatura de 50-55°C. La mezcla se enfrió luego hasta 30°C, se filtró en un embudo de

Buchner, y los precipitados se lavaron con 700 mL de éter isopropílico. La porción acuosa del filtrado se extrajo con 900 mL de EtOAc-hexano (2:1), y el extracto se combinó con la porción de éter del filtrado. Los orgánicos combinados se lavaron con 300 mL de 20% de NaCl acuoso, luego se extrajeron con una solución de 36 g de NaOH en 2,2 L de agua. El extracto acuoso enfriado se acidificó con 100 mL de HCl 12 N y se extrajo con Et_2O (3 x 800 mL). El extracto se lavó con salmuera, se secó sobre $MgSO_4$ anhidro, y se evaporó al vacío para dejar el compuesto del título **ILb** 98 g (88%) como una goma. H^1RMN ($CDCl_3$) δ 2,39 (m, 2), 2,28 (m,2), 2,19 (s, 3), 1,1,12 (s, 3), 0,90 (m, 2), 0,63 (s, 3).

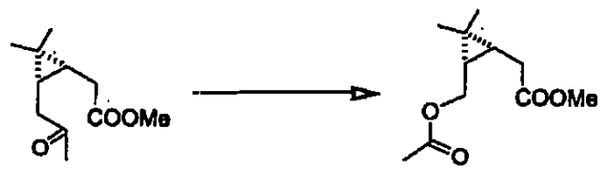
Paso 2. 2,2-DIMETIL-3-(2-OXOPROPIL)CICLOPROPAN-ACETATO DE (1R,3S)-METILO.



ILb **ILc**

Una solución de 98 g de **ILb**, el producto del Paso precedente y 0,55 L de DMF se trató con 98 g de Cs_2CO_3. La mezcla se agitó durante 10 minutos, se agregó 41,5 mL de MeI, y la mezcla se agitó a 40°C durante 1 hr. La mezcla se enfrió y se filtró en un embudo de Buchner. El filtrado se inactivó con 2,5 L de 18% de NaCl acuoso, la fase orgánica se separó, y la solución acuosa se extrajo con Et_2O-hexano (1:1; 2 x 1 L). La fase orgánica combinada y los extractos se lavaron con agua, se secaron sobre $MgSO_4$ anhidro, se filtraron y se evaporaron al vacío para dejar el compuesto del título **ILc** como 91 g (86%) de aceite espeso. H^1RMN ($CDCl_3$) δ 3,67 (s, 3), 2,3 (m, 4), 2,17 (s, 3), 1,12 (s, 3), 0,97 (m, 2), 0,91 (s, 3).

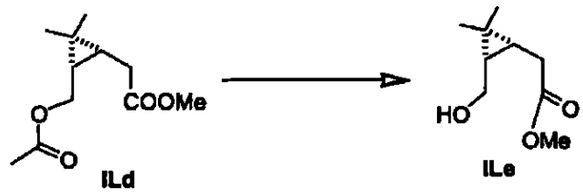
Paso 3. 3-(ACETOXIMETIL)-2,2-DIMETILCICLOPROPANACETATO DE (1R,3S)-METILO.



ILc ILd

Una solución de **ILc**, 91 g del producto del Paso precedente y 0,7 L de 1,1,2.tricloroetano se trató con 165 g de 70% ácido m-cloroperbenzoico. La mezcla se agitó a temperatura ambiente durante 1 hr., luego se calentó con un baño de aceite para mantener una temperatura de reacción de 65-70°C durante 1 hr., y luego se calentó a 75°C durante 1 hr. más. La mezcla se enfrió, se filtró en un embudo de Buchner, y la torta del filtro se lavó con tricloroetano fresco. El filtrado combinado y los lavados se concentraron al vacío a 0,5 L, y el residuo se diluyó con 2,5 L de hexano-Et_2O (3:1). La solución orgánica se lavó reiteradamente con una solución de 3,5% de $K2CO_3$ acuoso-salmuera (3:1; 8 x 0,9 L), luego con salmuera, luego se secó sobre $MgSO_4$ anhidro, se filtró y se evaporó al vacío para dejar el compuesto del título **ILd** como 98 g (100%) de aceite espeso. H^1RMN ($CDCl_3$) δ 4,1-3,9 (m, 2), 3,68 (s, 3), 2,34 (d, 2), 2,04 (s, 3), 1,12 (s, 3), 1,04 (m, 2), 1,00 (s, 3).

Paso 4. 3-(HIDROXIMETIL)-2,2-DIMETILCICLOPROPANACETATO de (1R,3S)-METILO

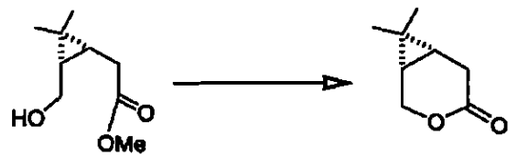


ILd ILe

Una solución de 98 g de **ILd** del producto del Paso precedente y 1 L de metanol se trató con 19 g de K_2CO_3, y la mezcla se agitó a 30°C durante 1 hr. La mezcla se concentró al vacío para quitar 0,6 L de metanol, el residuo se inactivó con 10 % de KH_2PO_4 acuoso frío, y la mezcla se extrajo con EtOAc. El extracto

se lavó con salmuera, se secó sobre $MgSO_4$ anhidro, se filtró y se evaporó al vacío para dejar 70 g (89%) del compuesto del título **ILe** como una goma. H^1RMN ($CDCl_3$) δ 3,80 (q, 1), 3,73 (s, 3), 3,52 (m, 1), 2,68 (d de d, 1), 2,23 (d de d, 1), 1,09 (s, 3), 1,1-0,9 (m, 2), 0,98 (s,3).

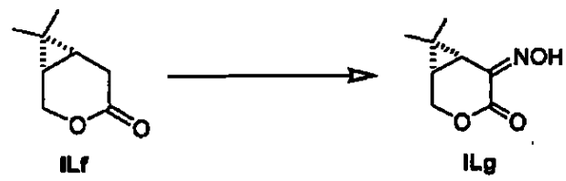
Paso 5. (1S,6R)-7,7-DIMETIL-3-OXABICICLO[4,1,0]HEPTAN-4-ONA.



ILe **ILf**

Una solución de ILe 70 g del producto del Paso precedente y 1,1 L de xilenos se trató con 30,8 g de DBU. La solución se calentó hasta un suave reflujo durante 18 hr. a medida que el metanol se eliminaba del destilado. La solución se enfrió, se lavó con HCl 1N frío, luego con salmuera; se secó sobre $MgSO_4$ anhidro, se filtró y se evaporó al vacío. El residuo se cromatografió en 600 g de sílice gel usando un gradiente de CH_2Cl_2 a 1:10 de EtOAc-CH_2Cl_2 para obtener el compuesto del título **ILf** como 54 g (94%) de aceite. H_1RMN ($CDCl_3$) δ 4,71 (d de d, 1), 4,04 (d de d, 1), 2,75 (d de d, 1), 2,16 (d de d, 1), 1,16 (s, 3), 1,25 (m, 1), 1,12 (s, 3).

Paso 6. (1S,6R,5E)-7,7-DIMETIL-3-OXABICICLO[4,1,0]HEPTAN-4,5-DIONA, 5-OXIMA.

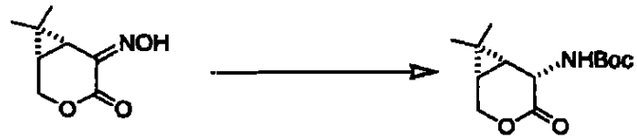


ILf **ILg**

Una solución de 42 g del producto del Paso precedente **ILf** y 300 mL de tolueno anhidro se trató con 102 mL de 90% de ter-butilnitrito. La mezcla agitada se calentó y se enfrió en forma alternada según la necesidad a medida que se

agregaban 45 g de terbutóxido de potasio en 6 porciones durante 20 minutos a 30-35°C. Luego se agregó 180 mL de metanol anhidro, la temperatura se elevó a 40°C, y se continuó la agitación a 40°C durante 2,5 hr. La mezcla se enfrió, se inactivó con una solución fría de 1,1 L de 10% de HCl acuoso y 20 mL de HCl 12N, luego se extrajo con EtOAc-tolueno (3:1). Los extractos se lavaron con 5% de $NaCHO_3$ acuoso, luego salmuera; se secaron sobre $MgSO_4$ anhidro, se filtraron y se evaporaron al vacío. El residuo (25 g) se cromatografió sobre 150 g sílice gel usando un gradiente de CH_2Cl_2 a 35:65 EtOAc-CH_2Cl_2 para obtener 15 g (29%) del compuesto del título **ILg** como un aceite. H^1RMN ($CDCl_3$) δ 4,82 (d de d, 1), 4,55 (d de d. 1), 2,40 (d, 1), 1,49 (m, 1), 1,27 (s, 3), 1,18 (s, 3).

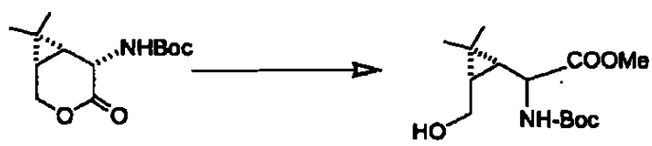
Paso 7.



ILg **ILh**

Una solución de 18 g del producto del Paso precedente **ILg** y 400 mL EtOAc se trató con 32 g de di-ter-butildicarbonato (Boc_2O), y 2,0 g de 10% de Pd sobre carbón. La mezcla se hidrogenó a 2,5 atm durante 18 hr., se filtró, y el filtrado se evaporó para dejar 36 g del compuesto del título mezclado con Boc_2O, que se llevó directamente al paso siguiente. Una porción se cromatografió para obtener **ILh** como compuesto del título puro: H^1RMN (DMSO-d_6) δ 7,28 (d, NH), 4,764,64 (m, 2), 4,44 (d, 1), 1,40 (s, 9), 1,24 (m, 1), 1,11 (m, 2), 1,07 (s, 3), 0,99 (s, 3).

Paso 8. ALFA(S)-[[(1,1-DIMETILETOXI)CARBONIL]AMINO]-3-(HIDROXIMATIL)-2,2-DIMETILCICLOPROPANACETATO DE (1R,3S)-METILO

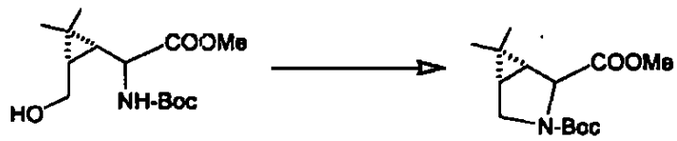


ILh **ILI**

Una solución de 35 g de **ILh** la mezcla producto del Paso precedente y 350 mL de metanol anhidro se trató con 12 g de K_2CO_3 anhidro finamente molido. La mezcla se agitó vigorosamente durante 2 hr., se concentró al vacío con un baño a 25°C, y luego se inactivó con 0,6 L de 10% de KH_2PO_4 acuoso. La solución se extrajo con EtOAc-hexano (95:5; 2 x 200 mL), los extractos se lavaron con salmuera, se secaron sobre $MgSO_4$ anhidro, se filtraron, y el filtrado se evaporó al vacío para dejar **ILi** 22 g (70%) del compuesto del título como una mezcla gomosa de los dos epímeros en una relación α-S/α-R de 8:2, que no tuvo que separarse para el presente fin. Una porción se cromatografió con Et_2O-hexano (60:40) para obtener un epímero α-S puro del compuesto del título: H^1RMN ($CDCl_3$) δ 5,2 (br s, 1), 4,05 (br s, 1), 3,81 (m, 1), 3,76 (s, 3), 3,65 (m, 1), 1,43 (s, 9), 1,14 (s, 3), 1,06 (s, 3), 1,05 (m, 1), 0,86 (m, 1). Rotación óptica: $[\alpha]_D^{25}$ -62,9° (c=1, MeOH). Análisis elemental: teoría C 58,52, H 8,77, N 4,87; encontrado C 58,48, H 8,75, N 5,10.

La elución adicional proveyó el epímero α-R del compuesto del título: H^1RMN ($CDCl_3$) δ 4,95 (br d, 1), 4,03 (m, 1), 3,82 (m, 1), 3,78 (s, 3), 3,71 (m, 1), 1,44 (s, 9), 1,13 (m, 1), 1,10 (s, 3), 1,08 (s, 3), 0,86 (m, 1). Rotación óptica: $[\alpha]_D^{25}$ -32,8° (c=1, MeOH). Análisis elemental: teoría C 58,52, H 8,77, N 4,87; encontrado C 58,46, H 8,69, N 4,74.

Paso 9. 3-(1,1-DIMETILETIL)-2-METIL ÉSTER DEL ÁCIDO (1R,5S)-6,6-DIMETIL-,3-AZABICICLO[3,1,0]HEXANO-2(S),3-DICARBOXÍLICO



ILi **ILj**

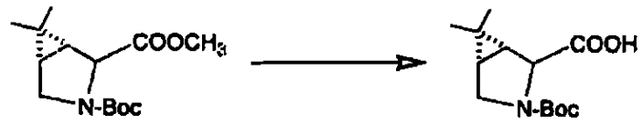
Una solución de 21,6 g de trifenilfosfina y 250 mL de THF anhidro se enfrió hasta -10°C y se trató gota a gota con 16,2 g de diisopropilazodicarboxilato a

medida que la temperatura de la reacción se elevó hasta +5°C. Luego de 5 minutos de agitación adicional, la mezcla se trató una solución de 19,7 g de **ILi** la mezcla producto del Paso precedente en 35 mL THF. Luego de 10 minutos de agitación adicional, la mezcla se calentó a reflujo durante 3 hr., se enfrió y se evaporó al vacío. El residuo se transfirió a un embudo de separación con un total de 450 mL de metanol-agua (1:1), y la mezcla de dos fases se extrajo con hexano (7 x 225 mL). Los extractos combinados se lavaron con 20 mL de metanol-agua (1:1), luego salmuera; se secaron sobre Na_2SO_4 anhidro, se filtraron, y el filtrado se evapora al vacío. El residuo se absorbió en 400 mL de hexano, se filtró por succión a través de un tapón de 30 g de sílice gel, y el tapón de sílice se eluyó con un adicional de 210 mL de EtOAc-hexano (1:9). Los filtrados combinados se evaporaron al vacío para dejar 12,8 g (69%) del compuesto del título **ILj** como una mezcla gomosa de 2 epímeros, contaminados con una pequeña cantidad de diisopropilhydrazindicarboxilato, aunque apropiados para las reacciones posteriores.

El epímero S puro del Paso precedente se trató de la misma manera para lograr el epímero S puro del compuesto del título: H^1RMN ($CDCl_3$) δ 4,21 y 4,09 (s+s, 1), 3,75 (s, 3), 3,65 (m, 1), 3,41 (m, 1), 1,44 y 1,39 (s+s, 9), 1,38 (m, 2), 1,03 (s, 3), 0,98 y 0,97 (s+s, 3). Análisis elemental: teoría C 62,43, H ,8,61, N 5,20; encontrado C 61,82, H 8,67, N 5,15.

El epímero R del Paso precedente se trató de la misma manera para lograr el epímero R del compuesto del título: H^1RMN ($CDCl_3$) δ 4,49 y 4,30 (d+d, 1), 3,62 (s, 3), 3,59 (m, 1), 3,42 (m, 1), 1,65 (m, 1), 1,45 y 1,39 (s+s, 9), 1,36 (m, 1), 1,10 (s, 3), 0,99 (s, 3).

Paso 10.

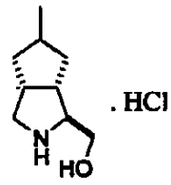


ILj IL

Una solución de 14,5 g de la mezcla producto ILj del Paso precedente y 270 mL de 1,4-dioxano se trató con 135 mL de LiOH acuoso 1M, y la mezcla se calentó a 80°C durante 4 hr. La mezcla se enfrió, se concentró al vacío hasta la mitad del volumen, se diluyó con 200 mL agua, y se extrajo con hexano. La fase de agua se congeló y se trató con una solución de 9 ml de HCl 12N en 50 mL de 10% de KH_2PO_4 acuoso, y luego se extrajo con EtOAc. El extracto se lavó con salmuera, se secó sobre Na_2SO_4 anhidro, se filtró, y el filtrado se evapora al vacío para dejar el compuesto del título IL como 10,8 g (78%) de goma, > 90% químicamente y diateroméricamente pura por PMR, y apropiada para la síntesis posterior: H^1RMN ($CDCl_3$) δ 4,20 y 4,11 (s+s, 1), 3,62 (m, 1), 3,44 (m, 1), 1,68 y 1,45 (d+unk, 1), 1,46 y 1,40 (s+s, 9), 1,45 (m enterrado bajo 1,46, 1), 1,07 (s+s, □ □= 2 Hz, 3), 0,99 y 0,95 (s+s, 3).

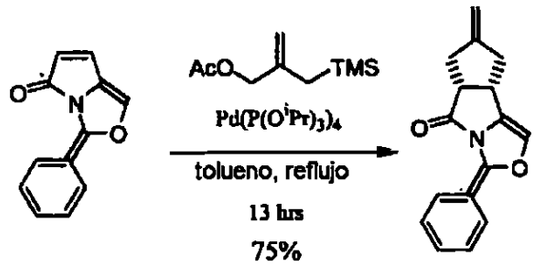
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios IL se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo L Preparación del intermediario de Fórmula L



L

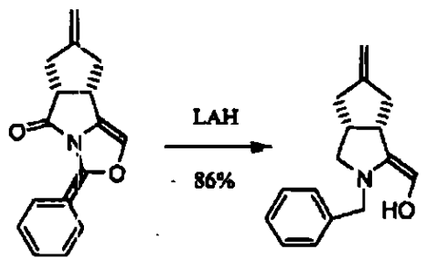
Paso 1



La **Lb**

A una mezcla de **La** (10,0 g, 50,0 mmole), acetato de 2-[(trimetilsilil)metil]-2-propanen-1-ilo (22,0 g, 118 mmole) y fosfito de triisopropilo (18,6 g, 89,2 mmole) en tolueno (50 ml) se agregó acetato de paladio (II) (2,5 g, 11 mmole) con agitación a temperatura ambiente bajo una atmósfera de Ar. Se calentó hasta 120°C (baño de aceite) durante trece horas. El enfriamiento hasta alcanzar la temperatura ambiente seguido de cromatografía flash (CH_2Cl_2: Hexano = 4:1) proveyó 9,55 gramos de **Lb** (75%). $[\square]^{25}$ = +132 ° ($CHCl_3$). HRMS (FAB) Calculado para $C_{16}H_{18}NO_2$ (MH+): 256,1338; encontrado: 256,1340.

Paso 2

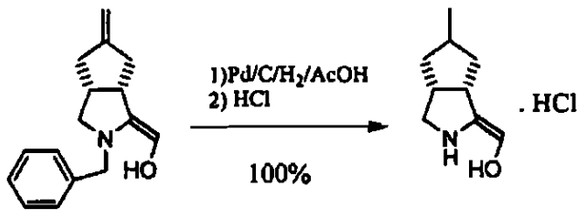


Lb **Lc**

A una solución de **Lb** (2 g, 7,8 mmol) en THF anhidro (50 ml) se agregó LAH (1,13 g, 28,9 mmol) en pequeñas porciones a 0°C. La mezcla luego se reflujó durante seis horas antes de enfriar hasta 0°C. A la reacción se agregaron cuidadosamente 2 ml de H_2O, 2 ml de 15% de NaOH y 6 ml de H_2O. El sólido se eliminó por filtración y el filtrado concentrado se cromatografió (2% de MeOH en

CH_2Cl_2) para dar 1,33 gramos de **Lc** (70%). HRMS (FAB) Calculado para $C_{18}H_{22}NO$ (MH+): 244,1701; encontrado: 244,1697.

Paso 3

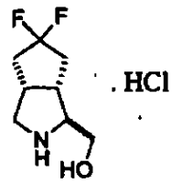


Lc **L**

Una mezcla del compuesto **Lc** (1,33 g, 5,46 mmol) y 10% de Pd sobre carbón (1,3 gram) en ácido acético (20 ml) se hidrogenó a 60 psi durante tres días. El catalizador se eliminó por filtración y el filtrado se concentró al vacío. El residuo se disolvió en 20 ml de HCl 4N en dioxano y la solución se evaporó hasta secar. El compuesto L se obtuvo en 1,04 gramos (100%) como una mezcla a 1:1 de dos epímeros. HRMS (FAB) Calculado para $C_8H_{18}NO$ (MH+): 156,1388; encontrado: 156,1390.

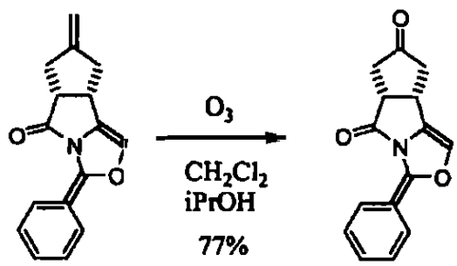
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios L se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LI Preparación del intermediario de Fórmula LI



LI

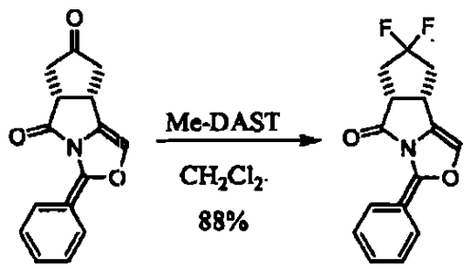
Paso 1



Lb **LIa**

El Compuesto Lb (2,6 g, 10,2 mmol) en una mezcla de CH_2Cl_2 (30 ml) y ^iPrOH (10 ml) se ozonizó a -78°C hasta que persistió un color azulado (Aprox. 40 minutos). Se agregó sulfuro de dimetilo (10 ml) y la solución se agitó a temperatura ambiente durante la noche. El solvente se eliminó al vacío y el residuo se repartió entre agua y EtOAc. La fase orgánica se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. La cromatografía flash (2% de MeOH en CH_2Cl_2) proveyó 2,32 gramos de **LIa** (77%). MS (MH+, FAB) = 257.

Paso 2

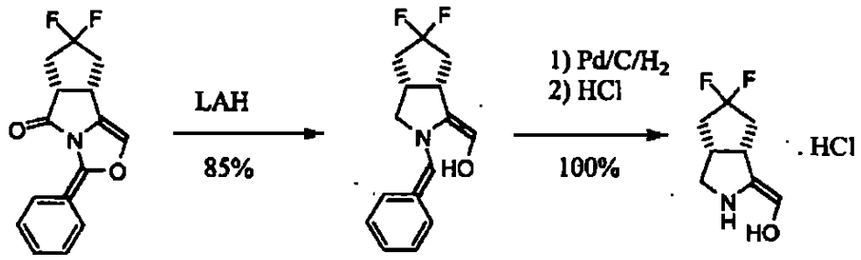


LIa **LIb**

A una solución de **LIa** (0,86 g, 3,35 mmol) en CH_2Cl_2 anhidro (30 ml) se agregó trifluoruro de dimetilaminoazufre (DAST de metilo, 2,23 g, 16,8 mmol) a temperatura ambiente. La solución se agitó a temperatura ambiente durante dos días. Se agregó con cuidado a una mezcla de hielo y $NaCHO_3$ saturado y se extrajo con EtOAc. La solución de EtOAc se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. El residuo se cromatografió (0,8 % de MeOH en CH_2Cl_2)

para dar **LIb** (0,82 g, 88%). HRMS (FAB) Calculado para $C_{15}H_{16}NO_2F_2$ (MH+): 280,1149; encontrado: 280,1152.

Paso 3

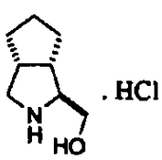


LIb **LIc** **LI**

Siguiendo los mismos procedimientos que se describen para la preparación de **L** a partir de **Lb** hasta **L** 0,44 gramos de **LIb** proveyeron 0,31 gramos de **LI** (92% en dos pasos). HRMS (FAB) Calculado para $C_8H_{14}NOF_2$ (MH+): 178,1043; encontrado: 178,1042.

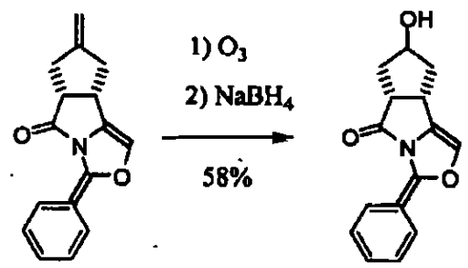
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios **LI** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LII Preparación del intermediario de Fórmula LII



LII

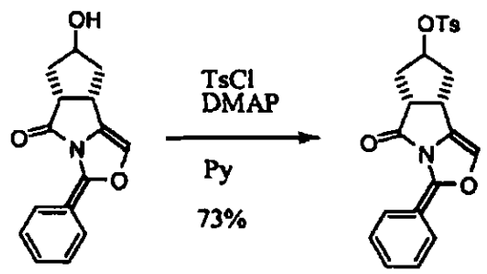
Paso 1



Lb **LIIa**

El Compuesto **Lb** (3,74 g, 14,7 mmol) en CH_2Cl_2 (30 ml) se ozonizó a -78°C hasta que persistió un color azulado (Aprox. 60 minutos). Se purgó con N_2 durante 5 min, y se agregó a una solución fría de $NaBH_4$ (4,44 g, 117 mmol) en 50 ml de EtOH/H_2O (1:1). Se agitó durante 12 hrs. a temperatura ambiente luego se extrajo dos veces con EtOAc. La fase orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4 y se concentró. El residuo se cromatografió (2% de MeOH en CH_2Cl_2) para dar **LIIa** (2,19 g, 58%). HRMS (FAB) Calculado para $C_{15}H_{18}NO_3$ (MH+): 260,1287; encontrado: 260,1283.

Paso 2

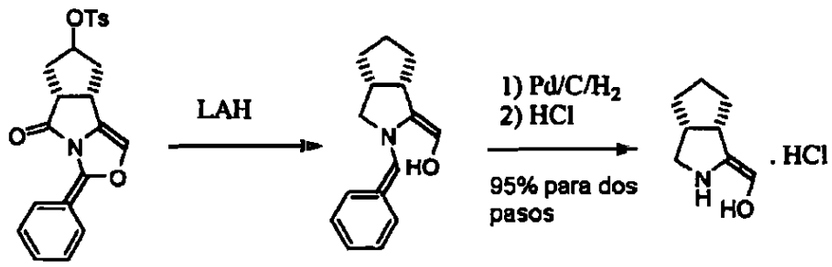


LIIa **LIIb**

A una solución de LIIa (2,18 g, 8,40 mmol) en piridina anhidra (50 ml) se agregaron cloruro de toluensulfonilo (3,2 g, 16,8 mmol) y N, N-dimetilaminopiridina (1,03 g, 8,40 mmol). Se agitó a temperatura ambiente durante 3 días y se concentró al vacío. El residuo se repartió entre 3% de ácido

cítrico y EtOAc. La fase orgánica se lavó con 3% ácido cítrico nuevamente, seguido de salmuera. Luego de quitar el solvente el residuo se cromatografió para dar **LIIb** (2,54 g, 73%). HRMS (FAB) Calculado para $C_{22}H_{24}SNO_5$ (MH+): 414,1375; encontrado: 414,1378.

Paso 3

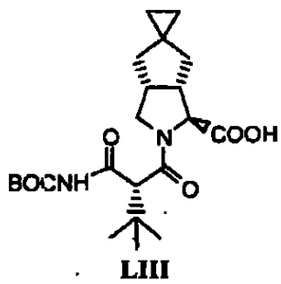


LIIb **LIIc** **LII**

Siguiendo los mismos procedimientos que se describen para la preparación de **L** a partir de **Lb** hasta **L**, 2,53 gramos de **LIIb** proveyeron 1,03 gramos de **LII** (95% en dos pasos). HRMS (FAB) Calculado para $C_8H_{16}NO$ (MH+): 142,1232; encontrado: 142,1233.

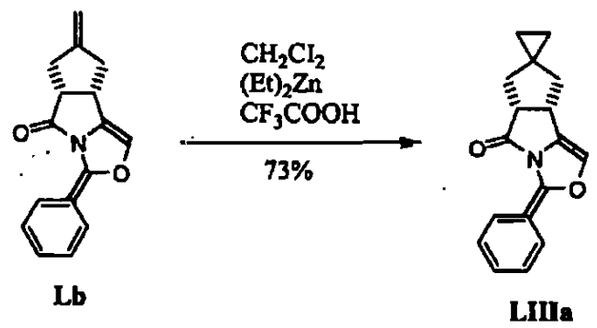
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios **LII** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LIII Preparación del intermediario de Fórmula LIII



LIII

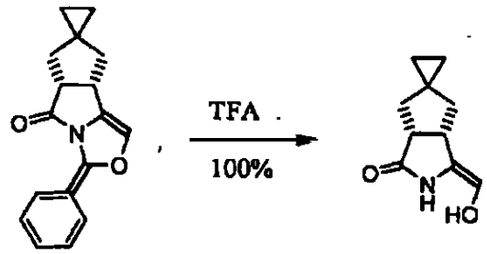
Paso 1



Lb **LIIIa**

A 7,84 mmol de dietil zinc (1N en hexano) en CH_2Cl_2 anhidro (30 ml) se agregó ácido trifluoroacético (0,893 g, 7,84 mmol) gota a gota a 0°C. Luego de agitar durante un adicional de 20 min se agregó diiodometano (2,10 g, 7,84 mmol), seguido de **Lb** (1 g, 3,92 mmol) en 5 ml de CH_2Cl_2 en 20 min. El baño de hielo se eliminó y la mezcla se agitó a temperatura ambiente durante 14 horas. La reacción se inactivó a través de NH_4Cl y se extrajo con EtOAc. La solución de EtOAc se lavó con Na_2SO_4 saturado, seguido de salmuera y se concentró al vacío. El residuo se cromatografió para dar **LIIIa** (4,61 g, 73%). HRMS (FAB) Calculado para $C_{17}H_{20}NO_2$ (MH+): 270,1494; encontrado: 270,1497.

Paso 2

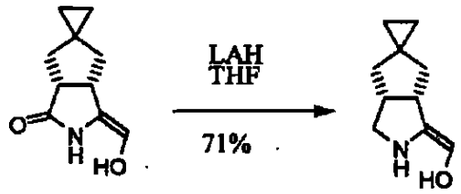


LIIIa **LIIIb**

Se agregó ácido trifluoroacético (TFA, 10 ml) a una solución de **LIIIa** (4,6 g, 17,1 mmol) en THF (20 ml) y H_2O (20 ml) a temperatura ambiente. Luego de agitar durante la noche los solventes se eliminaron al vacío. El residuo se repartió entre $NaCHO_3$ saturado y EtOAc. La fase de agua se extrajo nuevamente con EtOAc cinco veces. La fase orgánica combinada se secó sobre Na_2SO_4 y se

concentró. El residuo se cromatografió para dar **LIIIb** (3,1 g, 100%). HRMS (FAB) Calculado para $C_{10}H_{16}NO_2$ (MH+): 182,1181; encontrado: 180,1182.

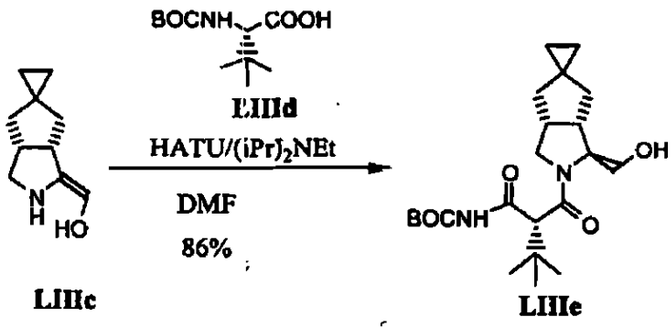
Paso 3



LIIIb **LIIIc**

LAH (1,76 g, 46,3 mmol) se agregó a **LIIIb** en THF anhidro (50 ml) en pequeñas porciones a 0°C. La mezcla luego se reflujó durante seis horas antes de enfriar hasta 0°C. A la reacción se agregaron cuidadosamente 2 ml de H_2O, 2 ml de 15% de NaOH y 6 ml de H_2O. El sólido se eliminó por filtración y el filtrado concentrado se cromatografió (30% de MeOH en CH_2Cl_2 con 1 % de NH_4OH) para dar 0,39 gramos de **LIIIc** (71 %). HRMS (FAB) Calculado para $C_{10}H_{18}NO$ (MH+): 168,1388; encontrado: 168,1389.

Paso 4

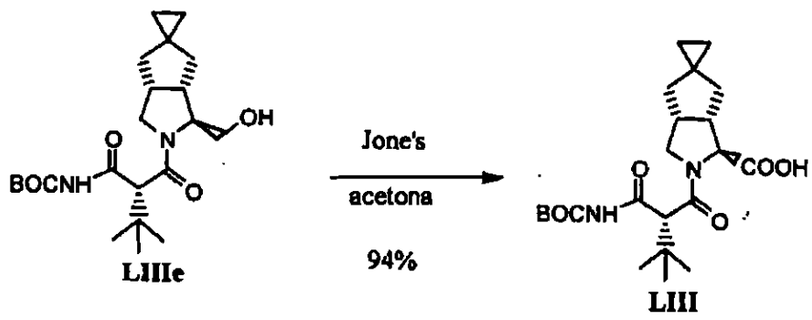


LIIIc **LIIIe**

A una mezcla de **LIIIc** (0,5 g, 2,99 mmol), **LIIId** (0,69 g, 2,99 mmol) y HATU (1,14 g, 3 mmol) en DMF anhidra (20 ml) se agregó N, N-diisopropiletilamina (1 ml, 5,89 mmol)) a 0°C. Se agitó a temperatura ambiente durante 3 hrs. La mezcla de reacción se repartió entre H_2O y EtOAc. La fase orgánica se lavó

sucesivamente con 3% de ácido cítrico, $NaHSO_4$ saturado y salmuera, se secó sobre Na_2SO_4 y se concentró. El producto **LIIIe** (0,9788, 86%) así obtenido fue lo suficientemente puro para el paso siguiente. HRMS (FAB) Calculado para $C_{21}H_{37}N_2O_4$ (MH+): 381,2910; encontrado: 381,2749.

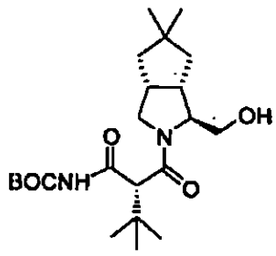
Paso 5



A una solución de **LIIIe** (0,49 g, 1,29 mmol) en acetona (20 ml) se agregó reactivo de Jones (2 ml de solución 2,5M, 5 mmol) a 0°C. Se agitó a 0 °C durante 20 min, luego a temperatura ambiente durante 30 hrs. A esta mezcla se agregaron sucesivamente EtOAc (50 ml), Na_2SO_4 anhidro (3 g), celite (2 g) y ^iPrOH (1 ml). Se agitó vigorosamente durante 20 min. El sólido se eliminó por filtración. El filtrado se lavó con 3% de ácido cítrico, se secó sobre Na_2SO_4 y se concentró al vacío. El residuo se cromatografió (3% de MeOH en CH_2Cl_2, 0,5% de ácido acético) para dar **LIII** (0,48 g, 94%). HRMS (FAB) Calculado para $C_{21}H_{35}N_2O_5$ (MH+): 395,2546; encontrado: 395,2543.

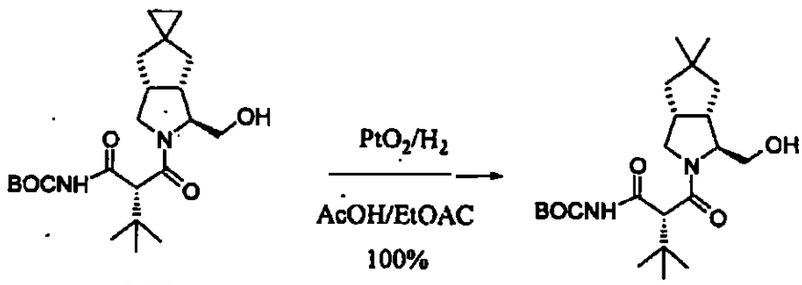
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios LIII se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LIV Preparación del intermediario de Fórmula LIV



LIV

Paso 1

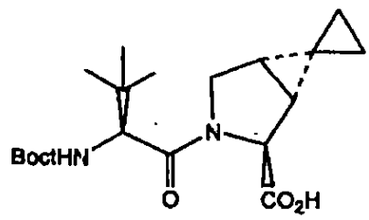


LIIIe **LIV**

El Compuesto **LIIIe** (0,41 g, 1,08 mmol) en una mezcla de solvente de AcOH (10 ml) y EtOAc (20 ml) que contenía PtO_2 (1 g) se hidrogenó bajo 1 atm de H_2 durante 3 hrs. El catalizador se eliminó por filtración y el filtrado se concentró al vacío para dar **LIV** (0,41 g, 100%). HRMS (FAB) Calculado para $C_{21}H_{39}N_2O_5$ (MH+): 383,2910; encontrado: 383,2906.

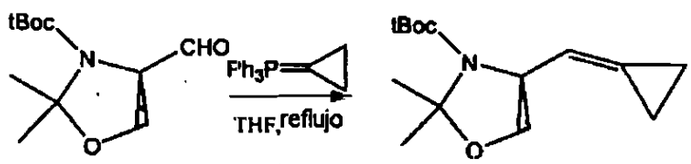
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios LIV se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LV Preparación del intermediario de Fórmula LV



LV

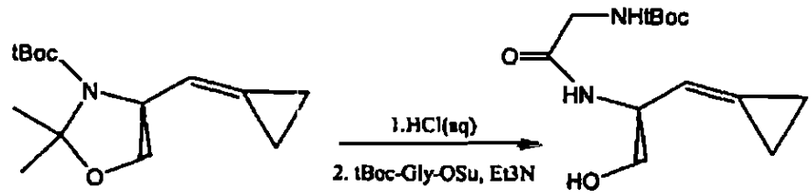
Paso 1



LVa **LVb**

Se agregó bis(trimetilsilil)amida de potasio (158 ml de una solución 0,5M en tolueno; 79 mmol) a una suspensión agitada de bromuro de ciclopropiltrifenilfosfonio (33,12 g; 86,4 mmol) en tetrahidrofurano anhidro (130 ml) y la mezcla naranja resultante se agitó bajo una atmósfera de nitrógeno a temperatura ambiente durante un período de 1 h., antes del agregado del aldehído **LVa** (9,68 g; 42,2 mmol) en THF (8 ml). La reacción luego se reflujó bajo una atmósfera de nitrógeno durante un período de 2h. Luego de enfriar, se agregaron metanol, éter dietílico y sal de Rochelles. La fase orgánica se separó, se lavó con salmuera, se secó y se concentró bajo presión reducida. El producto de reacción en bruto se purificó a través de cromatografía en columna sobre gel de sílice usando EtOAc-hexano (1:99) a EtOAc-hexano (5:95) para dar el alqueno **LVb** (8,47 g) como un aceite amarillo.

Paso 2

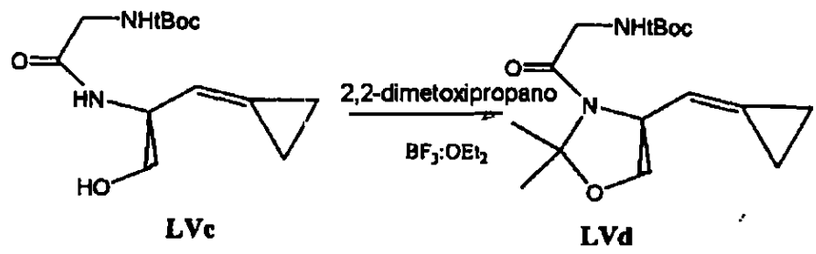


LVb **LVc**

Una solución de HCl 1M en MeOH/MeOAc se preparó a través del agregado de 14,2 ml de cloruro de acetilo gota a gota en metanol frío y la disolución de la solución resultante a 200 ml a temperatura ambiente. El carbamato **LVb** (9,49 g; 37,5 mmol) se disolvió en metanol (12 ml) y se agregó a HCl 1M en MeOH/MeOAc (150 ml) mientras se enfriaba en un baño de hielo. La mezcla resultante se mantuvo a esta temperatura durante 1 h., luego el baño de hielo se eliminó y se continuó la agitación durante la noche a temperatura ambiente. Los volátiles se eliminaron bajo presión reducida para dar como rendimiento un aceite amarillo que se usó en el paso siguiente sin purificación.

El aceite amarillo se disuelven en una mezcla de THF (30 ml) y MeOH (20 ml) y se trató con trietilamina (15 ml; 108 mmol) hasta que la solución tuvo un pH = 9-10. Luego de colocar en un baño de hielo, la mezcla se trató con N-Boc-Gly-OSu (11,22 g; 41 mmol). El baño de hielo se retiró y la reacción se agitó a temperatura ambiente durante 1 h. Los volátiles se eliminaron bajo presión reducida y el residuo se purificó a través de cromatografía en columna sobre gel de sílice usando metanol (1-3%) en diclorometano proveyendo la amida deseada **LVc** (9,09 g).

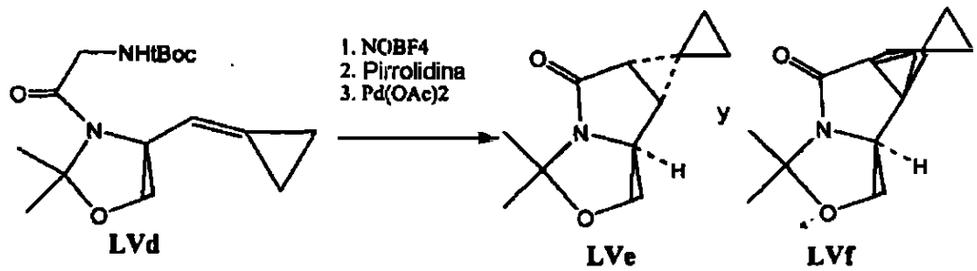
Paso 3



LVc **LVd**

El alcohol **LVc** (9,09 g; 33,6 mmol) se disolvió en acetona (118,5 ml) y se trató con 2,2-dimetoxipropano (37,4 ml;304 mmol) y BF_3:Et_2O (0,32 ml; 2,6 mmol) y la mezcla resultante se agitó a temperatura ambiente durante un período de 5,5 h. La solución de la reacción se trató con algunas gotas de trietilamina y los volátiles se eliminaron bajo presión reducida. El residuo se purificó a través de cromatografía en columna sobre gel de sílice usando 5-25% de EtOAc en hexanos para dar el N,Oacetal **LVd** (8,85 g).

Paso 4



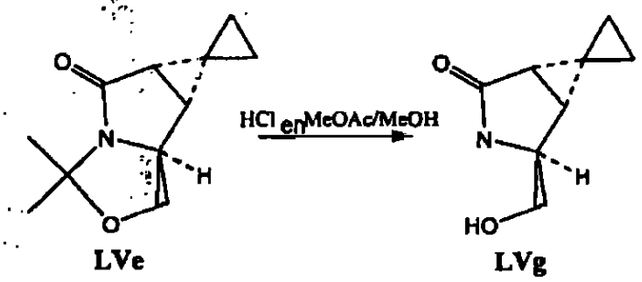
LVd **LVe** **LVf**

El carbamato **LVd** (8,81 g; 28,4 mmol) se disolvió en acetonitrilo (45 ml) y la solución se enfrió hasta -40°C bajo una atmósfera de nitrógeno. Se agregaron piridina (6,9 ml; 85,3 mmol) seguido de tetrafluoroborato de nitrosio (6,63 g; 56,8 mmol) y la mezcla de reacción resultante se mantuvo por debajo de 0°C hasta que la TLC indicó que no quedaban restos de material inicial (aprox. 2,25 h.). Se agregó pirrolidina (20 ml; 240 mmol) y el baño de frío se retiró y se continuó con la agitación a temperatura ambiente durante 1 h. y luego los volátiles se

eliminaron bajo presión reducida. El residuo se pasó rápidamente a través de un tapón de sílice gel para dar un aceite amarillo.

El aceite amarillo se disolvió en benceno anhidro (220 ml) y se agregó acetato de paladio (0,317 g; 1,41 mmol) antes de calentar la mezcla resultante hasta el reflujo, bajo una atmósfera de nitrógeno durante un período de 1,5h. Luego de enfriar, los volátiles se eliminaron bajo presión reducida y el residuo oscuro se purificó a través de cromatografía en columna sobre gel de sílice usando EtOAc-hexano (1:4) para dar I) la trans- pirrolidinona **LVe** (1,94 g) seguido de ii) la cis-pirolidinona **LVf** (1,97 g).

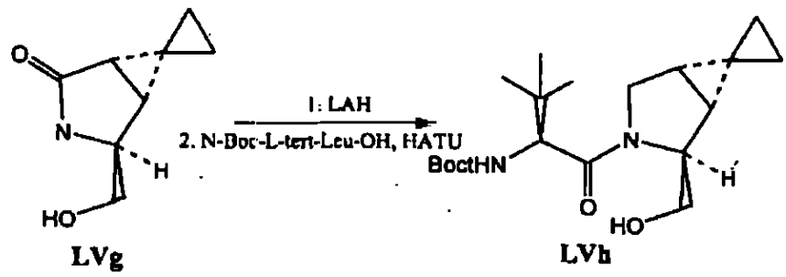
Paso 5



LVe **LVg**

Se agregó HCl 1M recién preparado en MeOAc/MeOH (10 ml; como se describió con anterioridad) al N,O-acetal **LVe** y se agitó a temperatura ambiente durante 1 h. El solvente se eliminó bajo presión reducida y el residuo se purificó a través de cromatografía en columna sobre gel de sílice usando 0-4% de MeOH en diclorometano como eluyente para dar el alcohol deseado **LVg** (1,42 g), un aceite amarillo.

Paso 6

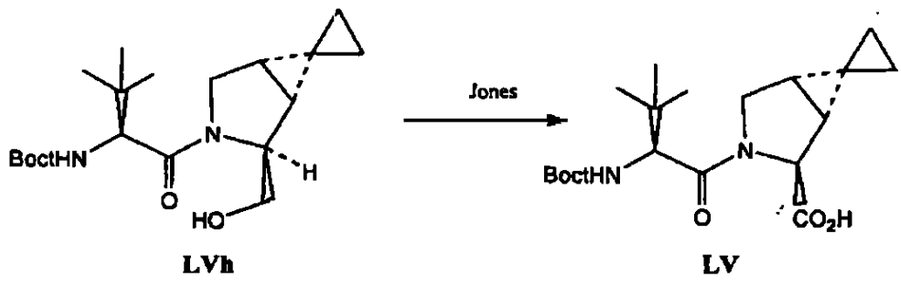


LVg LVh

A una solución de la lactama **LVg** (1,29 g; 8,44 mmol) en tetrahidrofurano anhidro (55 ml) se agregó hidruro doble de litio y aluminio (2,40 g; 63,2 mmol) y la mezcla resultante se reflujó durante 8 h. Luego de enfriar, se agregaron agua, seguido de 15% de NaOH acuoso y la mezcla resultante se filtró a través de celite y el sólido se lavó minuciosamente con THF y MeOH. El solvente se eliminó bajo presión reducida y el residuo se disolvió nuevamente en diclorometano, se secó y se concentró bajo presión reducida para dar la pirrolidina, usada sin purificación.

Se agregó base de Hunigs (4,5 ml; 25,8 mmol) a una mezcla de N-Boc-L-ter-Leu-OH (1,76 g; 7,6 mmol), La pirrolidina en bruto y HATU (2,89 g; 7,6 mmol) en diclorometano anhidro (50 ml) a -60°C, bajo una atmósfera de nitrógeno. La reacción resultante se dejó llegar hasta alcanzar la temperatura ambiente lentamente, durante la noche. Se agregó EtOAc y la solución amarilla se lavó con HCl acuoso diluido, bicarbonato de sodio acuoso saturado, agua, salmuera. La fase orgánica se secó y se concentró bajo presión reducida. El residuo se purificó a través de cromatografía en columna sobre gel de sílice usando EtOAc:hexanos (1:3) para dar la amida deseada **LVh** (2,00 g).

Paso 7

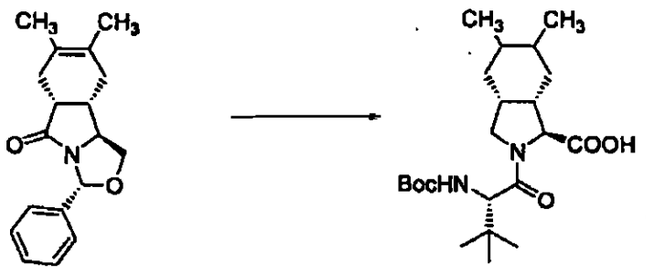


LVh **LV**

El alcohol **LVh** (2,00 g; 5,67 mmol) se disolvió en acetona (116 ml) y se enfrió en un baño de hielo durante 10 min. Esta solución luego se agregó a un reactivo de Jones enfriado (14,2 ml; aprox. 2 mmol/ml) y la mezcla resultante se agitó a 5°C durante 0,5h y el baño de frío se eliminó. La reacción se agitó durante un adicional de 2h. a temperatura ambiente, antes de agregar al sulfato de sodio (28,54 g), celite (15 g) en EtOAc (100 ml). Se agregó isopropanol (15 ml) luego de 1 min y luego se agitó durante un adicional de 10 min. y se filtró. El filtrado se concentró bajo presión reducida, proveyendo un aceite marrón que se disolvió en EtOAc. Esta solución se lavó con agua, 3% de ácido cítrico acuoso, salmuera, se secó y se concentró para dar el ácido carboxílico deseado **LV** (1,64 g) como un sólido blanco.

NOTA: Alternativamente el ácido XXIVc, el ácido XXVIg, XXVIII, pudieron sintetizarse siguiendo el procedimiento mencionado anteriormente en buenos rendimientos. Un número de inhibidores descritos en la Tabla 6 usando los intermediarios LV se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LVI Preparación del intermediario de Fórmula LVI

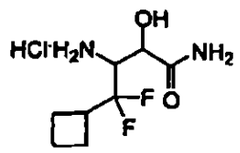


LVIa LVI

La síntesis de **LVIa** se logró siguiendo el procedimiento reportado en Bailey, J, H.; Cherry, D, T.; Crapnell, K, M.; Moloney, M. G.; Shim, S. B.; Bamford, M. J.; Lamont, R. B. Tetrahedron (1997), 53, 11731. Éste se convirtió en **LVI** similar al procedimiento para **LIII** (Paso 2 to Paso 5)

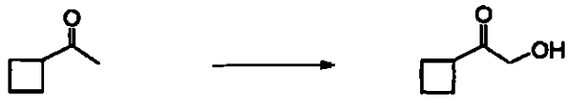
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios LVI se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LVII Preparación del intermediario de Fórmula LVII



LVII

Paso 1

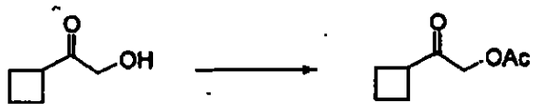


LVIIa **LVIIb**

A la solución agitada de TFA (22,6 mL, 305 mmol), agua (120 mL) y [bis(trifluoroacetoxi)iodo]benceno (131 g, 305 mmol) en acetonitrilo (600 mL) se agregó ciclobutil metil cetona **LVIIa** (15,0 g, 153 mmol). La solución resultante se calentó hasta el reflujo y se agitó durante 4 h. El acetonitrilo se eliminó al vacío.

Se agregó agua (120 mL) y la mezcla se extrajo con éter dietílico (2 X 500 mL). La solución orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El producto en bruto se purificó a través de cromatografía flash con 30% de Et_2O/hexano para dar 8,82 g de **LVIIb** (51 %).

Paso 2



LVIIb **LVIIc**

A la solución de **LVIIb** (1,4 g, 12,3 mmol), anhídrido acético (1,3 mL, 13,5 mmol) y trietilamina (3,4 mL, 24,5 mmol) en CH_2Cl_2 (50 mL) se agregó DMAP (0,67 g, 5,5 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 4 h antes de agregar 5% de H_3PO_4 (50 mL). Luego de que las fases se separaron, la fase de agua se extrajo con CH_2Cl_2 (2 X 50 mL). La solución orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío to 2,0 g producto en bruto **LVIIc.**

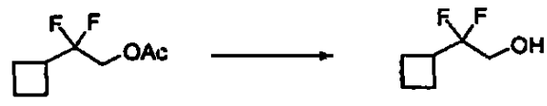
Paso 3



LVIIc **LVIId**

La mezcla de **LVIIc** (1,9 g, 12,2 mmol) y DAST (trifluoruro de dietilamino azufre, 3,0 mL, 22,3 mmol) se calentó hasta 50°C y se agitó durante 2 h. La mezcla se vertió luego lentamente en agua helada (50 mL), y se extrajo con éter dietílico (3 X 50 mL). La solución orgánica combinada se secó ($MgSO_4$), se filtró y se concentró al vacío. El producto en bruto se purificó a través de cromatografía flash con 10-40% de Et_2O/hexano para dar 0,62 g de **LVIId** (29%) y 0,68 g de material inicial **LVIIc**.

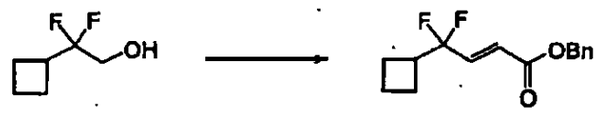
Paso 4



LVIId **LVIIe**

La mezcla de **LVIId** (3,10 g, 17,4 mmol) e hidróxido de litio (0,84 g, 34,8 mmol) en agua (10 mL) se agitó vigorosamente a temperatura ambiente durante 6 h antes de diluir con agua (50 mL) y se extrajo con éter dietílico (3 X 60 mL). La solución orgánica combinada se secó ($MgSO_4$), se filtró y se concentró cuidadosamente al vacío para dar **LVIIe** 2,68 g producto en bruto.

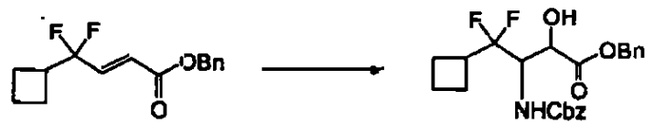
Paso 5



LVIIe **LVIIf**

La solución del compuesto **LVIIe** y reactivo de Dess-Martin en CH_2Cl_2 se agitó a temperatura ambiente durante 1 h antes de agregar $Ph_3P{=}CHCO_2Bn$ y se continuó la agitación durante otras 20 h. Se agregó éter dietílico seguido de soluciones saturadas de NaS_2O_3 y $NaCHO_3$. Luego de agitar durante 15 min, las fases se separaron. La solución orgánica se lavó con $NaCHO_3$ saturado y salmuera, se secó ($MgSO_4$), se filtró y se concentró al vacío. El producto en bruto se purificó a través de cromatografía flash para dar el producto deseado **LVIIf**.

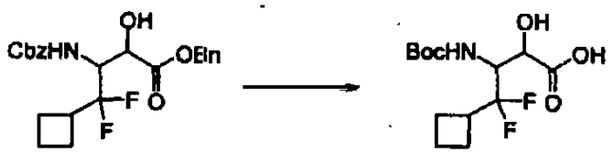
Paso 6



LVIIf **LVIIg**

El Compuesto **LVIIg** se preparó como se describió con anterioridad (Paso 4, Ejemplo XXXXIII) con cantidades apropiadas de reactivos.

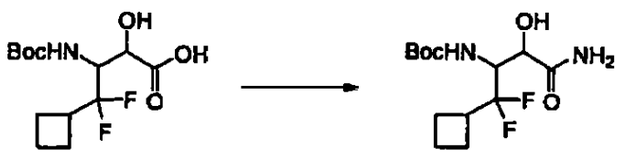
Paso 7



LVIIg **LVIIh**

La hidrogenación catalítica de **LVIIg** sobre 10% de Pd/C en MeOH seguido de tratamiento con BOC_2O en $NaCHO_3$/THF/agua producirá **LVIIh**.

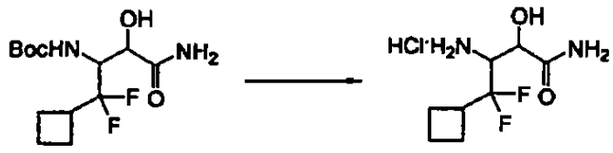
Paso 8



LVIIh **LVIIi**

La conversión de **LVIIh** en el compuesto **LVIIi** seguirá los procedimientos descritos anteriormente (Paso 5, Ejemplo XXVIII).

Paso 9

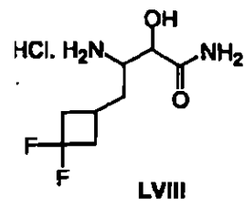


LVIIi **LVII**

La conversión de **LVIIi** en el compuesto **LVII** sigue los procedimientos descritos anteriormente (Paso 9, Ejemplo XXIII).

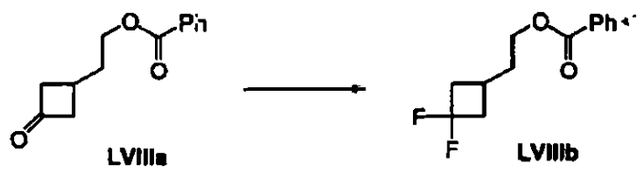
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios **LVII** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LVIII Preparación del intermediario de Fórmula LVIII



LVIII

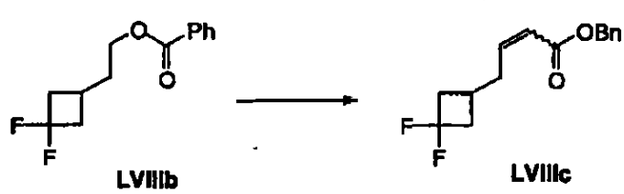
Paso 1



LVIIIa **LVIIIb**

A una solución del compuesto **LVIIIa** [para la preparación de **LVIIIa** ver J. Ramnauth y E. Lee-Ruff, Can. J. *Chem.,* 2001, 79, 114-120] (3 g) en diclorometano (75 mL) se agregó DAST (Trifluoruro de dietilamino azufre, 9,1 mL) lentamente y la reacción se agitó a temperatura ambiente durante la noche. La mezcla se vertió lentamente en hielo/ solución saturada de bicarbonato de sodio (100/200 mL) con agitación. Se agregó 200 mL de diclorometano y la fase orgánica se separó y se lavó con solución fría saturada de bicarbonato de sodio, salmuera, se secó (Na_2SO_4) y se concentró. La purificación a través de cromatografía en columna (5/95 EtOAc/hexanos) produjo 2,59 g de **LVIIIb.**

Paso 2

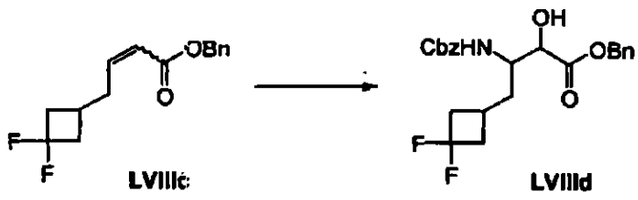


LVIIIb **LVIIIc**

El Compuesto **LVIIIb** (3,42 g) se disolvió en THF/MeOH (1/1, 50 mL). A este se agregó una solución de carbonato de potasio (1,97 g) en agua (25 mL). La mezcla de reacción se agitó a temperatura ambiente durante 4 hrs. y luego se

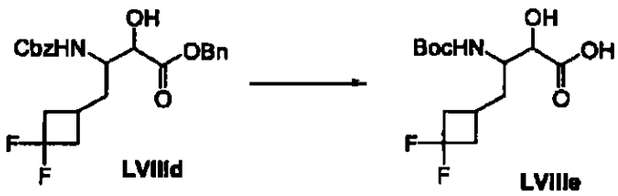
almacenó en el congelador (10°C) durante la noche. La mezcla de reacción se entibió hasta alcanzar la temperatura ambiente durante 3 hrs. cuando la TLC indicó el consumo completo de **LVIIIb.** Se agregó salmuera (100 mL) a la mezcla de reacción y se extrajo con éter etílico (3 x 100 mL). La fase de éter se combinaron, se secaron (Na_2SO_4) y se concentraron para lograr un residuo (2,77 g) que se procesó en forma adicional sin purificación. El residuo así obtenido se disolvió en CH_2Cl_2/DMSO (6/1, 140 mL). A esta solución se agregó (trifenilfosforaniliden)acetato de bencilo (11,7 g) y luego periodinano de Dess-Martin (12,09 g, en tres porciones iguales) con cuidado. La mezcla de reacción se agitó a temperatura ambiente durante 4 hrs. y se inactivó con solución fría de bicarbonato de sodio (200 mL) y se diluyó con CH_2Cl_2 (100 mL). La fase de CH_2Cl_2 se separó y se lavó con solución al 10% de $Na_2S_2O_3$ (125 mL), solución $NaCHO_3$ (125 mL), agua (125 mL), se secó (Na_2SO_4) y se concentró. El residuo se purificó a través de cromatografía en columna usando 50/50 de CH_2Cl_2/hexanos para lograr el compuesto requerido, LVIIIc (2,25 g).

Paso 3



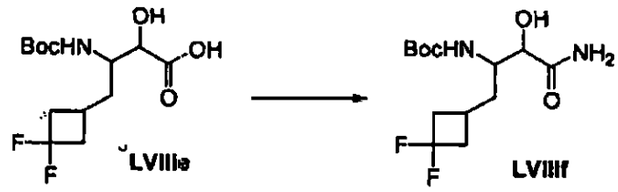
El Compuesto **LVIIId** se preparó como se describió con anterioridad (Paso 4, Ejemplo XXXXIII) con cantidades apropiadas de reactivos.

Paso 4



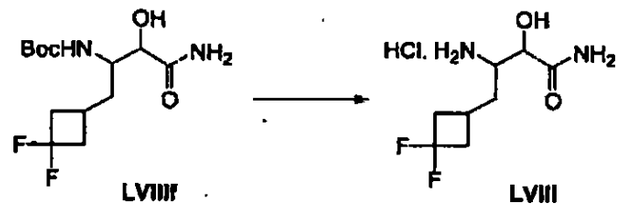
La hidrogenación catalítica de **LVIIId** sobre 10% de Pd/C en MeOH seguido del tratamiento con BOC_2O en $NaCHO_3$/THF/agua producirá **LVIIIe**.

Paso 5



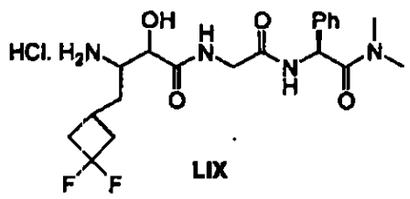
La conversión de **LVIIIe** en el compuesto **LVIIIf** seguirá los procedimientos descritos anteriormente (Paso 5, Ejemplo XXVIII).

Paso 6



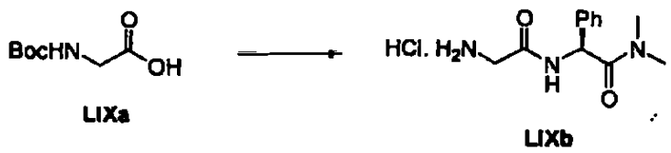
La conversión de **LVIIIF** en el compuesto **LVIII** seguirá los procedimientos descritos anteriormente (Paso 9, Ejemplo XXIII). Un número de inhibidores descritos en la Tabla 6 usando los intermediarios **LVIII** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LIX Preparación del intermediario de Fórmula LIX



LIX

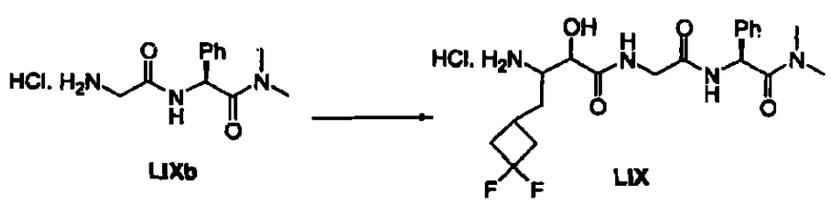
Paso 1



LIXa **LIXb**

La glicina protegida con N-Boc comercial **LIXa** se reaccionó con la amina **XV** del Ejemplo XV del modo previamente descrito en el Ejemplo XXI, Paso 4. El intermediario resultante se trató luego con HCl del modo previamente descrito en el Ejemplo XXIII, Paso 9 para lograr el producto **LIXb**.

Paso 2

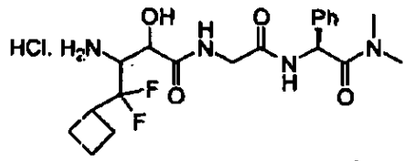


LIXb **LIX**

El ácido **LVIIIe** (del paso anterior) puede reaccionarse con **LIXb** del modo previamente descrito en el Ejemplo XXI, Paso 4. El intermediario resultante puede tratarse luego con HCl del modo previamente descrito en el Ejemplo **XXIII,** Paso 9 para lograr el producto **LIX**.

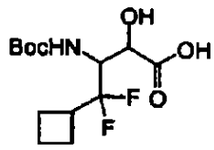
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios **LIX** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIX, y XXXX**

Ejemplo LX Preparación del intermediario de Fórmula LX

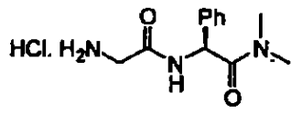


LX

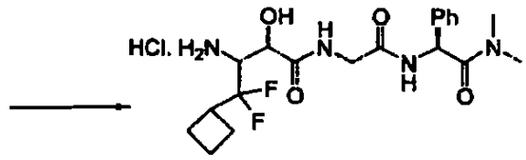
Paso 1



LVIIh



LIXb

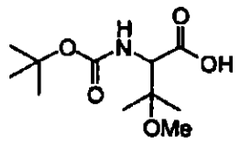


LX

El ácido **LVIIh** (del paso anterior) se reaccionó con **LIXb** del modo previamente descrito en el Ejemplo XXI, Paso 4. El intermediario resultante se trató luego con HCl del modo previamente descrito en el Ejemplo XXIII, Paso 9 para lograr el producto LX.

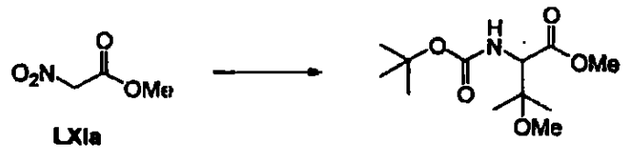
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios **LIX** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIX, y XXXX**

Ejemplo LXI Preparación del intermediario de Fórmula LXI



LXI

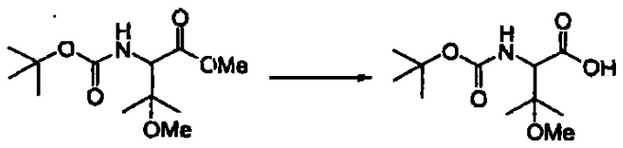
Paso 1



LXIa **LXIb**

A una solución del nitroacetato de metilo **LXIa** (3 g) en benceno (15 mL) se agregó dimetoxi propano (6,2 mL) y anhídrido acético (4,87 mL). La mezcla se reflujó durante la noche. La mezcla de reacción se concentró. Se sometió nuevamente a las condiciones anteriores. El residuo después de la concentración se llevó en EtOAc (100 mL) y se lavó con solución fría saturada de bicarbonato de sodio (3 x 75 mL), salmuera (100 mL), se secó (Na_2SO_4) y se concentró. El residuo del paso anterior se llevó en MeOH (150 mL). Se agregaron BOC_2O (6 g) y 10% de Pd/C (150 mg) y la mezcla se hidrogenó usando un globo lleno con hidrógeno gaseoso. Luego de 24 horas, se agregó algo más de 10% de Pd/C y se repitió el procedimiento. La mezcla de reacción luego se filtró a través de celite, se concentró, y se purificó a través de cromatografía en columna usando 5/95 hasta 10/90 EtOAc/hexanos para lograr 2,2 g de LXIb.

Paso 2

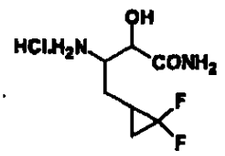


LXIb **LXI**

El Compuesto **LXIb** se preparó a partir de **LXI** en rendimiento cuantitativo usando procedimientos descritos con anterioridad para la conversión de **XXVIg** en **XXVIh** (ver Ejemplo XXVI).

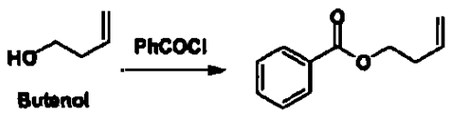
Un número de inhibidores descritos en la Tabla 6 usando los intermediarios **LVIII** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LXII Preparación del intermediario de Fórmula LXII



LXII

Paso 1:

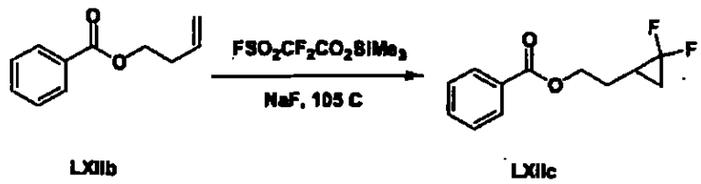


Butenol

LXIIa **LXIIb**

El butenol **LXIIa** se reaccionó del modo previamente descrito en el Ejemplo de Preparación XXXXIII paso 1 para lograr el producto **LXIIb**

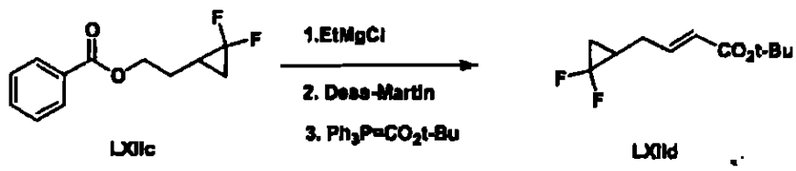
Paso 2:



LXIIb LXIIc

A 5,3 g (30 mmol) de **LXIIb** producto del paso 1 se agregó 25 mg de NaF. A 110°C, se agregó a través de un bombeador de jeringa 1,6 equiv (48 mmol, 12 g) de TMSfluorosulfonildifluoroacetato (TFDA) en 2h. Luego de 2h, la reacción se enfría hasta la temperatura ambiente. La purificación a través de cromatografía flash (3% EtOAc, Hexano, sílice) logró **LXIIc**, Producto del paso 2 (4,93 g).

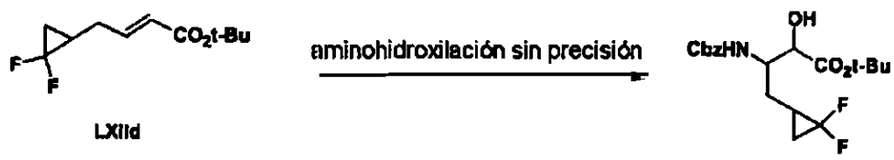
Paso 3:



LXIIc LXIId

El producto del paso 2, **LXIIc** (1 g) se trató del modo previamente descrito en el Paso 3 del Ejemplo de Preparación XXXXIII para lograr **LXIId**, Producto del paso 3 (0,89 g)

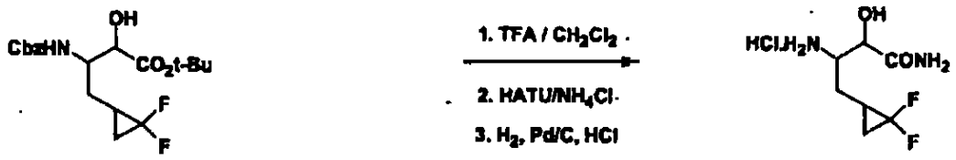
Paso 4:



LXIId LXIIe

El producto del paso 3, **LXIId** (3,2 g) se trató del modo previamente descrito en el Paso 4 del ejemplo de preparación XXXXIII para lograr el producto **LXIIe** (1,4 g).

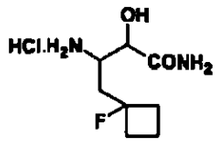
Paso 5:



LXIIe LXIIf

El producto del paso 4, **LXIIe** (0,54 g) se trató del modo previamente descrito en el Paso 5 luego paso 6 y finalmente paso 7 del Ejemplo de Preparación XXXXIII para lograr el producto **LXIIf** (0,24 g). Un número de inhibidores descritos en la Tabla 6 usando el intermediario **LXII** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LXIII Preparación del intermediario de Fórmula LXIII



LXIII

Paso 1:

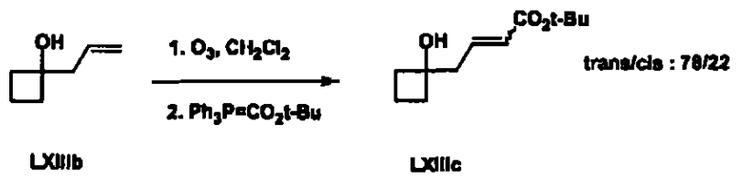


LXIIIa LXIIIb

A una solución a -78°C ciclobutanona (15 g, 214 mmol) en THF (100 mL) se agrega gota a gota Cloruro de alilmagnesio (2,0 M en THF, 1,1 equiv, 118 mL). Luego de 1 hora, la reacción se interrumpe a través del agregado de hielo y HCl 1,0 N (100 mL). La mezcla se diluyó con acetato de etilo (~200 ml) y la fase orgánica se separó; se lavó con salmuera y se secó sobre $MgSO_4$ anhidro. La

concentración al vacío y la purificación a través de cromatografía sobre gel de sílice (10% de acetato de etilo en n-hexano) proveyó el producto **LXIIIb** (21 g).

Paso 2:

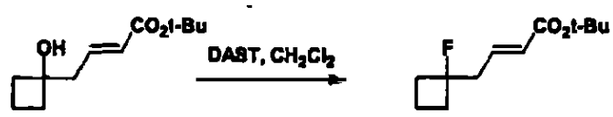


LXIIIb LXIIIc

A una solución a -78°C del producto del paso 1, **LXIIIb** (11,2 g) en CH_2Cl_2 (200 mL) se burbujea Ozono hasta que se observó un color azul persistente (luego de 1 hora). Se interrumpió el Ozono y N_2 se aplicó a la mezcla de reacción durante 10 minutos. Se agregó Me_2S (10 equiv., 7,3 mL) y la reacción se entibió en forma gradual hasta alcanzar la temperatura ambiente durante la noche.

Luego de 18 horas, se agregó $Ph_3P{=}CHCOOtBu$ (40 g). Se continuó la agitación durante ~24 hrs. La evaporación al vacío dio el producto en bruto que se cromatografió sobre gel de sílice (10% de acetato de etilo en n-hexano) para dar el producto **LXIIIc** como una mezcla de isómeros (6,65 g de isómero trans) y (1,9 g de cis olefina).

Paso 3:

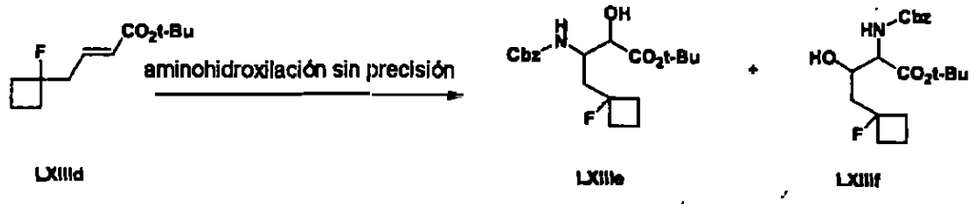


LXIIIc LXIIId

A una solución a 0°C de producto del paso 2, **LXIIIc** (0,21 g) en CH_2Cl_2 (3 mL) se agrega DAST (1,1 equiv., 0,135 mL). Luego de 15 minutos, la reacción se interrumpió a través del agregado una solución saturada, fría de Na_2CO_3 (150 ml). La mezcla se diluyó con acetato de etilo (~10 ml) y luego de agitar durante ~30 min la fase orgánica se separó; se lavó con salmuera y se secó sobre $MgSO_4$

anhidro. La concentración al vacío y la purificación a través de cromatografía sobre gel de sílice (5% hasta 10% de CH_2Cl_2 en n-hexano) dio **LXIIId** (0,1 g; 47%).

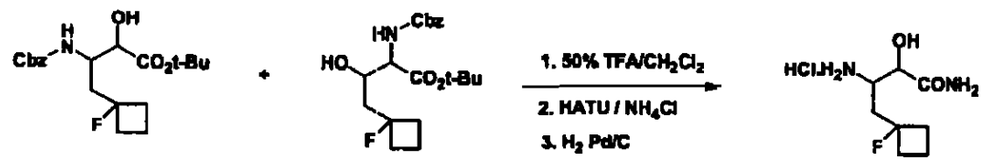
Paso 4:



LXIIId LXIIIe LXIIIf

El producto del paso 3, **LXIIId** (3,5 g) se trató del modo previamente descrito en el Paso 4 del ejemplo de preparación XXXXIII para lograr los productos **LXIIIe y LXIIIf** como una mezcla (3,25 g).

Paso 5:

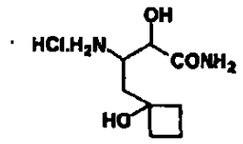


LXIIIe LXIIIf LXIII

Los productos del paso 4 (**LXIIIe+LXIIIf**) (2,3 g) se trataron del modo previamente descrito en el Paso 5 luego paso 6 y finalmente paso 7 del Ejemplo de Preparación XXXXIII para lograr el producto **LXIII** (0,47 g).

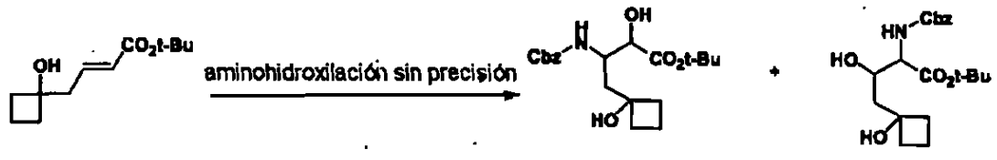
Un número de inhibidores descritos en la Tabla 6 usando el intermediario **LXII** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LXIV Preparación del intermediario de Fórmula LXIV



LXIV

Paso 1:



LXIIIc
"isómero trans"

LXIVa

LXIVb

El producto LXIIIc (1,36 g) se trató del modo previamente descrito en el Paso 4 del Ejemplo de Preparación XXXXIII para lograr los productos **LXIVa y LXIVb** como una mezcla (1,3 g).

Paso 2:



LXIVa

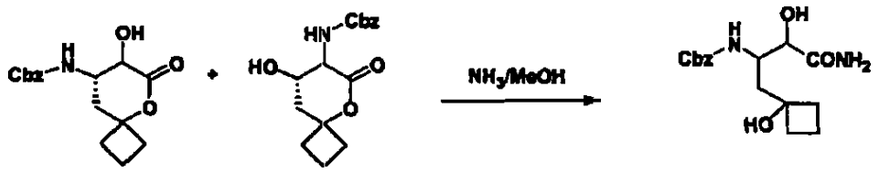
LXIVb

LXIVc

LXIVd

Una solución agitada de los productos del paso 1 (**LXIVa+LXIVb**) (1,2 g) en CH_2Cl_2 (40 ml) se trató con ácido trifluoroacético (40 ml). Luego de 45 minutos la mezcla de reacción se concentró hasta secar al vacío. El residuo se cromatografió sobre gel de sílice (2% de MeOH en CH_2Cl_2) para dar los productos **LXIVc y LXIVd** como una mezcla (0,97 g).

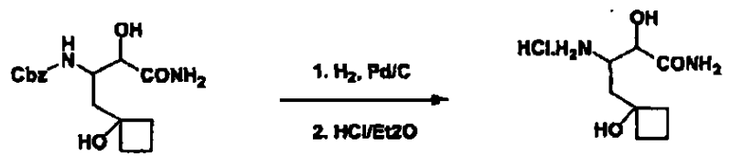
Paso 3:



LXIVc LXIVd LXIVe

A los productos del paso 2 (**LXIVc+LXIVd**) (0,4 g) se agregó 30 mL de NH_3 (2,0 M en MeOH). Luego de 4 horas, la mezcla de reacción se concentró hasta secar al vacío. El residuo se sometió a cromatografía preparativa sobre gel de sílice (100% de CH_3CN) para dar el producto deseado **LXIVe** (0,3 g).

Paso 4:

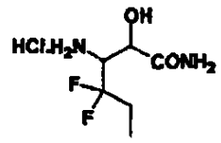


LXIVe LXIV

El producto del paso 3 **LXIVe** (0,054 g) se trató del modo previamente descrito en el Paso 7 del Ejemplo de Preparación XXXXIII para lograr el producto **LXIV** (0,032 g)

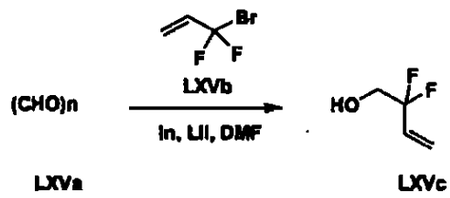
Un número de inhibidores descritos en la Tabla 6 usando el intermediario **LXII** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Ejemplo LXV Preparación del intermediario de Fórmula LXV



LXV

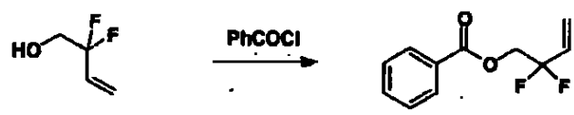
Paso 1:



LXVa LXVc

A una solución a temperatura ambiente de paraformaldehído **LXVa** (12 g, 400 mmol) y 1-bromo-1,1-difluorop-2-eno **LXVb** (6,3 g, 40 mmol) en DMF (100 mL) se agregó In(0) (6,5 g, 57 mmol) y LiI (0,4 g, 3 mmol). La emulsión resultante se agitó a temperatura ambiente durante 48 h . Luego de 48 h, la reacción se filtró a través de un tapón de celite. El filtrado se diluyó con EtOAc (250 mL) y se lavó con H_2O (3 veces) luego salmuera. La fase orgánica se separó y finalmente se secó sobre $MgSO_4$ anhidro. La evaporación al vacío dio el producto **LXVc**, que se usó como es directamente en el paso siguiente.

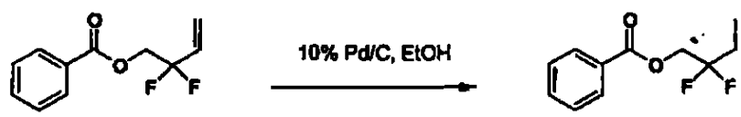
Paso 2:



LXVc LXVd

El producto del paso 1, **LXVc**, (4 g, 37 mmol) se reaccionó del modo previamente descrito en el Ejemplo de Preparación XXXXIII paso 1 para lograr luego de la purificación a través de cromatografía sobre gel de sílice (10% a 50% de CH_2Cl_2 en n-hexano) el producto **LXVd** (4,3 g).

Paso 3:

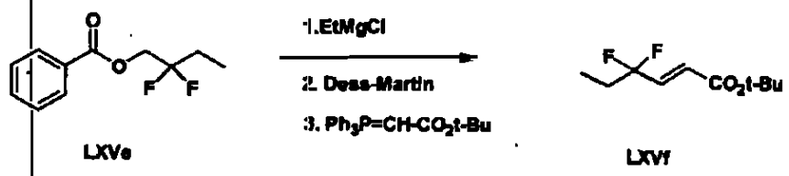


LXVd LXVe

A una solución del producto del Paso 2, **LXVd** (3,8 g) en etanol (30 ml) se agregó 10% de Catalizador de Pd/C (0,76 g). La suspensión resultante se

hidrogenó hasta que el experimento de RMN indicó el consumo completo del material inicial (~4 hrs.). El catalizador se eliminó por filtración a través de un tapón celite y se lavó con etanol. El filtrado combinado y los lavados se evaporaron al vacío hasta secar para dar el producto deseado, **LXVe** (3,8 g).

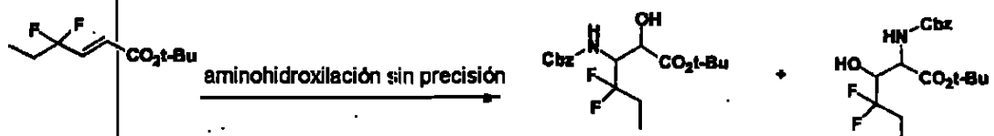
Paso 4:



LXVe LXVf

El producto del paso 3, **LXVe** (3,4 g) se trató del modo previamente descrito en el Paso 3 de XXXXIII para lograr el producto **LXVf** (2,5 g).

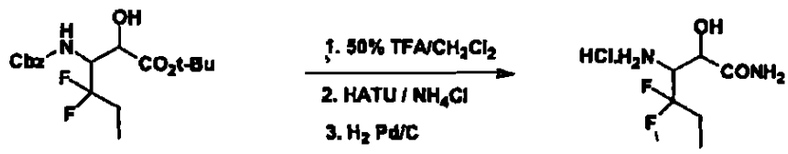
Paso 5:



LXVf LXVg LXVh

El producto del paso 4, **LXVf** (2 g) se trató del modo previamente descrito en el Paso 4 del Ejemplo de Preparación XXXXIII para lograr luego de la purificación a través de cromatografía sobre gel de sílice (30% de EtOAc en n-hexano) dar **LXVg** (0,27 g) y **LXVh** (0,26 g).

Paso 6:



LXVg LXV

El producto del paso 5 **LXVg** (0,17 g) se trató del modo previamente descrito en el Paso 5 luego paso 6 y finalmente paso 7 del Ejemplo de Preparación XXXXIII para lograr el producto **LXV** (0,025 g).

Un número de inhibidores descritos en la Tabla 6 usando el intermediario **LXV** se sintetizaron siguiendo los procedimientos definidos para los Ejemplos de Preparación **XXIII, XXIV, XXVIII, XXIX, y XXXX**

Separación de los diaterómeros: Los diasterómeros que surgen del centro α de la cetoamida se separaron usando tanto cromatografía (SiO_2) como HPLC (columna de diol YMC) con Hexano/ CH_2Cl_2/ Isopropanol/ CH_2CN = 85/7,5/6,5/1 como solvente, como es sabido para los expertos en el arte.

Valoración de la Actividad Inhibidora de la Proteasa de HCV

Valoración Espectrofotométrica: La valoración espectrofotométrica de la proteasa serina de HCV se realizó sobre los compuestos de la invención siguiendo el procedimiento descrito por R. Zhang *et al, Analytical Biochemistry*, 270 (1999) 268-275, cuya descripción se incorpora aquí a modo de referencia. La valoración basada en la proteólisis de los sustratos cromogénicos del éster es apropiada para el monitoreo continuo de la actividad de la proteasa NS3 de HCV. Los sustratos se derivaron del lado P de la secuencia de unión NS5A-NS5B (Ac-DTEDVVX(Nva), donde X = A o P) cuyos grupos carboxilo C-terminales se esterificaron con uno de cuatro alcoholes cromofóricos diferentes (3- ó 4-nitrofenol, 7-hidroxi-4-metil-cumarina, o 4-fenilazofenol). Se presenta a continuación la síntesis, la caracterización y la aplicación de estos nuevos sustratos de éster espectrofotométricos a selección de alto rendimiento y evaluación cinética detallada de los inhibidores de proteasa NS3 de HCV.

Materiales y Métodos:

Materiales: Los reactivos químicos para la valoración se obtuvieron de Sigma Chemical Company (St. Louis, Missouri). Los reactivos para la síntesis de los péptidos fueron de Aldrich Chemicals, Novabiochem (San Diego, California); Applied Biosystems (Foster City, California) y Perseptive Biosystems (Framingham, Massachussets). Los péptidos se sintetizaron en forma manual o en un sintetizador automático ABI modelo 431A (de Applied Biosystems). El espectrómetro de UV/VIS modelo LAMBDA 12 fue de Perkin Elmer (Norwalk, Connecticut) y las placas de UV de 96 receptáculos se obtuvieron de Corning, New York). El bloque de precalentamiento fue de USA Scientific (Ocala, Florida) y el aparato de vórtex de placa de 96 receptáculos fue de Labline Instruments (Melrose Park, Illinois). Un lector de placas de microtitulación Spectramax Plus con monocrómetro se obtuvo de Molecular Devices (Sunnyvale, California).

Preparación de las Enzimas: Se preparó la proteasa de HCV NS3/NS4A recombinante heterodimérica (cepa 1a) usando los procedimientos publicados previamente (D. L. Sali *et al. Biochemistry,* 37 (1998) 3392-3401. Las concentraciones de las proteínas se determinaron a través del método de coloración de Biorad usando estándares de proteasa de HCV recombinante cuantificados anteriormente a través del análisis de aminoácidos. Antes de iniciar el ensayo, se cambió el buffer de almacenamiento (fosfato de sodio 50 mM pH 8,0, NaCl 300 mM, 10% de glicerol, 0,05% de maltosida de laurilo y DTT 10 mM) por el buffer del ensayo (MOPS 25 mM pH 6,5, NaCl 300 mM, 10% de glicerol, 0,05% de maltosida de laurilo, 5 µM de EDTA y 5µM de DTT) usando una columna pre envasada Biorad Bio-Spin P-6.

Síntesis y Purificación del Sustrato: La síntesis de los sustratos se realizó como se informó en R. Zhang *et al, (ibid).* y se inició anclando Fmoc-Nva-OH a la resina de cloruro de 2-clorotritilo usando un protocolo estándar (K. Barlos *et al, Int. J. Pept. Protein Res.*, 37 (1991), 513-520). Los péptidos se ordenaron

posteriormente, usando la química de Fmoc, ya sea en forma manual como en un sintetizador de péptidos ABI modelo 431. Los fragmentos de péptidos N-acetilados y totalmente protegidos se disociaron de la resina ya sea con 10% de ácido acético (HOAc) o 10% de trifluoroetanol (TFE) en diclorometano (DCM) durante 30 minutos, o a través de 2% de ácido trifluoroacético (TFA) en DCM durante 10 min. El filtrado combinado y el lavado de DCM se evaporó en forma azeotrópica (o se extrajo en forma reiterada con solución acuosa de Na_2CO_3) para eliminar el ácido usado en la disociación. La fase de DCM se secó sobre Na_2SO_4 y se evaporó.

Los substratos de éster se ordenan usando procedimientos estándares de acoplamiento de ácido-alcohol (K. Holmber *et al, Acta Chem. Scand.*, B33 (1979) 410-412). Los fragmentos de péptidos se disolvieron en piridina anhidra (30-60 mg/ml) a la cual se agregaron 10 equivalentes molares de cromóforo y una cantidad catalítica (0,1 eq.) de ácido para-toluensulfónico (pTSA). Se agregó diciclohexilcarbodiimida (DCC, 3 eq.) para hincar las reacciones de acoplamiento. La formación de producto se monitoreó a través de HPLC y se encontró que estaba completa luego de 12-72 horas de reacción a temperatura ambiente. El solvente de piridina se evaporó al vacío y se quitó en forma adicional a través de evaporación azeotrópica con tolueno. El éster peptídico se desprotegió con 95% de TFA en DCM durante dos horas y se extrajo tres veces con éter etílico anhidro para quitar el exceso de cromóforo. El sustrato desprotegido se purificó por HPLC de fase inversa en una columna C3 o C8 con un 30% hasta un 60% de gradiente de acetonitrilo (usando seis volúmenes de columna). El rendimiento general luego de la purificación por HPLC fue de aproximadamente 20-30%. La masa molecular se confirmó a través de espectrometría de masa con ionización por electroaspersión. Los substratos se almacenaron en forma de polvo seco con desecación.

Espectros de los Sustratos y los Productos: Los espectros de los sustratos y los correspondientes productos cromóforos se obtuvieron en el buffer de valoración con pH 6,5. Los coeficientes de extinción se determinaron en la longitud de onda óptima fuera del pico en cubetas de 1 cm (340 nm para 3-Np y HMC, 370 nm para PAP y 400 nm para 4-Np) usando diluciones múltiples. La longitud óptima fuera del pico se definió como aquella longitud de onda que produce la diferencia fraccional máxima en la absorbancia entre el substrato y el producto (OD de producto - OD de sustrato)/ OD de sustrato).

Valoración de Proteasa: Las valoraciones de proteasa del HCV se realizaron a 30°C usando una mezcla de reacción de 200 µl en una placa de microtitulación de 96 receptáculos. Las condiciones del buffer de valoración (MOPS 25 mM pH 6,5, NaCl 300 mM, 10% de glicerol, 0,05% de maltosida de laurilo, 5 µM de EDTA y 5 µM de DTT) se optimizaron para el heterodímero NS3/NS4A (D. L. Sali *et al, ibid.*)). Normalmente, se colocaron mezclas de buffer, sustrato e inhibidor en los receptáculos (concentración final de DMSO ≤4% v/v) y se dejó pre-incubar a 30°C durante aproximadamente 3 minutos. Luego se usaron cincuenta µls de proteasa precalentada (10 nM, 30°C) en buffer de valoración, para iniciar la reacción (volumen final 200 µl). Las placas se monitorearon mientras duró la valoración (60 minutos) para evaluar el cambio en la absorbancia a la longitud de onda apropiada (340 nm para 3-Np y HMC, 370 nm para PAP y 400 nm para 4-Np) usando un lector de placas de microtitulación Spectromax Plus equipado con un monocrómetro (los resultados aceptables pueden obtenerse con lectores de placas que utilicen filtros de corte). La disociación proteolítica de la ligadura de éster entre Nva y el cromóforo se monitoreó a la longitud de onda apropiada contra un blanco sin enzimas como control para la hidrólisis no enzimática. La evaluación de los parámetros de cinética de los sustratos se realizó en un rango de 30 concentraciones del sustrato (~6-200 µM). Las velocidades iniciales se determinaron usando

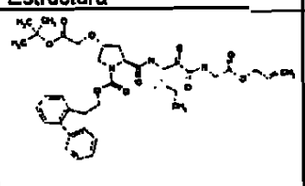
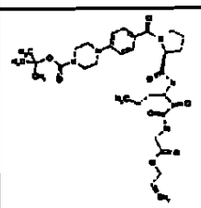
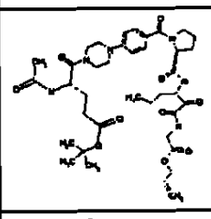
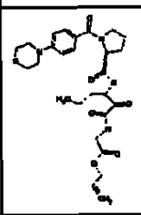
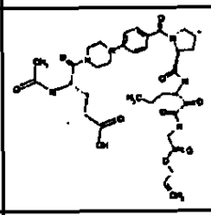
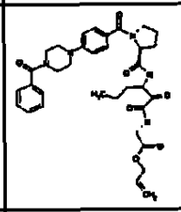
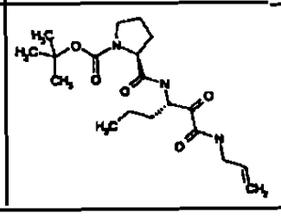
regresión lineal y las constantes cinéticas se obtuvieron adaptando los datos a la ecuación de Michaelis-Menten usando análisis de regresión no lineal (Mac Curve Fit 1.1, K. Raner). Las cifras de producción (K_{cat}) se obtuvieron suponiendo que la enzima estaba totalmente activa.

Evaluación de los Inhibidores e Inactivadores: La inhibición de las constantes (Ki*) para los inhibidores competitivos Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH y Ac-DTEDVVP(Nva)-OH se determinaron en forma experimental en concentraciones fijas de enzimas y sustrato trazando un gráfico de v_o/v_i versus la concentración de inhibidor ($[I]_o$) de acuerdo con la ecuación reordenada de Michaelis-Menten para la cinética de inhibición competitiva: $v_o/v_i = 1 + [I]_o / (Ki^* (1 + [S]_o/ K_m))$, donde v_o es la velocidad inicial no inhibida, v_i es la velocidad inicial en presencia de inhibición a cualquier concentración determinada de inhibidor, ($[I]_o$) y $[S]_o$ es la concentración de sustrato usada. Los datos resultantes se adaptaron usando regresión lineal y la pendiente resultante, $1/(Ki^*(1+[S]_o/K_m)$, se usó para calcular el valor de Ki*.

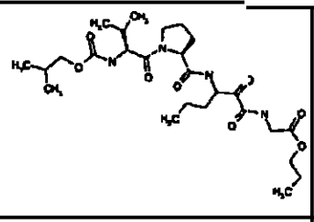
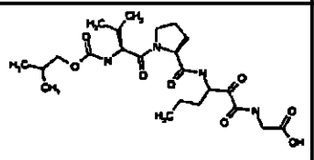
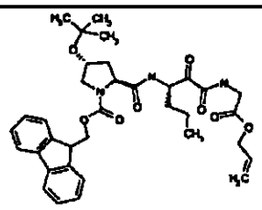
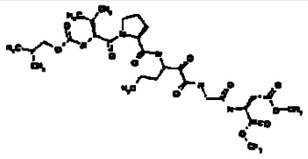
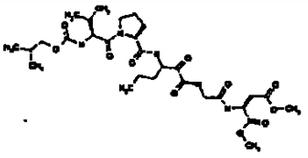
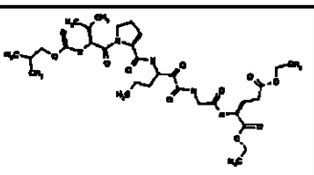
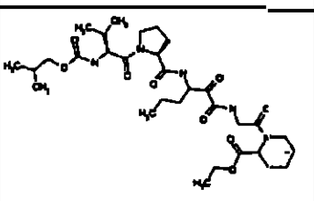
Los valores obtenidos de Ki* para los diferentes compuestos de la presente invención se dan en las Tablas antes mencionadas en las cuales los compuestos se han ordenado en el orden de rangos de valores de Ki*. A partir de estos resultados experimentales, resultará obvio para los expertos en el arte que los compuestos de la invención tienen una excelente utilidad como inhibidores de la proteasa serina NS3.

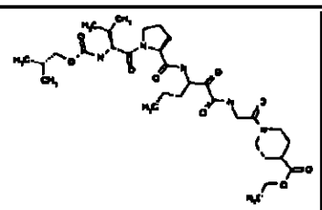
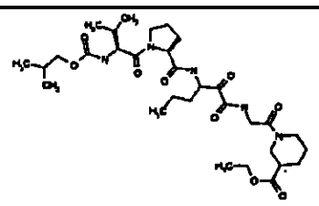
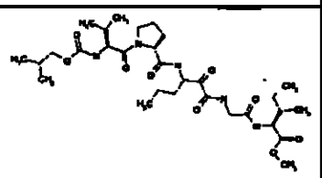
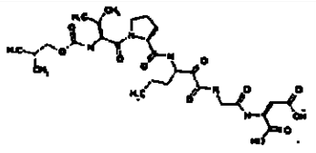
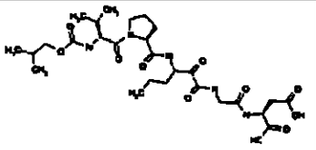
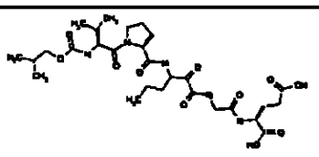
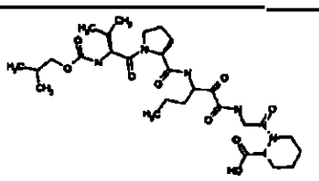
Mientras que la presente invención se ha descrito en conjunción con las realizaciones específicas indicadas anteriormente, muchas alternativas, modificaciones y otras variaciones a ésta resultarán obvias para aquellos expertos en el arte. Todas estas alternativas, variaciones y modificaciones caen dentro del espíritu y del alcance de la presente invención.

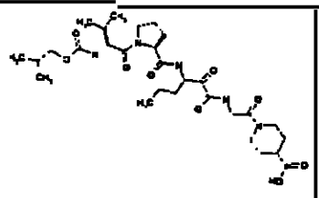
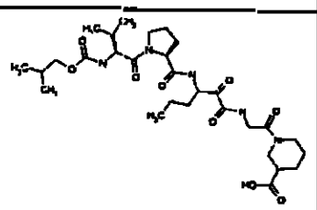
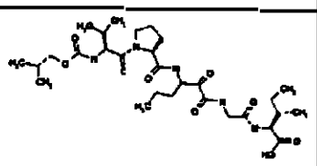
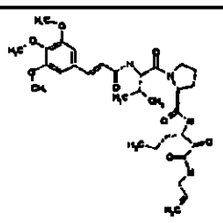
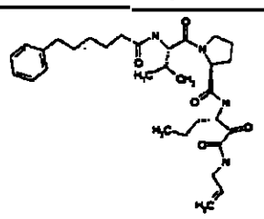
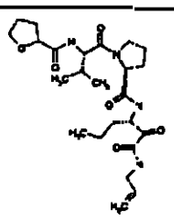
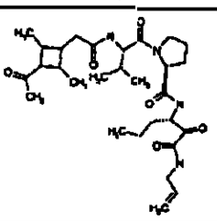
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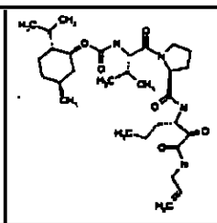
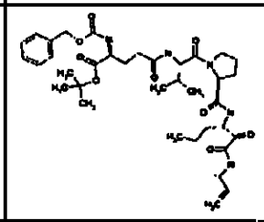
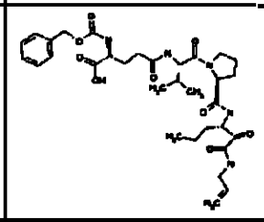
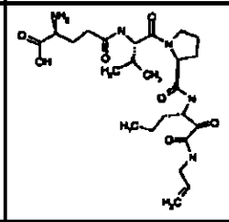
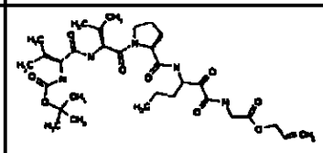
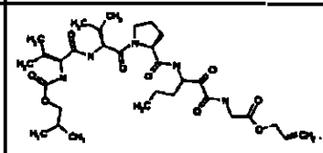
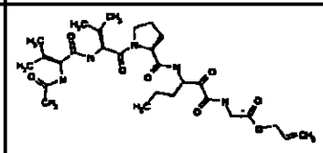
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4		527.6259
5		696.7799
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7		381.476

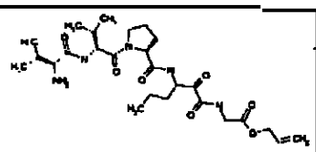
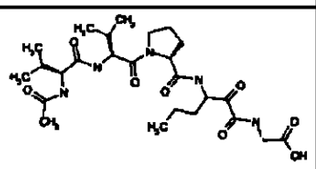
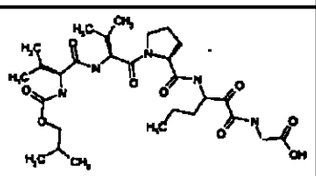
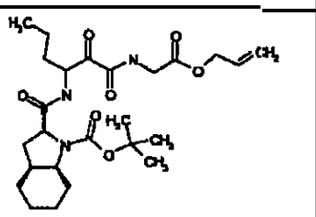
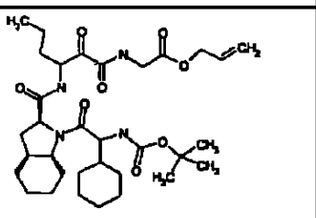
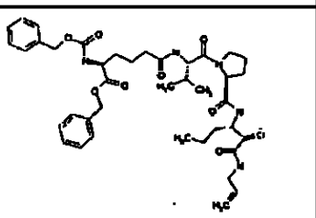
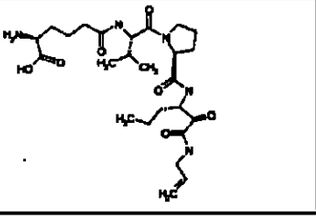
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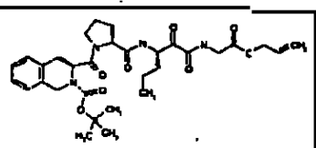
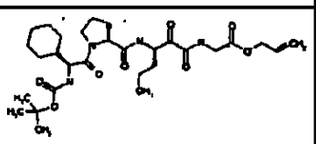
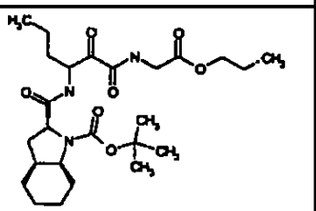
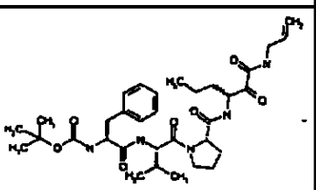
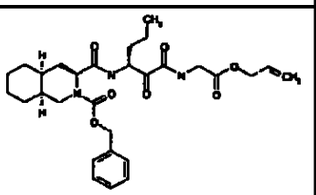
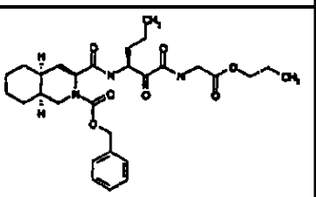
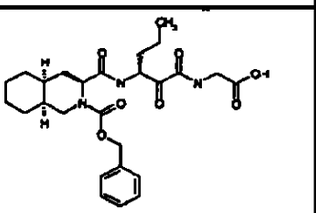
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12		641.7249
13		683.8061
14		637.7802

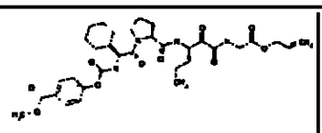
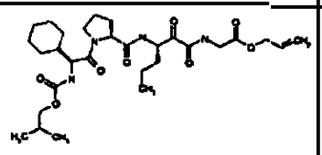
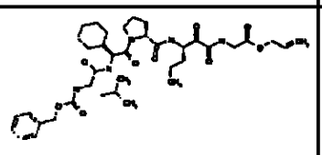
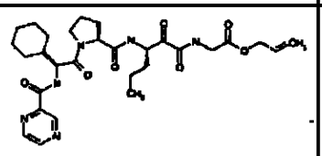
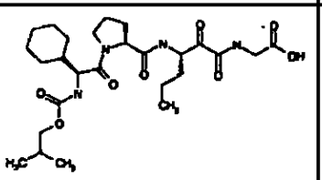
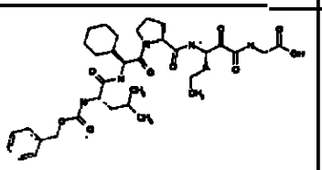
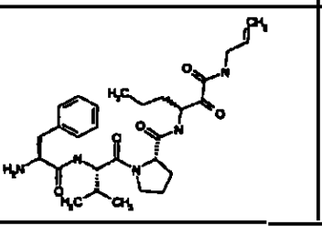
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19		613.6707
20		627.6978
21		609.726

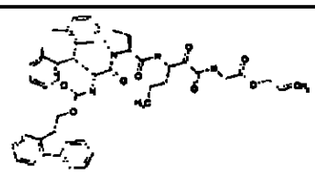
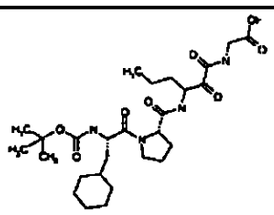
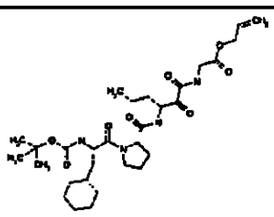
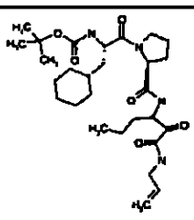
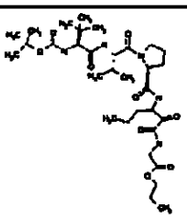
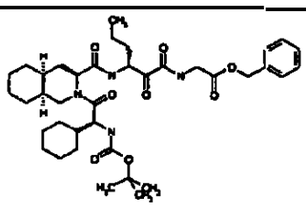
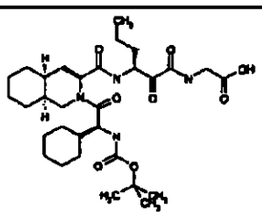
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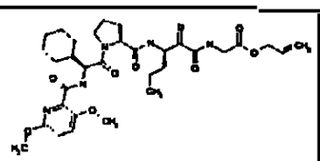
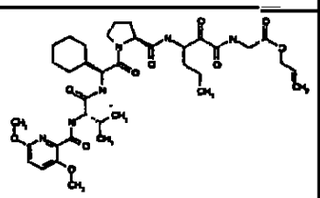
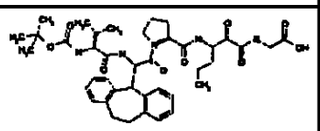
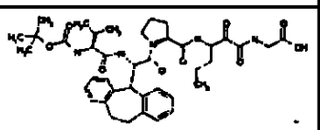
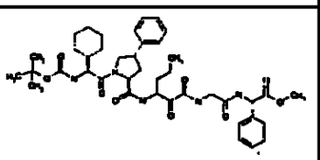
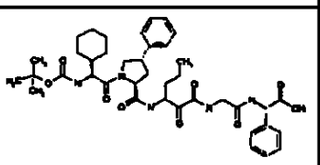
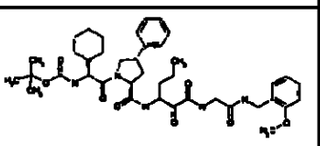
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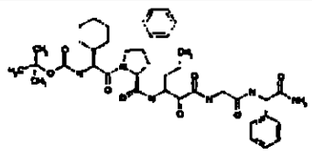
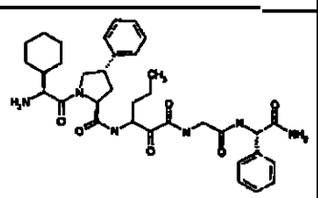
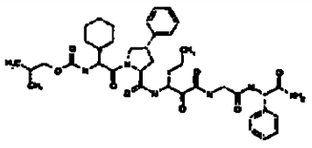
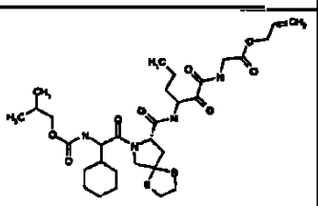
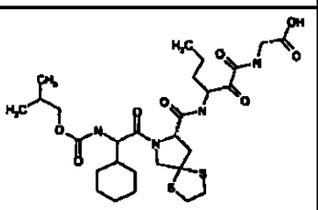
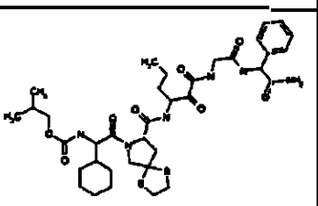
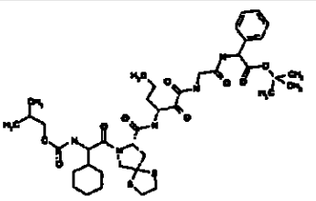
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38		597.7149
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40		632.8044
41		747.8965
42		523.6348

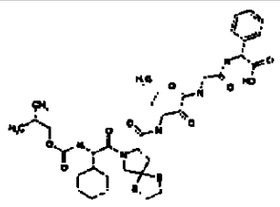
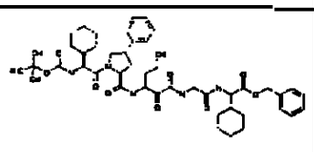
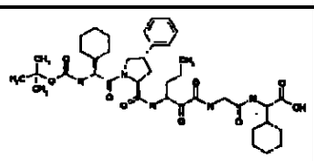
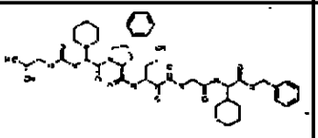
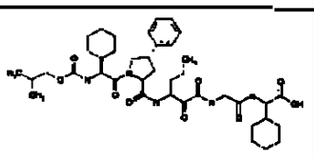
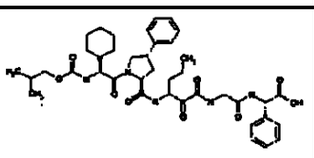
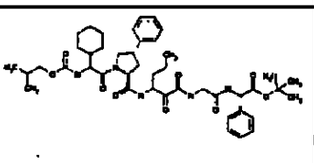
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44		578.712
45		495.6214
46		627.7878
47		541.6501
48		543.666
49		501.5847

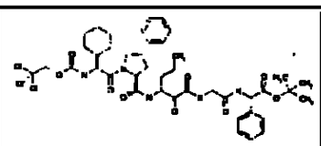
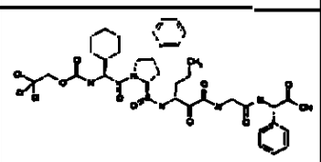
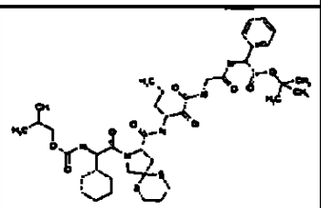
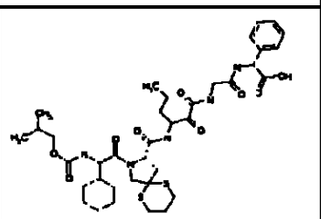
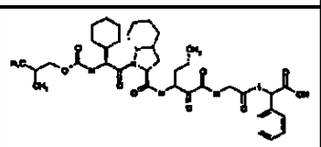
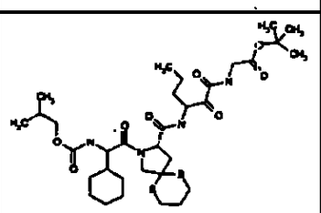
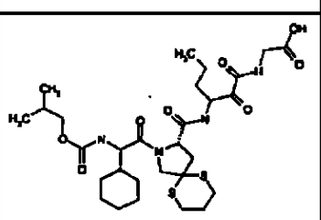
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52		725.8901
53		584.6782
54		538.6467
55		685.8248
56		527.6695

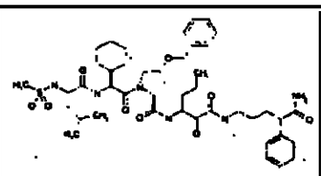
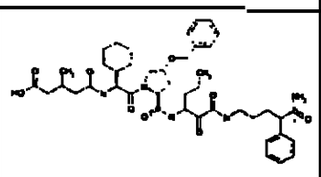
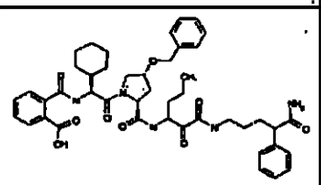
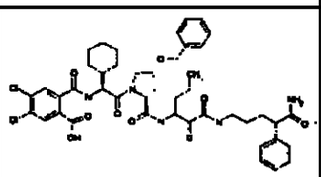
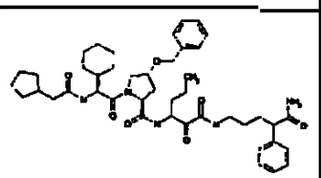
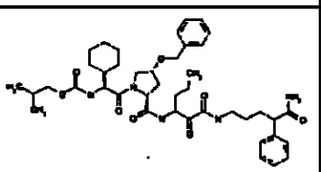
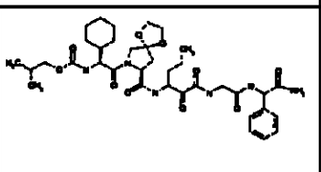
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59		592.7391
60		534.702
61		653.8232
62		696.892
63		606.7662

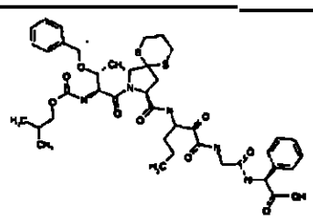
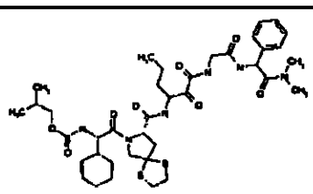
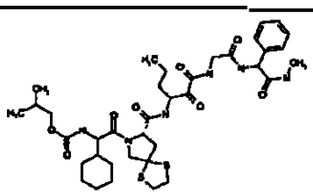
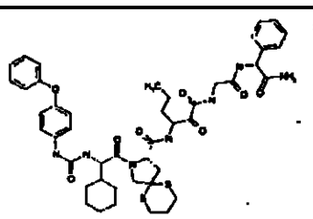
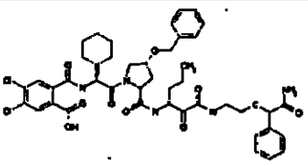
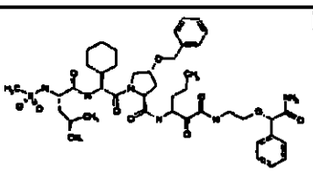
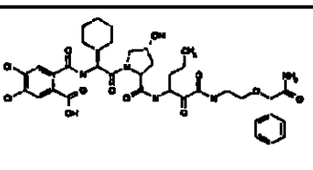
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70		733.913

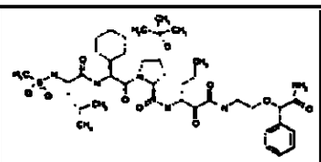
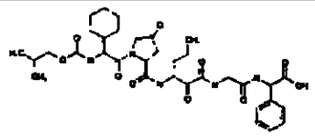
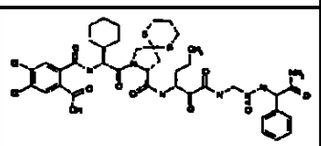
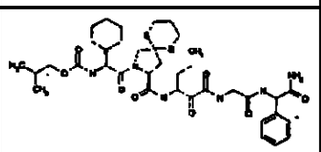
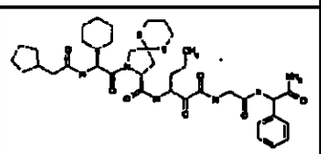
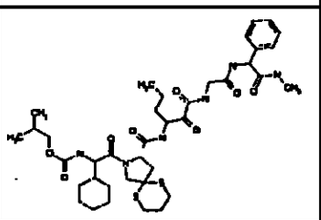
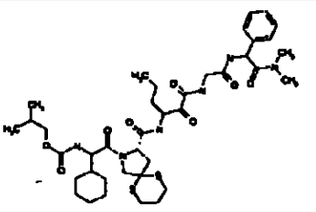
71		746.9118
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73		746.9118
74		668.8782
75		628.8129
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77		818.0723

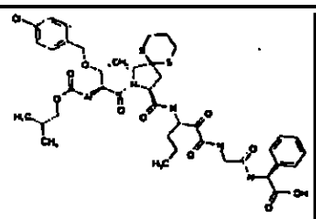
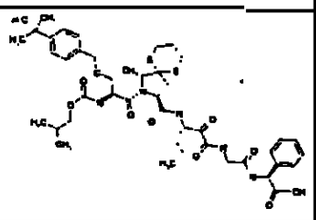
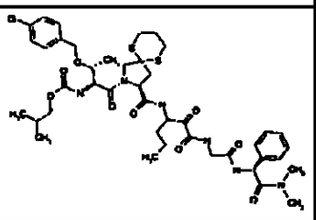
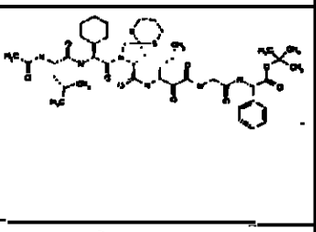
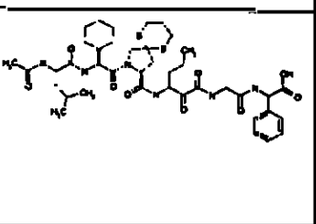
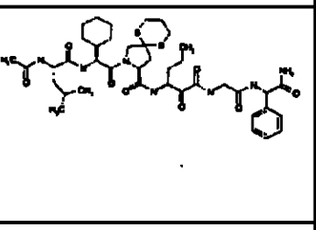
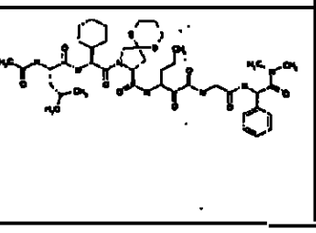
78		761.964
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84		804.0049

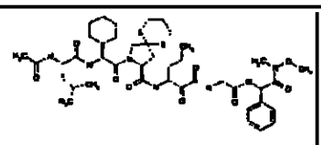
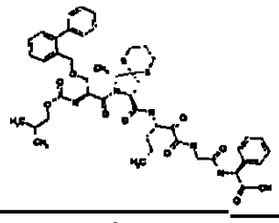
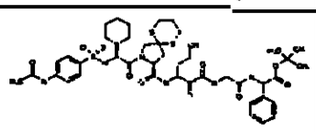
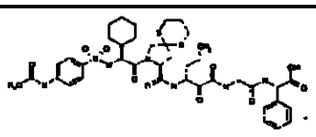
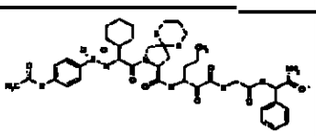
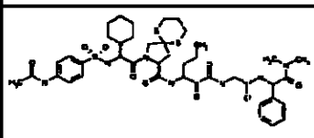
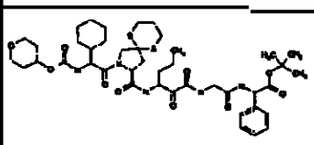
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87		832.0994
88		775.9911
89		725.8901
90		698.9483
91		642.84

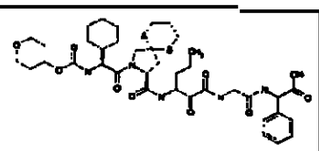
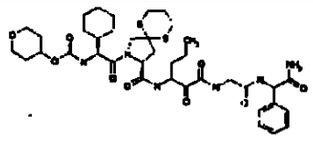
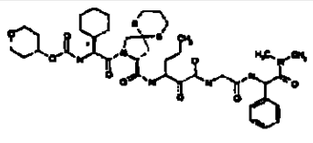
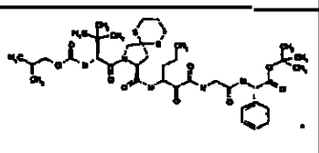
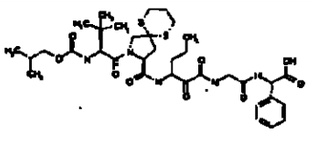
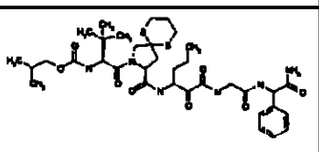
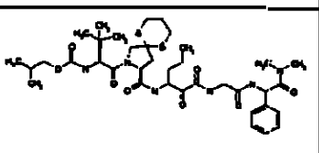
92		853.0995
93		789.9778
94		809.9682
95		878.8583
96		772.006
97		761.9672
98		728.85

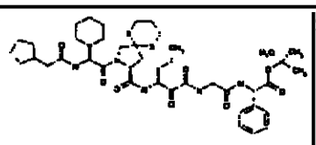
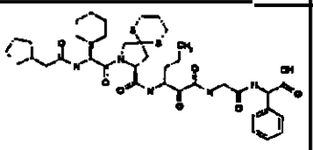
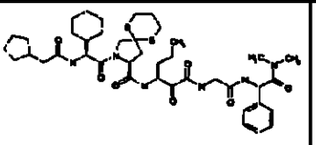
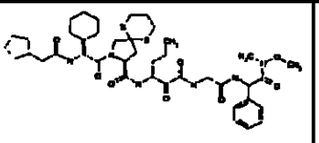
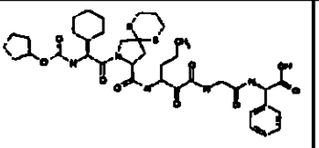
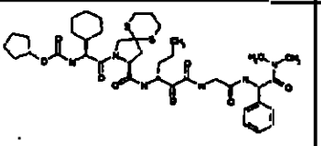
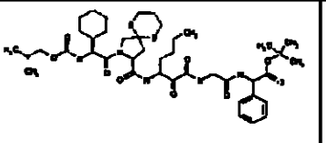
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105		790.7047

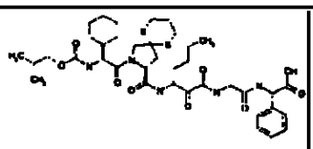
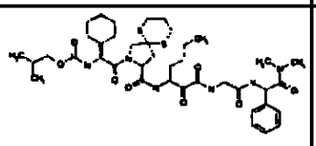
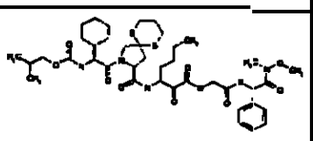
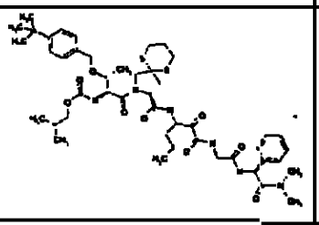
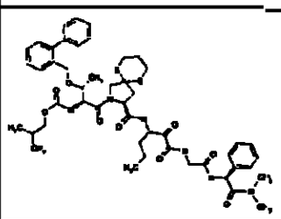
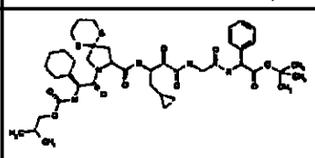
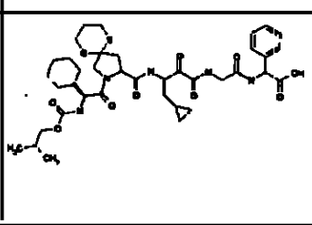
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108		891.8973
109		775.0063
110		785.0452
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112		803.0605

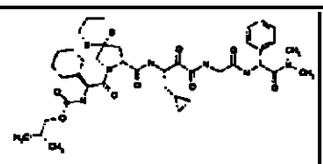
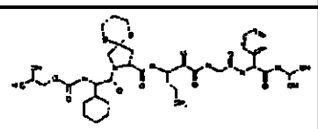
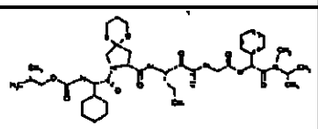
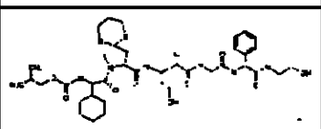
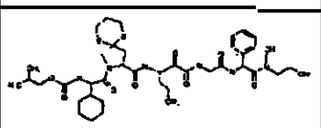
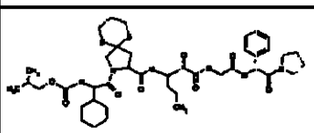
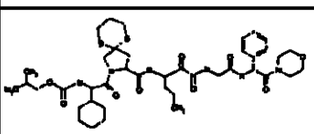
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117		831.071
118		830.0863
119		858.1405

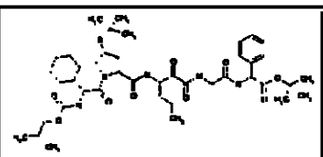
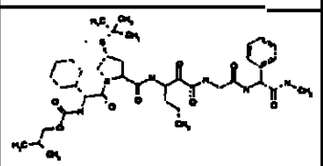
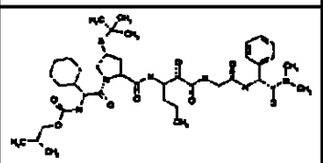
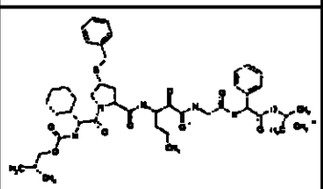
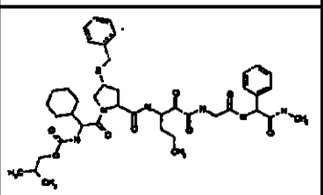
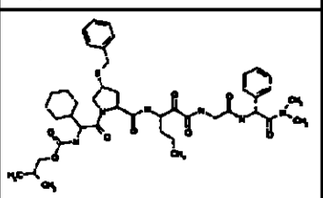
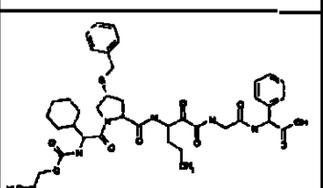
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126		860.11

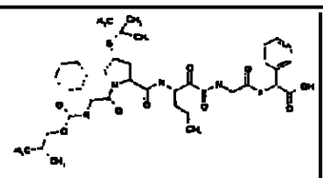
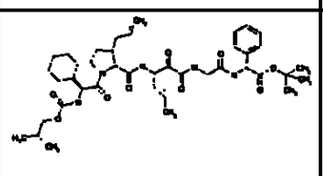
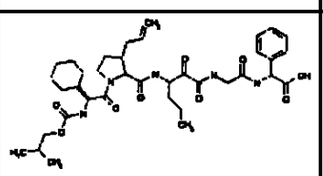
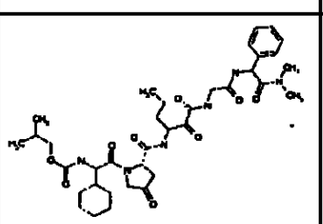
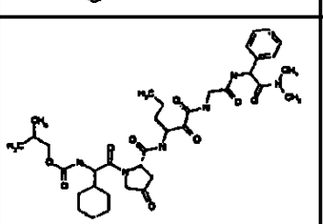
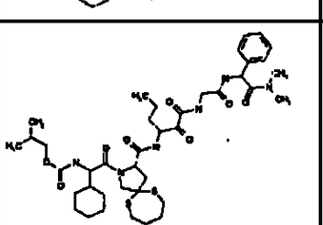
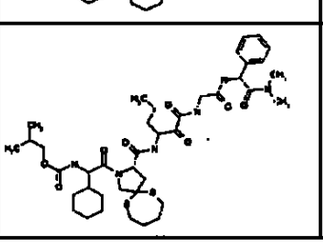
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133		777.0223

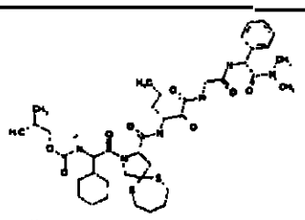
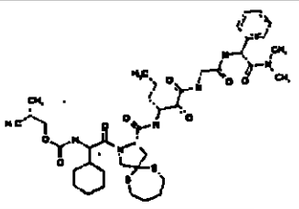
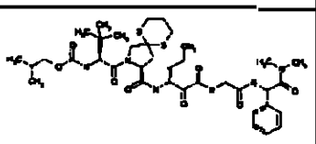
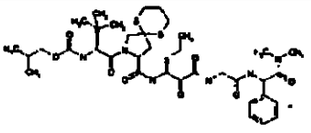
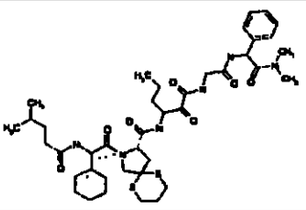
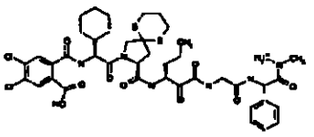
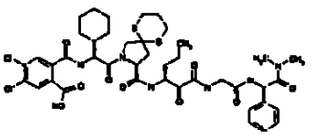
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140		846.1265

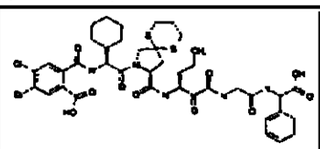
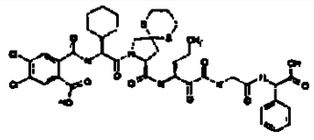
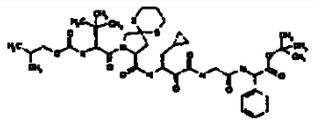
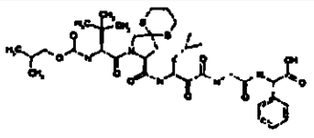
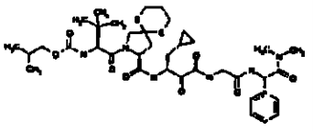
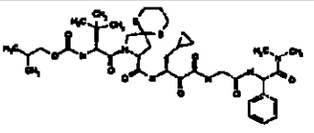
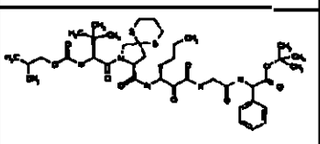
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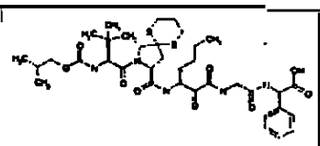
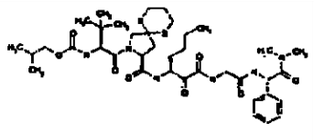
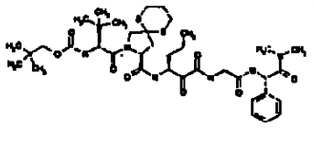
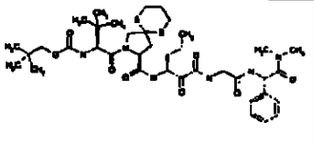
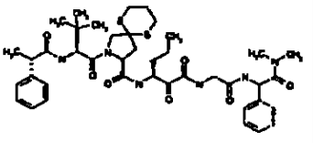
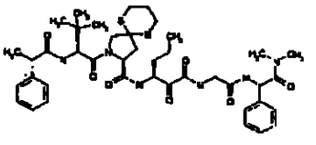
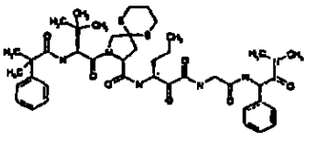
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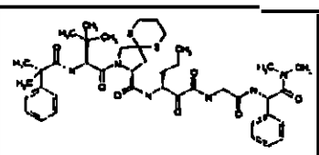
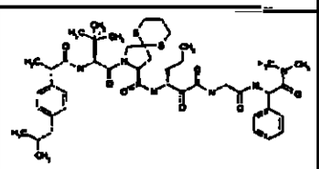
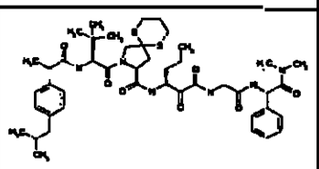
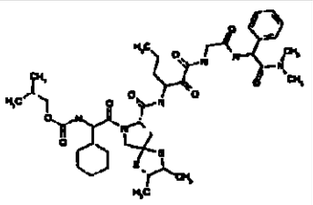
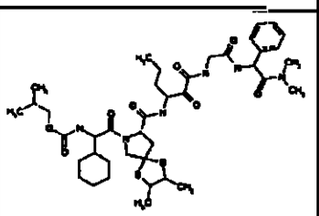
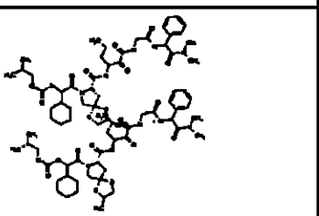
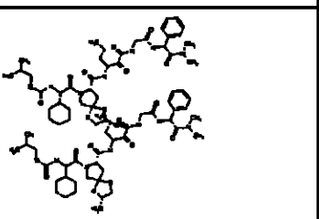
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159		807.03
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161		793.9876

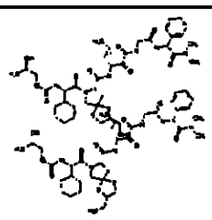
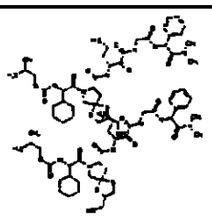
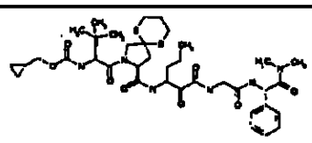
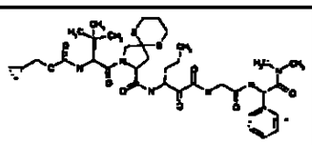
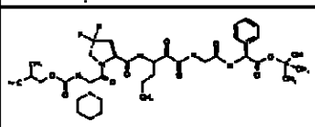
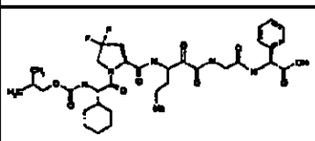
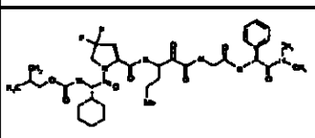
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166		712.8506
167		817.0876
168		817.0876

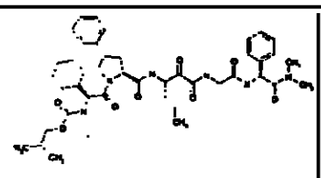
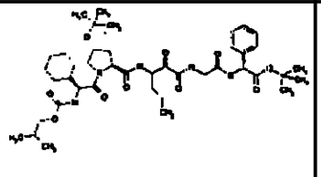
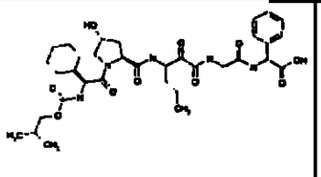
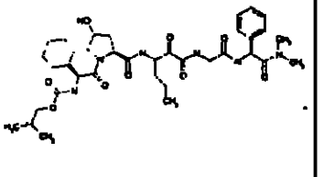
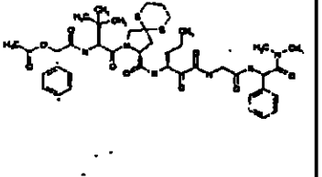
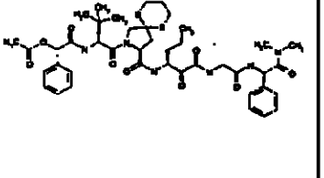
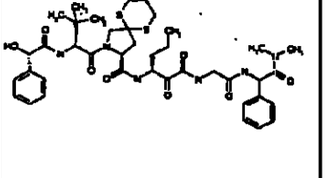
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173		801.0882
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175		919.9515

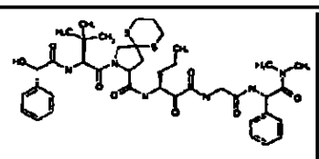
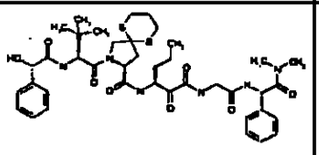
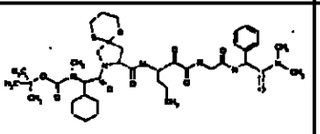
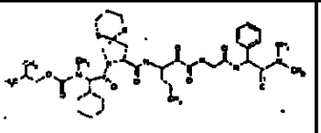
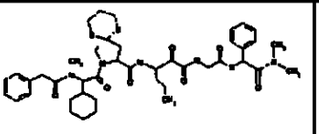
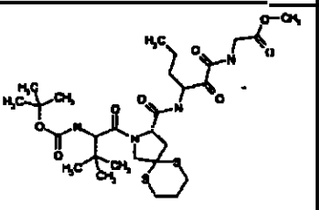
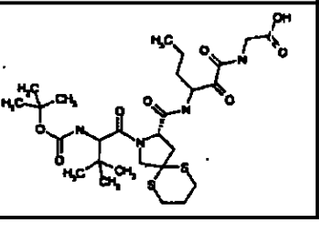
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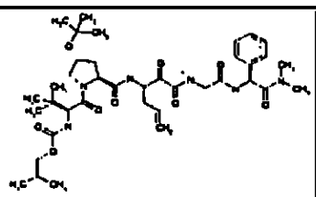
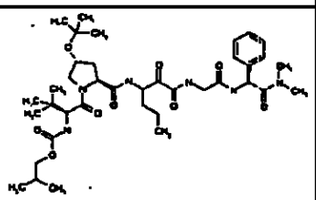
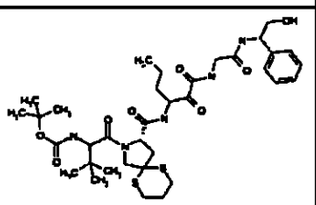
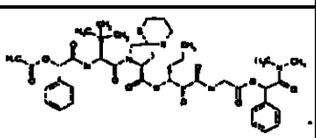
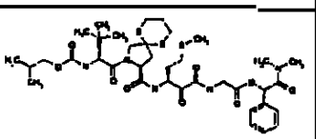
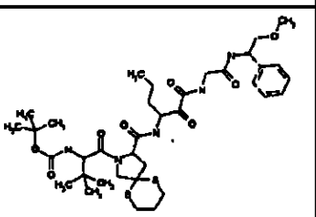
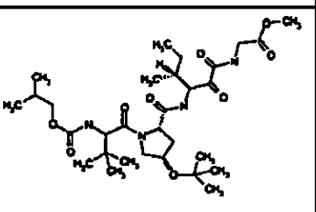
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189		823.0945

190		823.0945
191		865.1758
192		865.1758
193		817.0876
194		817.0876
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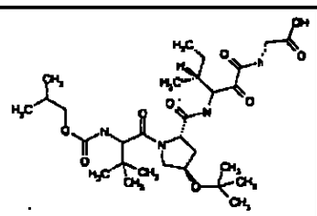
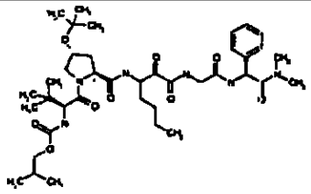
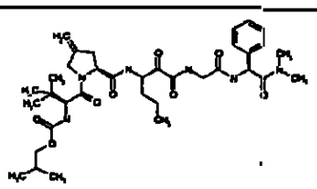
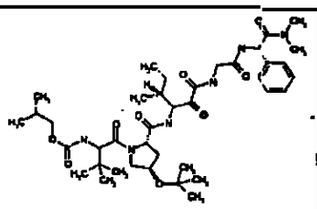
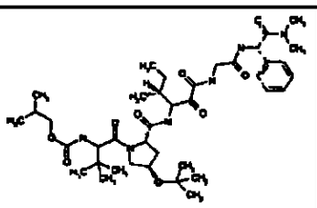
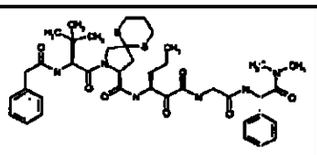
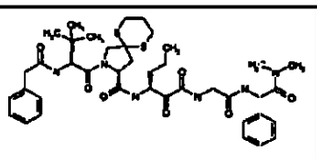
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203		734.848

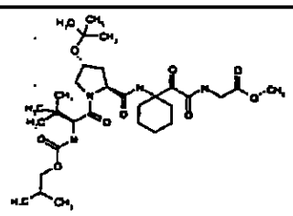
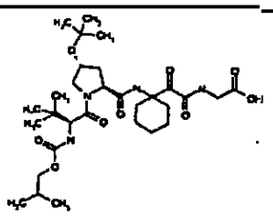
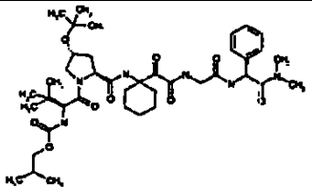
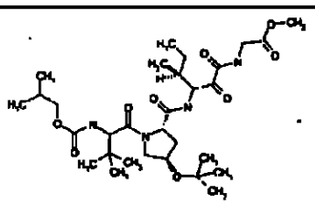
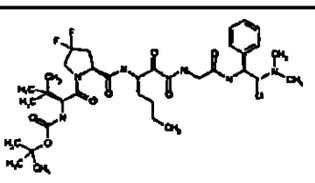
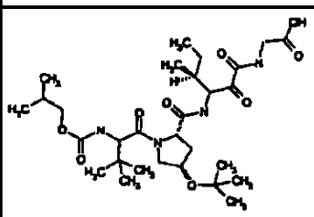
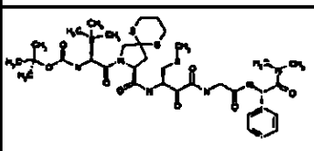
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210		811.0398

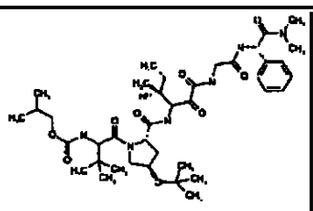
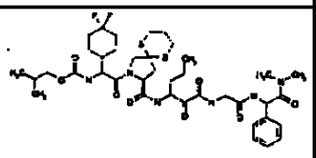
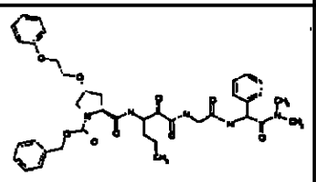
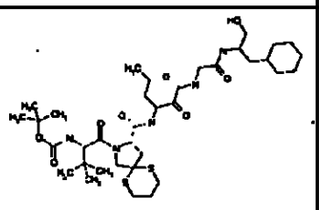
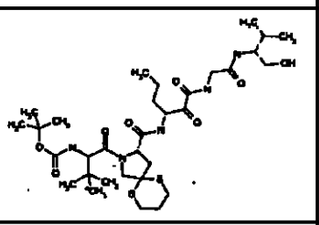
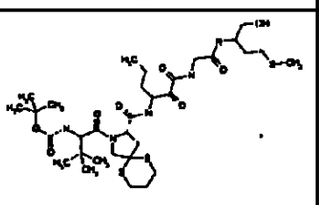
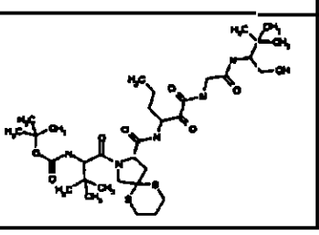
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215		835.1057
216		630.8288
217		616.8018

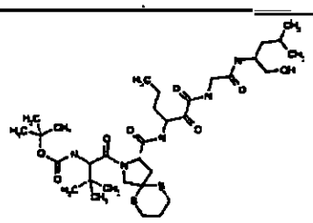
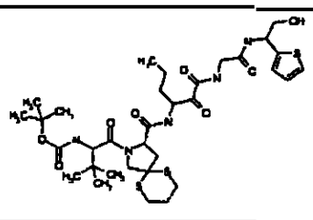
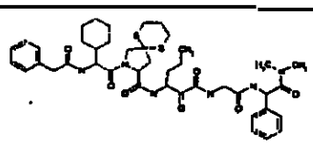
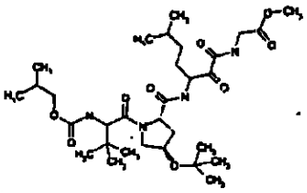
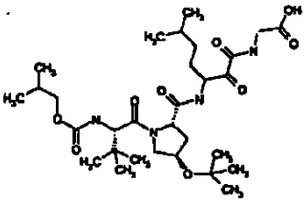
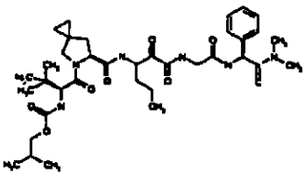
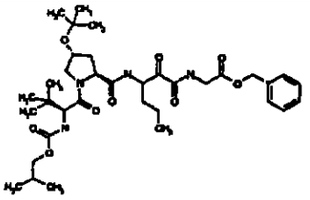
218		742.9208
219		744.9367
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222		809.0862
223		749.9965
224		612.7703

1020
A024

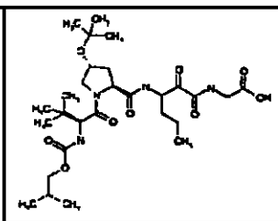
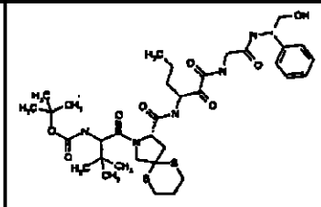
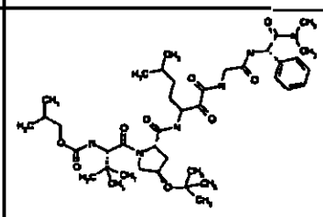
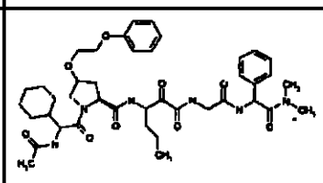
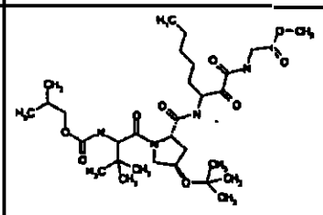
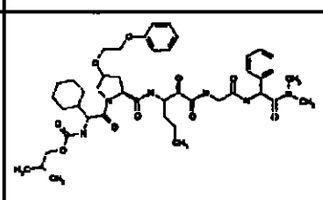
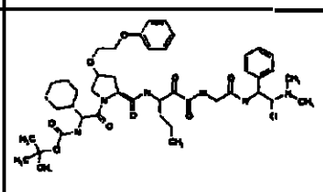
225		598.7432
226		758.9638
227		684.8401
228		758.9638
229		758.9638
230		795.0404
231		795.0404

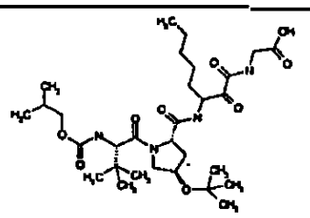
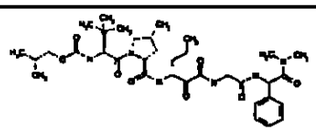
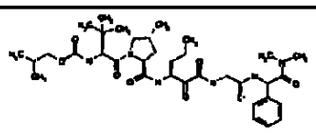
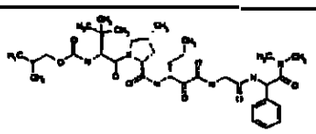
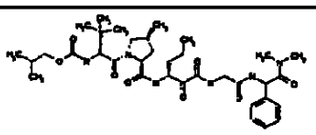
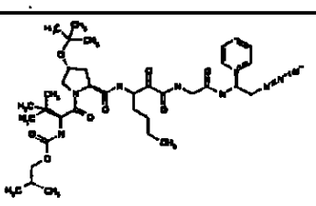
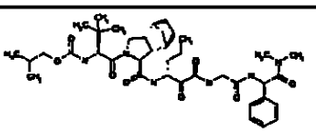
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233		610.7544
234		770.9749
235		612.7703
236		722.8369
237		598.7432
238		795.0592

239		758.9638
240		839.0414
241		729.8375
242		756.0443
243		701.9518
244		734.0159
245		715.9789

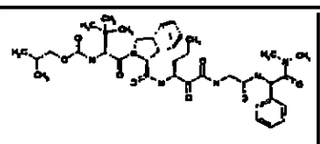
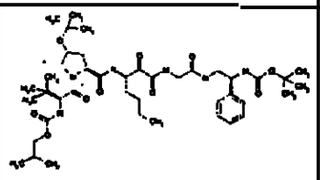
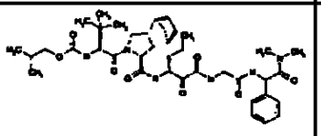
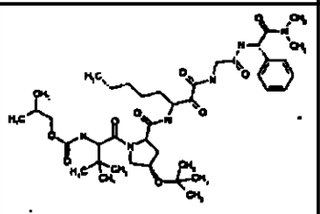
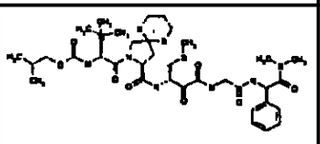
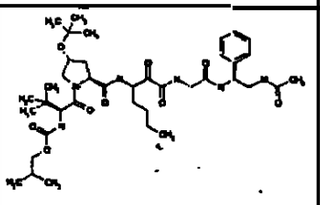
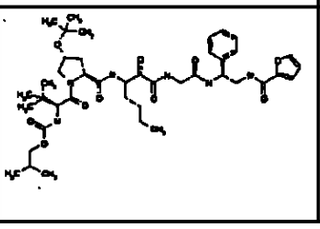
246		715.9789
247		741.9951
248		821.0786
249		626.7974
250		612.7703
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252		674.842

1024

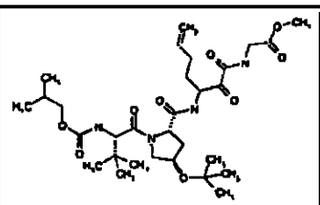
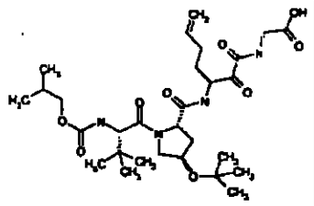
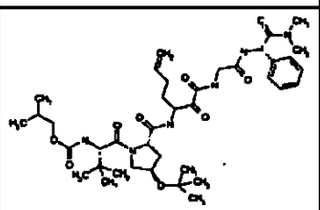
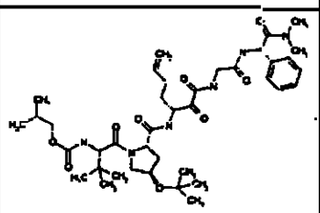
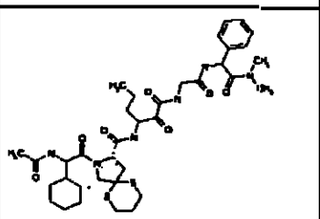
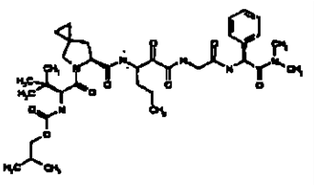
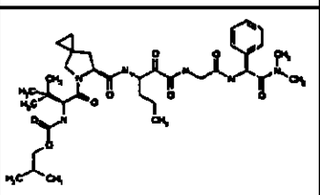
253		584.7162
254		735.9694
255		772.9909
256		776.9383
257		626.7974
258		835.0189
259		835.0189

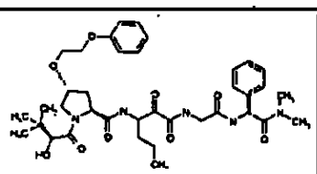
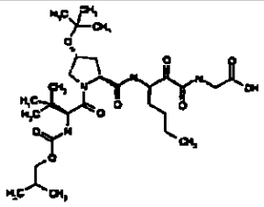
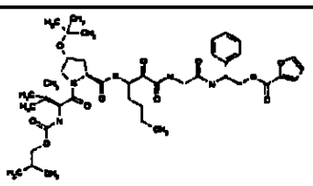
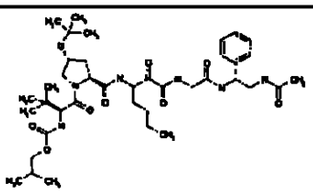
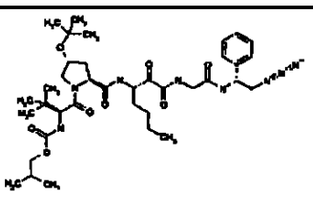
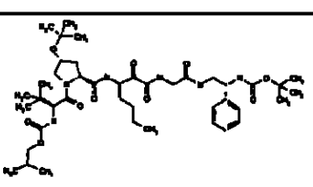
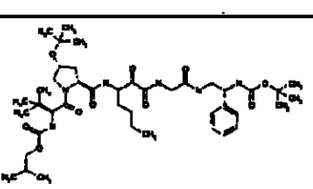
260		612.7703
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263		686.856
264		686.856
265		742.9236
266		738.9325

1026
1027

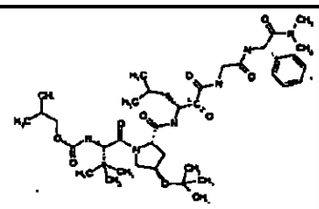
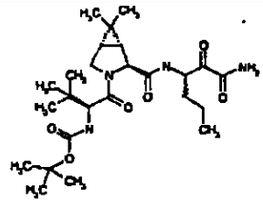
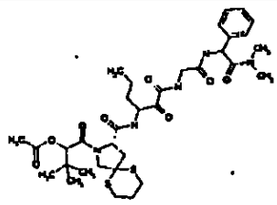
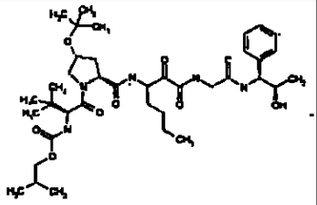
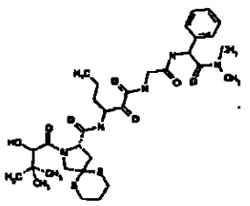
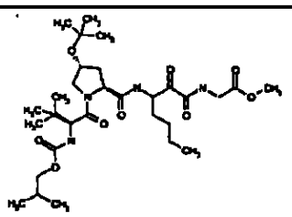
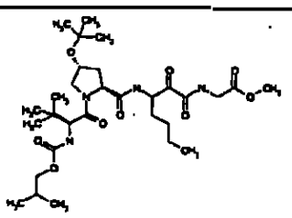
267		738.9325
268		817.0444
269		738.9325
270		772.9909
271		795.0592
272		758.9638
273		810.9966

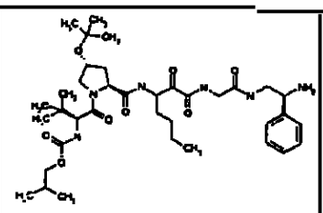
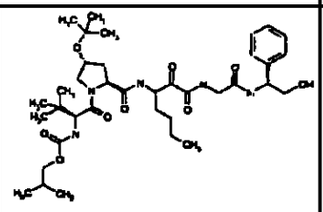
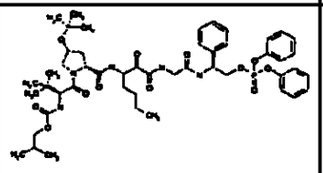
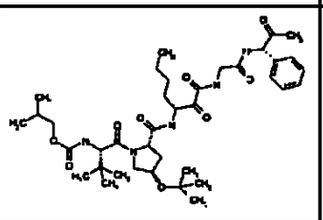
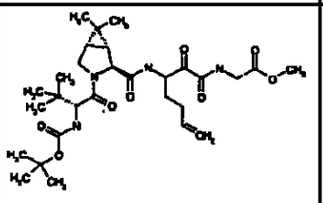
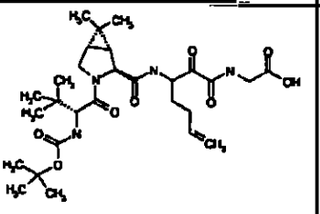
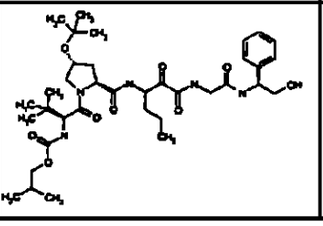
1027
A028

274		610.7544
275		596.7273
276		756.9479
277		756.9479
278		744.9799
279		698.8672
280		698.8672

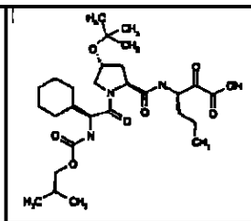
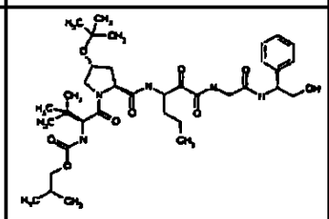
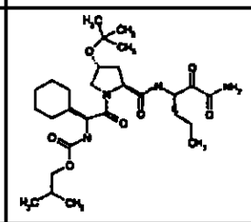
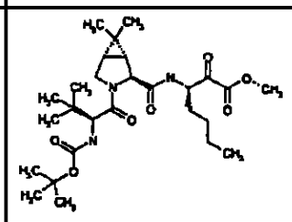
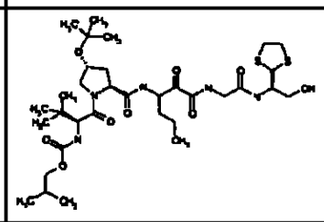
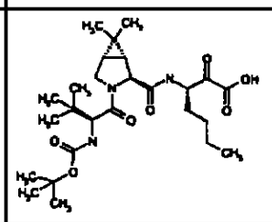
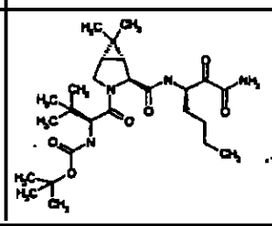
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283		810.9966
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285		742.9236
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287		817.0444

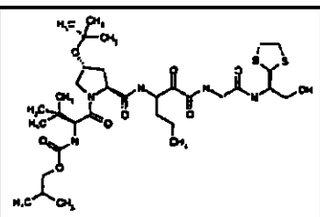
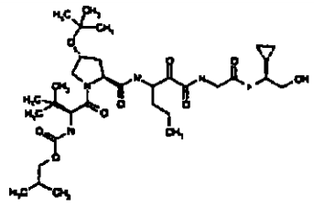
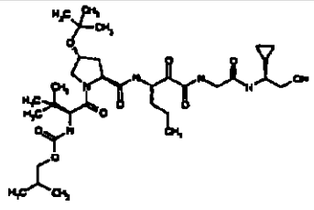
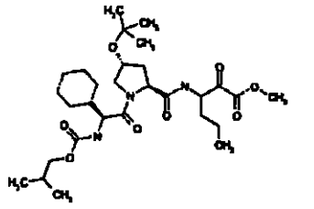
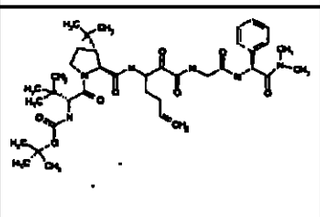
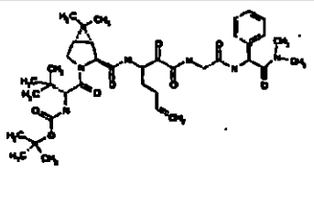
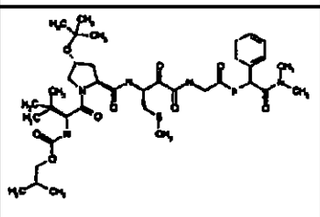
1029
1030

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290		719.9263
291		731.938
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293		612.7703
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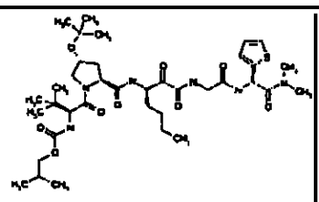
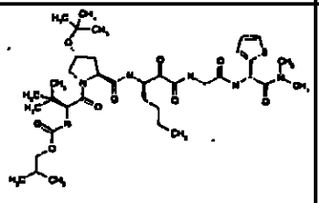
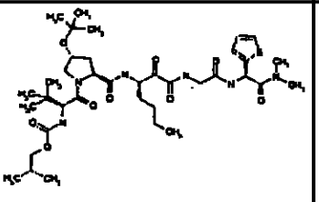
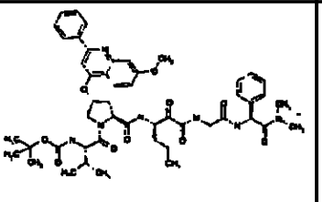
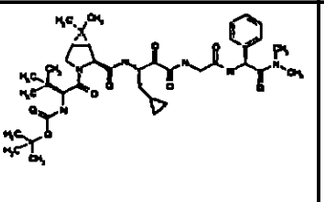
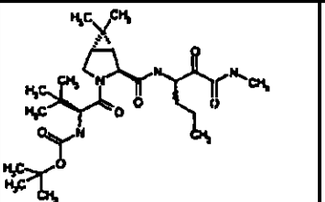
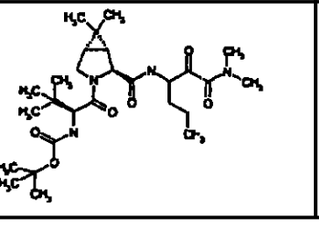
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297		950.0884
298		729.9221
299		578.712
300		564.6849
301		703.8838

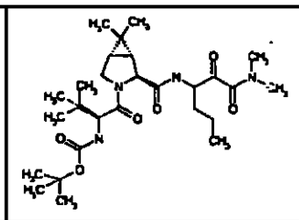
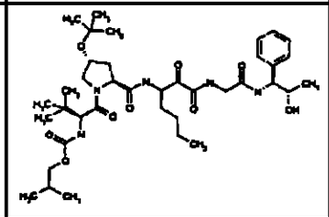
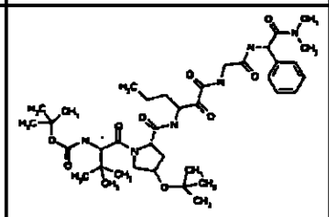
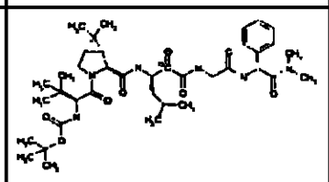
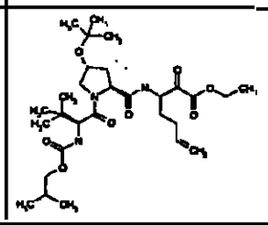
1031 1032

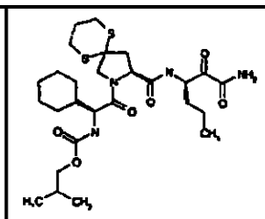
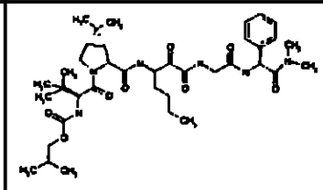
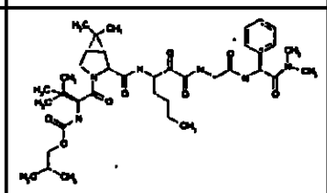
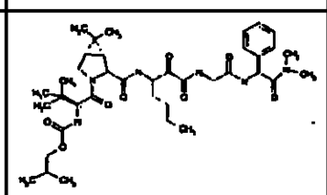
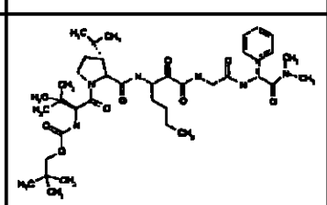
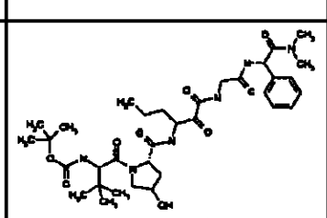
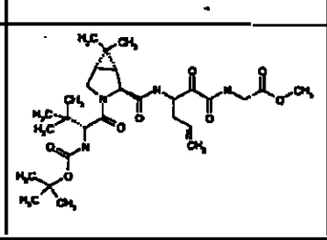
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306		731.9783
307		509.6485
308		508.6638

309		731.9783
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311		667.8503
312		567.7292
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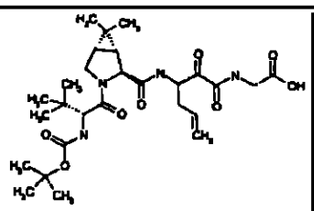
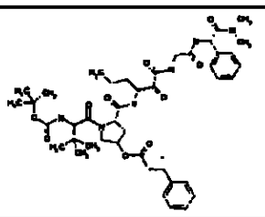
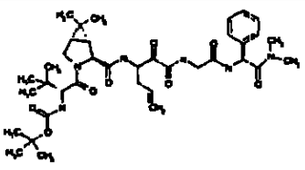
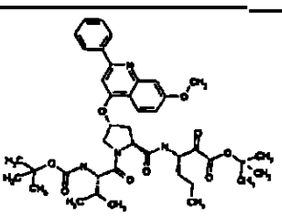
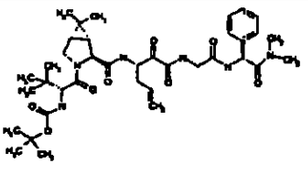
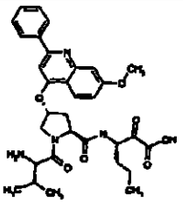
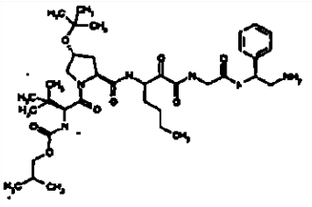
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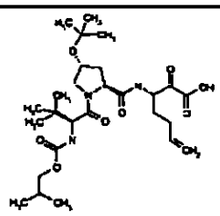
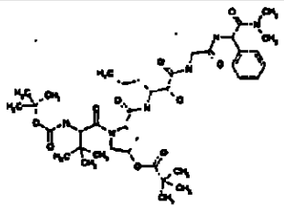
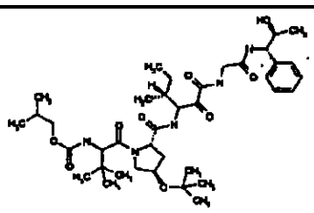
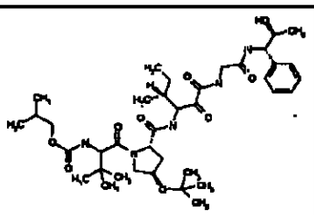
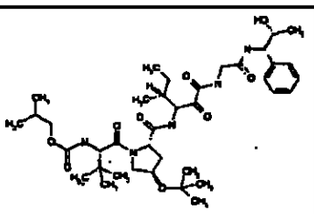
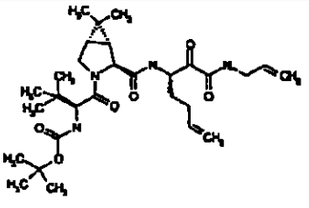
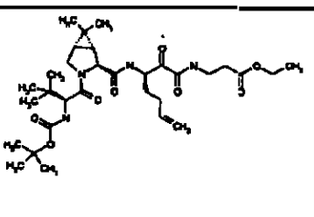
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318		764.9896
319		908.0734
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322		522.6909

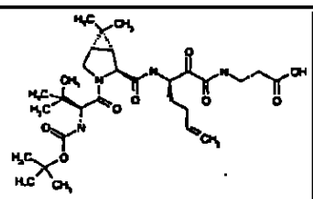
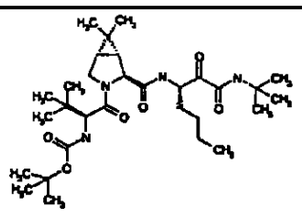
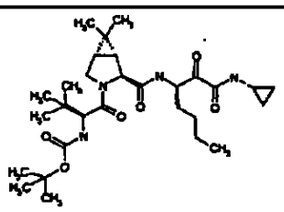
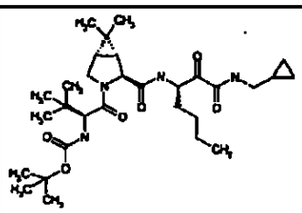
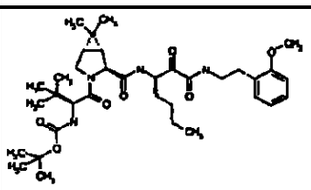
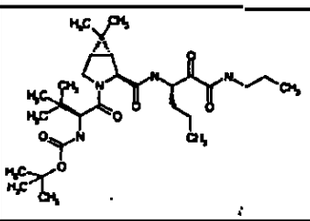
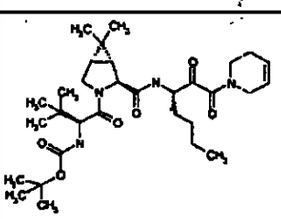
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324		731.938
325		744.9367
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327		567.7292

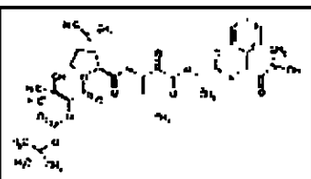
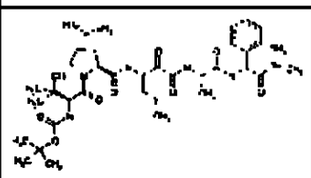
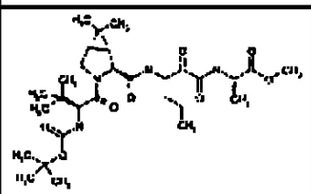
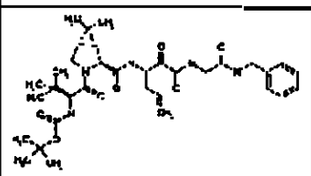
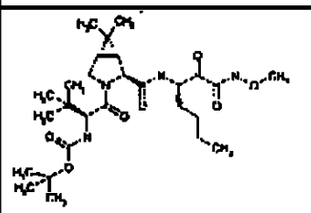
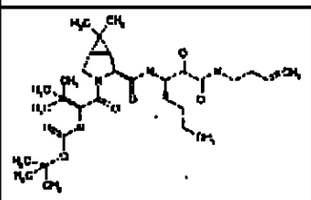
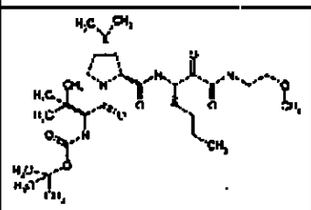
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1536
4037

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340		590.6823
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342		539.675
343		772.9473
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355		574.7673

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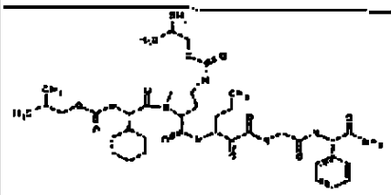
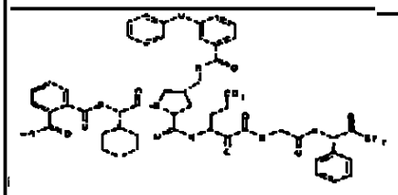
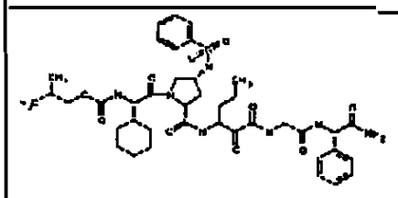
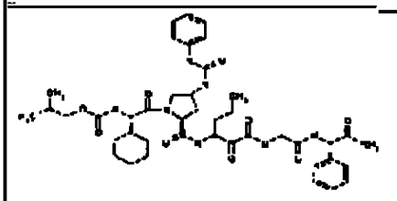
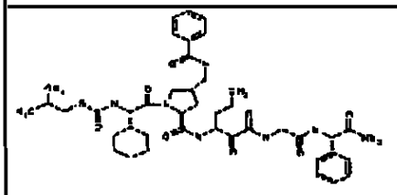
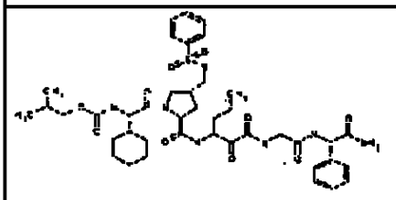
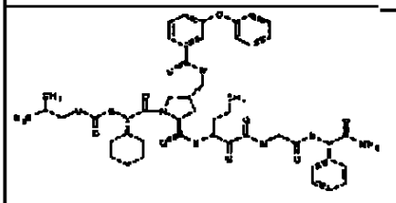
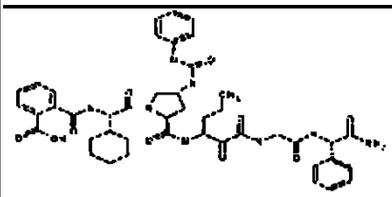
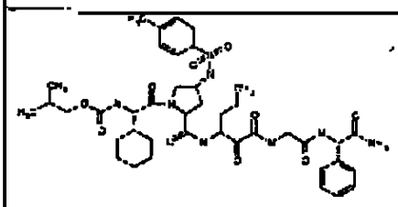
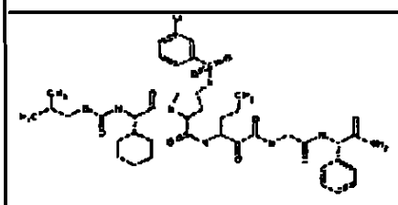
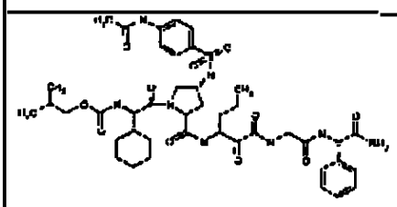
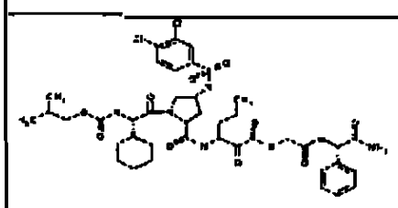
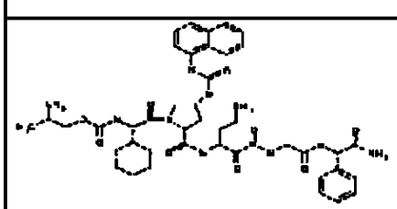
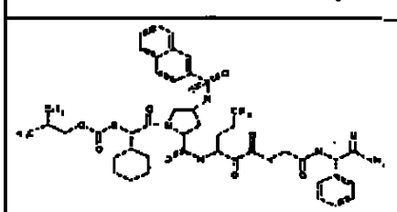
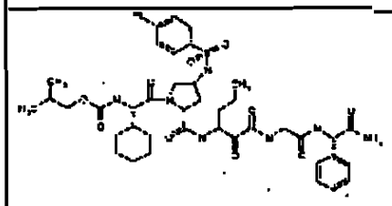
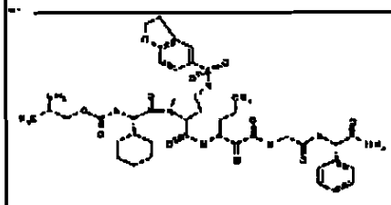
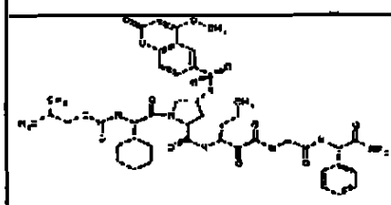
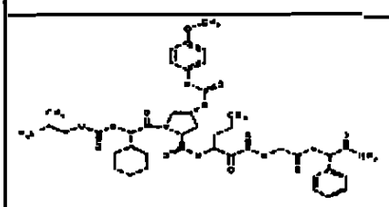
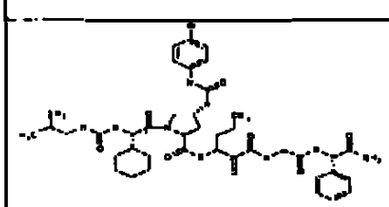
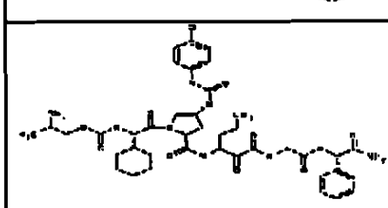
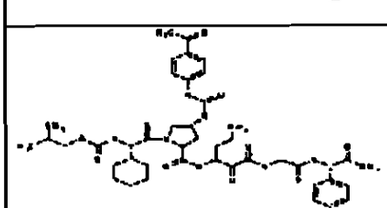
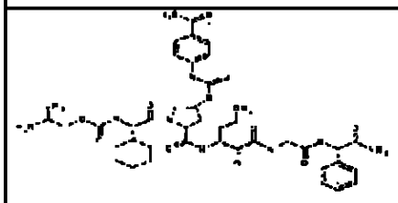
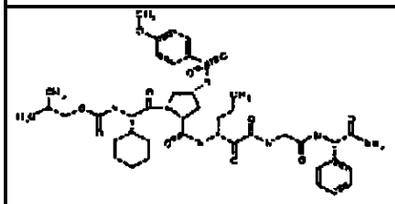
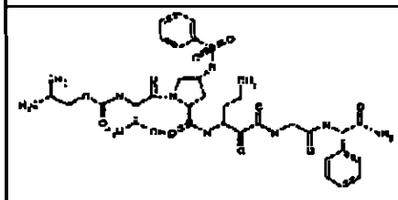
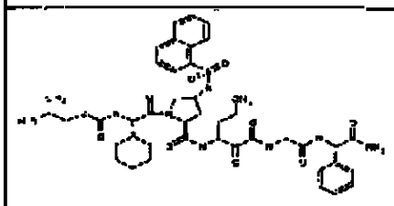
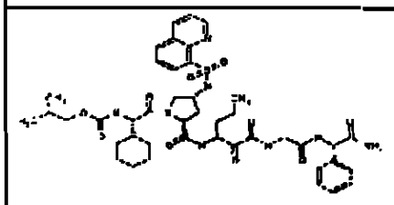
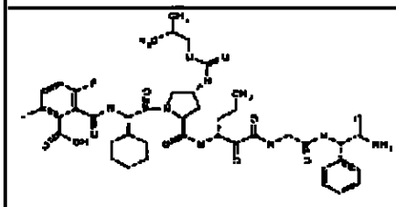
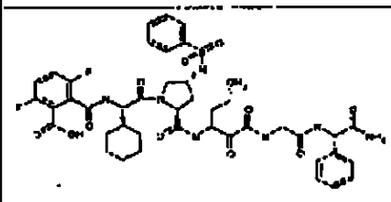
ESTRUCTURA	NOMBRE	Rango de Ki*
	iBoc-G(Chx)-P(4t-NHiBoc)-nV-(CO)-G-G(Ph)-Am	A
	(2-CO2)PhCO-G(Chx)-P(4t-MeNHCOPh(3-OPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-NHSO2Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-UreaPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHCOPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHSO2Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHCOPh(3-OPh))-nV-(CO)-G-G(Ph)-Am	B

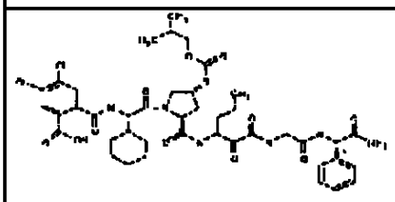
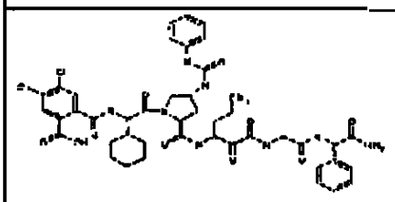
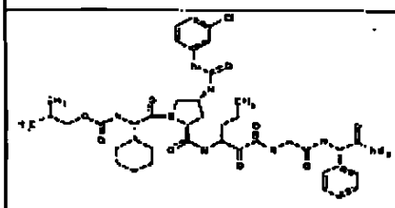
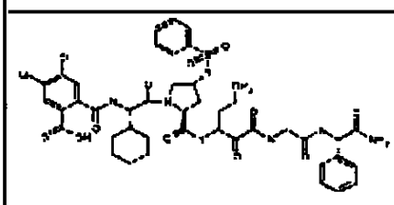
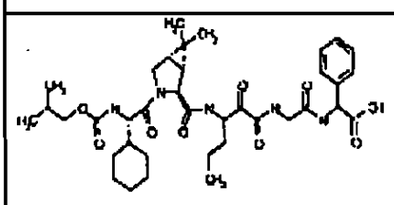
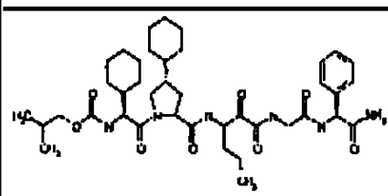
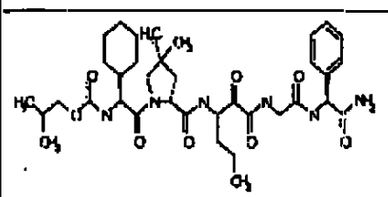
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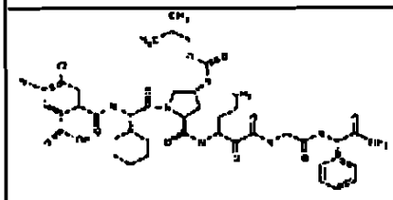
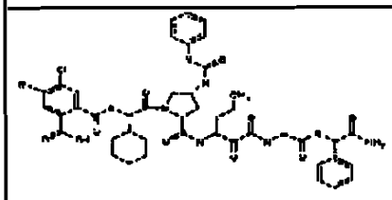
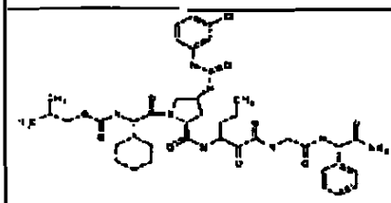
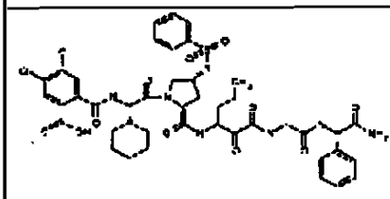
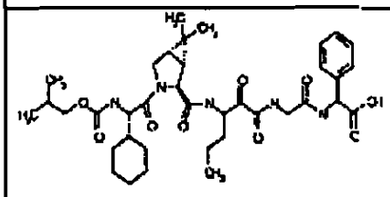
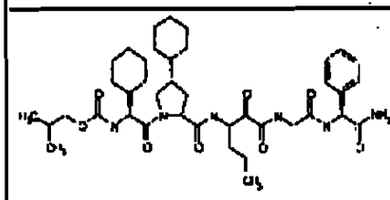
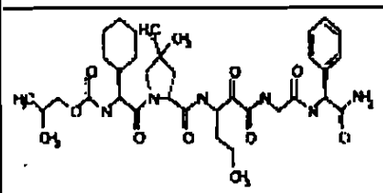
ESTRUCTURA	NOMBRE	Rango de Ki*
	(2-CO2)PhCO-G(chx)-P(4t-UreaPh)-nV-(CO)-G-G(ph)-Am	C
	iBoc-G(Chx)-P(4t-NHSO2-(4Me)Ph)-nV(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-(3Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-(4-NHAc)Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-NHSO2-(3,4-diCl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-1-Np)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-2-Np)-nV-(CO)-G-G(Ph)-Am	B

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4003

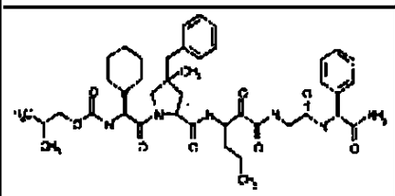
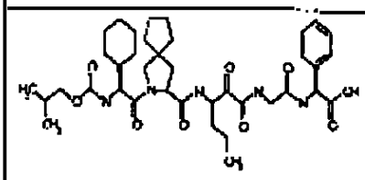
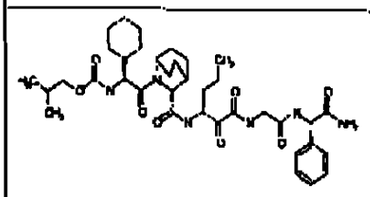
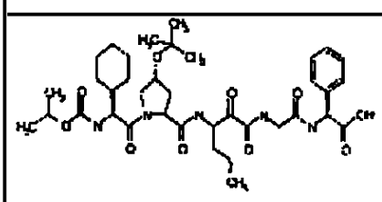
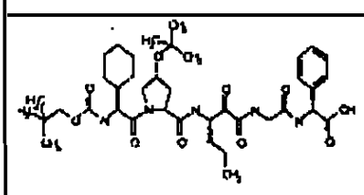
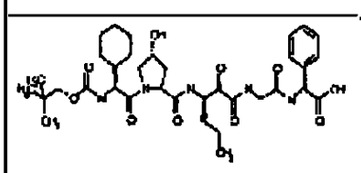
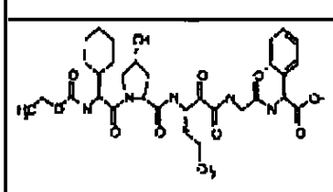
ESTRUCTURA	NOMBRE	Rango de Ki*
	iBoc-G(Chx)-P(4t-NHSO2-(4Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-5(2,3-dihidrobenzofuran))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-6(4-OMe)Cumarin)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-Ph(4-OMe))-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Cl))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Cl))-nV-(CO)-G-G(Ph)-Am	C
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Ac))-nV-(CO)-G-G(Ph)-Am	B

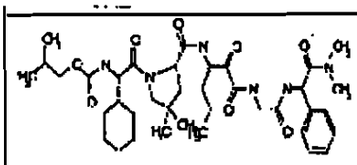
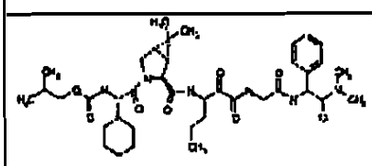
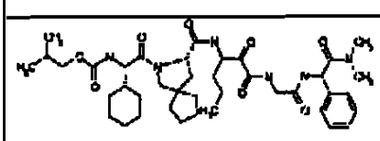
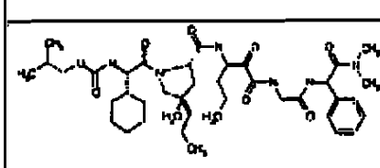
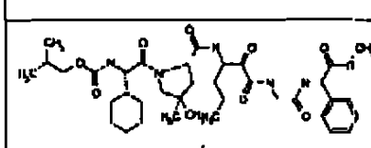
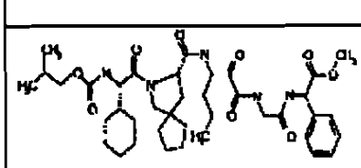
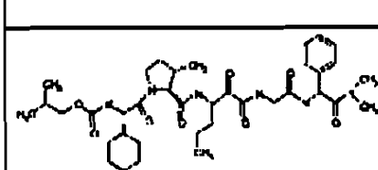
ESTRUCTURA	NOMBRE	Rango de Ki*
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Ac))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-Ph(4-OMe))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-V-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-1Np)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-8-quinolin)-nV-(CO)-G-G(Ph)-Am	B
	(2,5-diF-6-CO2)PhCO-G(Chx)-P(4t-NH-iBoc)-nV-(CO)-G-G(Ph)-Am	A
	(2,5-diF-6-CO2)PhCO-G(Chx)-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	A

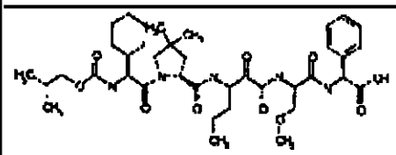
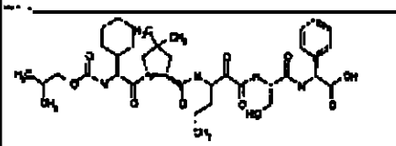
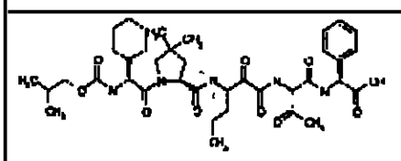
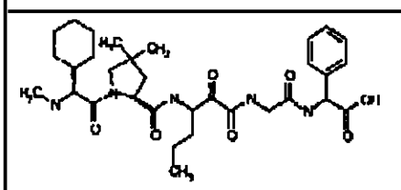
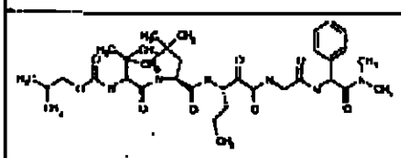
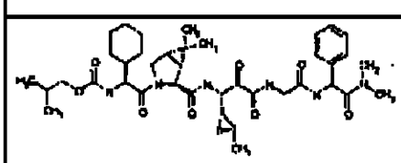
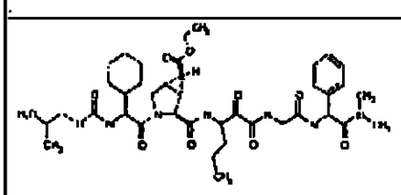
ESTRUCTURA	NOMBRE	Rango de Ki*
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-NH-iBoc)-nV-(CO)-G-G(Ph)-Am	A
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-UreaPh)-nV(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-Urea-(3-Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(3,4 iPr)-nV-(CO)-G-G(Ph)-OH	A
	iBoc-G(Chx)-P(4t-Chx)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4-diMe)-nV-(CO)-G-G(Ph)-Am	A

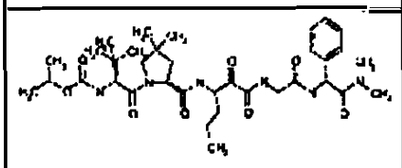
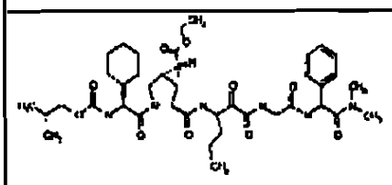
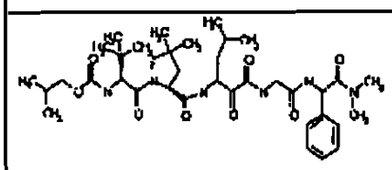
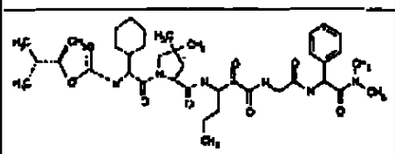
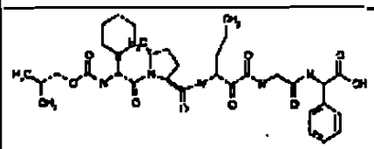
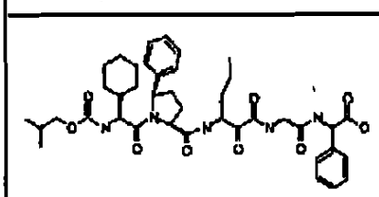
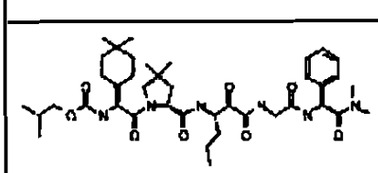
ESTRUCTURA	NOMBRE	Rango de Ki*
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-NH-iBoc)-nV-(CO)-G-G(Ph)-Am	A
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-UreaPh)-nV(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-Urea-(3-Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(3,4 iPr)-nV-(CO)-G-G(Ph)-OH	A
	iBoc-G(Chx)-P(4t-Chx)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4-diMe)-nV-(CO)-G-G(Ph)-Am	A

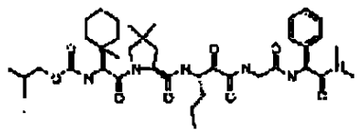
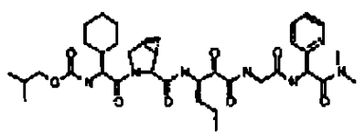
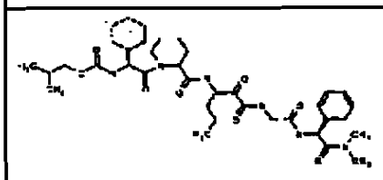
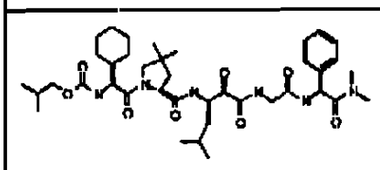
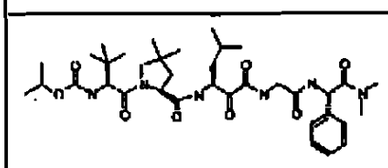
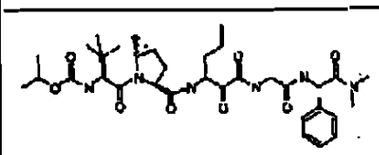
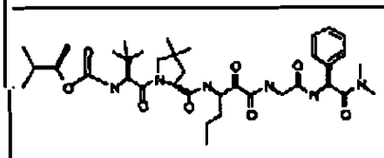
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ESTRUCTURA	NOMBRE	Rango de Ki*
	iBoc-G(Chx)-P(4-Bn,4-Me)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4-espirociclopentan)-nV-(CO)-G-G(Ph)-OH	A
	iBoc-G(Chx)-2-azabiciclo[2.2.2]octan -3-CO-nV-(CO)-G-G(Ph)-Am	B
	iPrOCO-G(Chx)-P(4-OtBu)-nV-(CO)-G-G(Ph)-OH	A
	Neopentoxi(CO)-G(Chx)-P(4-OtBu)-nV- (CO)-G-G(Ph)-OH	B
	Neopentoxi (CO)-G(Chx)-P(OH)-nV-(CO)-G- G(Ph)-OH	B
	Etoxi (CO)-G(Chx)-P(OH)-nV-(CO)-G- G(Ph)-OH	B

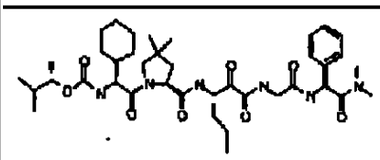
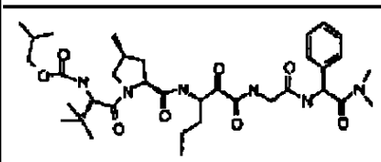
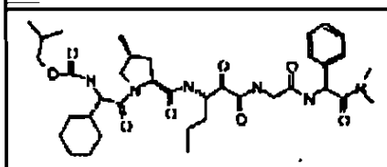
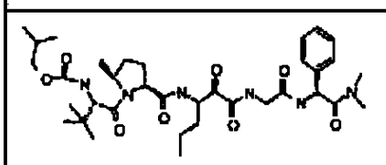
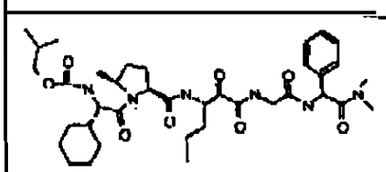
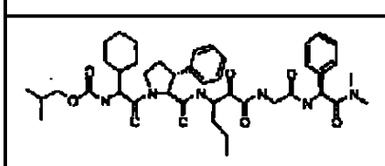
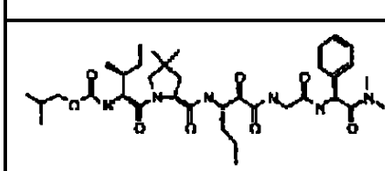
ESTRUCTURA	NOMBRE	Rango de Ki*
	iBoc-G(Chx)-P(4,4 diMe)-nV-(CO)- G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4 iPr)-nV-(CO)- G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4-espirociclopentan)- nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4c-Me,4t-Pr)- nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4,4 diMe)-nV-(CO)- G-G(Ph)-OMe	A
	iBoc-G(Chx)-P(4-espirociclopentan)- nV-(CO)-G-G(Ph)-OMe	A
	iBoc-G(Chx)-P(3t-Me)-nV-(CO)- G-G(Ph)-N(Me)2	A

ESTRUCTURA	NOMBRE	Rango de Ki*
	iBoc-G(Chx)-P(4,4 diMe)-nV-(CO)-S(Me)-G(Ph)-OH	A
	iBoc-G(Chx)-P(4,4 diMe)-nV-(CO)-S-G(Ph)-OH	B
	iBoc-G(Chx)-P(4,4 diMe)-nV-(CO)-G(Ac)-G(Ph)-OH	C
	N-Me-G(Chx)-P(4,4-diMe)-nV-(CO)-G- G(Ph)-CO2H	C
	iBoc-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4 (diMe-ciclopropil))-G((S,S)-Me-ciclopropil)-(CO)-G-G(Ph)-N(Me)	A
	iBoc-G(Chx)-P(6S-CEM)-nV-(CO)-G-G(Ph)-N(Me)2	A

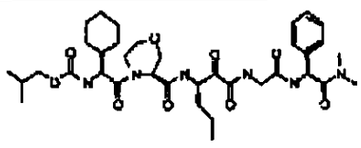
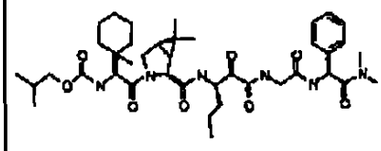
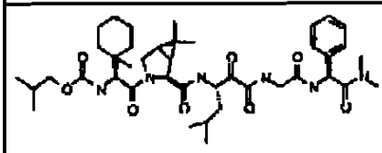
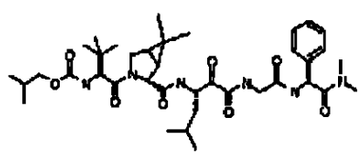
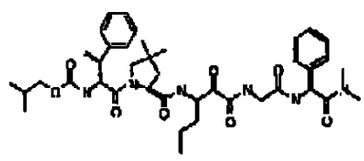
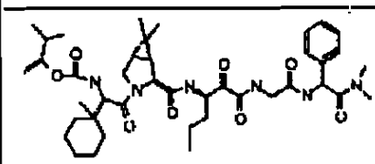
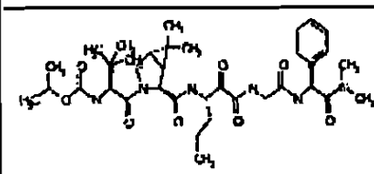
ESTRUCTURA	NOMBRE	Rango de Ki*
	iPoc-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(6R-CEM)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(4,4-diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me-iBoc)-G(Chx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(5-c/t-Me)-nV-(CO)-G-G(Ph)-CO2H	A
	iBoc-G(Chx)-P(5-cis-Ph)-nV-(CO)-G-G(Ph)-CO2H	B
	iBoc-G(4,4-diMeChx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

ESTRUCTURA	NOMBRE	Rango de Ki*
	iBoc-G(1-MeChx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4 CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-Chg-Pip-nV-(CO)-G-G(Ph)-N(Me)2	C
	iBoc-G(Chx)-P(4,4 diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(4,4-diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(5-c/t-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me-iBoc)-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

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ESTRUCTURA	NOMBRE	Rango de Ki*
	(S)-1-MeiBoc-G(Chx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(4-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(5-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(5-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(t-3Ph)-nV-(CO)-G-G(Ph)-N(Me)2	B
	iBoc-allo(Ile)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

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1.03

ESTRUCTURA	NOMBRE	Rango de Ki*
	iBoc-G(Chx)-Pip(4-morfolino)-nV-(CO)-G-G(Ph)-N(Me)2	B
	iBoc-G(1-MeChx)-P[3,4-(diMe-ciclopropil)]-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(1-MeChx)-P[3,4-(diMe-ciclopropil-)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P[3,4-(diMe-ciclopropil)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-erythro-D,L-F(beta-Me)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(1-MeChx)-P[3,4-(diMe-ciclopropil)]-nV-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P[3,4-(diMe-ciclopropil)]-nV-(CO)-G-G(Ph)-N(Me)2	A

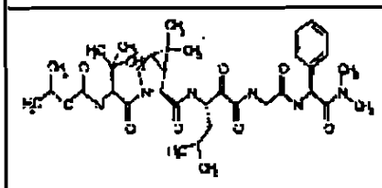
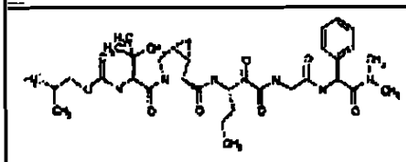
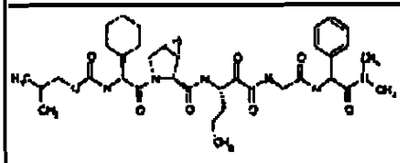
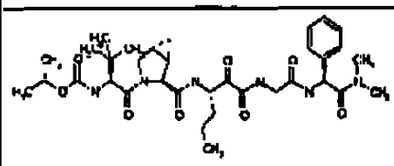
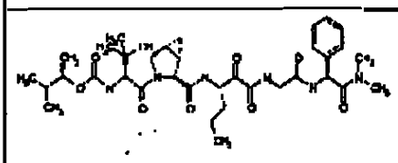
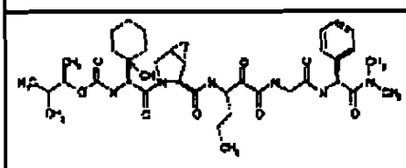
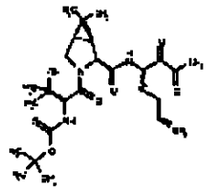
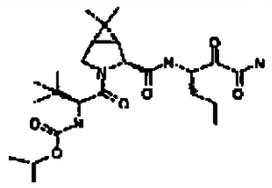
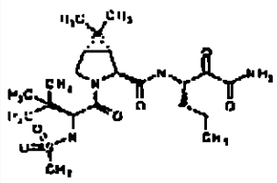
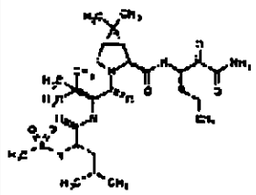
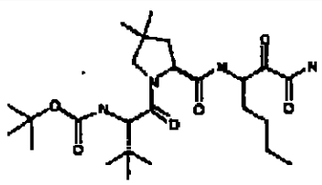
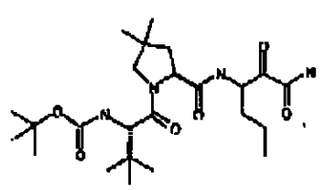
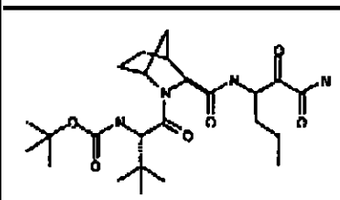
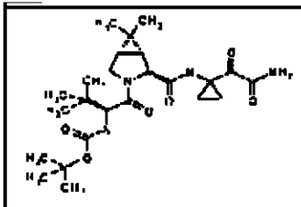
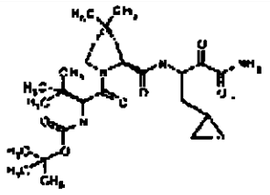
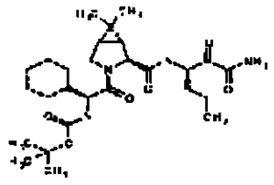
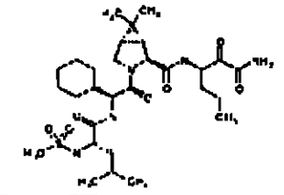
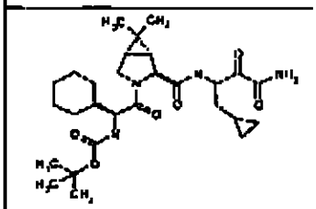
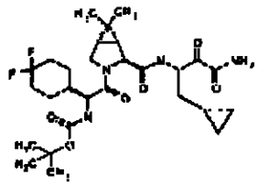
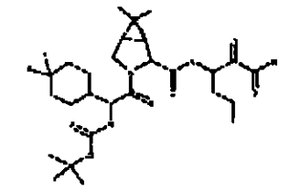
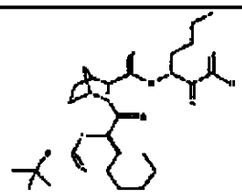
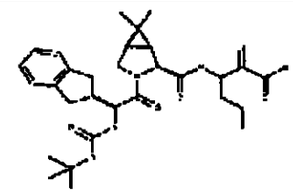
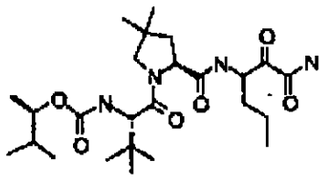
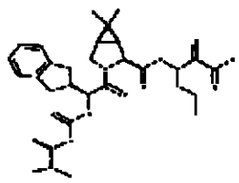
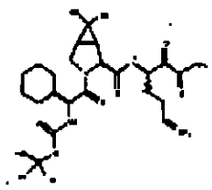
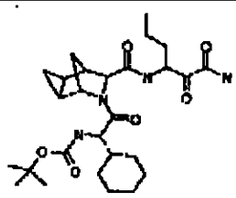
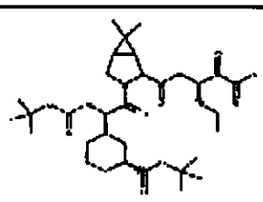
ESTRUCTURA	NOMBRE	Rango de Ki*
	iPoc-G(tBu)-P[3,4-(diMe-ciclopropil)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4 CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(1-MeChx)-P(3,4 CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A

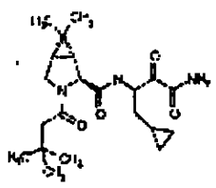
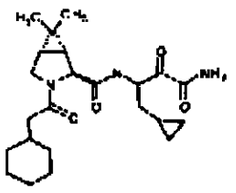
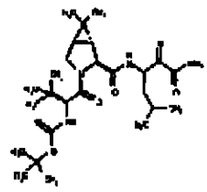
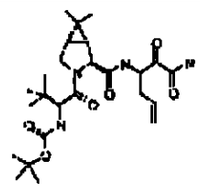
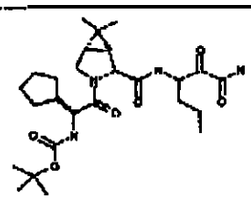
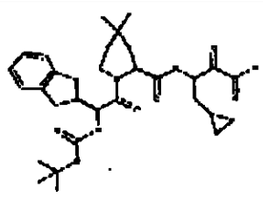
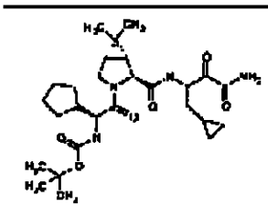
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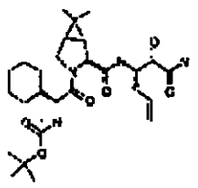
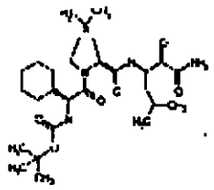
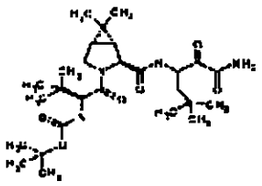
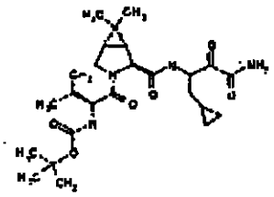
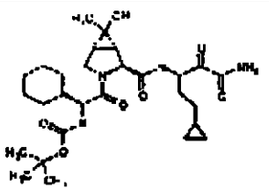
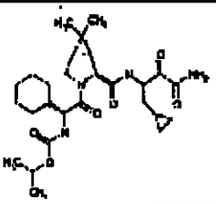
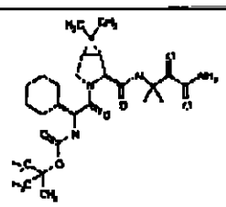
ESTRUCTURA	PM	Rango Ki*
	507	B
	481	B
	473	C
	586	B
	497	C
	483	C
	481	C

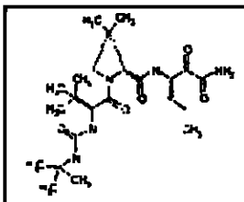
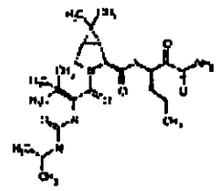
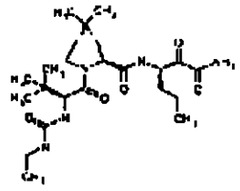
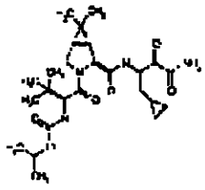
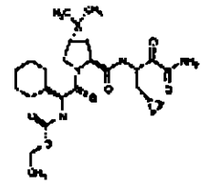
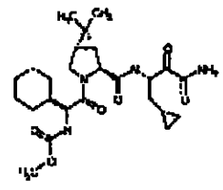
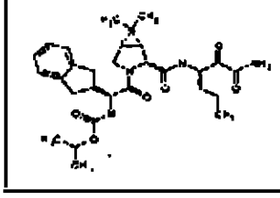
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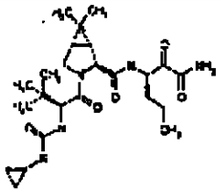
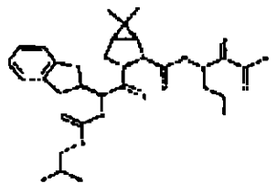
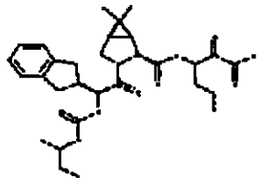
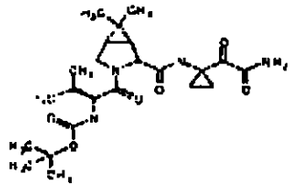
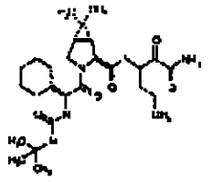
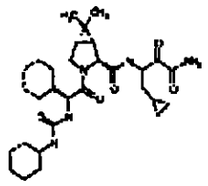
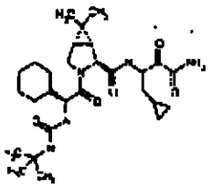
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1057

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	621	B

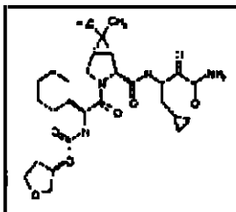
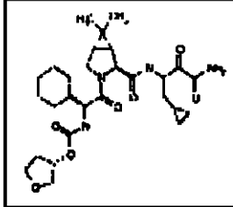
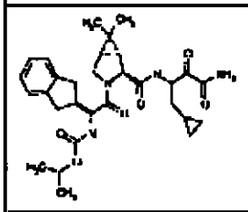
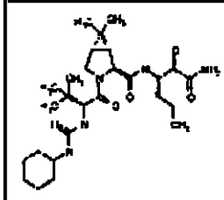
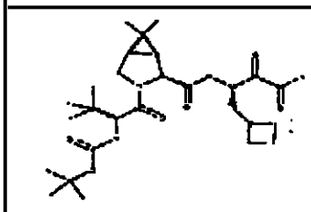
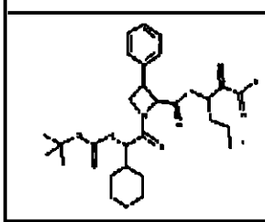
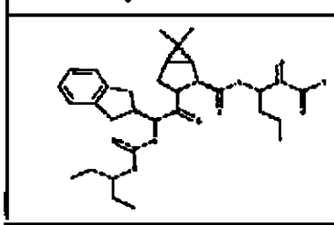
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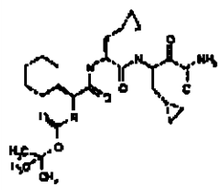
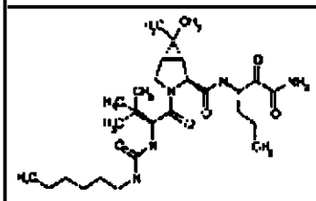
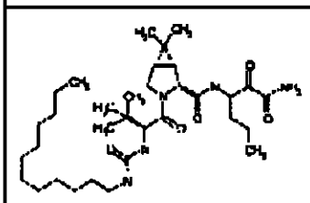
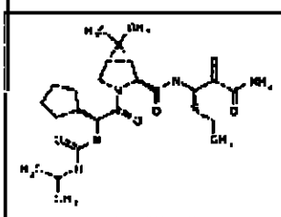
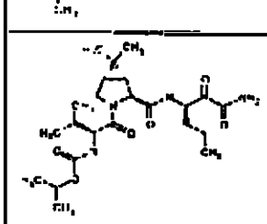
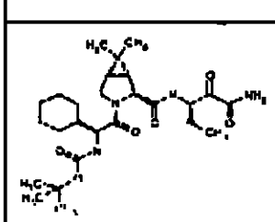
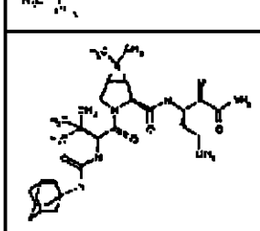
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	505	C

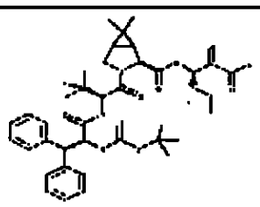
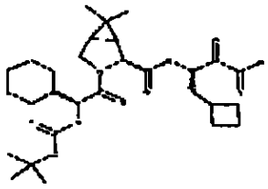
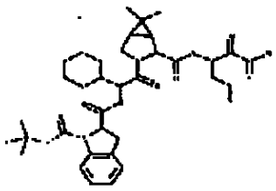
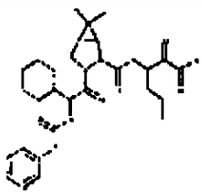
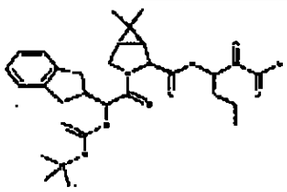
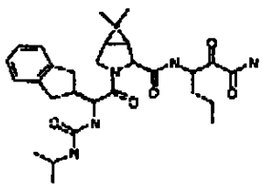
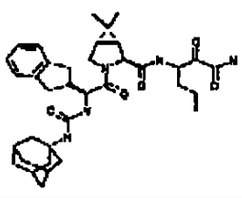
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	541	B

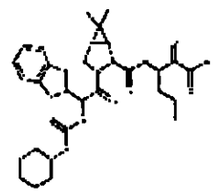
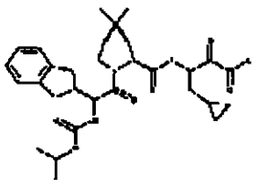
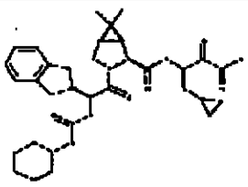
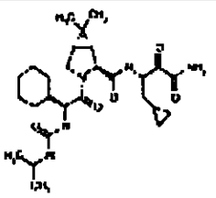
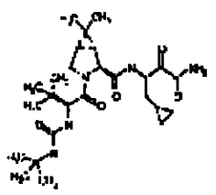
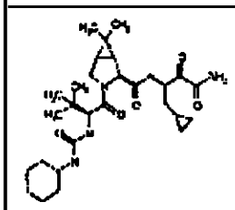
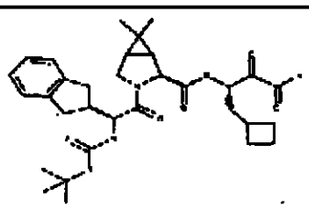
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	554	B
	465	C
	520	A
	558	A
	532	A

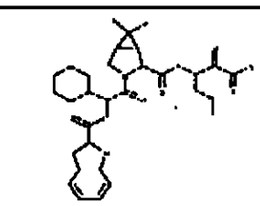
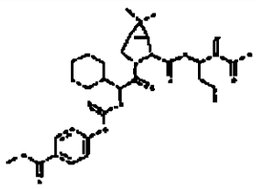
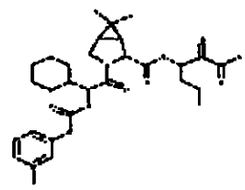
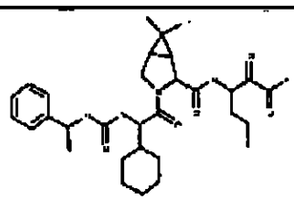
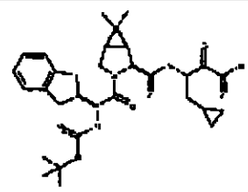
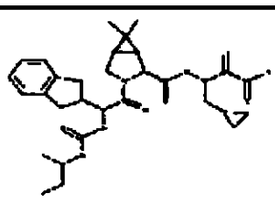
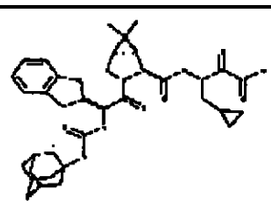
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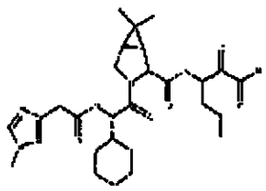
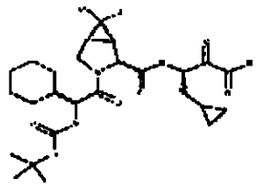
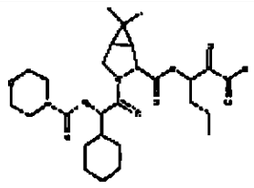
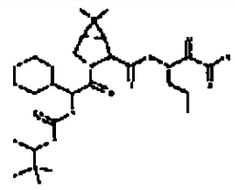
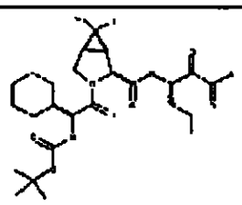
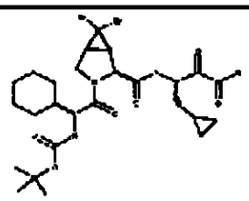
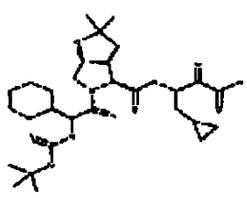
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	553	A
	520	B
	521	A
	543	C
	569	B

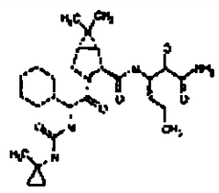
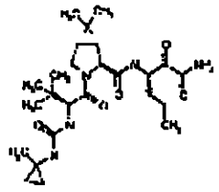
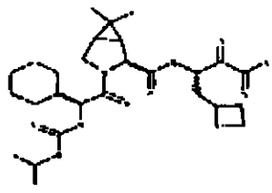
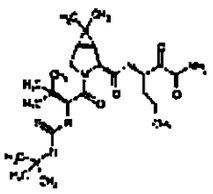
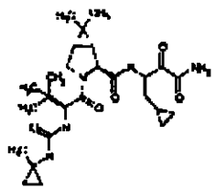
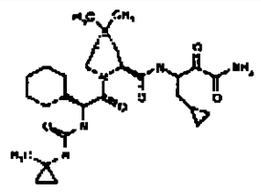
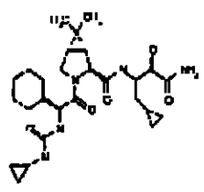
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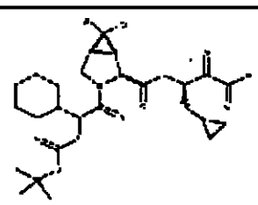
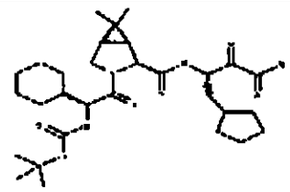
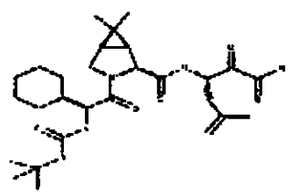
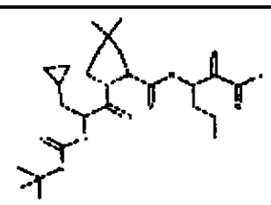
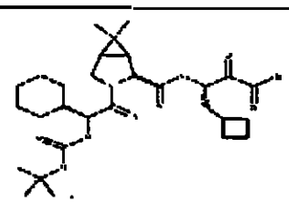
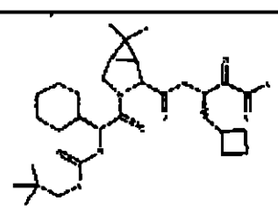
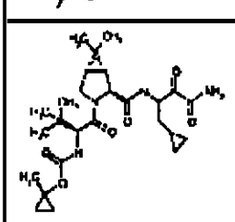
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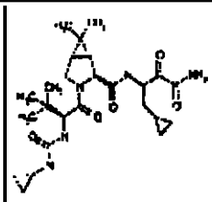
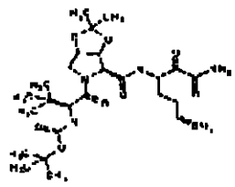
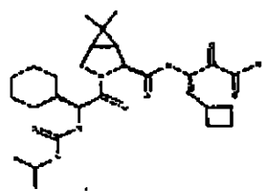
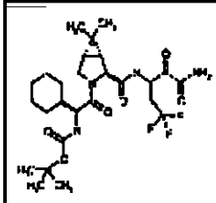
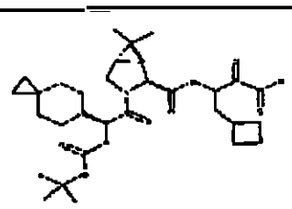
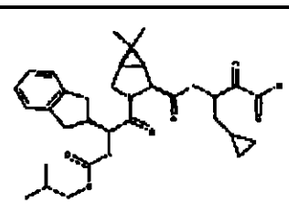
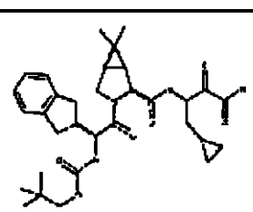
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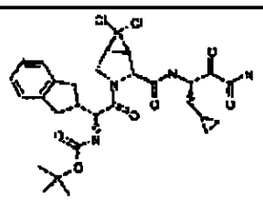
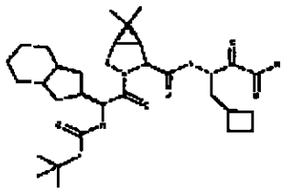
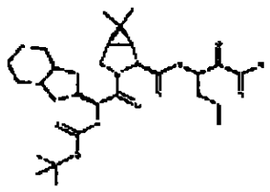
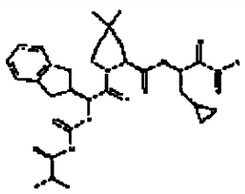
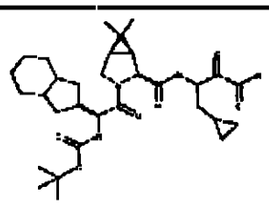
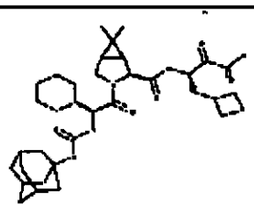
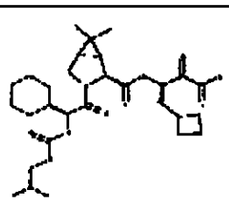
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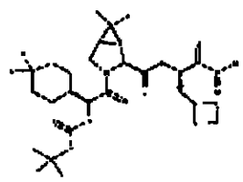
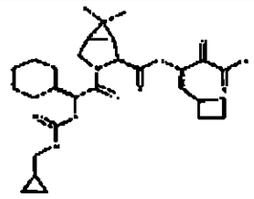
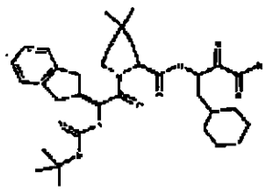
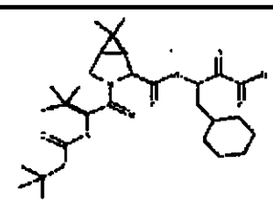
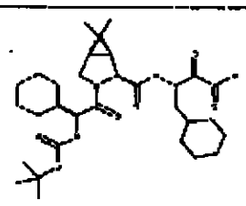
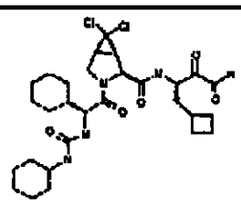
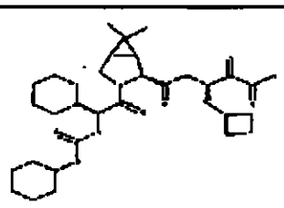
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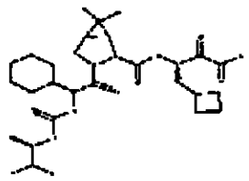
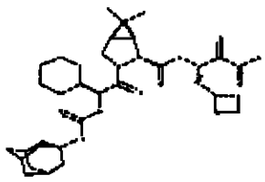
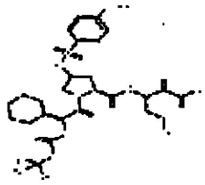
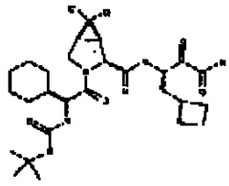
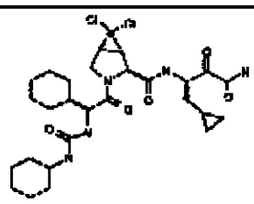
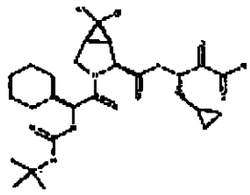
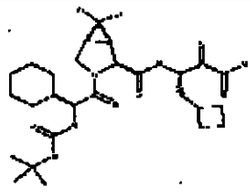
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	516	B

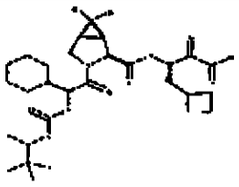
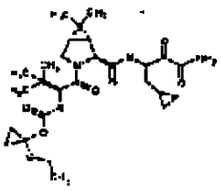
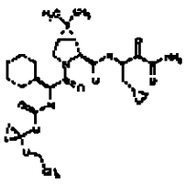
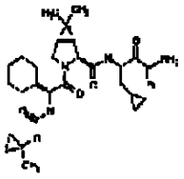
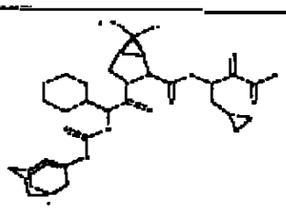
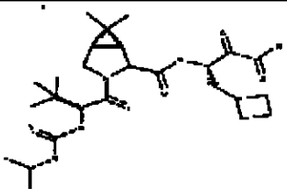
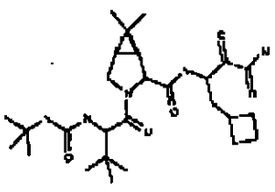
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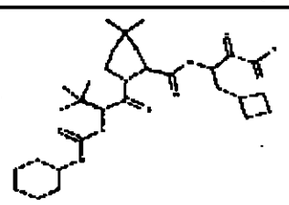
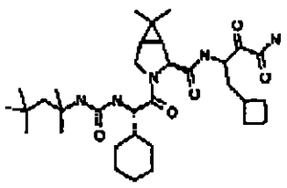
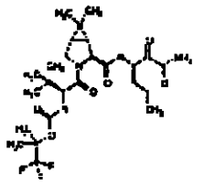
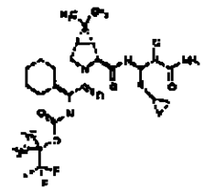
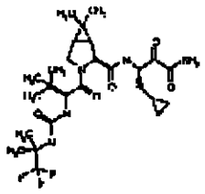
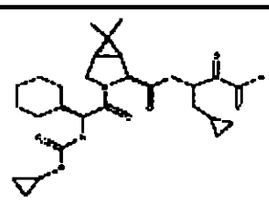
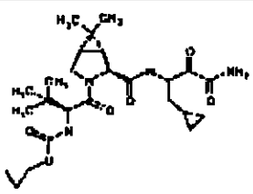
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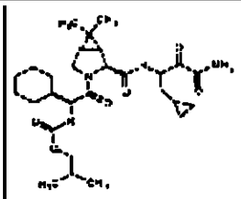
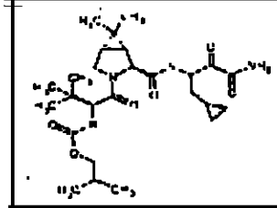
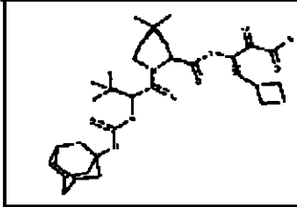
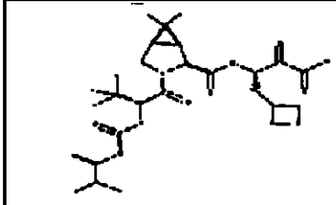
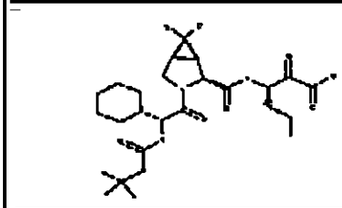
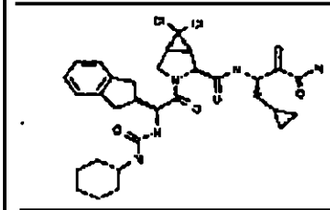
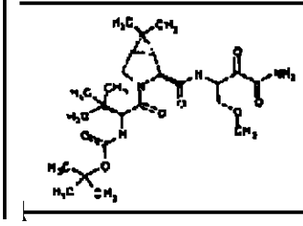
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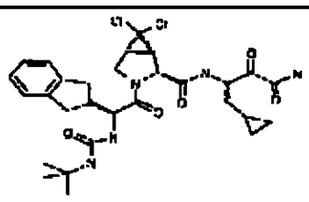
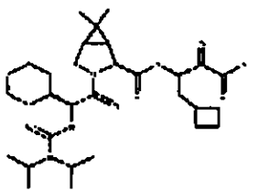
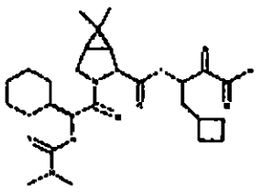
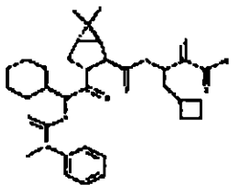
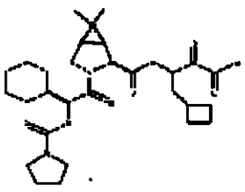
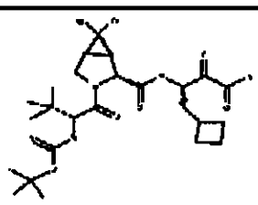
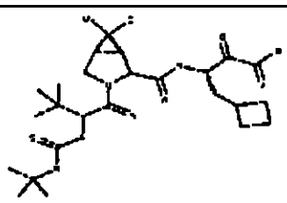
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	575	C
	613	A
	573	A

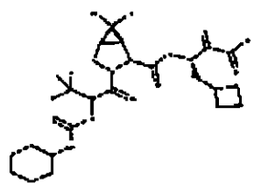
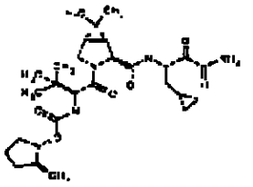
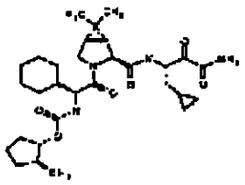
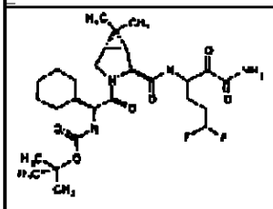
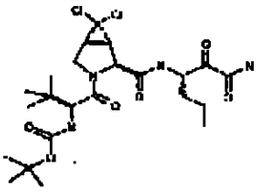
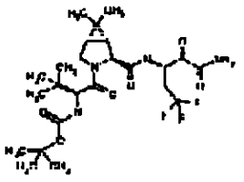
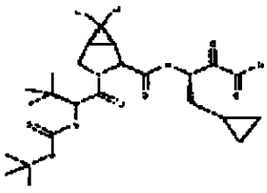
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	588	A
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	673	A
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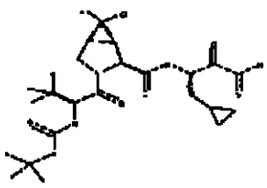
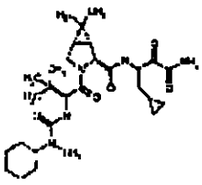
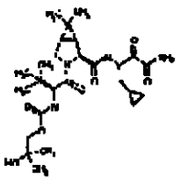
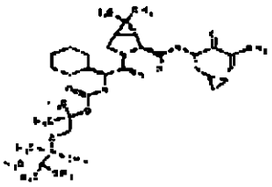
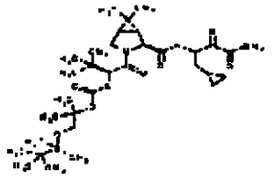
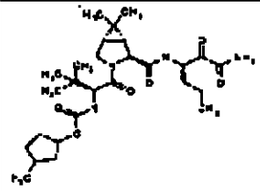
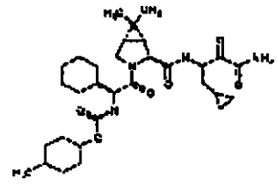
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	531	A
	551	A
	506	A
	520	A

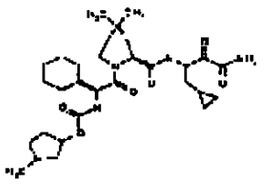
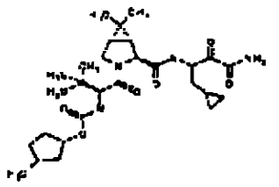
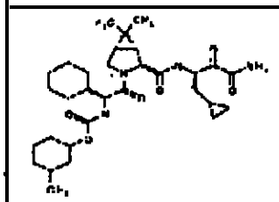
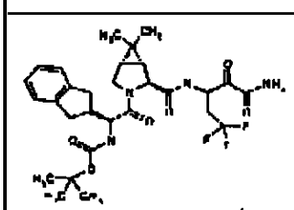
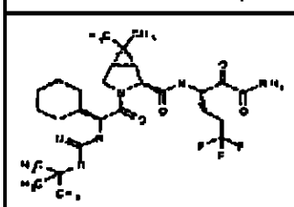
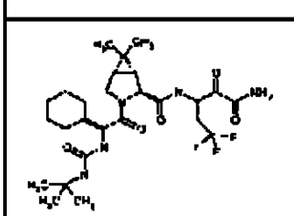
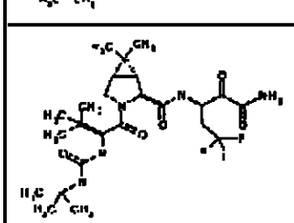
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	649	B
	587	A
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	491	B

	533	B
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	497	C

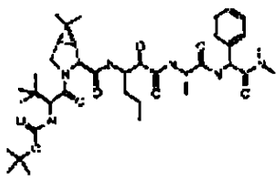
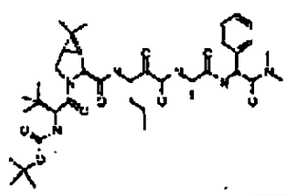
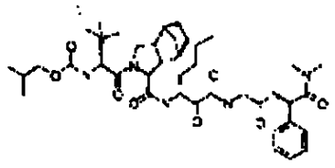
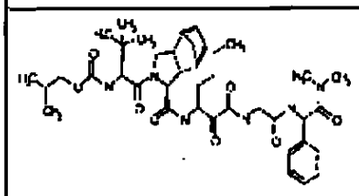
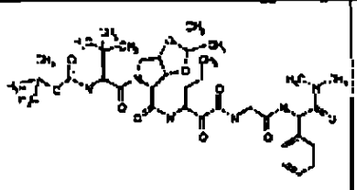
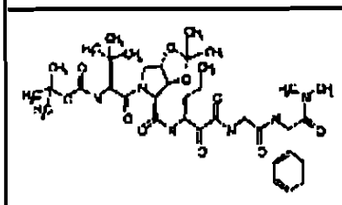
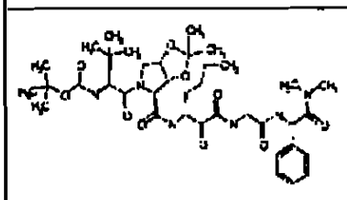
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	516	B
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	561	A

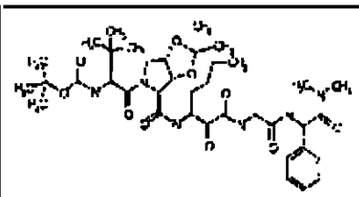
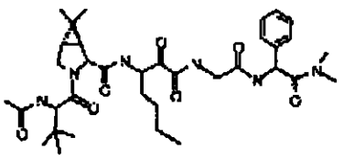
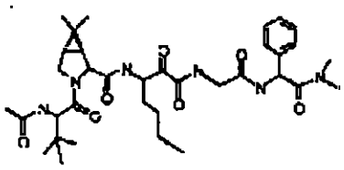
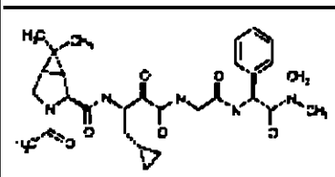
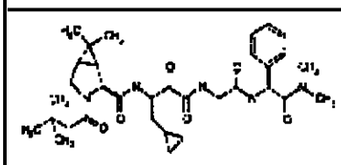
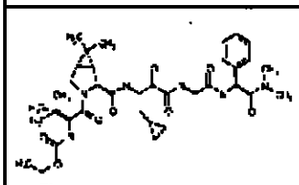
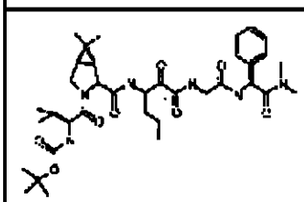
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	557	C
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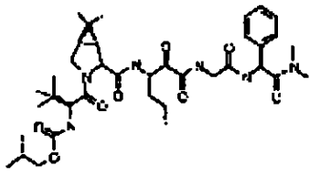
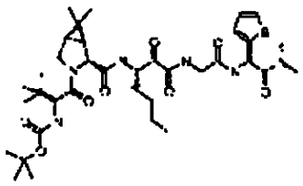
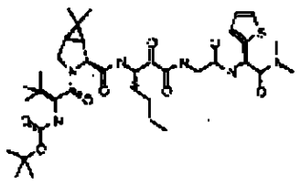
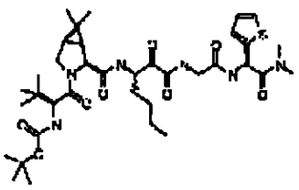
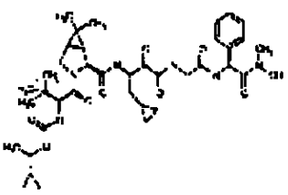
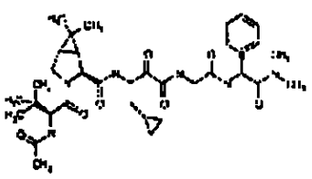
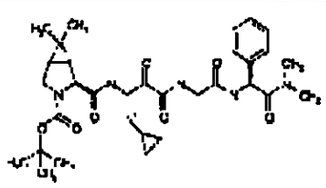
	546	A
	546	B
	523	B
	663	C
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	521	B
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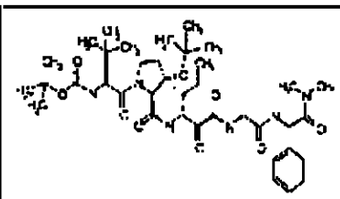
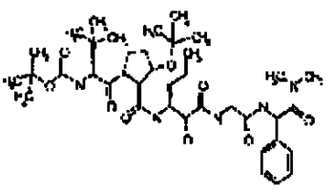
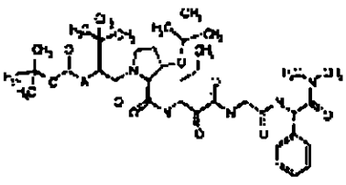
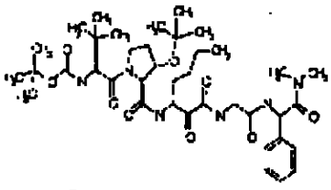
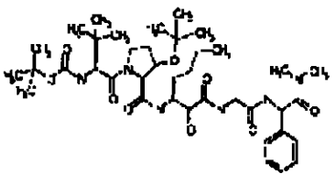
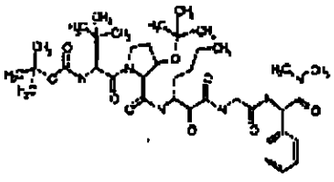
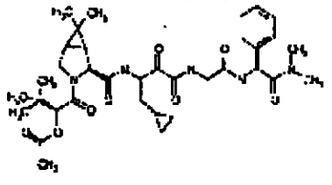
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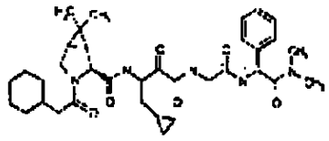
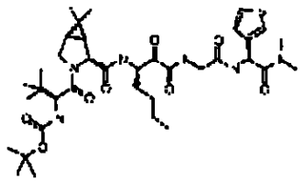
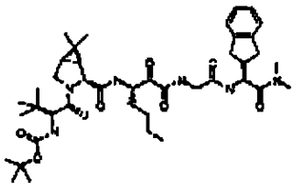
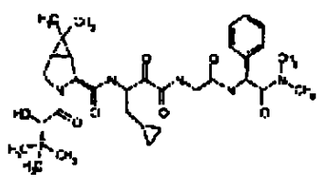
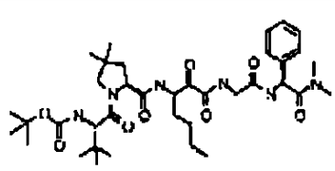
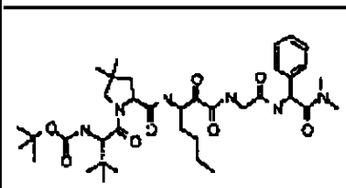
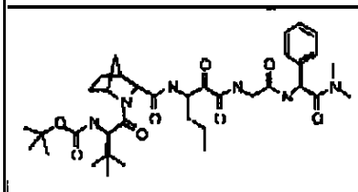
1080 1081

ESTRUCTURA	PM	Rango Ki*
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	753	C
	753	B
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	745	A
	759	C

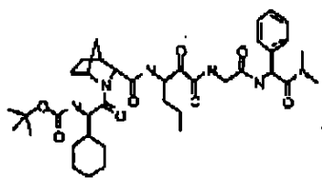
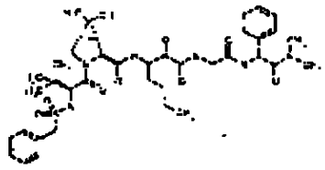
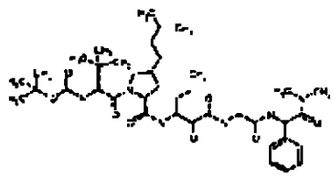
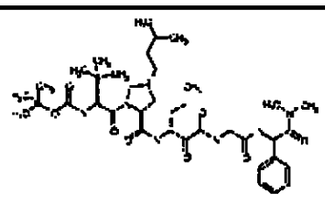
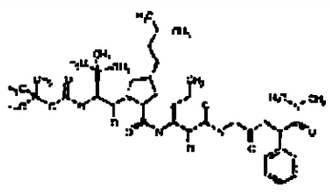
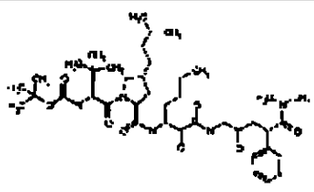
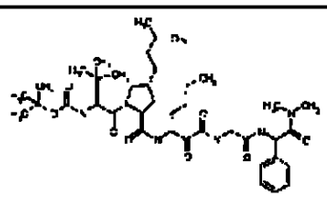
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	669	A
	554	C
	610	B
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	612	C

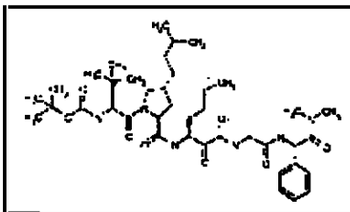
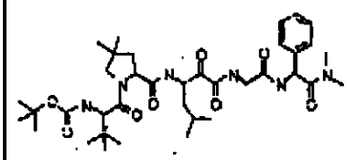
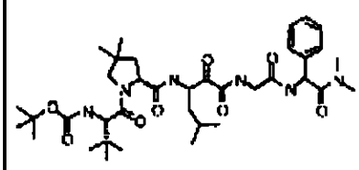
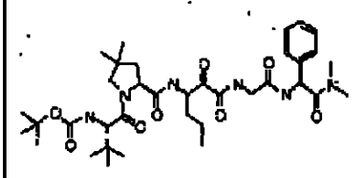
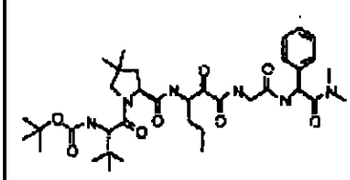
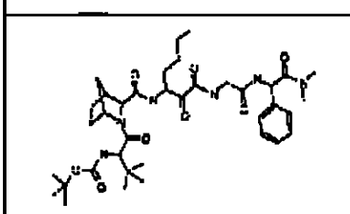
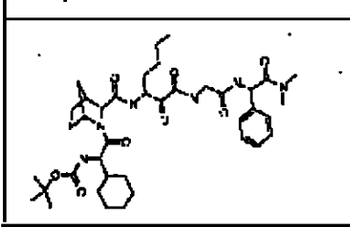
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	759	C
	759	C
	888	C

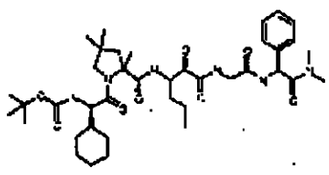
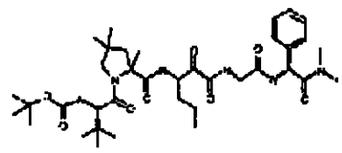
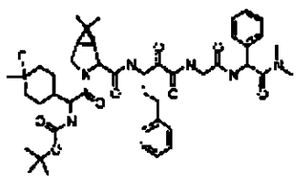
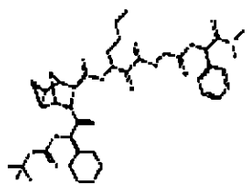
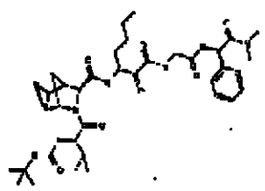
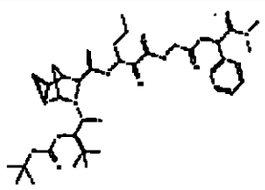
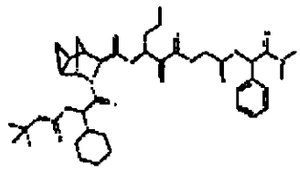
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	767	B
	626	B
	715	C
	715	A
	699	B

1085

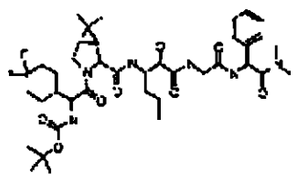
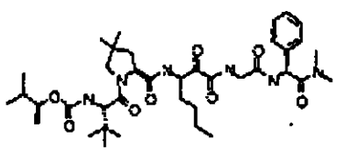
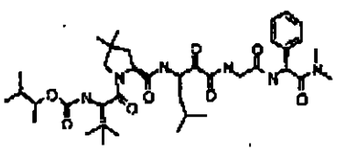
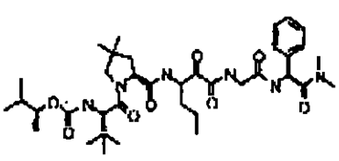
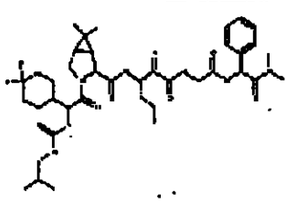
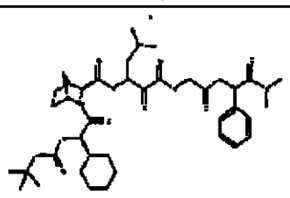
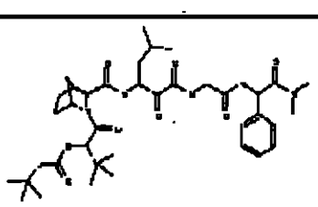
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	781	B
	743	B
	743	C
	743	A
	757	B
	757	C

1086

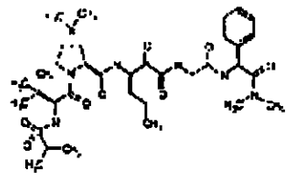
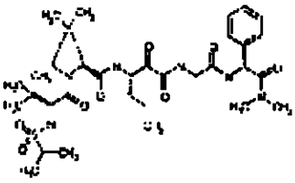
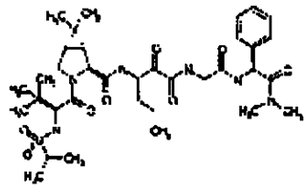
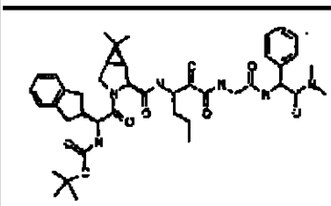
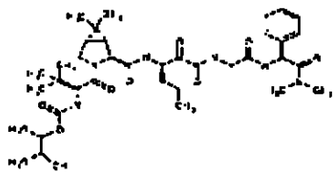
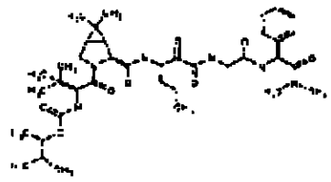
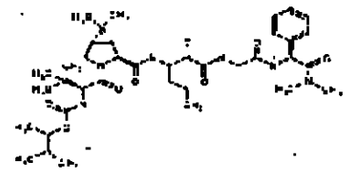
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	715	A
	715	A
	701	C
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	741	C
	715	C
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	711	C
	737	A

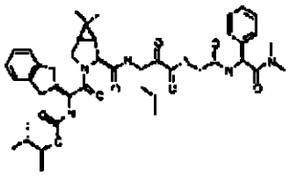
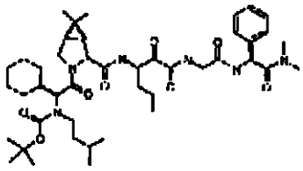
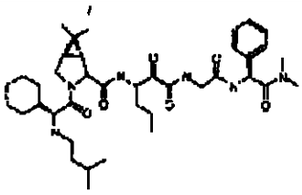
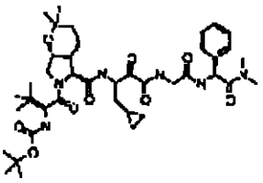
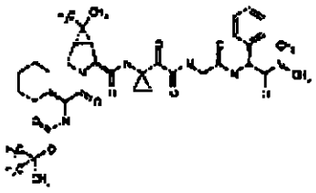
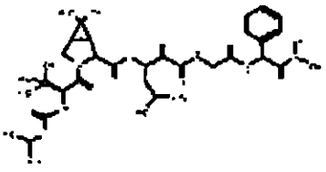
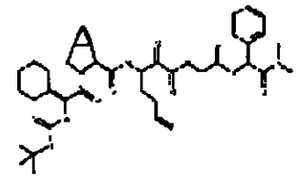
1088

	775	A
	729	A
	729	A
	715	A
	775	A
	739	A
	713	A

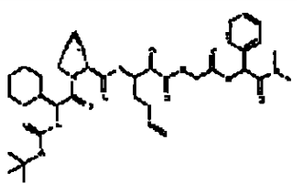
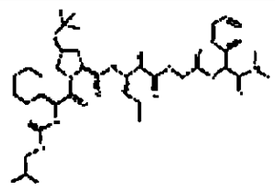
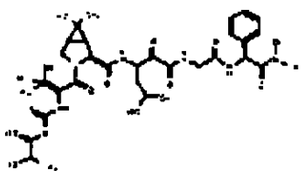
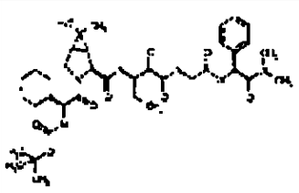
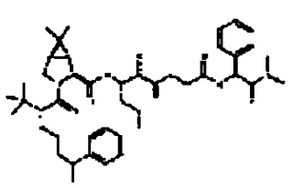
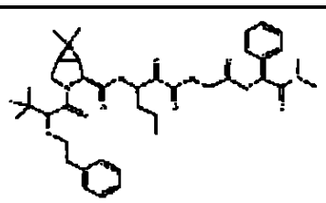
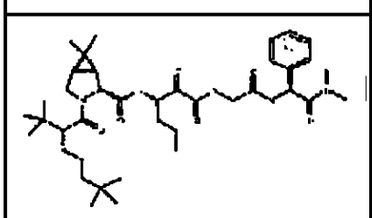
1089

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	727	A
	727	A

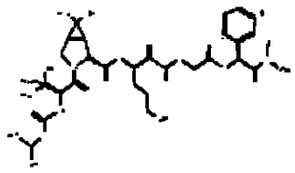
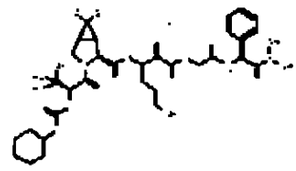
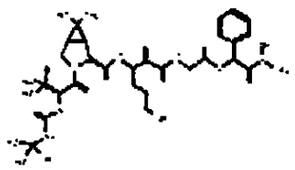
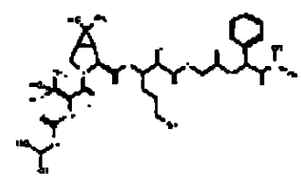
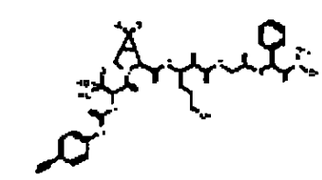
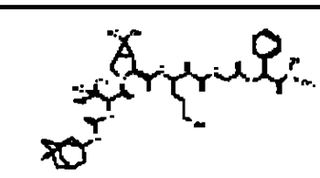
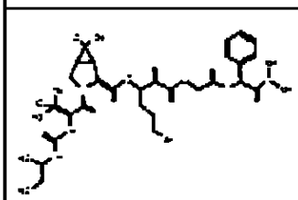
1090

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	809	C
	709	A
	769	B
	723	C
	713	A
	723	A

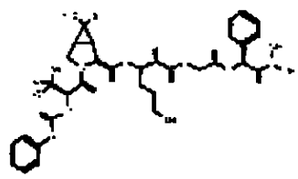
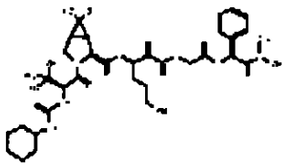
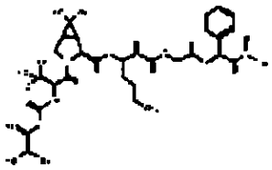
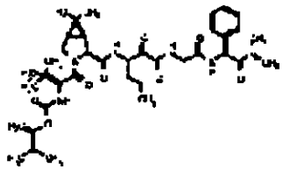
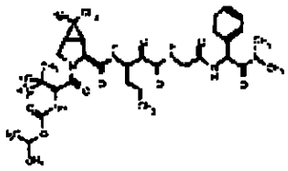
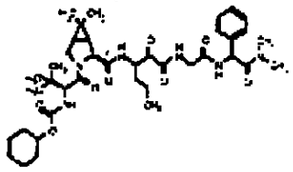
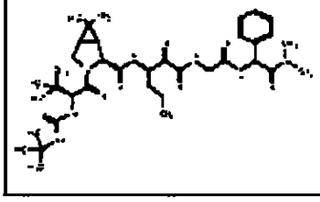
1092
1091

	723	B
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	716	A
	733	A

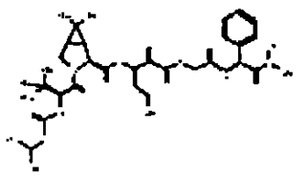
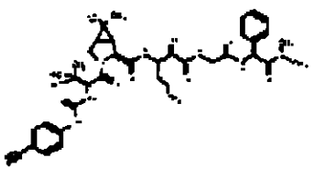
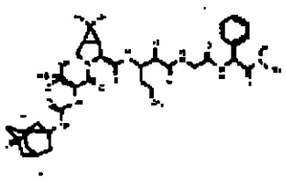
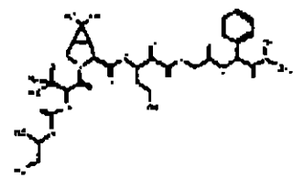
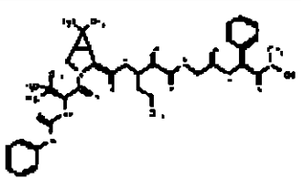
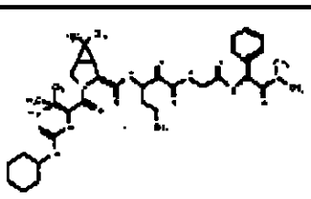
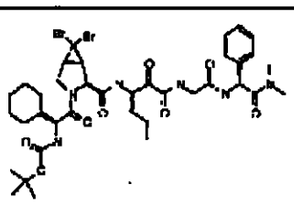
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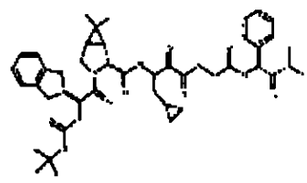
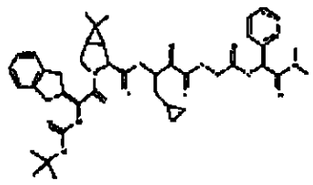
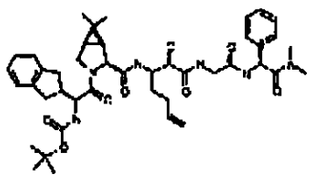
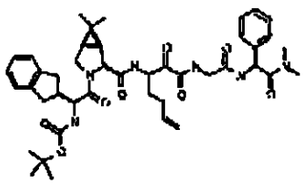
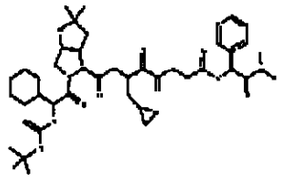
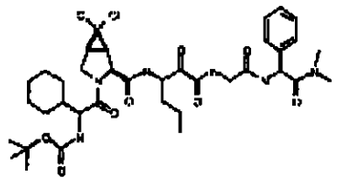
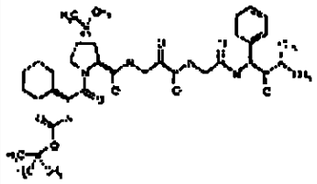
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	712	A
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	804	A
	726	A

1093

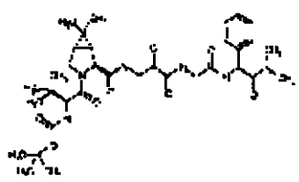
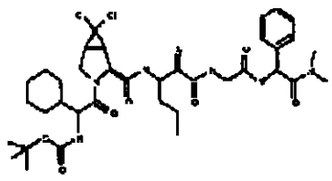
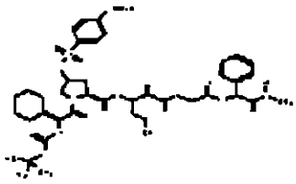
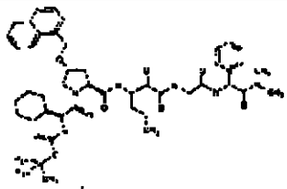
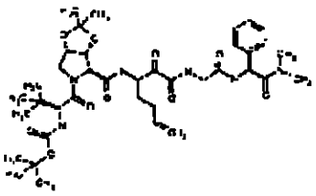
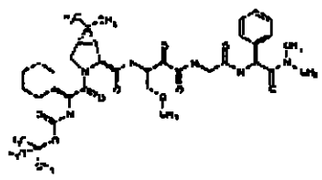
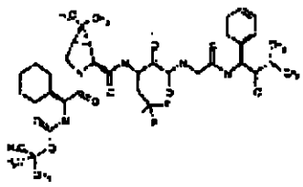
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	699	A
	739	A
	712	A

1094

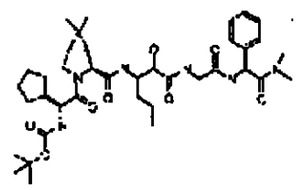
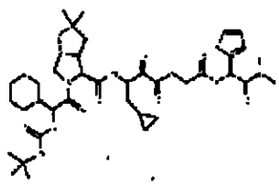
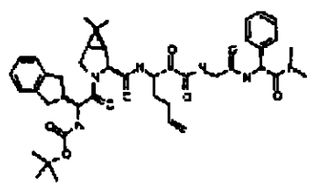
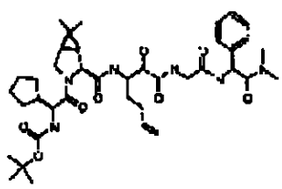
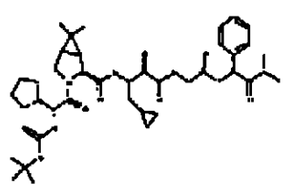
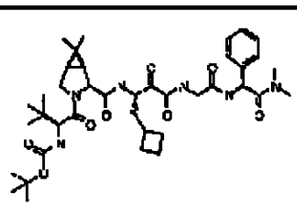
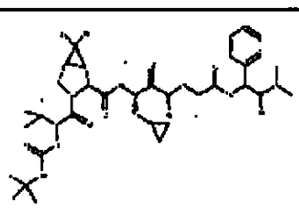
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	712	A
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	809	A

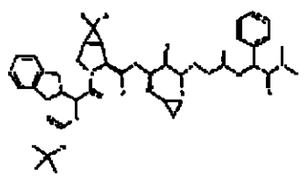
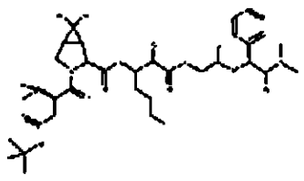
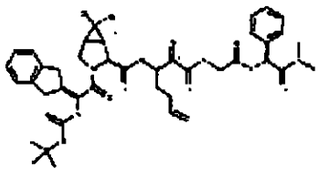
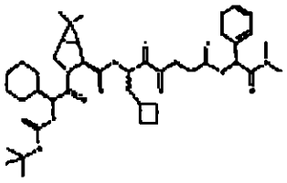
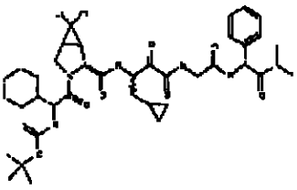
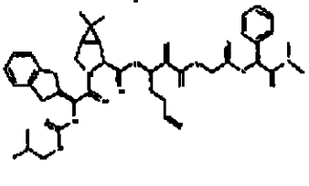
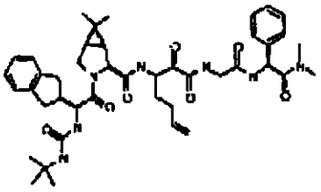
	785	A
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	785	A
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	781	A
	780	A
	607	C

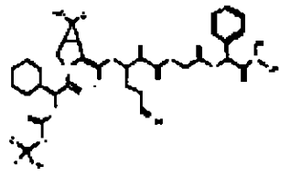
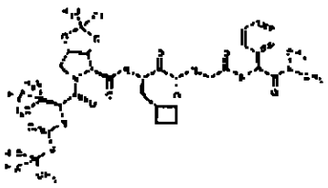
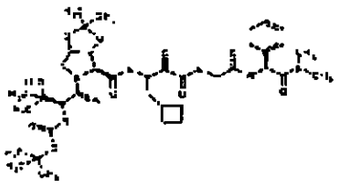
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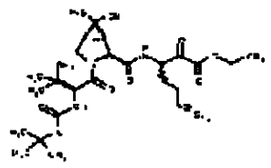
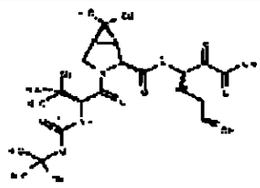
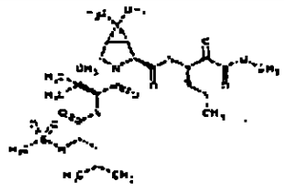
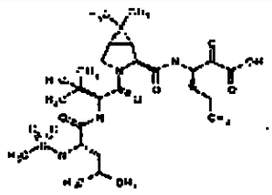
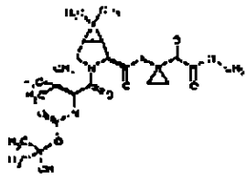
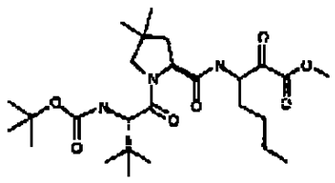
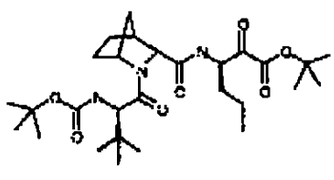
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1097

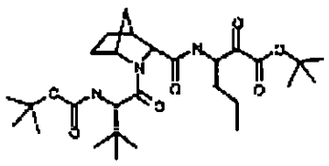
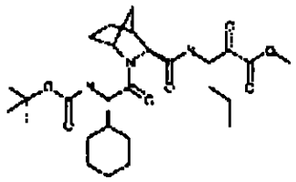
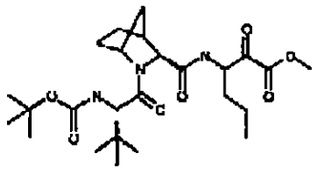
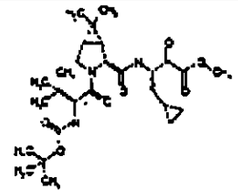
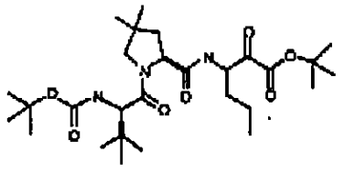
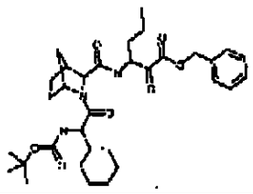
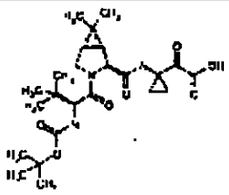
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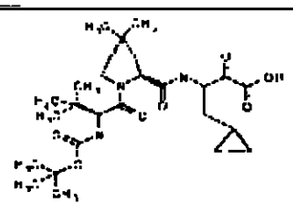
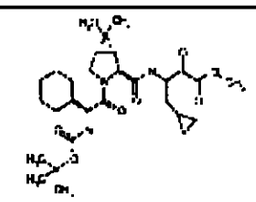
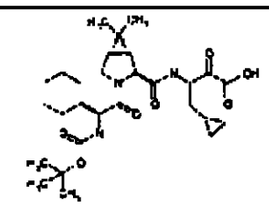
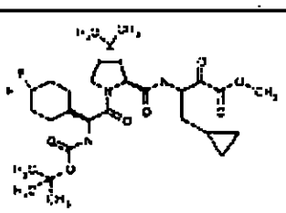
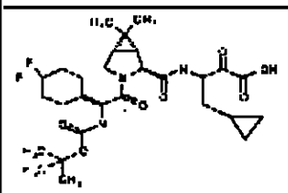
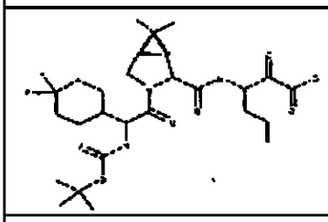
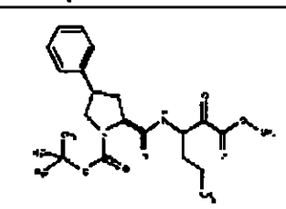
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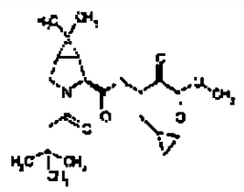
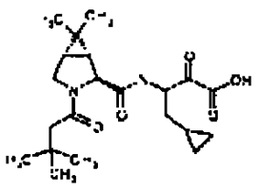
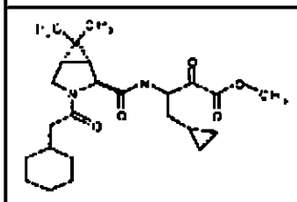
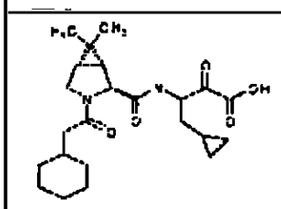
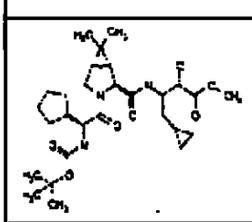
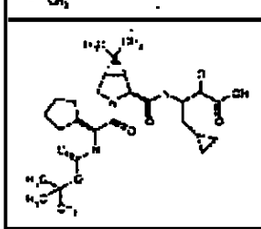
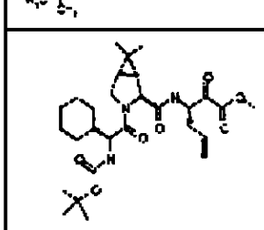
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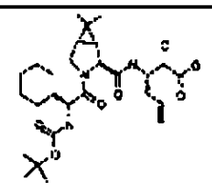
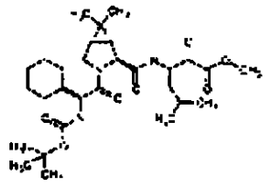
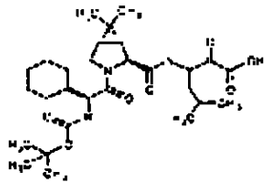
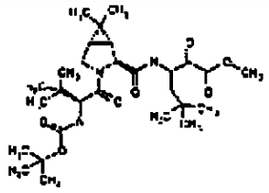
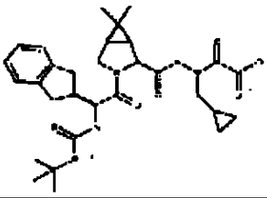
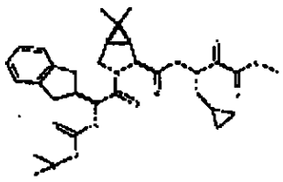
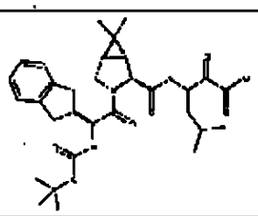
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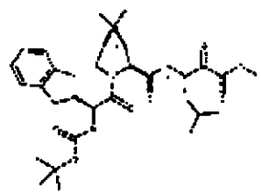
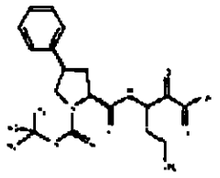
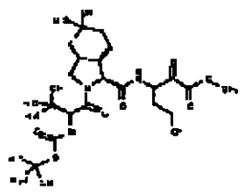
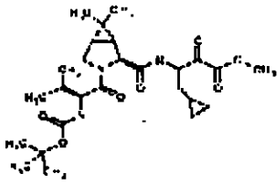
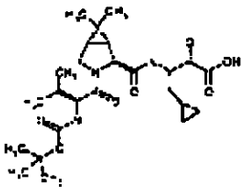
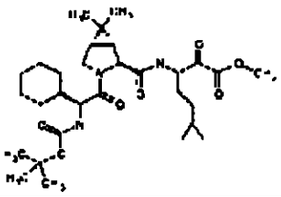
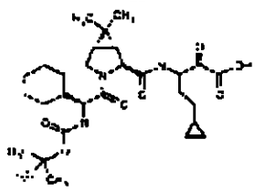
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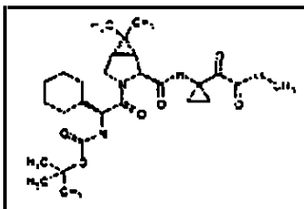
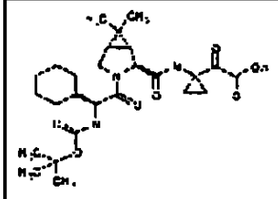
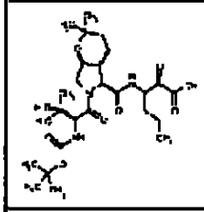
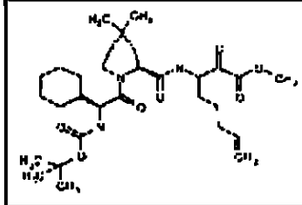
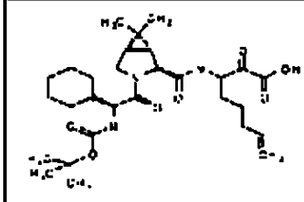
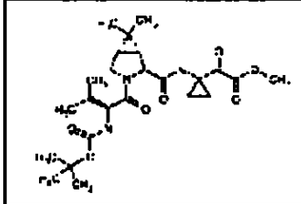
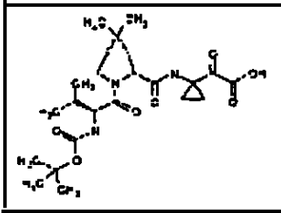
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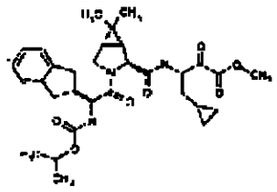
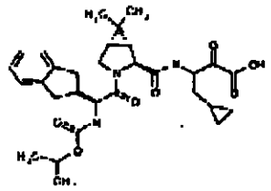
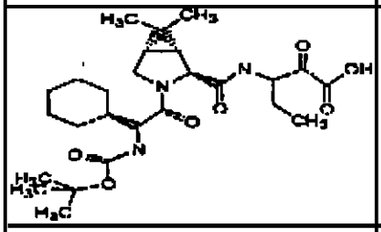
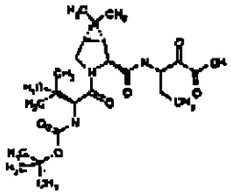
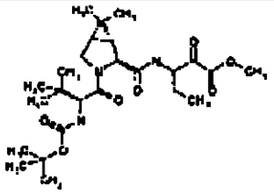
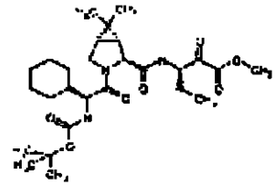
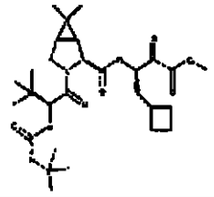
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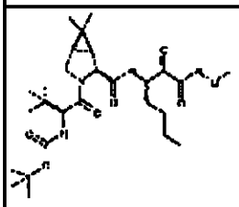
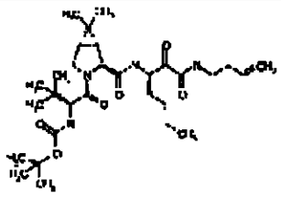
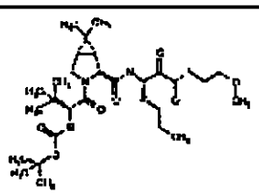
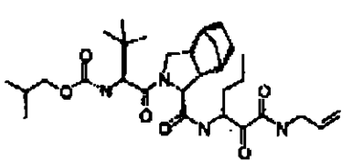
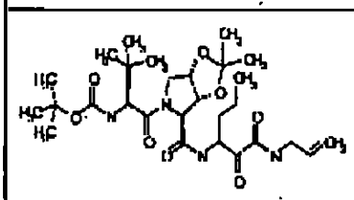
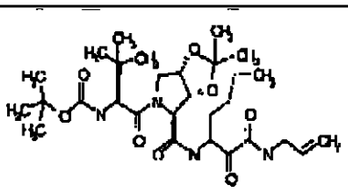
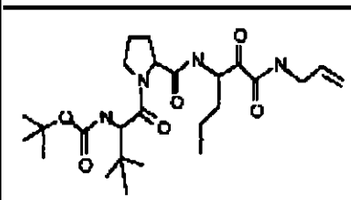
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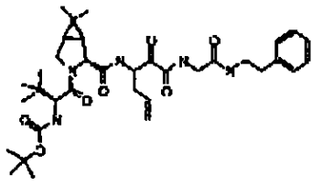
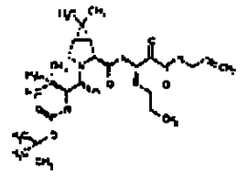
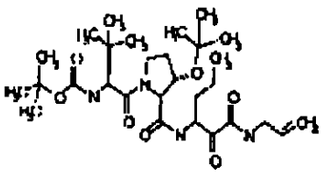
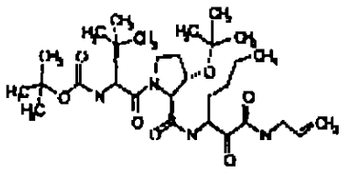
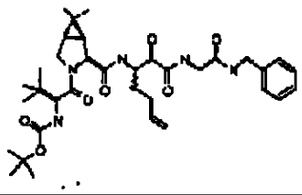
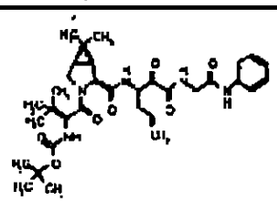
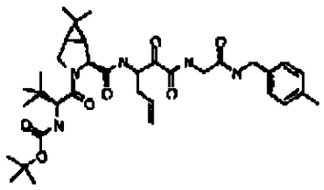
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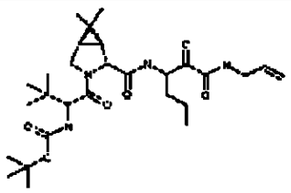
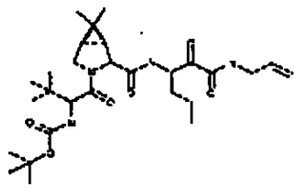
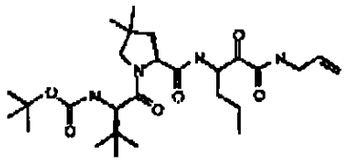
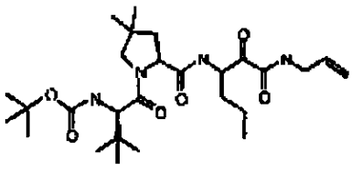
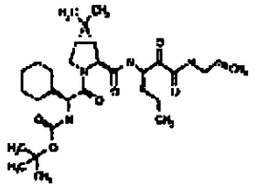
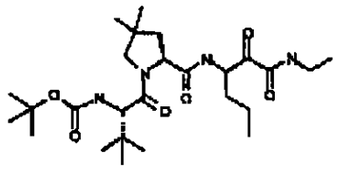
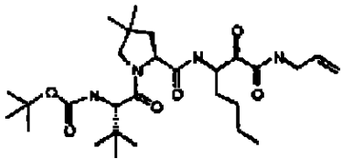
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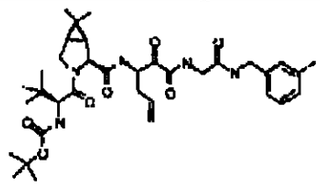
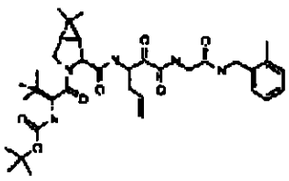
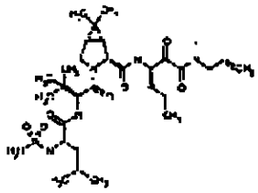
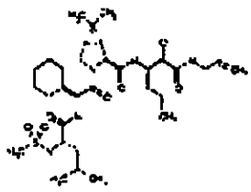
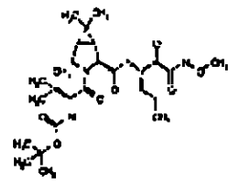
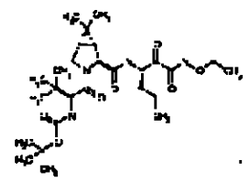
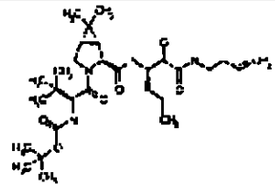
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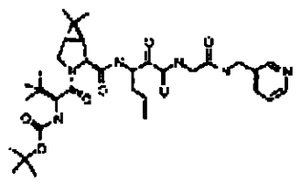
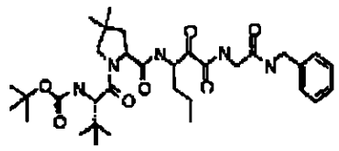
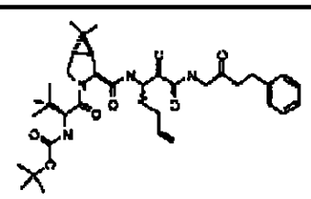
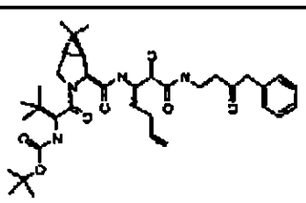
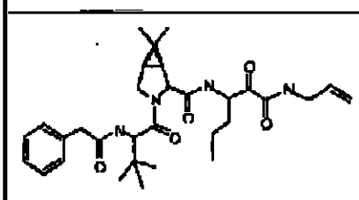
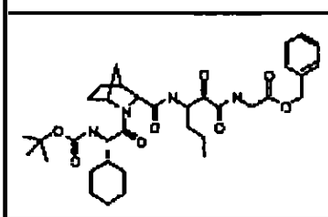
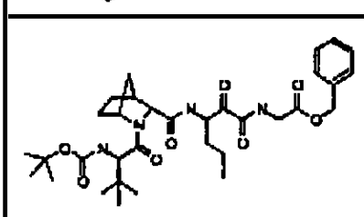
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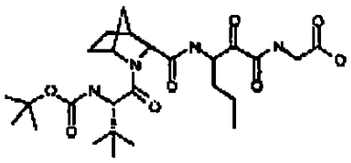
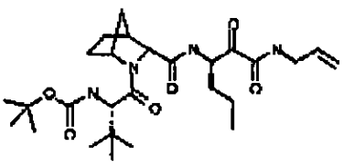
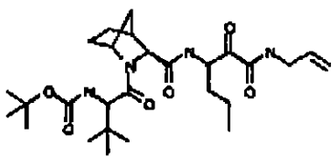
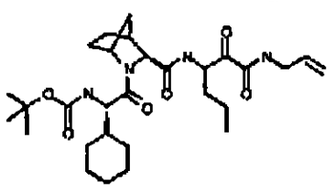
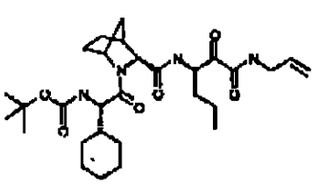
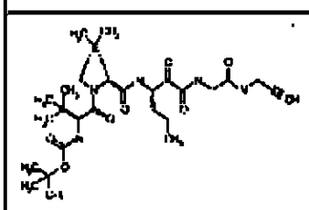
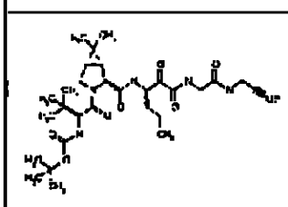
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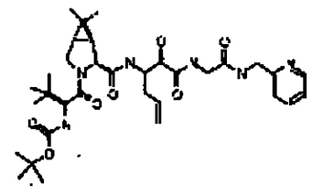
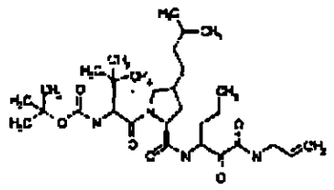
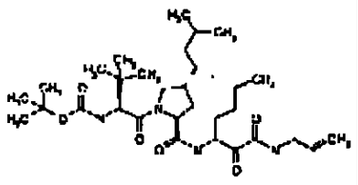
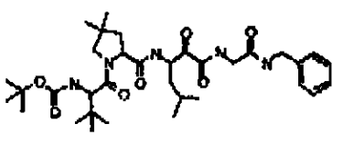
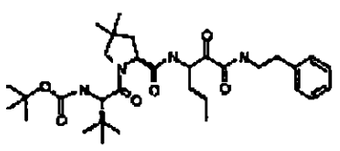
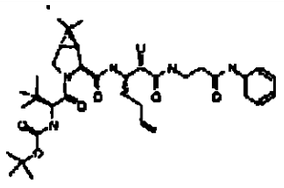
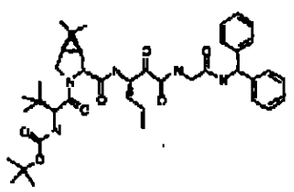
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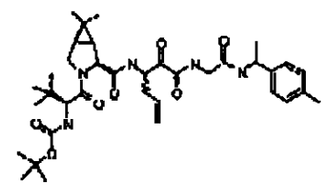
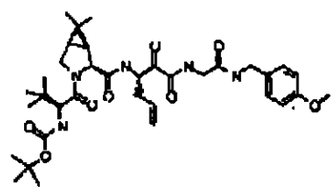
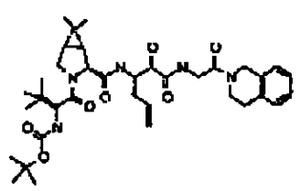
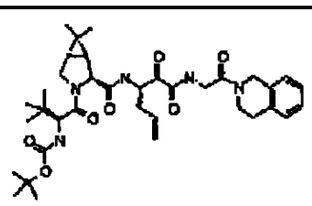
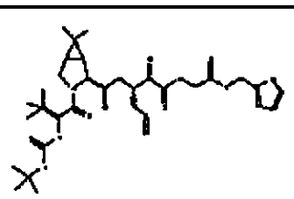
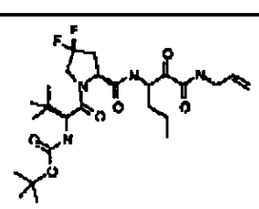
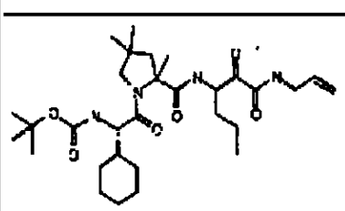
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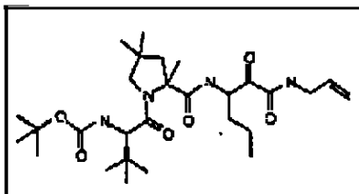
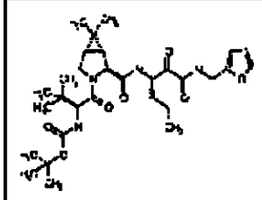
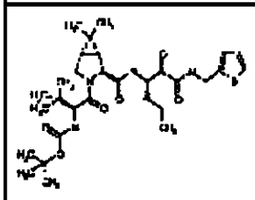
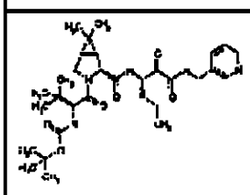
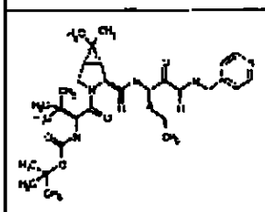
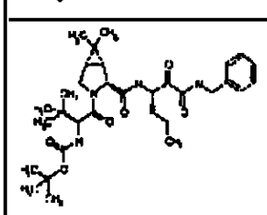
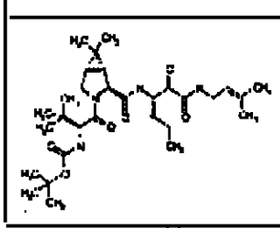
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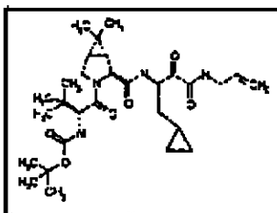
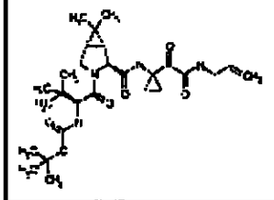
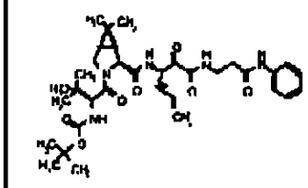
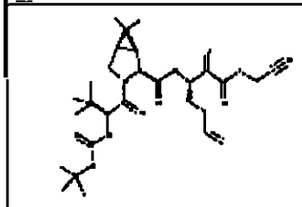
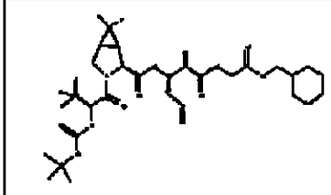
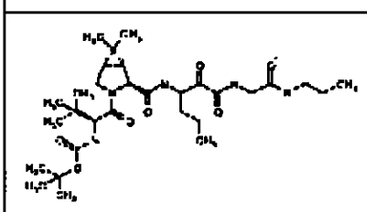
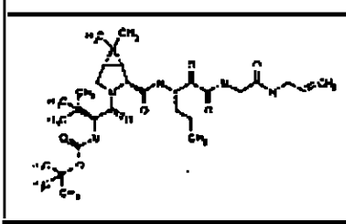
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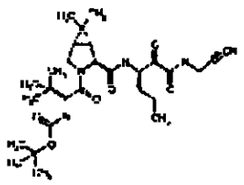
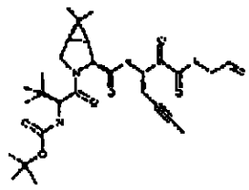
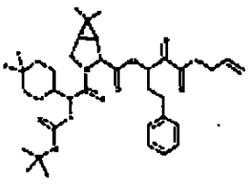
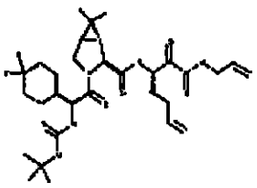
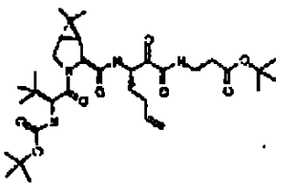
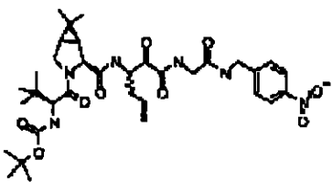
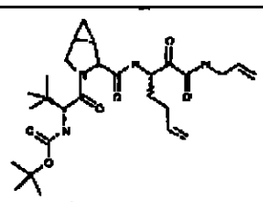
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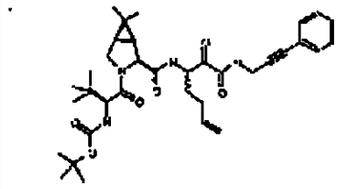
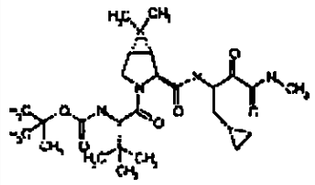
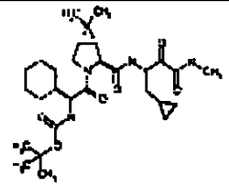
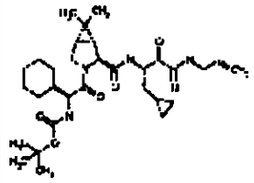
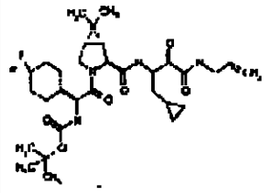
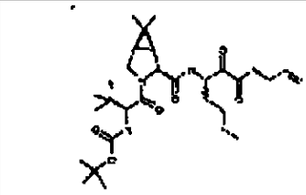
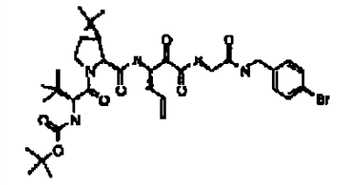
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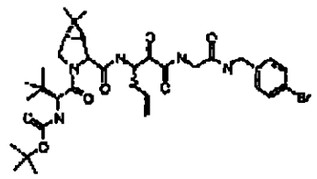
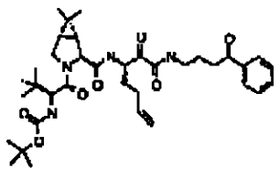
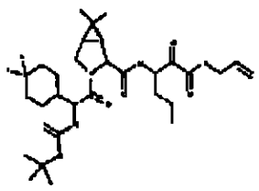
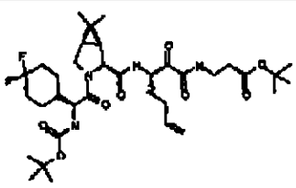
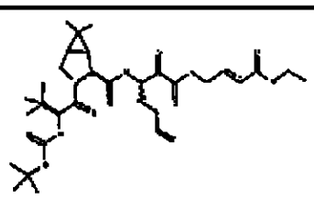
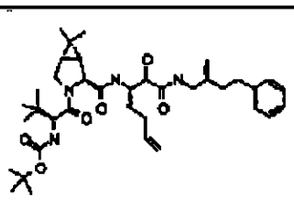
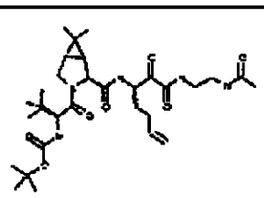
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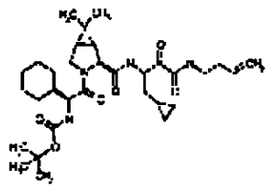
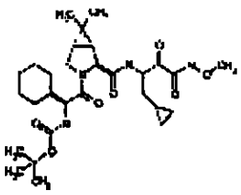
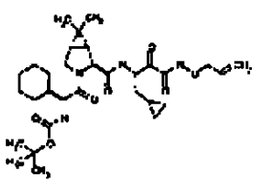
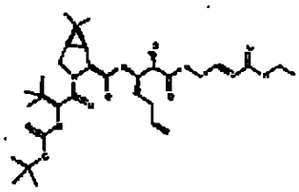
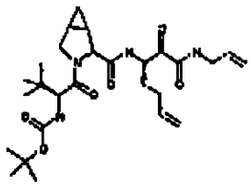
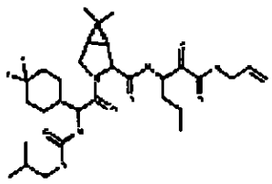
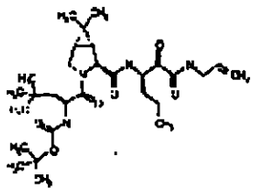
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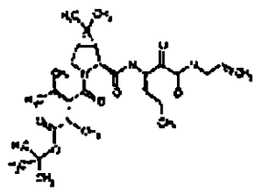
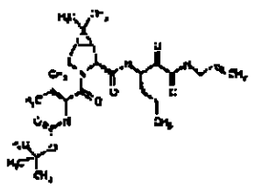
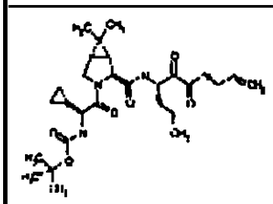
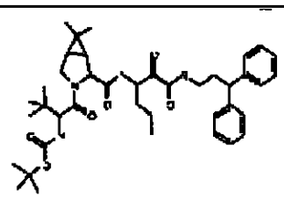
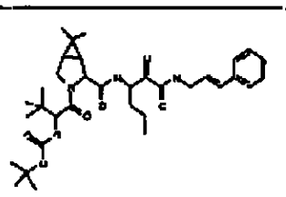
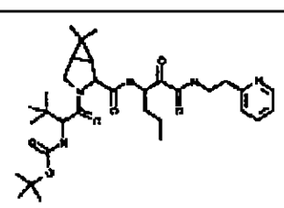
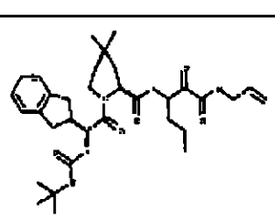
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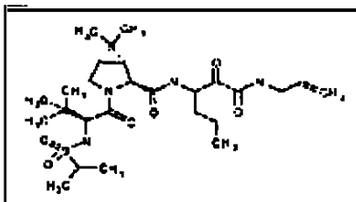
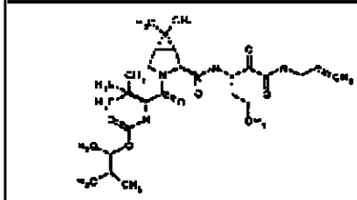
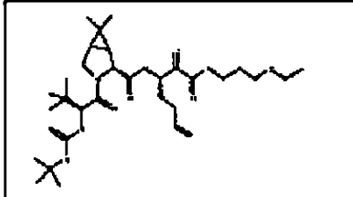
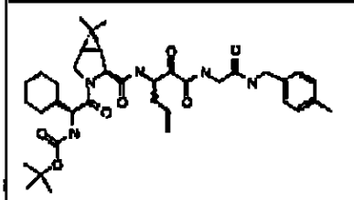
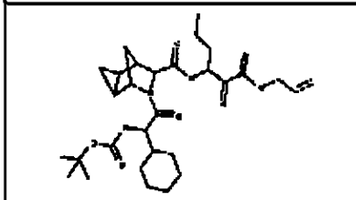
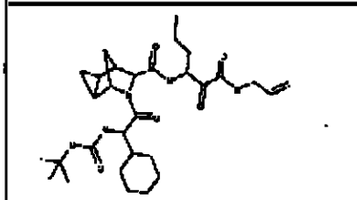
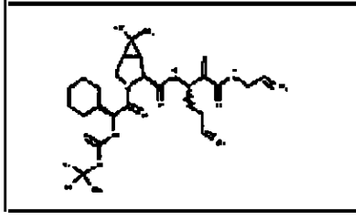
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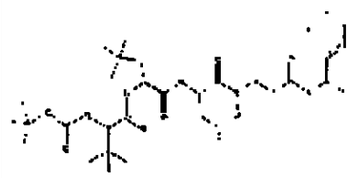
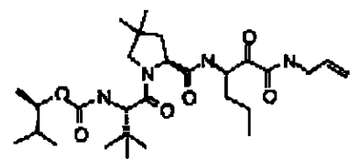
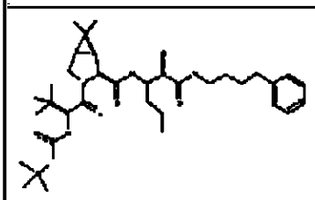
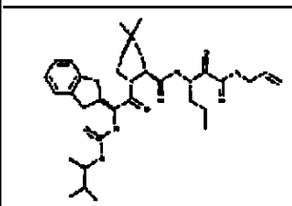
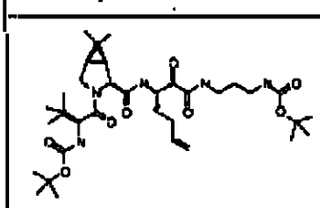
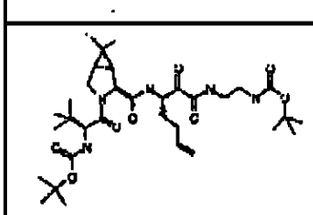
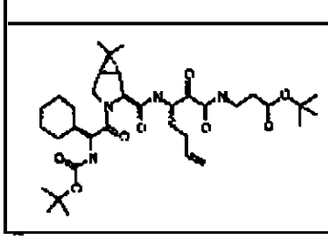
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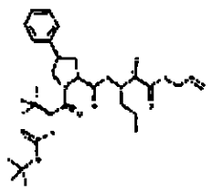
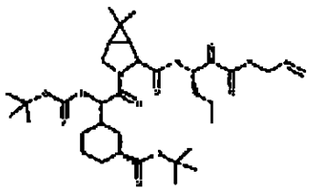
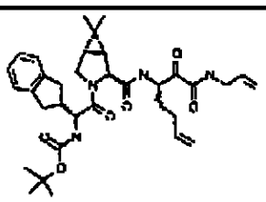
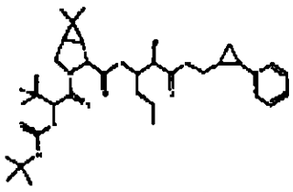
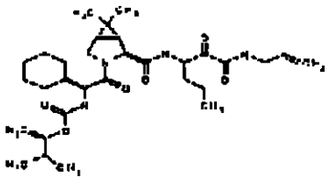
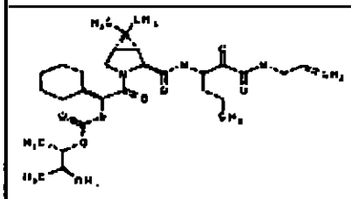
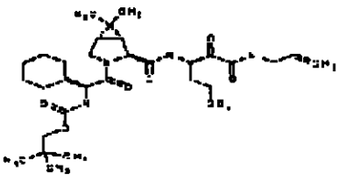
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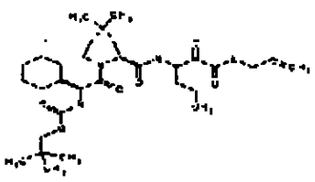
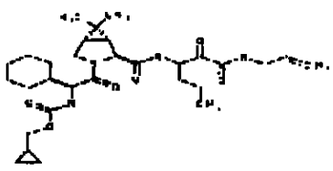
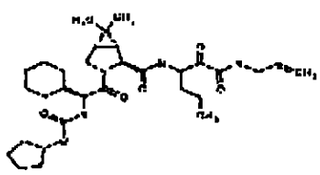
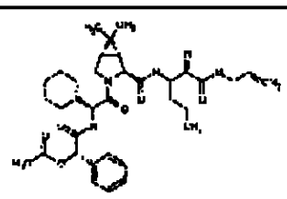
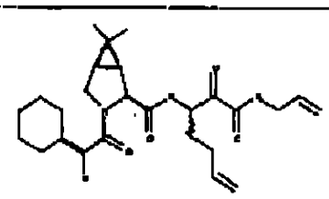
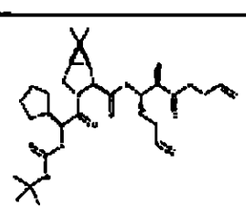
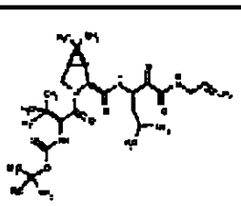
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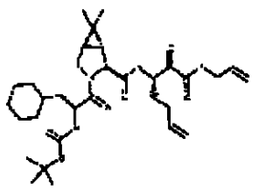
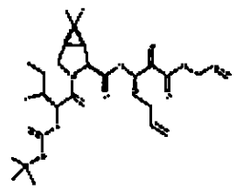
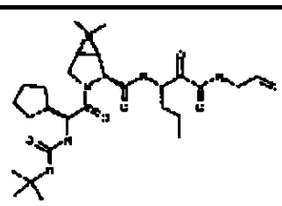
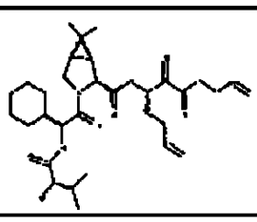
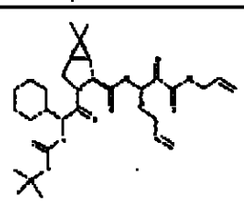
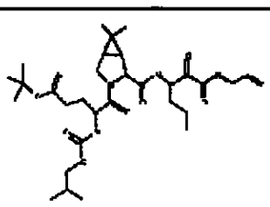
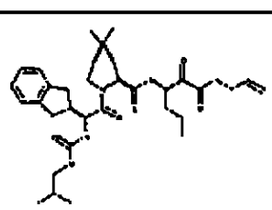
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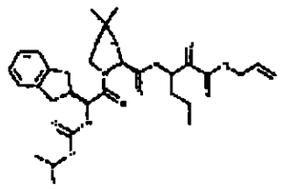
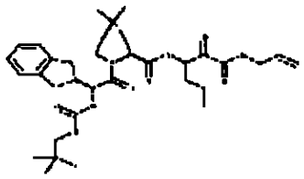
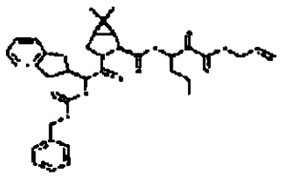
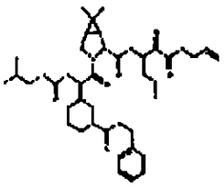
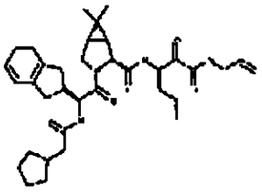
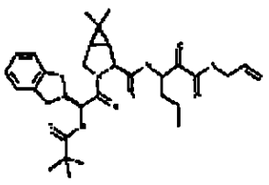
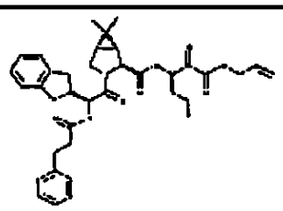
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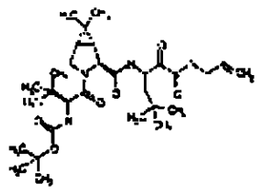
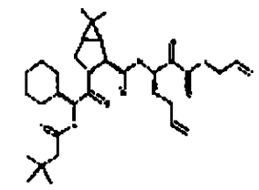
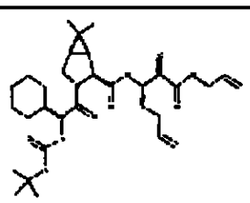
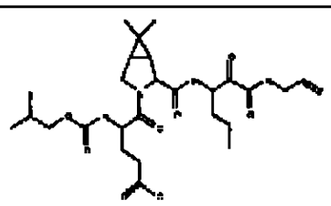
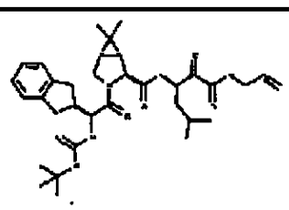
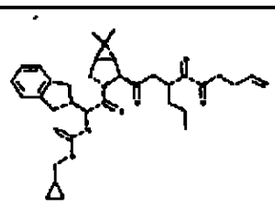
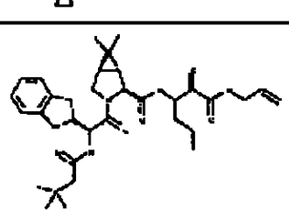
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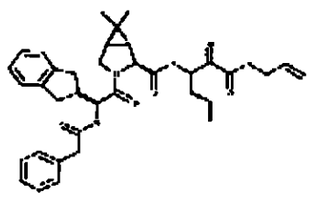
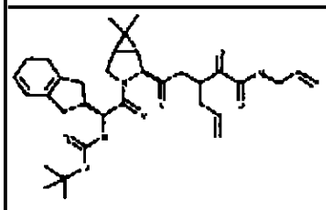
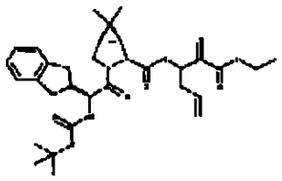
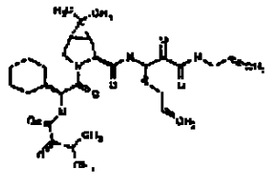
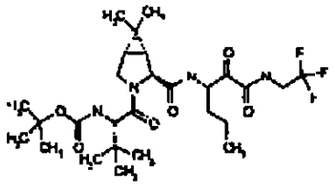
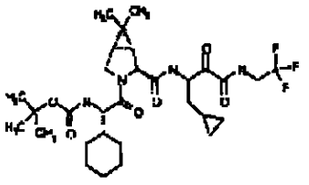
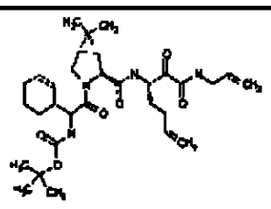
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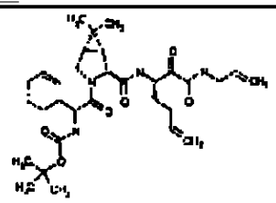
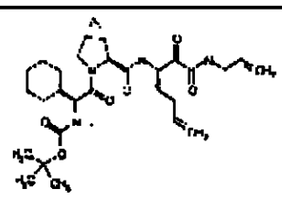
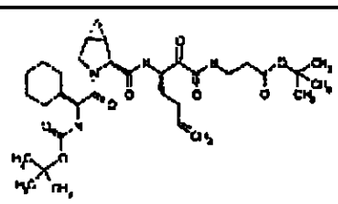
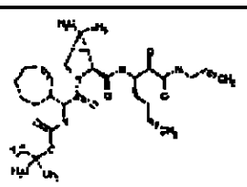
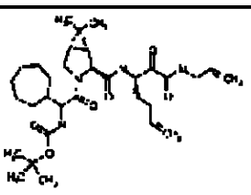
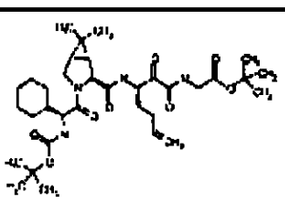
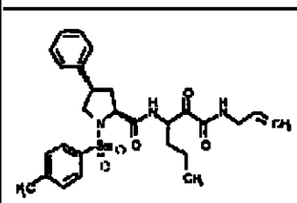
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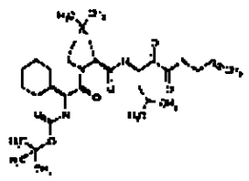
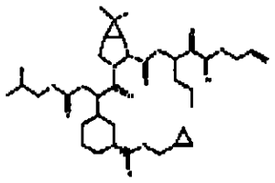
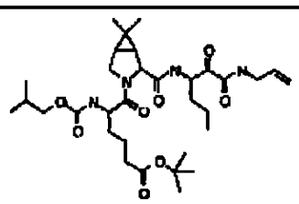
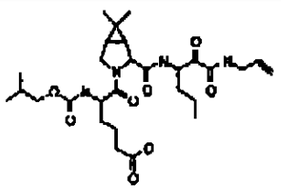
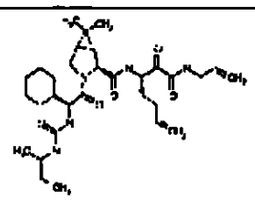
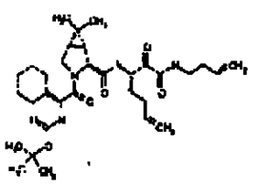
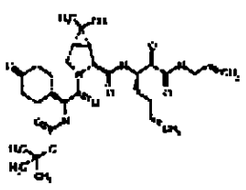
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	627	C

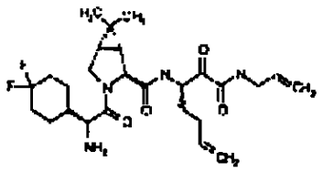
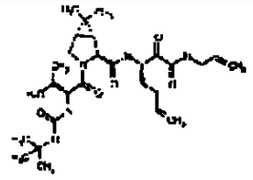
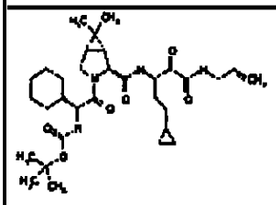
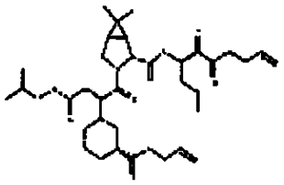
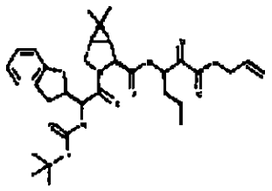
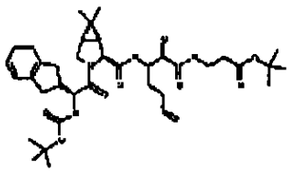
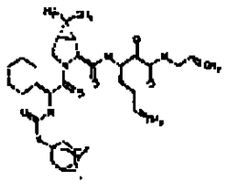
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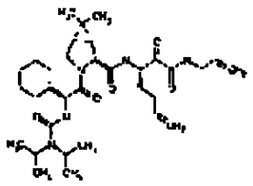
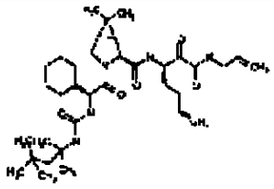
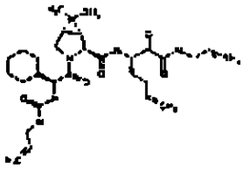
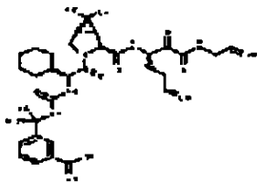
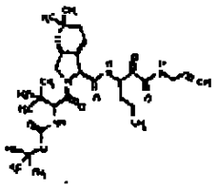
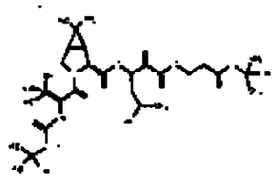
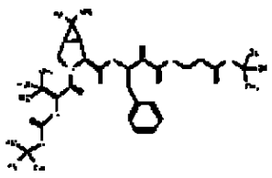
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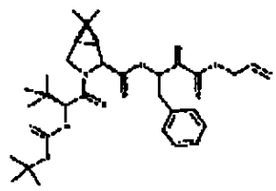
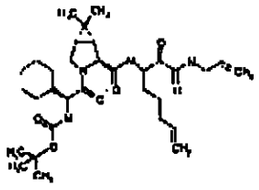
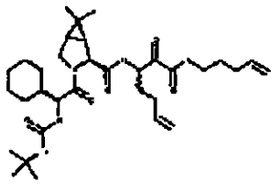
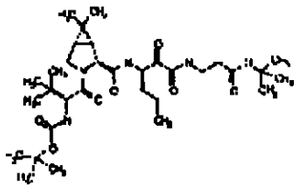
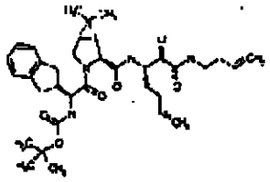
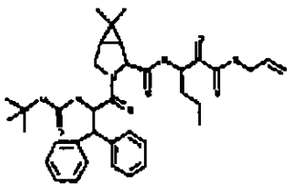
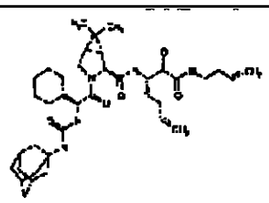
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	585	B
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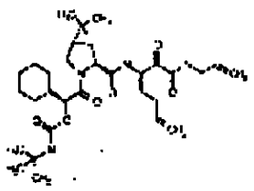
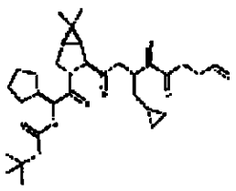
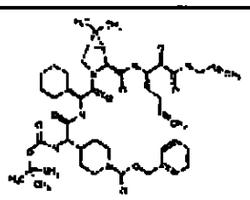
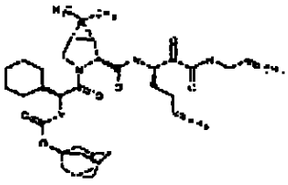
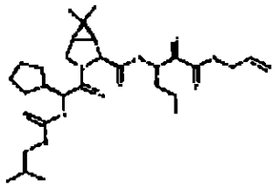
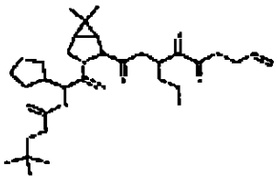
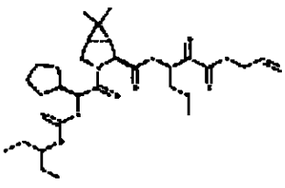
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9734

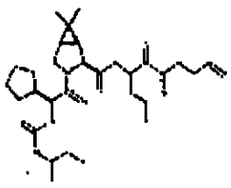
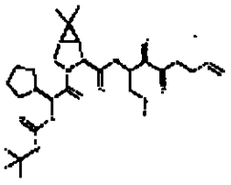
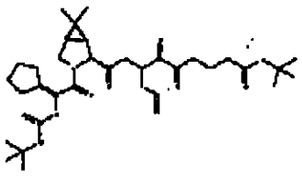
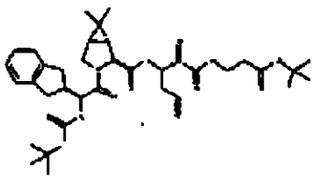
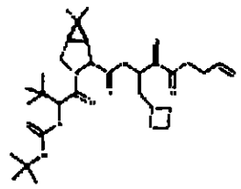
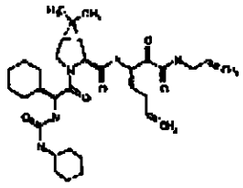
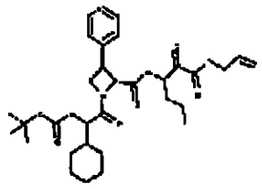
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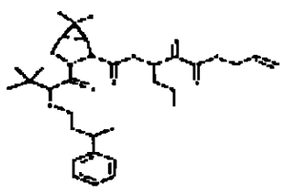
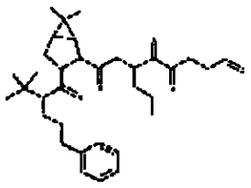
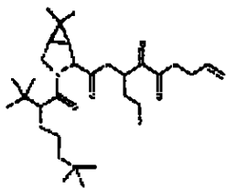
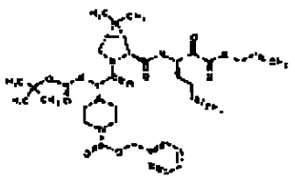
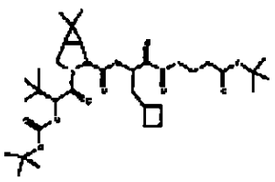
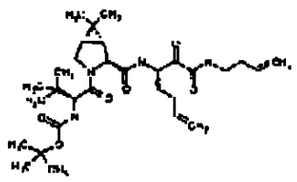
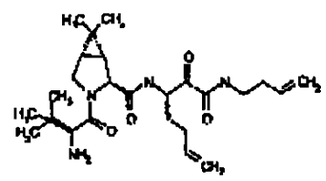
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	601	B
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	664	B

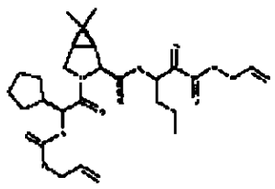
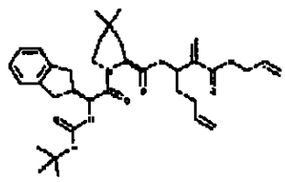
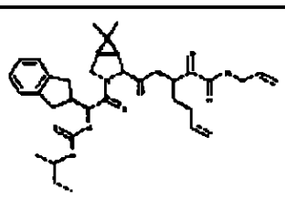
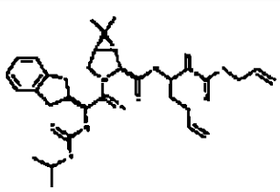
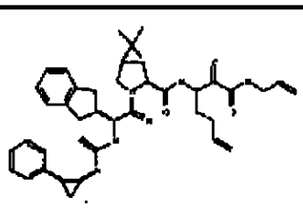
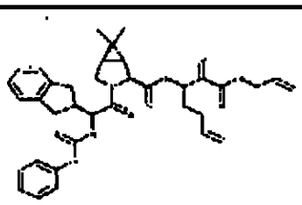
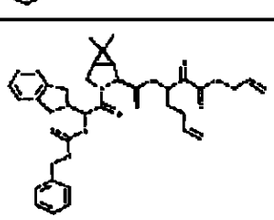
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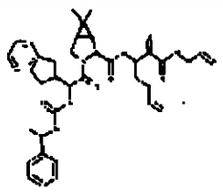
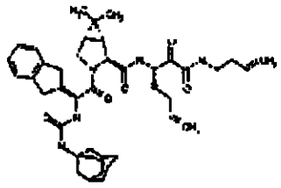
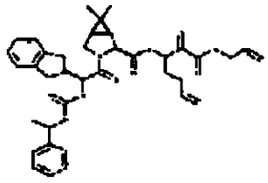
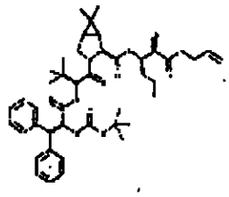
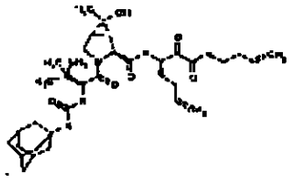
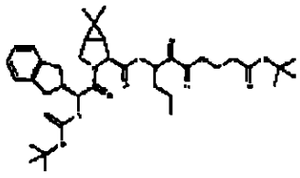
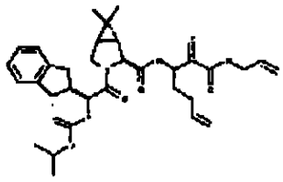
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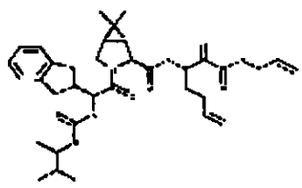
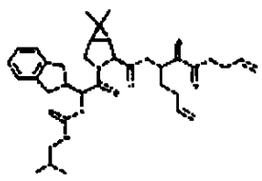
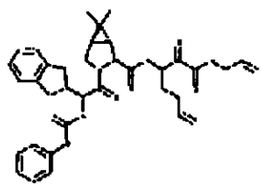
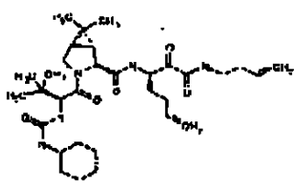
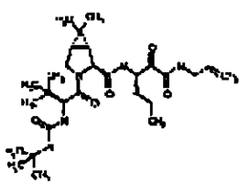
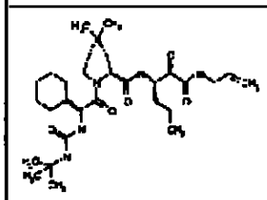
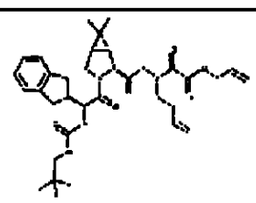
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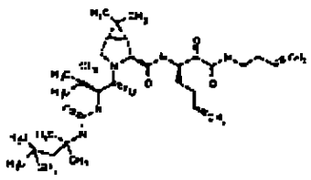
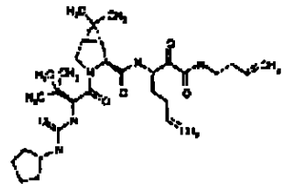
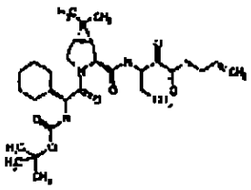
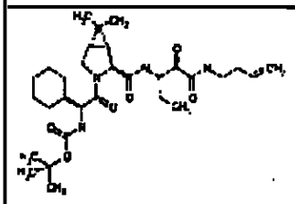
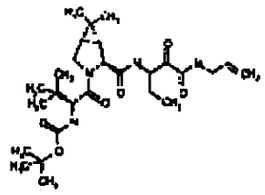
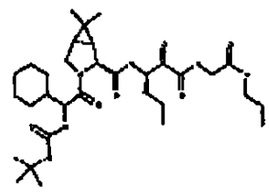
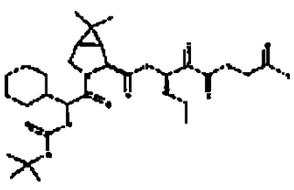
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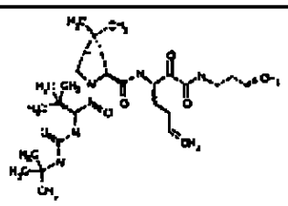
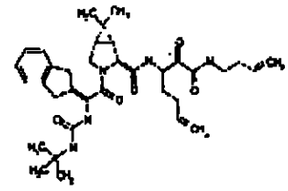
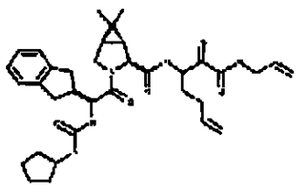
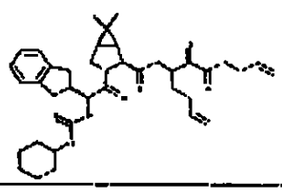
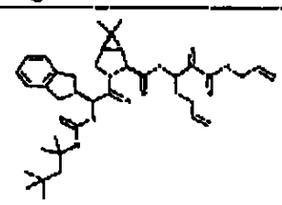
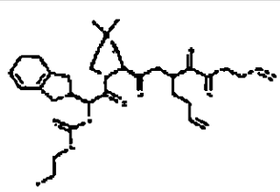
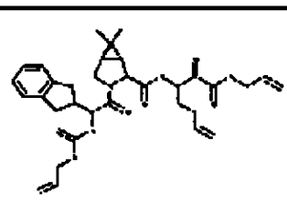
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	640	B

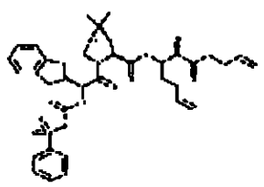
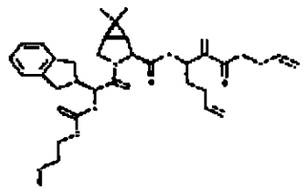
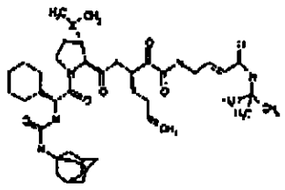
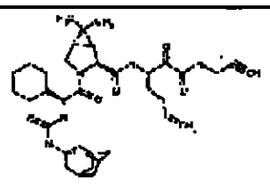
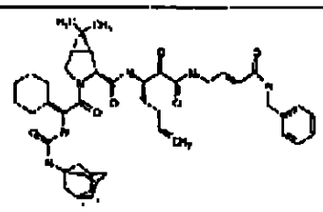
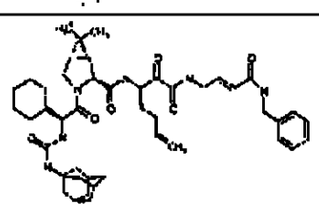
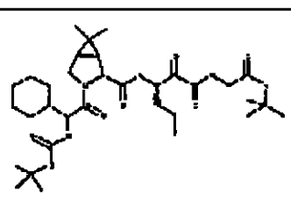
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	654	B
	768	C
	638	A
	683	B
	593	A

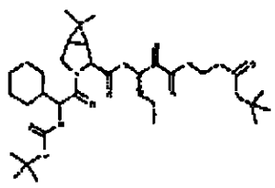
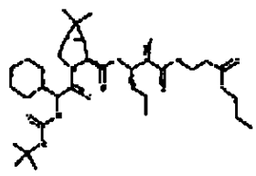
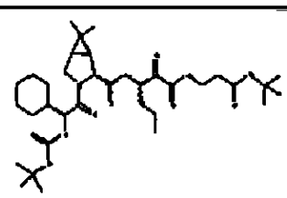
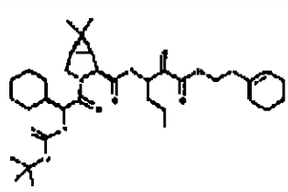
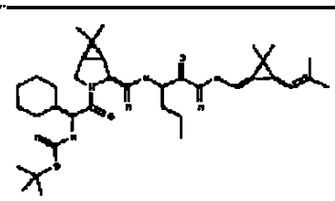
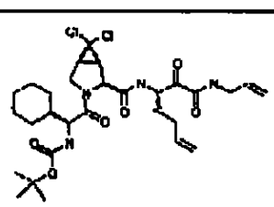
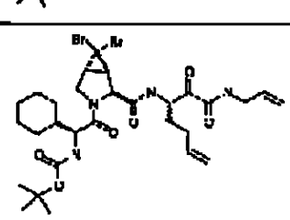
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	627	B
	586	A
	534	B
	560	C
	621	A

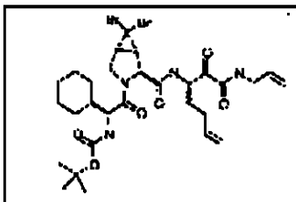
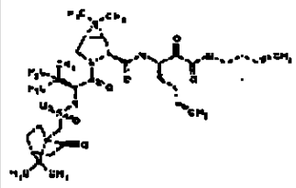
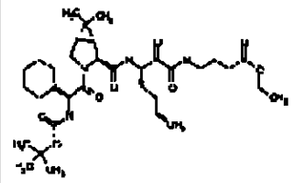
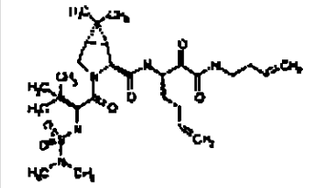
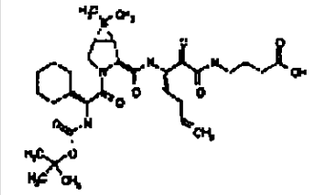
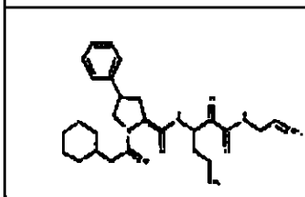
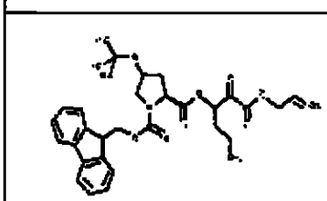
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	547	C
	561	C
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	620	B
	578	B

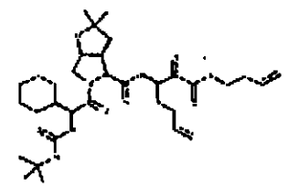
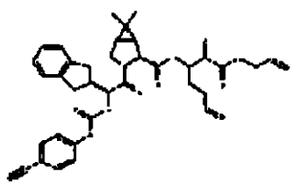
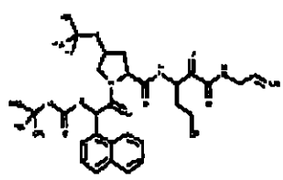
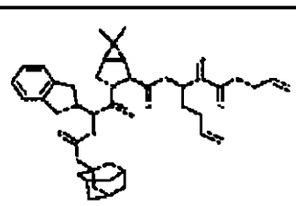
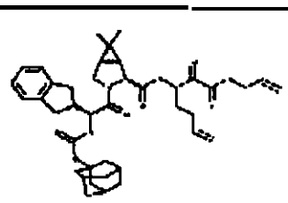
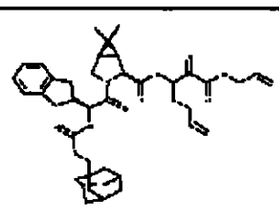
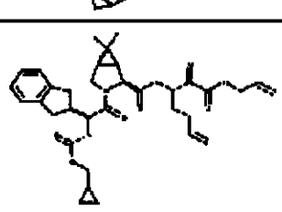
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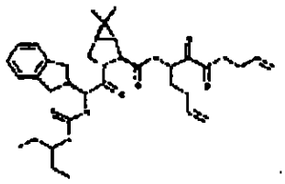
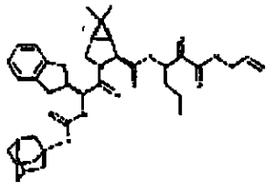
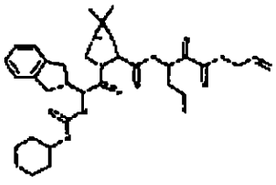
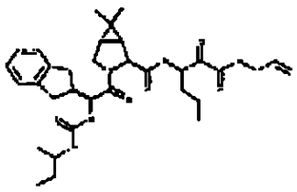
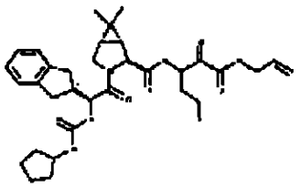
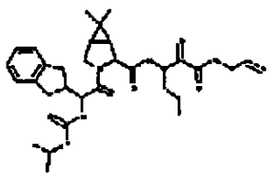
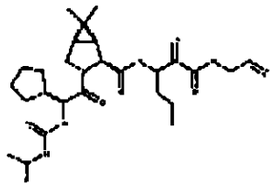
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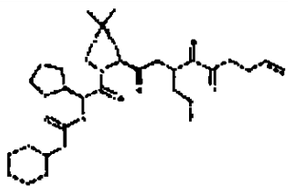
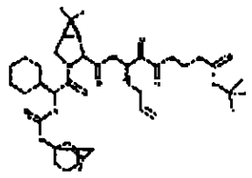
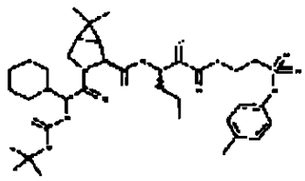
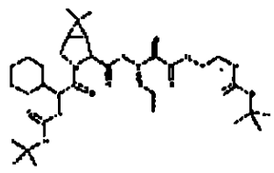
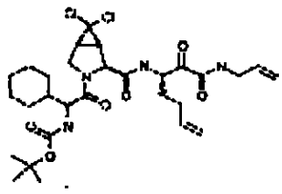
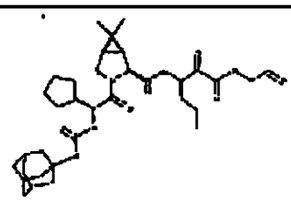
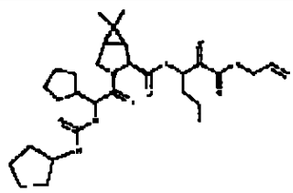
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	783	B
	783	B
	634	C

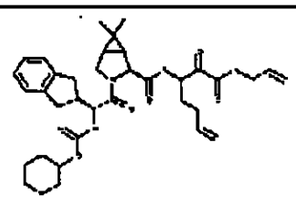
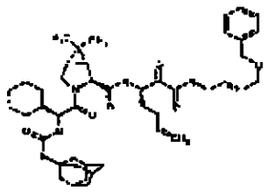
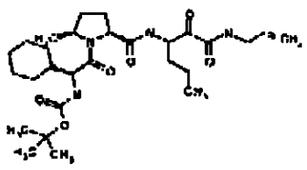
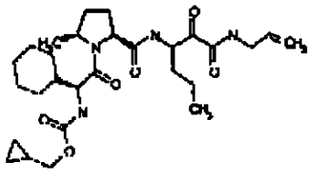
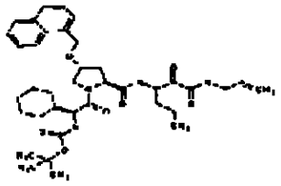
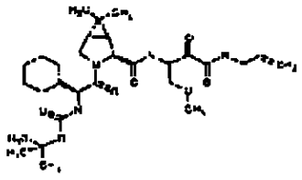
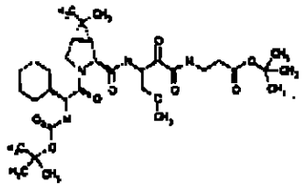
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	629	C
	657	C
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	702	B

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	588	C
	619	C
	482	C
	578	C

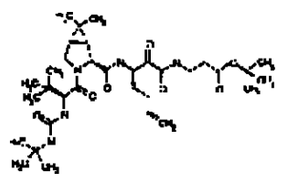
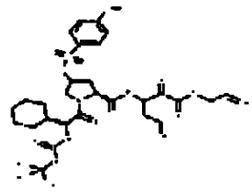
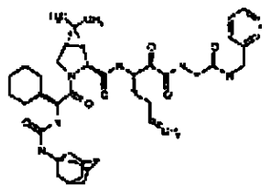
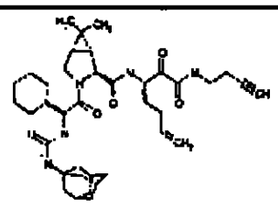
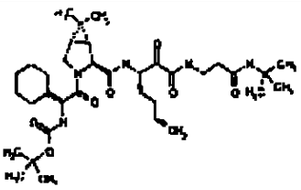
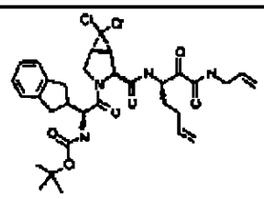
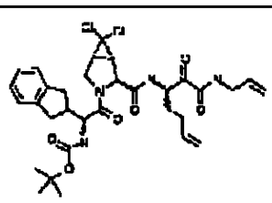
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	684	B
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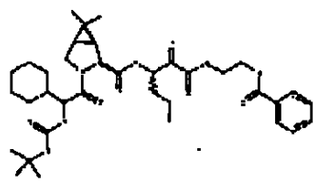
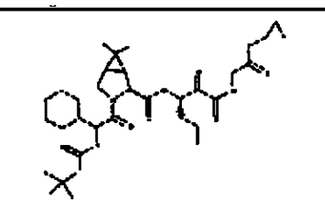
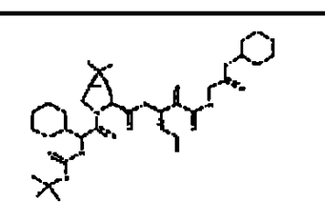
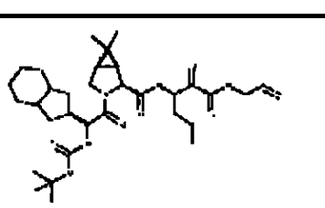
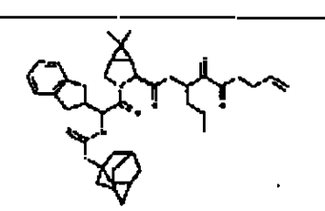
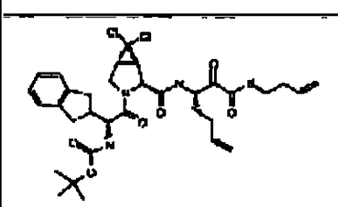
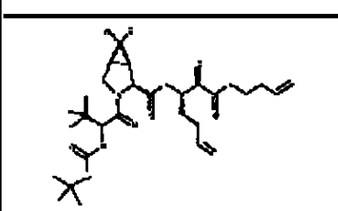
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	558	B

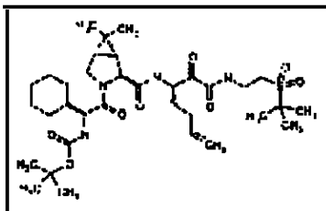
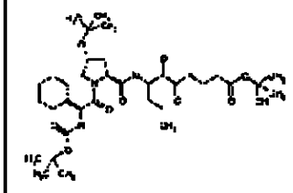
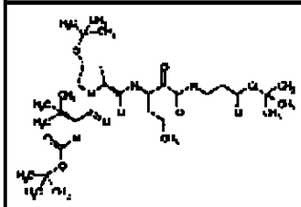
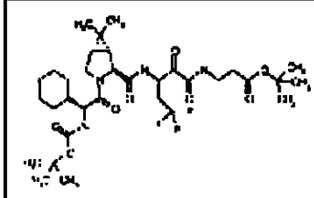
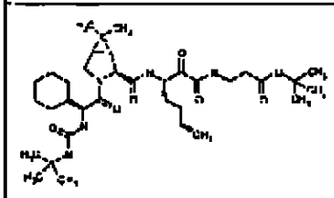
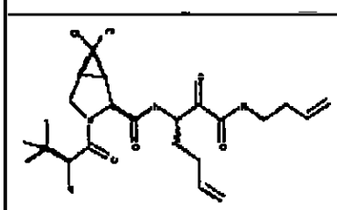
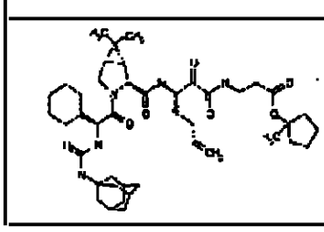
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	651	A

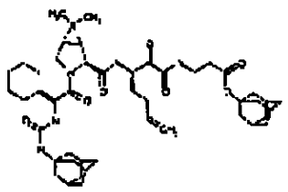
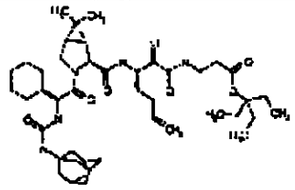
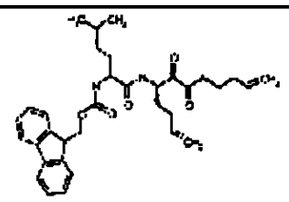
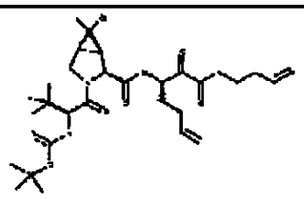
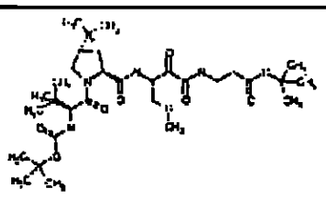
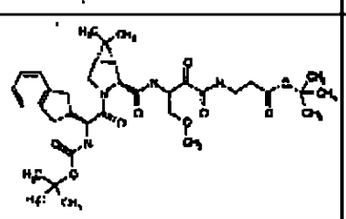
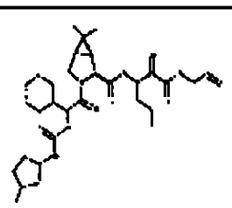
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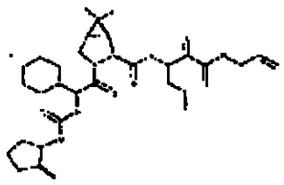
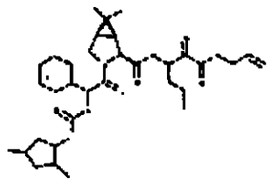
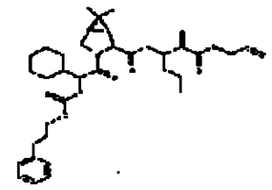
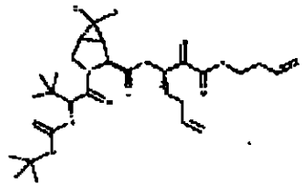
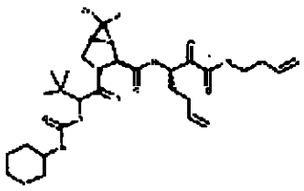
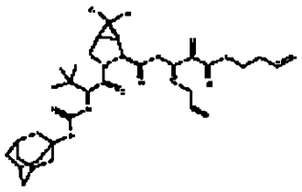
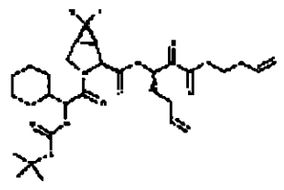
	634	A
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	757	A
	662	A
	690	A
	648	A
	648	C

9152

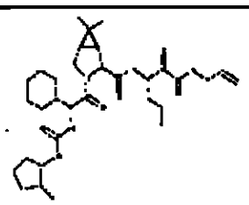
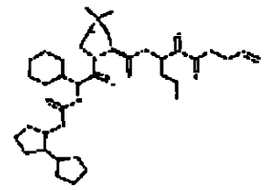
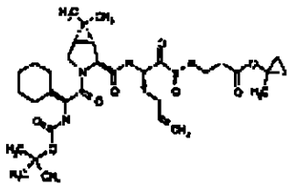
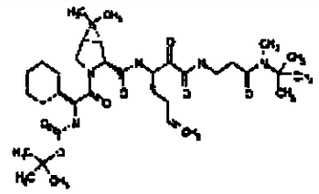
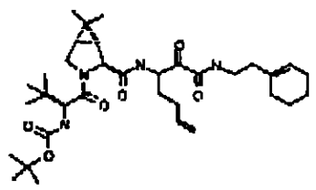
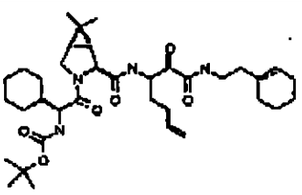
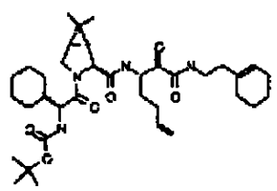
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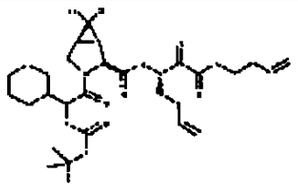
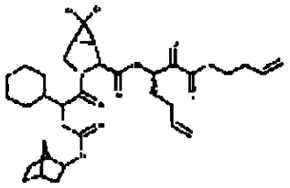
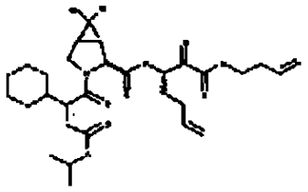
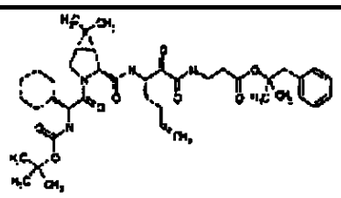
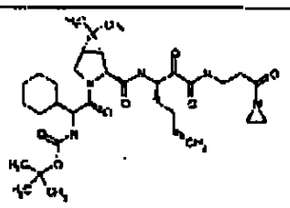
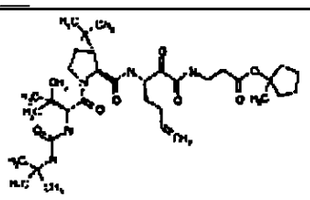
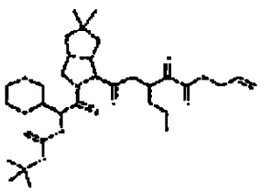
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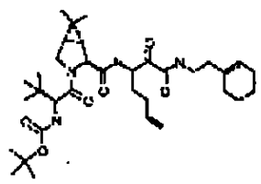
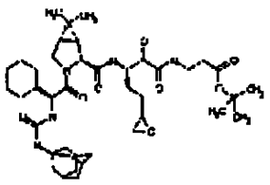
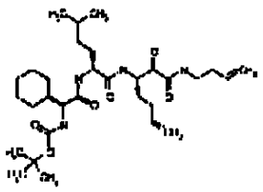
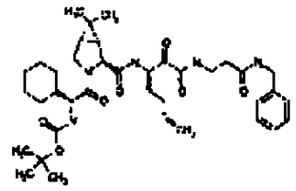
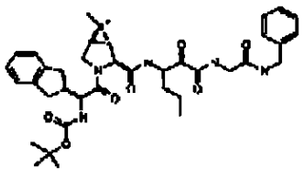
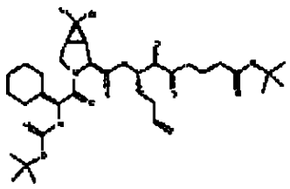
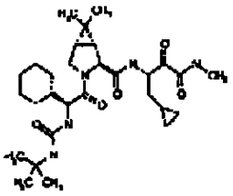
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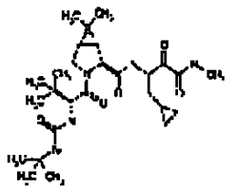
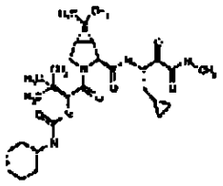
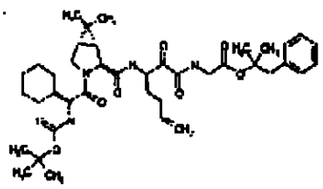
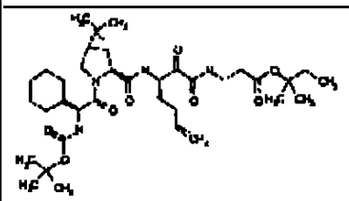
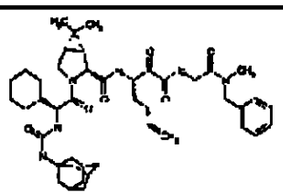
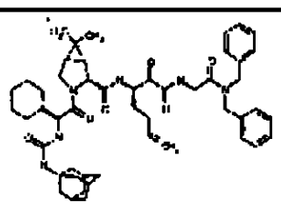
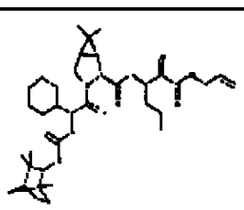
1156

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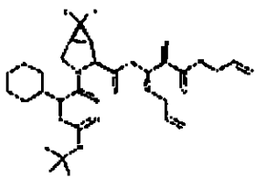
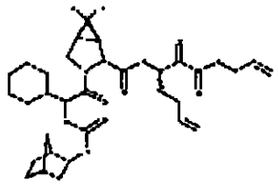
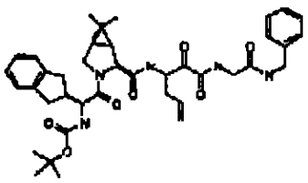
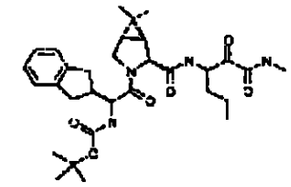
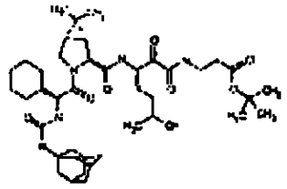
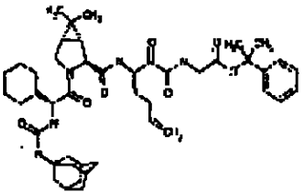
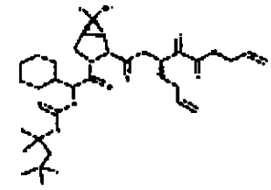
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4738

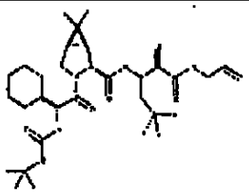
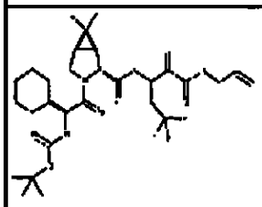
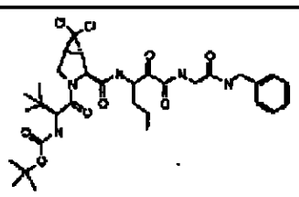
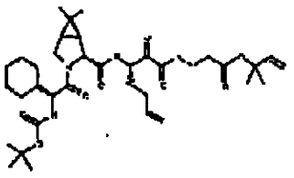
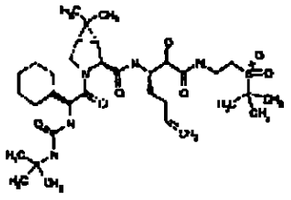
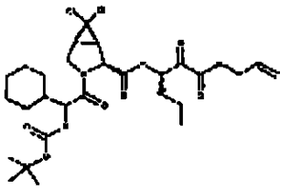
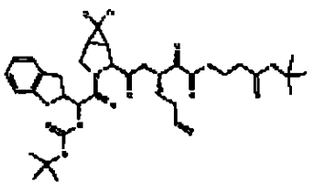
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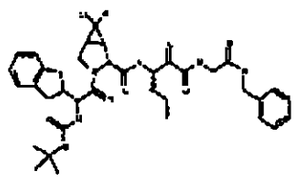
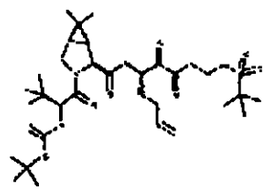
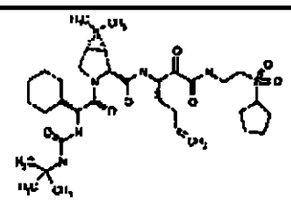
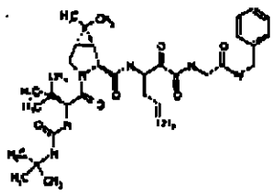
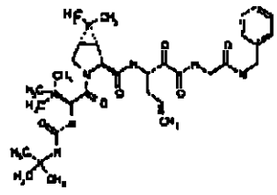
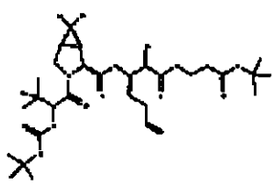
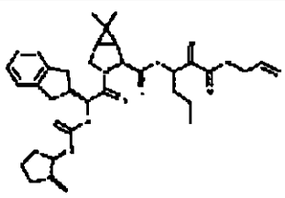
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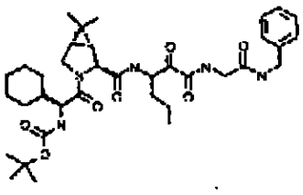
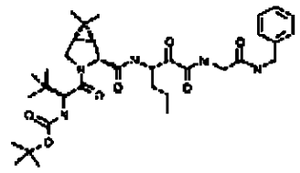
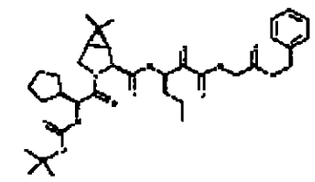
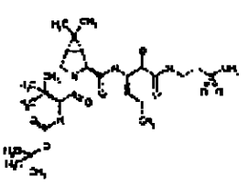
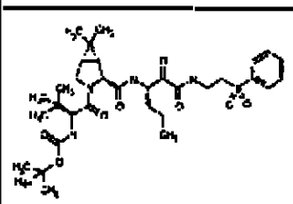
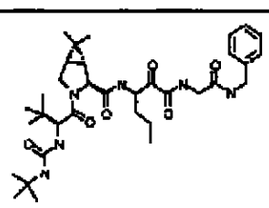
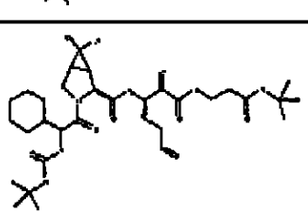
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	700	A
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	758	B
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	659	B

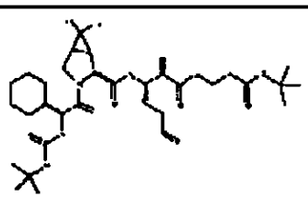
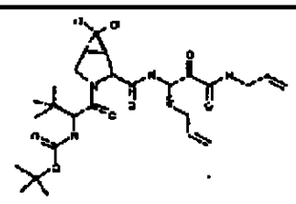
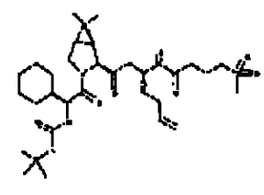
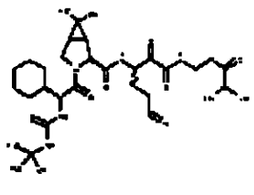
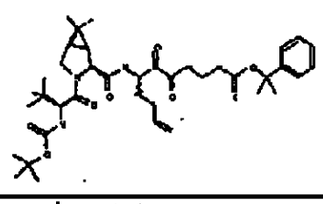
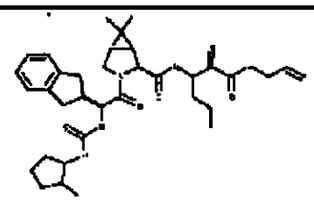
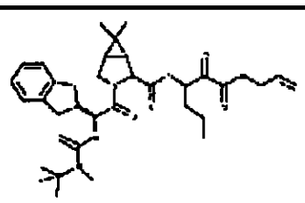
1161

	601	A
	601	B
	683	A
	673	A
	680	A
	602	A
	735	A

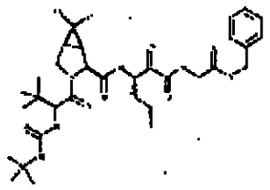
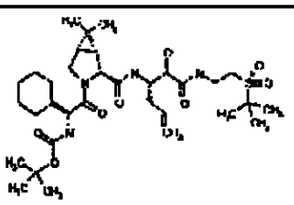
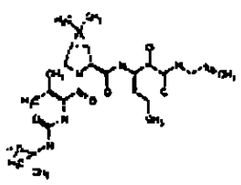
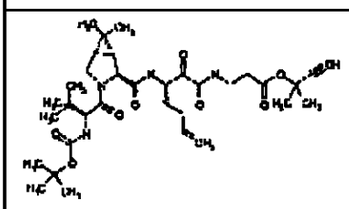
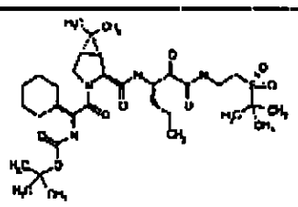
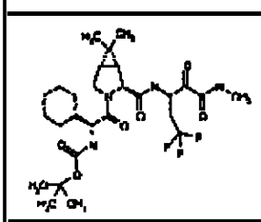
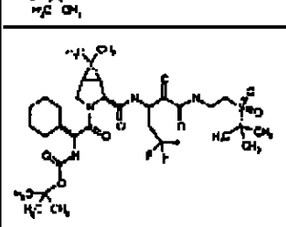
7162

	743	A
	655	B
	692	A
	638	A
	639	A
	675	A
	621	A

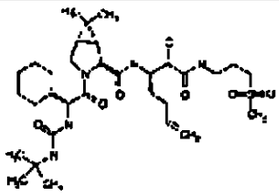
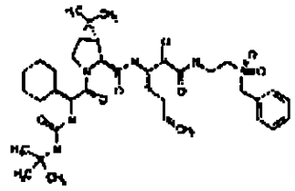
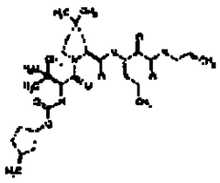
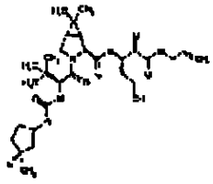
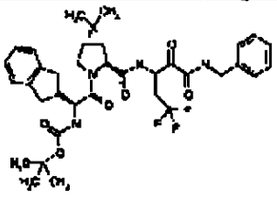
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	642	A
	654	A
	601	C
	653	B
	641	A
	702	A

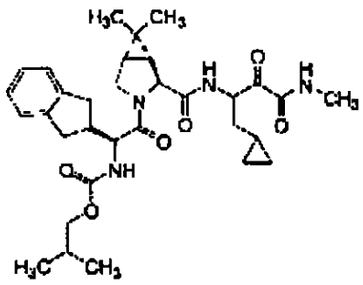
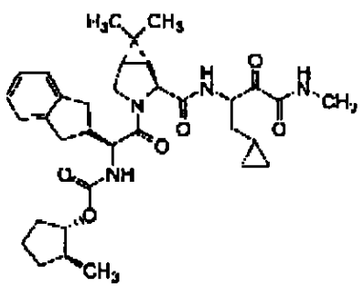
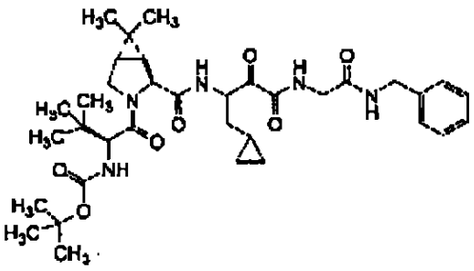
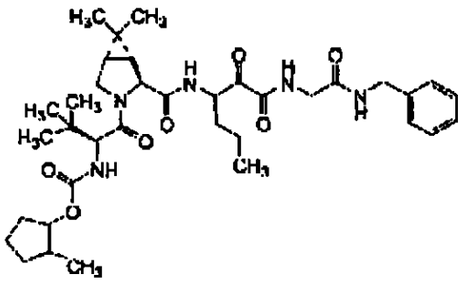
	701	A
	586	B
	638	A
	630	A
	697	A
	621	A
	608	B

1163

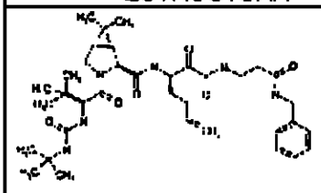
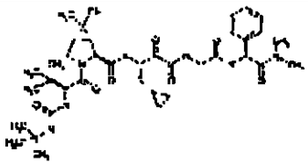
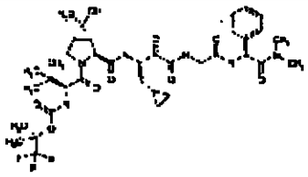
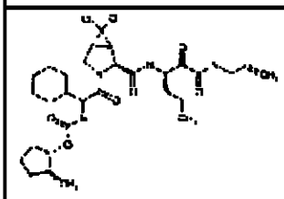
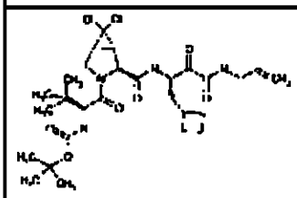
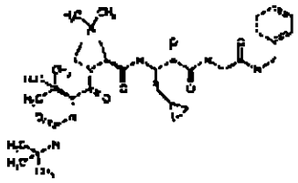
	682	A
	667	B
	620	B
	645	B
	689	C
	575	A
	709	B

1766

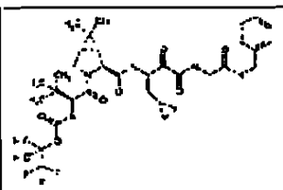
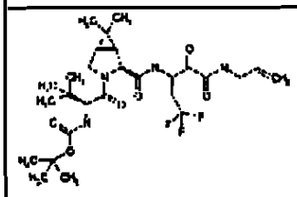
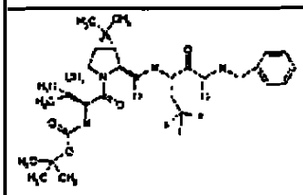
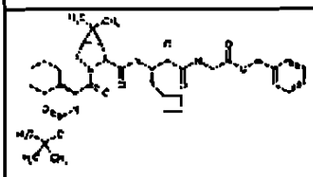
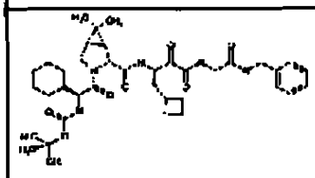
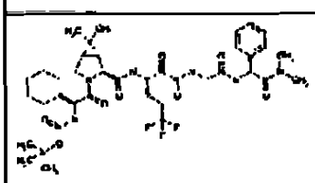
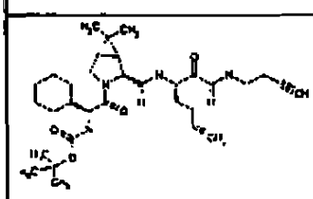
	652	B
	714	A
	561	B
	561	B
	685	B

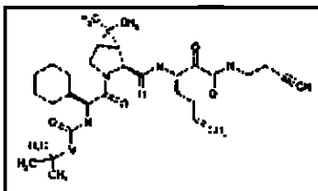
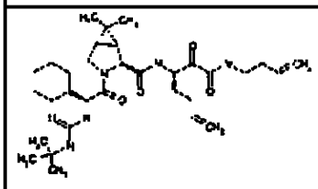
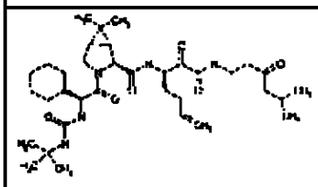
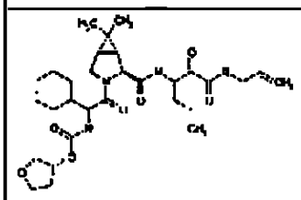
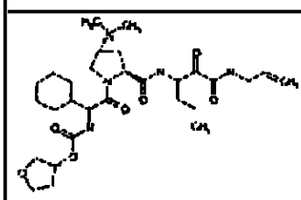
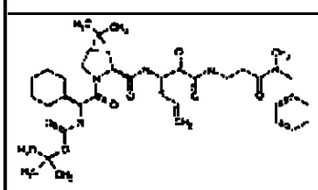
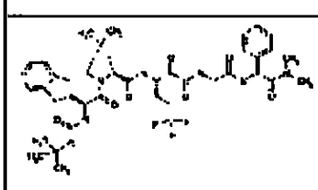
Estructura	PM	Rango Ki*
	580	A
	606	A
	653	A
	667	A

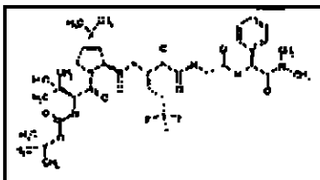
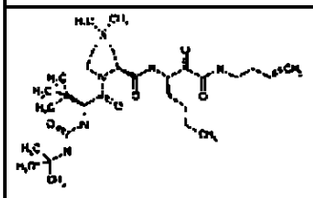
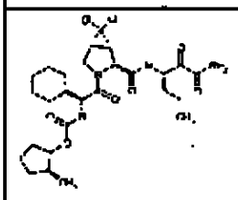
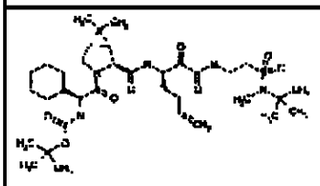
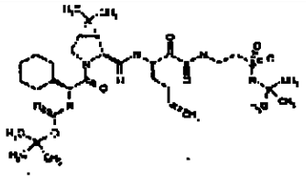
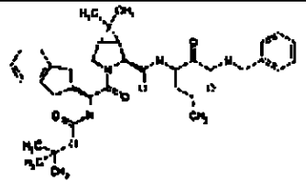
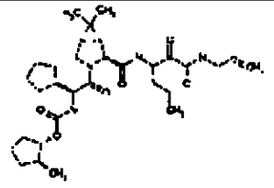
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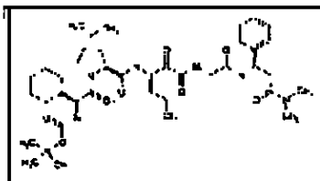
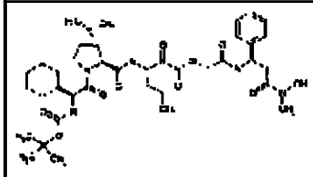
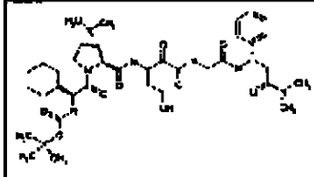
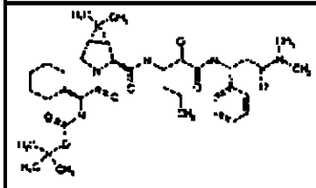
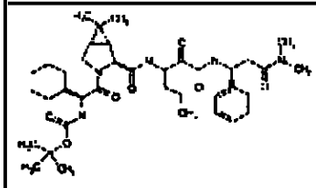
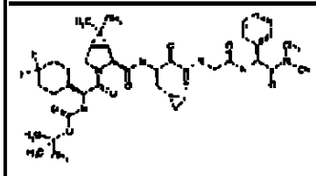
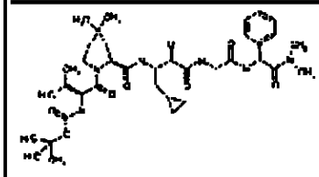
Tabla 6		
ESTRUCTURA	PM	KI* (nM)
	666.87	A
	723.92	A
	778.88	A
	627.81	A
	601.58	B
	652.84	A

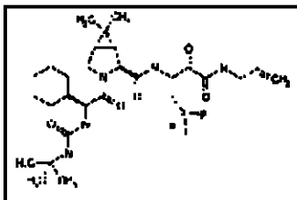
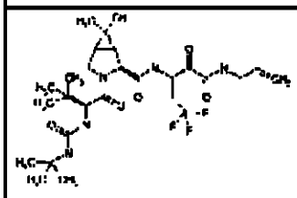
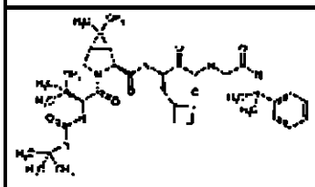
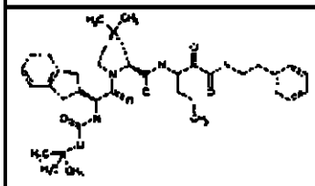
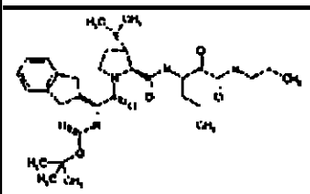
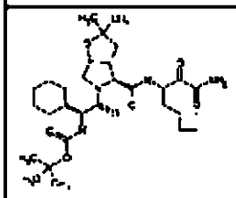
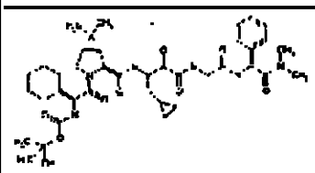
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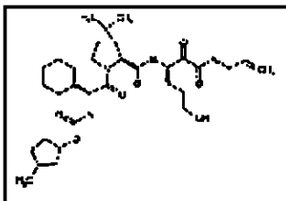
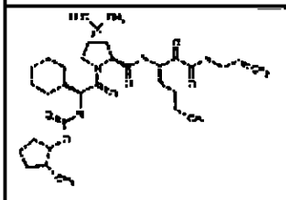
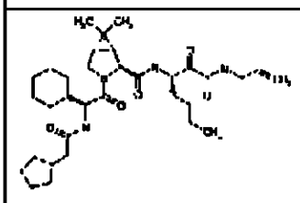
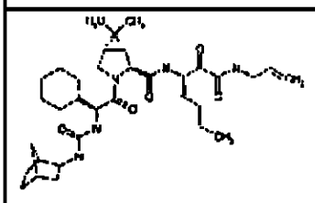
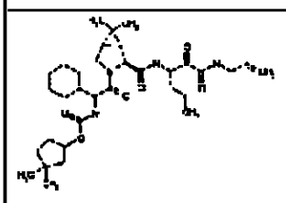
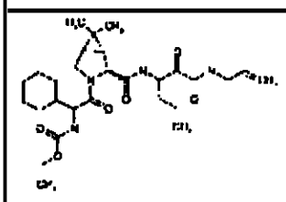
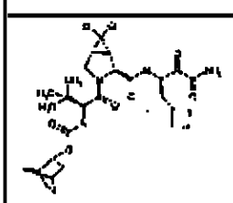
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	694.88	A
	693.89	B
	792.90	A
	584.76	A

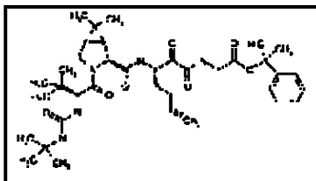
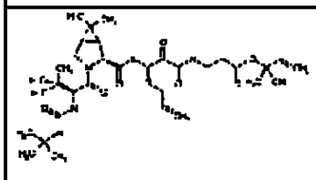
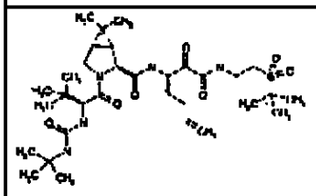
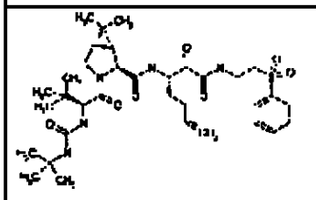
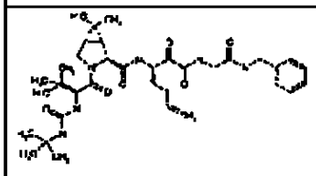
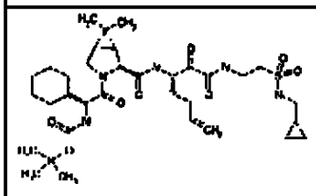
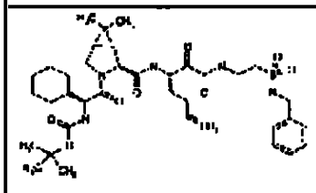
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	585.79	A
	643.87	A
	574.72	B
	574.72	B
	693.89	B
	826.92	A

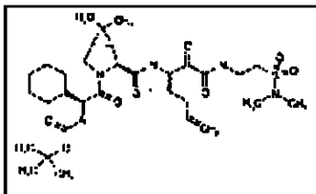
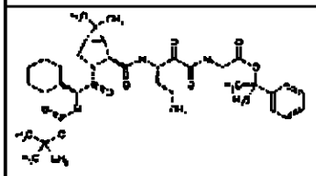
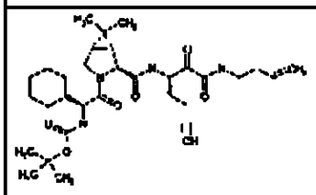
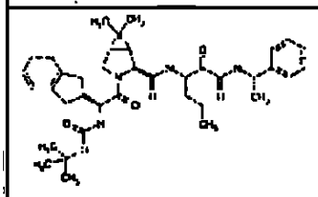
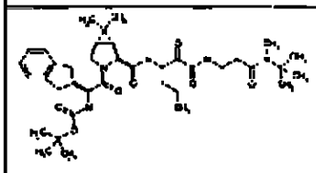
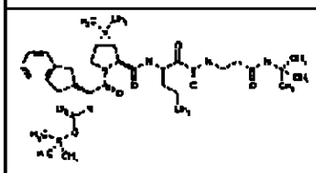
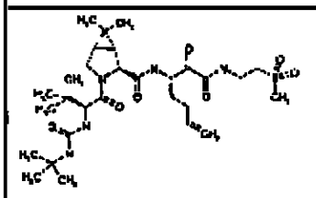
	766.87	A
	561.77	B
	587.55	A
	709.95	A
	695.93	B
	644.82	B
	572.75	A

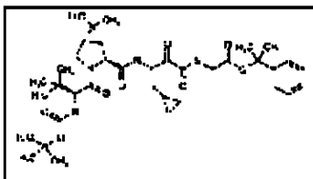
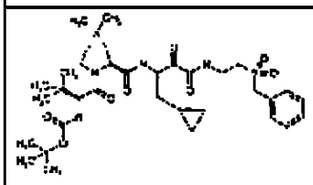
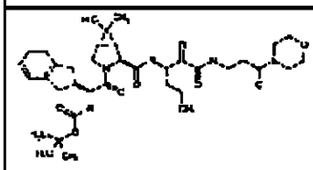
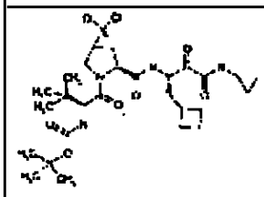
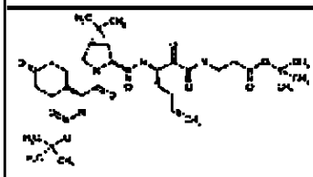
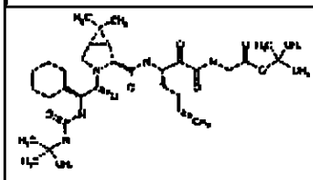
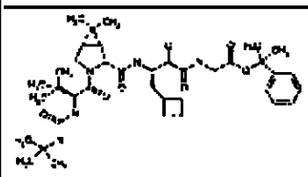
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	752.96	A
	752.96	A
	695.91	C
	695.91	B
	786.92	A
	710.88	A

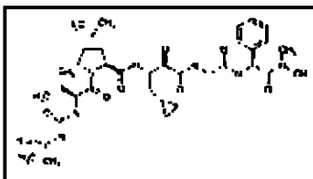
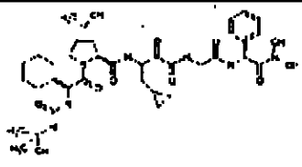
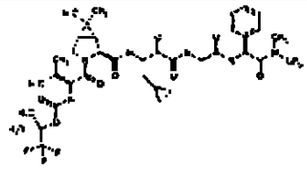
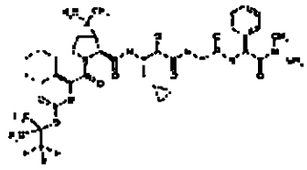
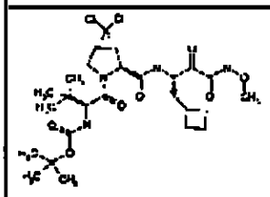
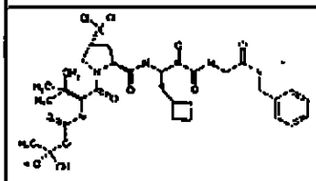
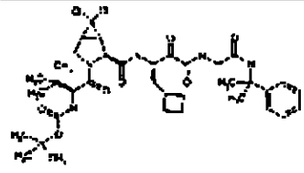
	599.70	A
	573.68	B
	694.92	B
	658.85	B
	596.77	B
	576.74	B
	750.94	A

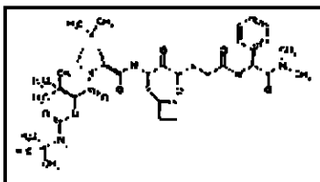
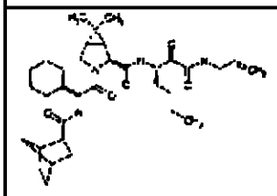
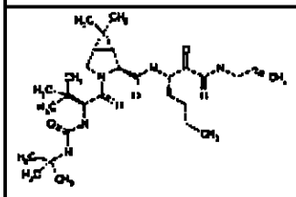
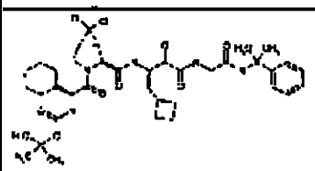
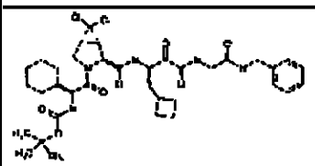
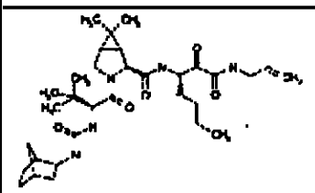
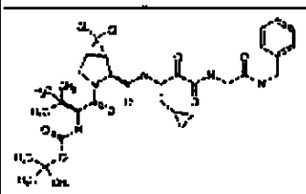
	600.81	B
	600.81	B
	584.81	B
	611.83	A
	600.81	B
	532.69	B
	599.56	A

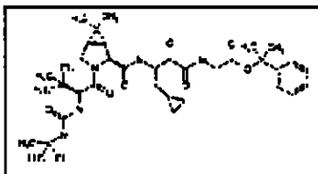
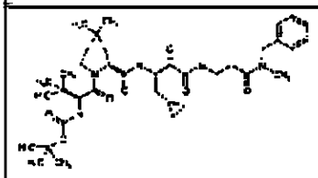
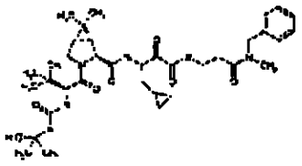
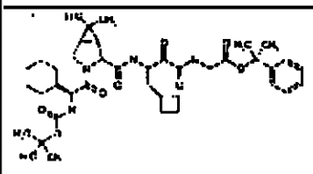
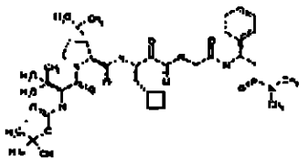
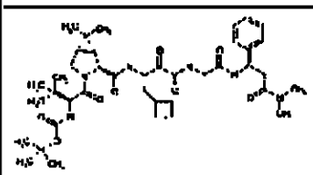
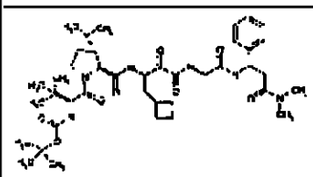
	681.88	A
	646.85	A
	653.89	B
	673.88	A
	652.84	A
	693.91	A
	729.84	A

	667.87	A
	696.89	A
	584.76	A
	658.85	A
	695.91	B
	681.88	B
	611.81	B

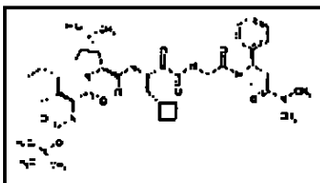
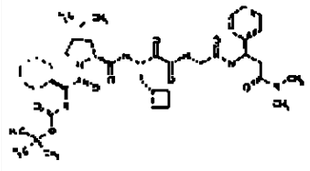
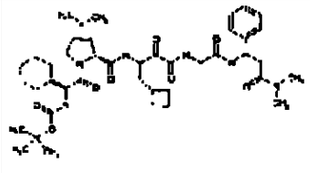
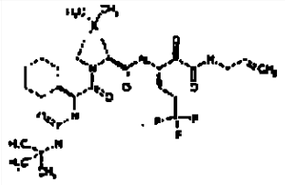
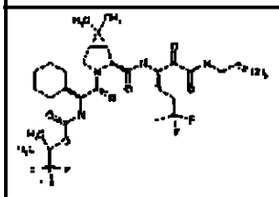
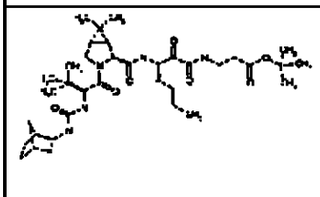
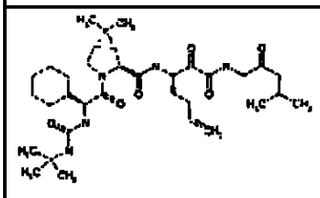
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	688.89	A
	695.86	B
	601.58	B
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	695.91	A

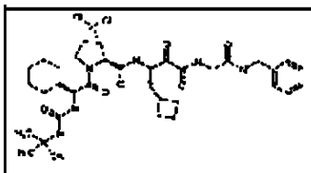
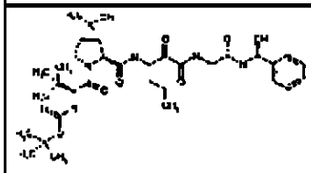
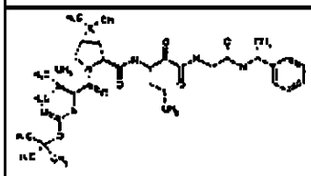
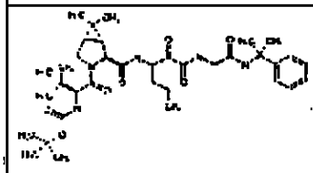
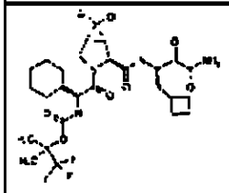
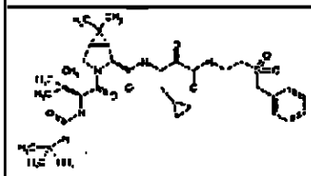
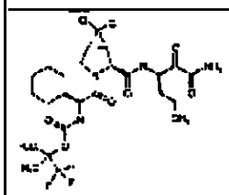
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	749.96	A
	764.85	A
	804.92	A
	591.54	A
	708.69	C
	736.74	C

	737.95	A
	596.82	B
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	762.78	C
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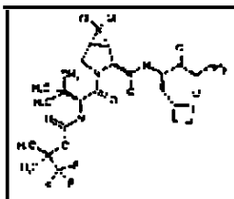
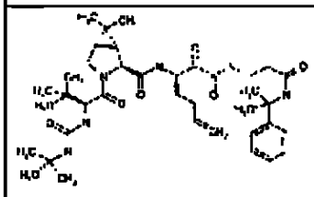
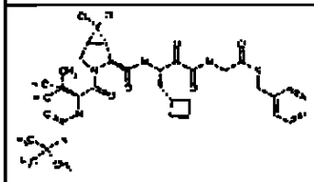
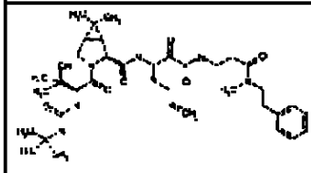
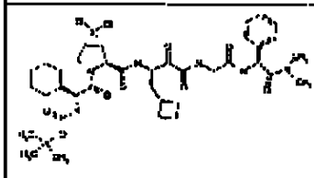
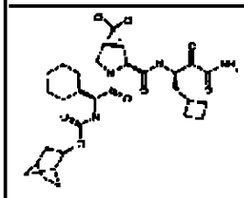
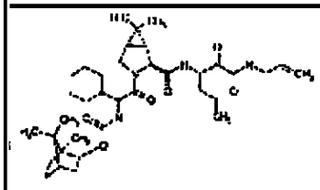
	681.88	A
	681.88	B
	680.90	B
	722.93	C
	752.96	A
	752.96	A
	752.96	A

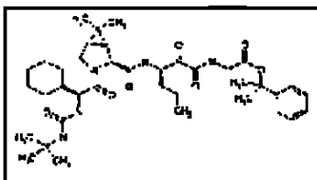
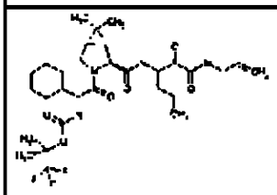
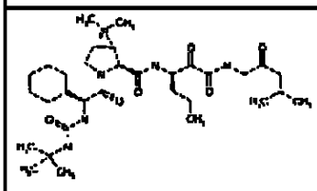
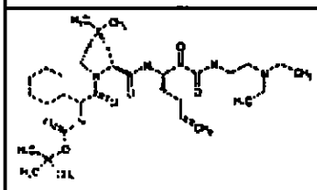
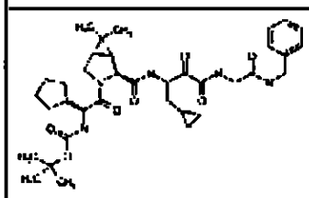
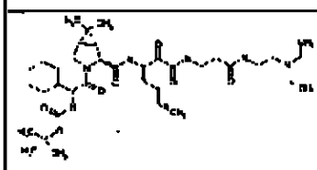
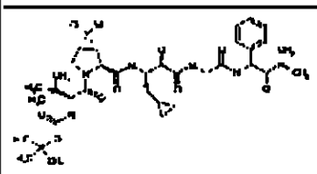
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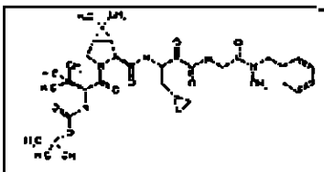
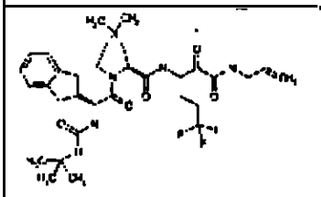
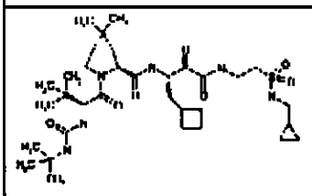
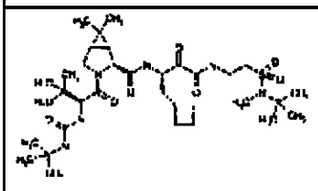
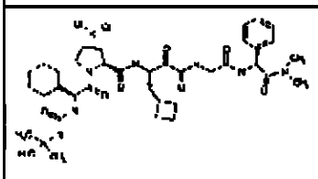
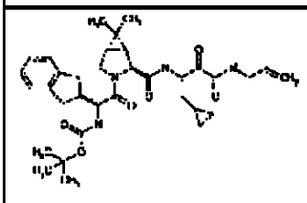
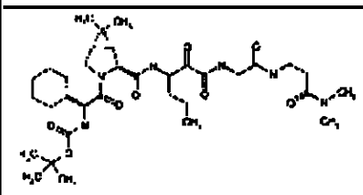
	779.00	A
	779.00	A
	779.00	A
	813.73	C
	656.68	A
	673.90	B
	829.85	B

	733.74	B
	855.84	B
	855.84	B
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	641.52	B
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	816.48	A

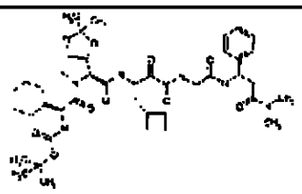
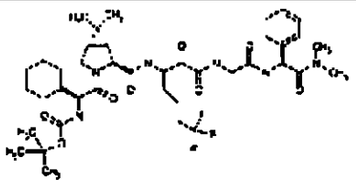
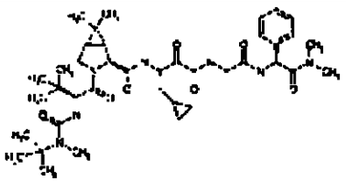
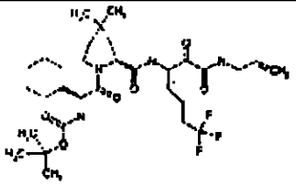
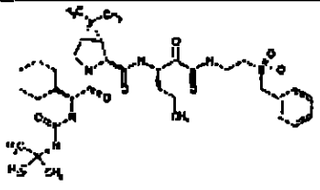
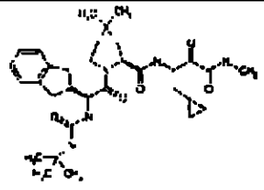
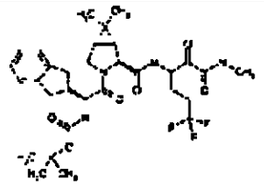
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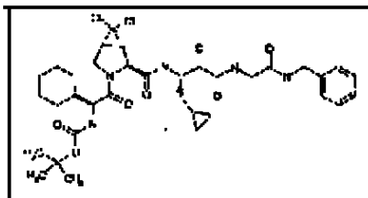
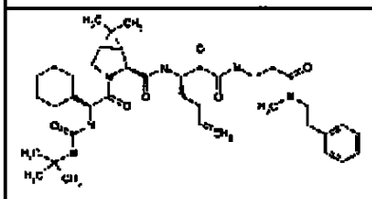
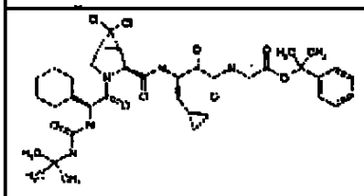
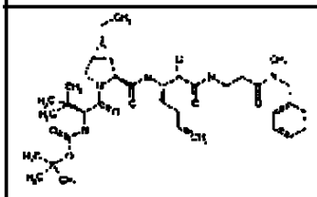
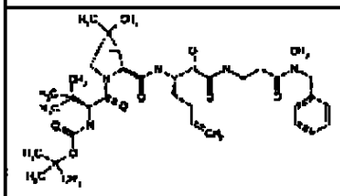
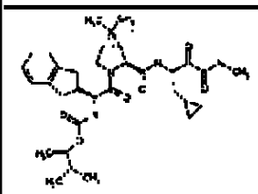
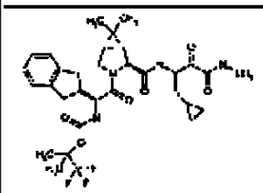
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	694.92	B
	707.70	A
	694.92	A
	805.81	A
	625.60	A
	840.87	B

	695.91	A
	614.71	B
	617.84	B
	631.86	C
	665.84	A
	702.94	C
	765.74	A

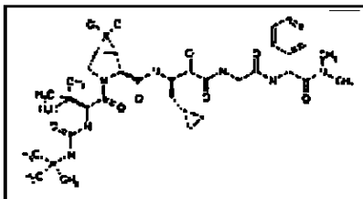
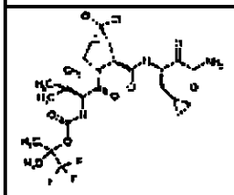
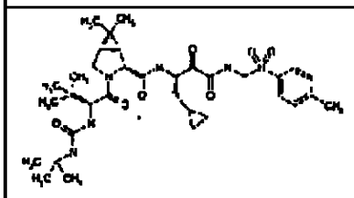
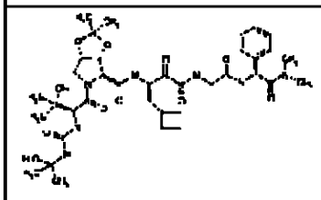
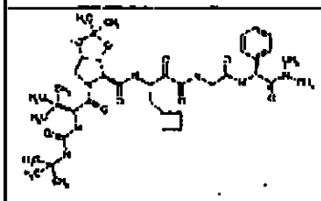
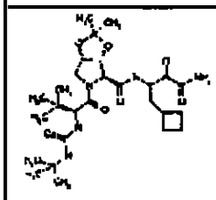
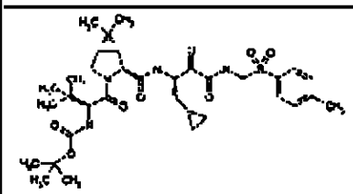
	667.85	C
	648.73	A
	680.91	B
	696.98	C
	804.82	A
	606.77	B
	676.86	A

1186

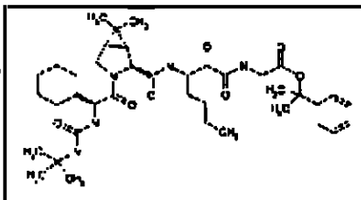
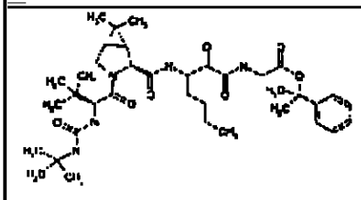
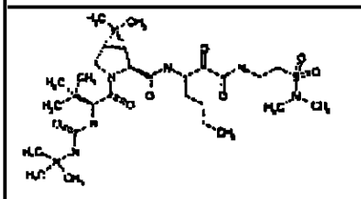
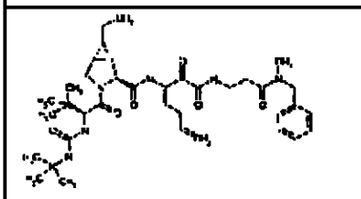
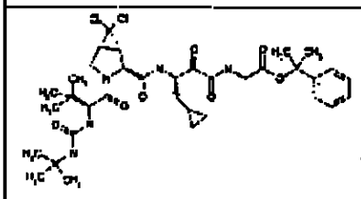
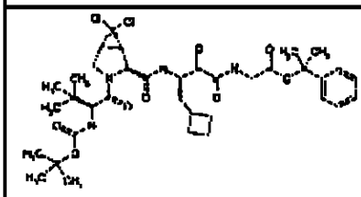
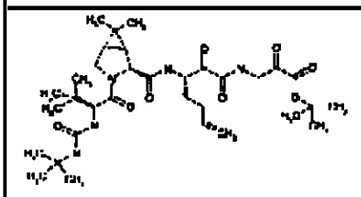
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	806.93	A
	737.95	A
	628.74	B
	701.93	A
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	622.69	B

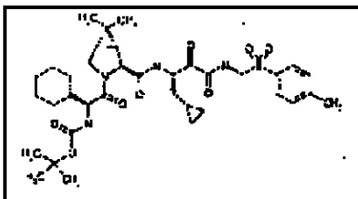
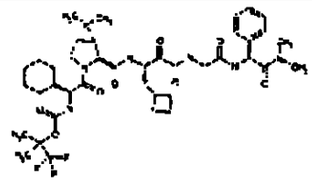
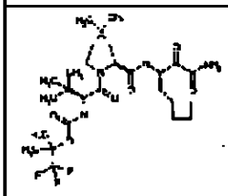
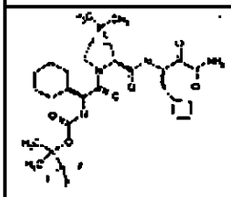
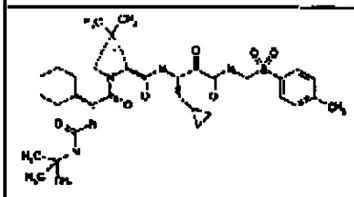
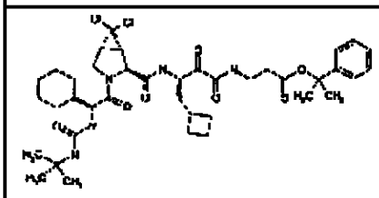
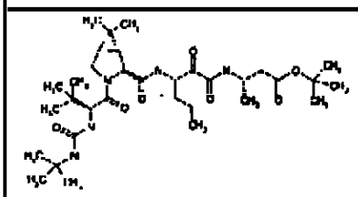
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	720.96	A
	748.75	A
	681.88	B
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	594.76	A
	634.70	A

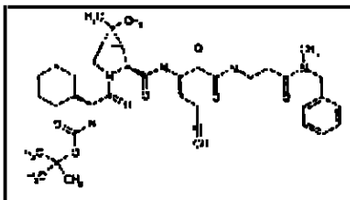
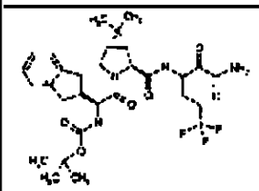
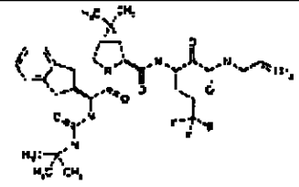
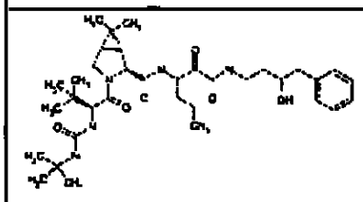
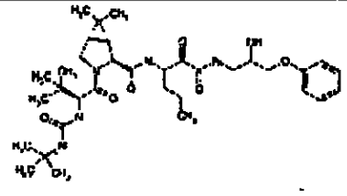
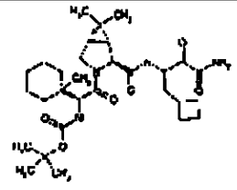
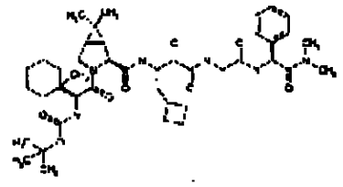
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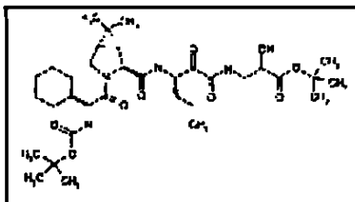
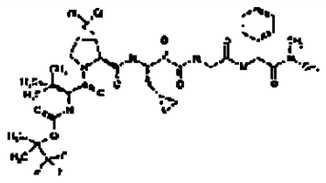
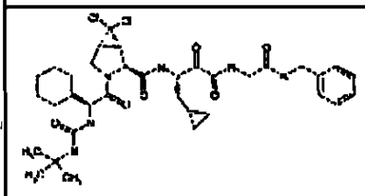
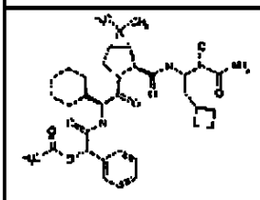
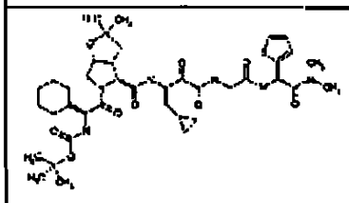
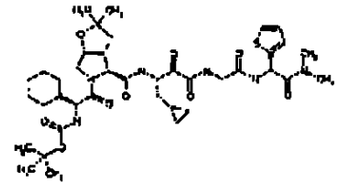
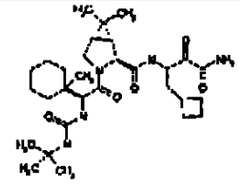
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	601.46	A
	673.88	A
	769.95	B
	769.95	A
	551.69	B
	674.86	B

1189

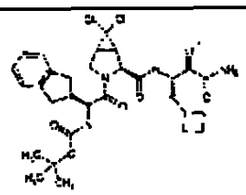
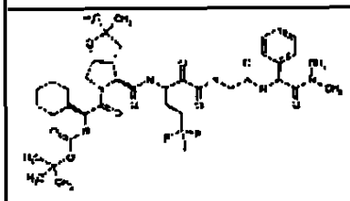
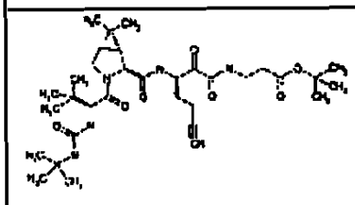
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	683.90	B
	642.87	B
	660.90	B
	722.72	A
	737.73	B
	647.82	B

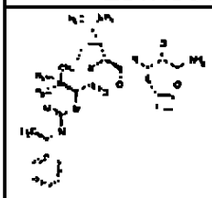
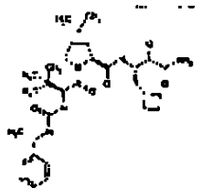
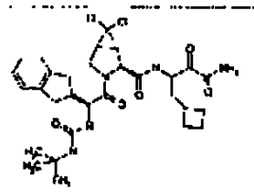
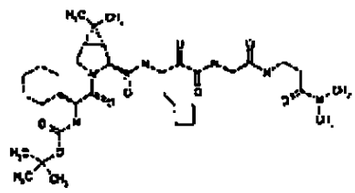
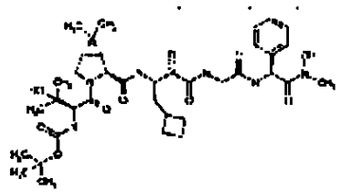
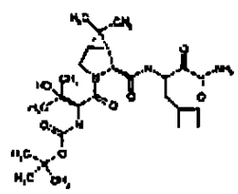
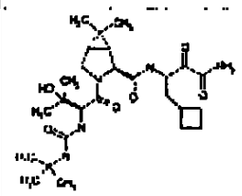
	700.90	A
	818.94	A
	574.65	B
	600.68	A
	699.92	B
	776.81	B
	635.85	A

	706.90	A
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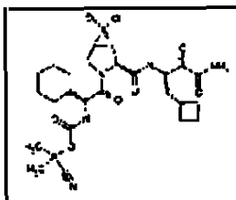
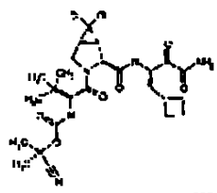
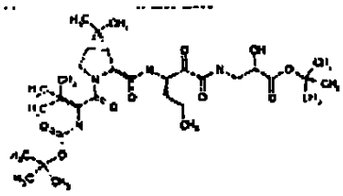
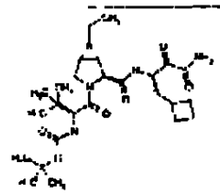
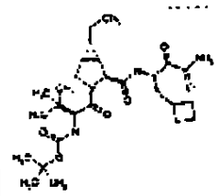
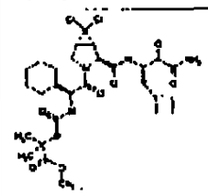
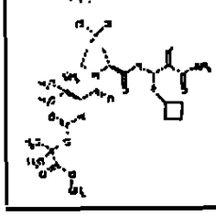
	684.85	A
	819.71	A
	719.72	A
	622.77	A
	787.00	A
	787.00	A
	559.76	A

A193

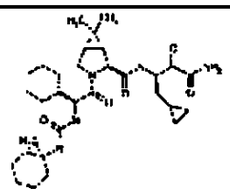
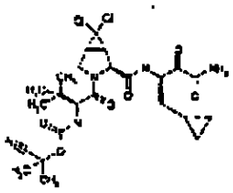
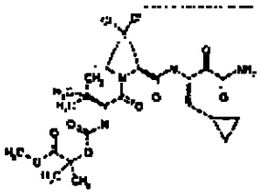
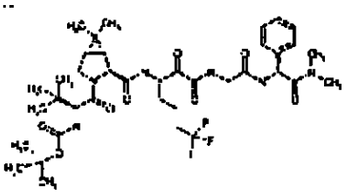
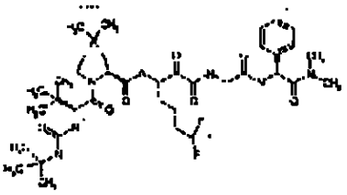
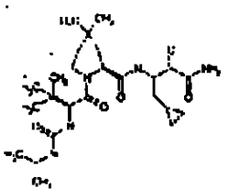
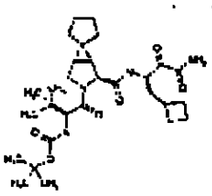
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	822.93	A
	631.82	A

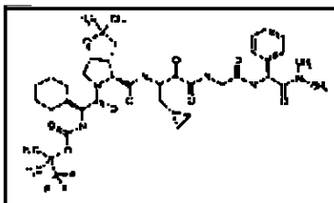
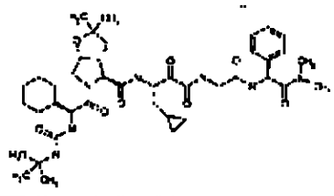
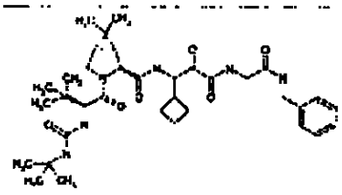
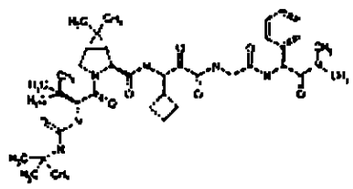
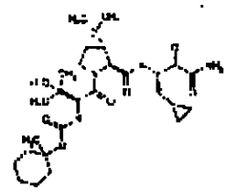
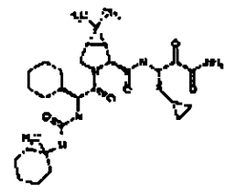
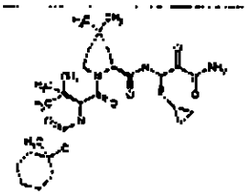
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	567.74	A
	620.58	A
	702.90	A
	740.91	A
	522.65	B
	521.66	B

1195

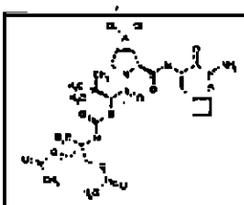
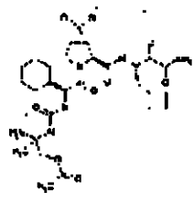
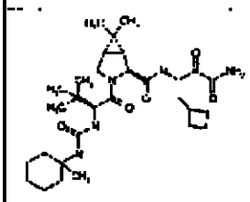
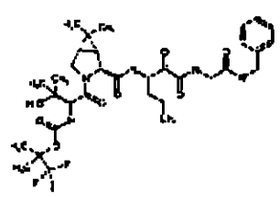
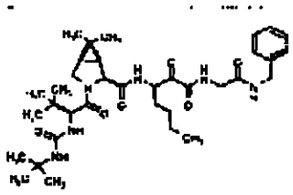
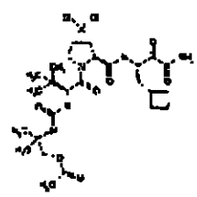
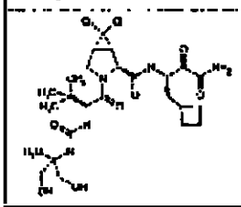
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	572.49	B
	638.81	B
	520.68	C
	520.68	B
	631.58	B
	605.52	B

1196

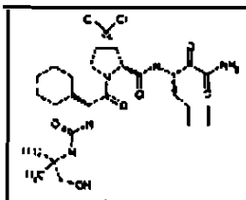
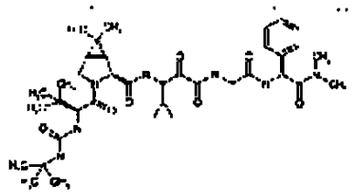
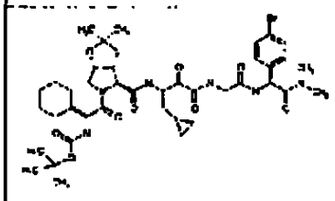
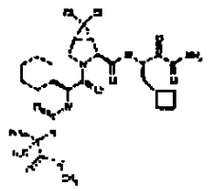
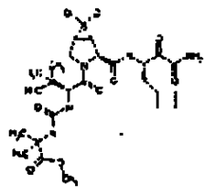
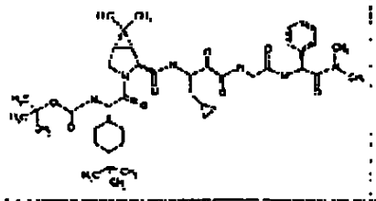
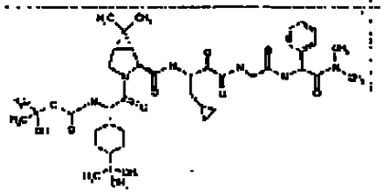
	571.77	A
	558.47	A
	581.49	A
	780.89	A
	779.91	A
	491.64	B
	546.71	B

	834.94	A
	779.99	A
	852.84	A
	723.92	A
	545.73	A
	572.75	A
	546.71	A

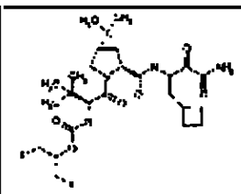
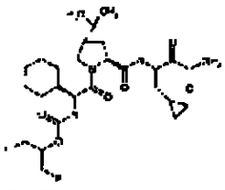
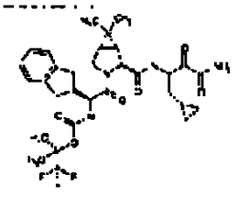
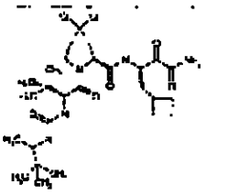
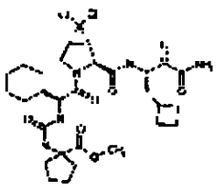
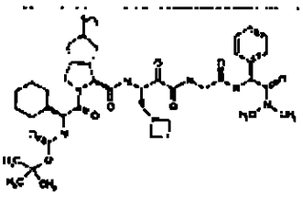
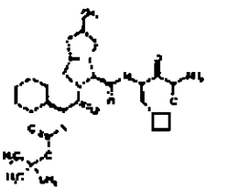
1198

	676.60	B
	644.60	B
	559.76	A
	695.79	A
	654.86	A
	618.56	B
	692.53	B

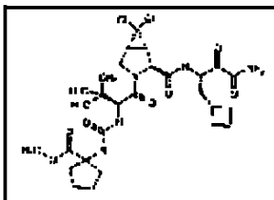
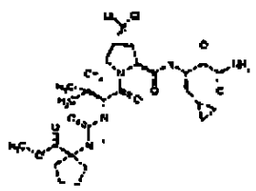
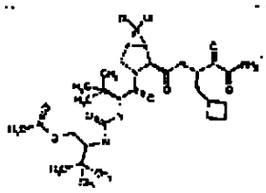
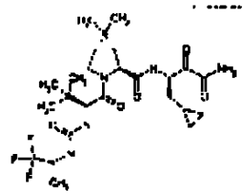
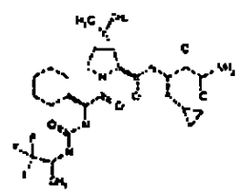
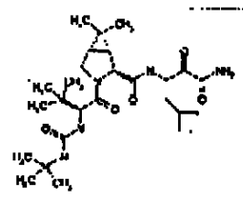
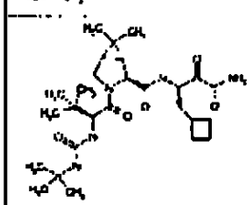
1 191

	602.56	B
	709.89	A
	659.87	A
	630.57	A
	604.54	A
	807.05	A
	807.05	A

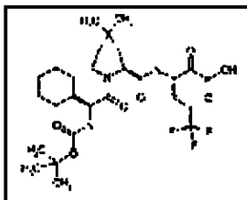
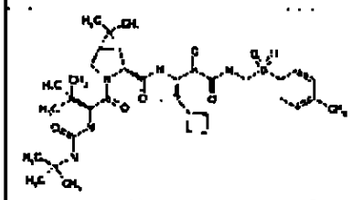
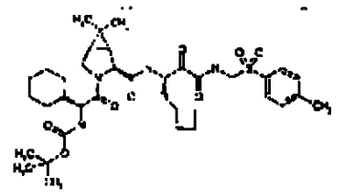
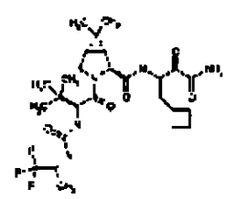
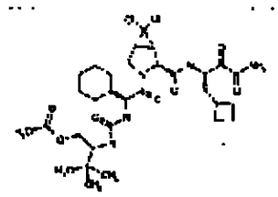
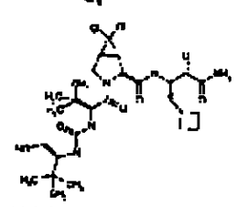
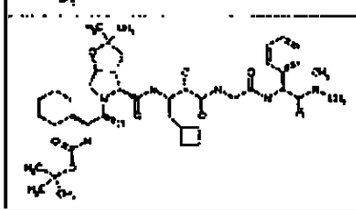
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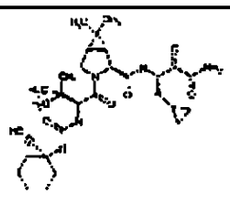
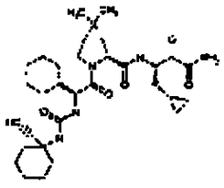
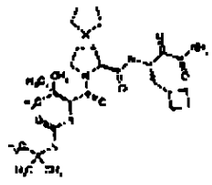
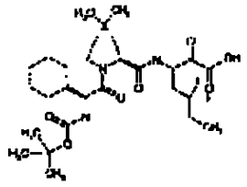
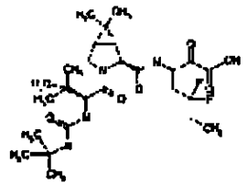
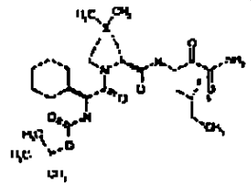
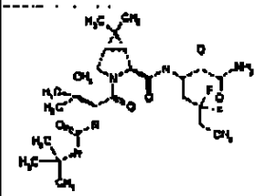
	542.63	B
	554.64	A
	620.68	A
	586.58	A
	656.81	B
	779.00	A
	560.74	B

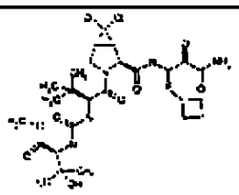
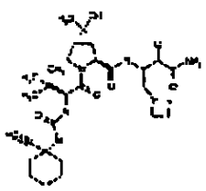
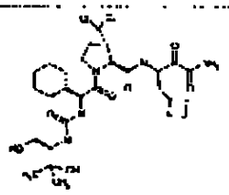
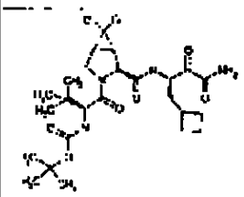
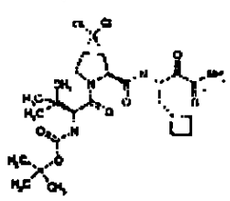
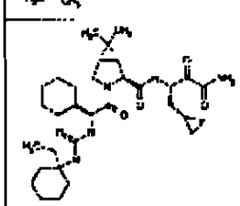
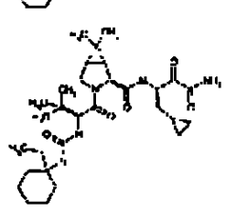
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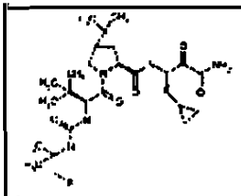
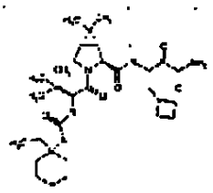
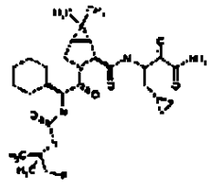
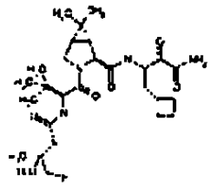
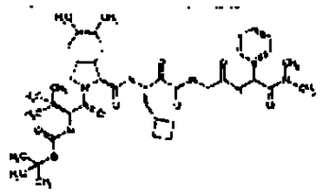
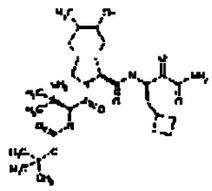
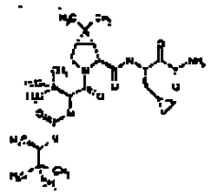
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	616.55	B
	646.62	A
	545.61	B
	571.65	B
	519.69	A
	519.69	B

1202

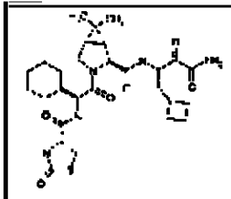
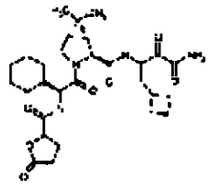
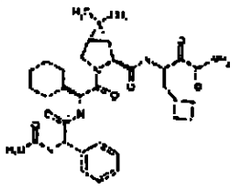
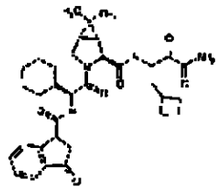
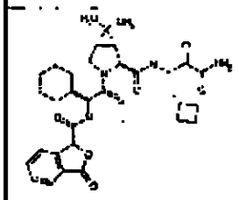
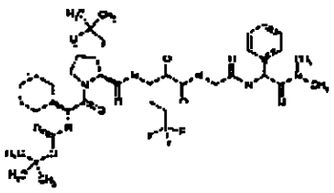
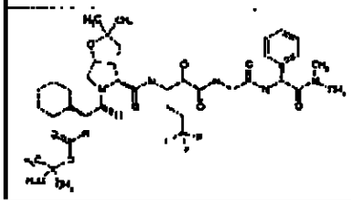
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	687.91	B
	714.93	B
	559.63	A
	672.66	A
	604.58	B
	795.00	A

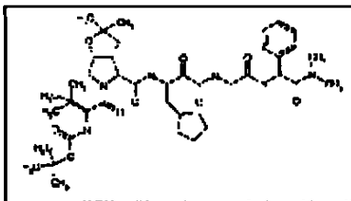
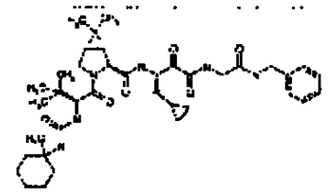
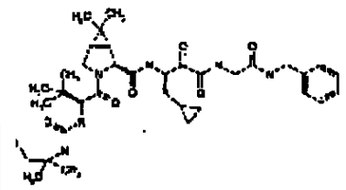
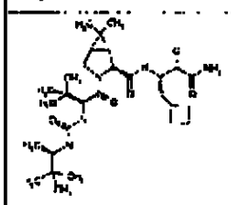
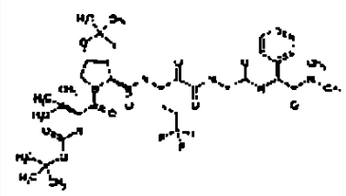
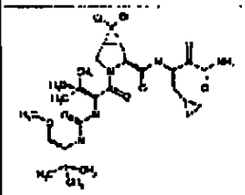
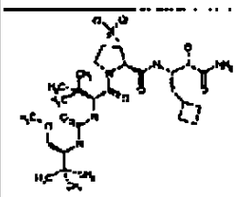
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	581.76	A
	545.73	B
	571.67	B
	644.65	B
	570.68	B
	543.66	B

	634.56	B
	569.75	A
	630.62	B
	561.51	C
	561.51	A
	585.79	A
	559.76	A

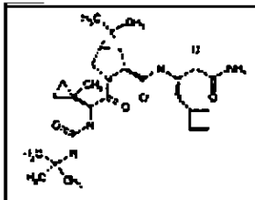
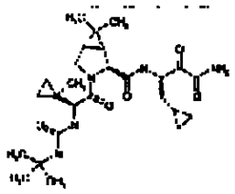
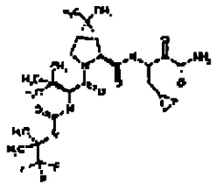
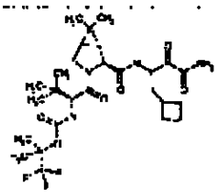
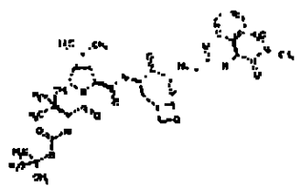
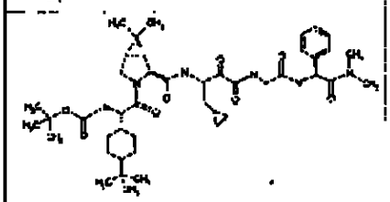
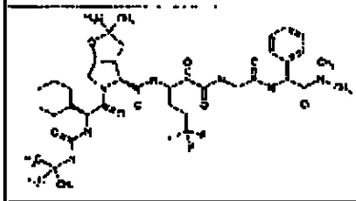
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	573.78	A
	549.69	A
	537.68	A
	781.01	A
	562.76	B
	633.72	A

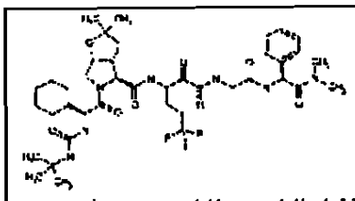
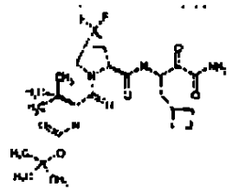
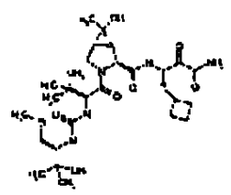
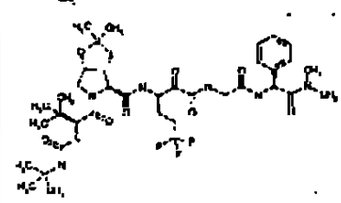
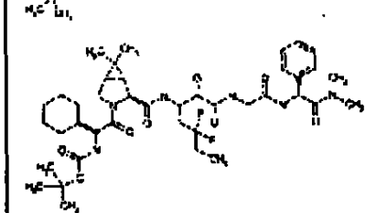
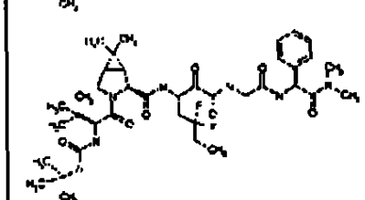
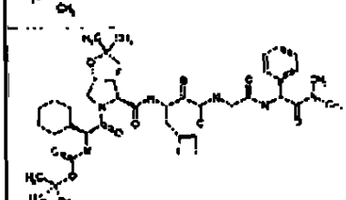
1206

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	558.68	A
	621.78	A
	604.75	B
	606.73	A
	822.93	A
	822.93	A

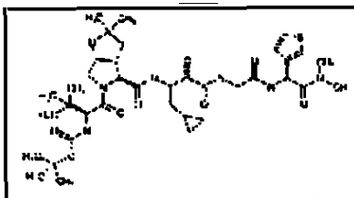
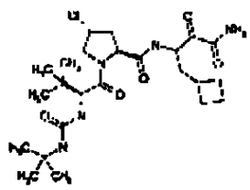
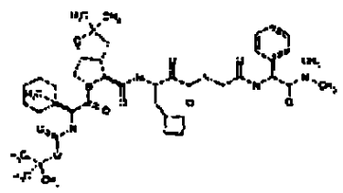
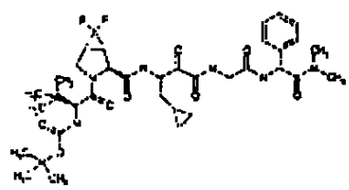
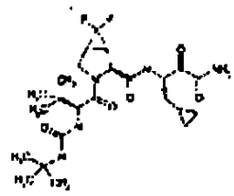
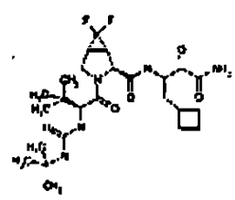
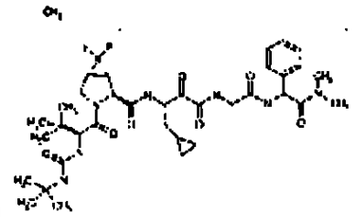
	782.99	A
	692.91	A
	670.83	A
	547.74	A
	796.89	A
	604.58	A
	618.61	A

1206

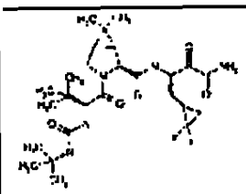
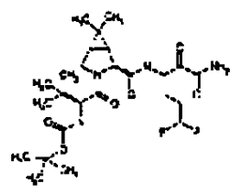
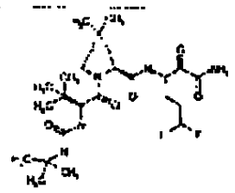
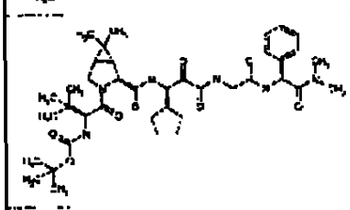
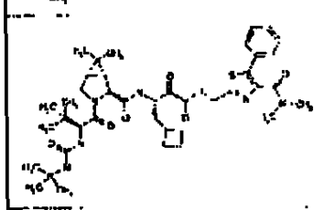
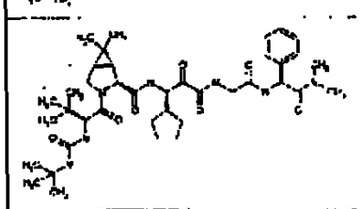
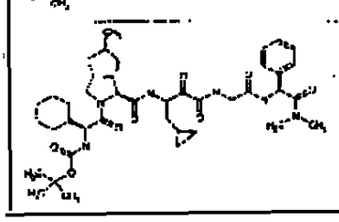
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	503.65	B
	559.63	A
	573.66	A
	739.92	A
	807.05	A
	821.95	A

	821.95	A
	528.60	B
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	795.91	A
	788.94	A
	761.92	A
	795.00	A

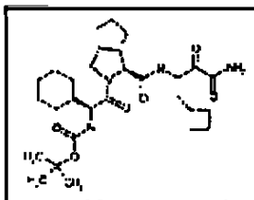
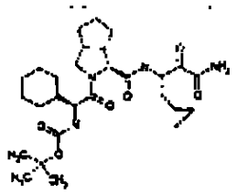
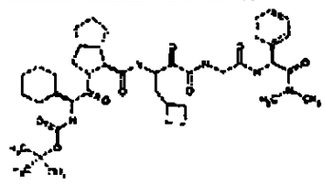
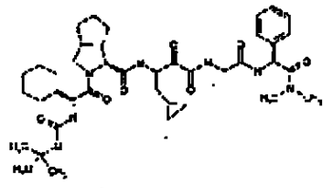
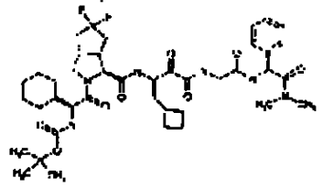
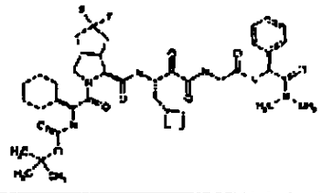
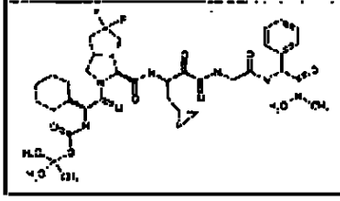
1210

	780.96	A
	514.07	B
	809.02	A
	732.83	A
	513.59	B
	627.62	B
	731.85	A

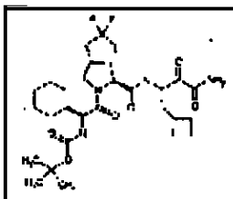
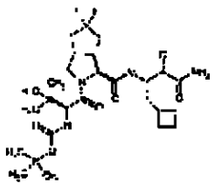
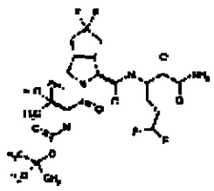
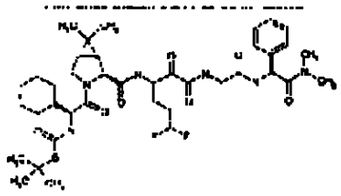
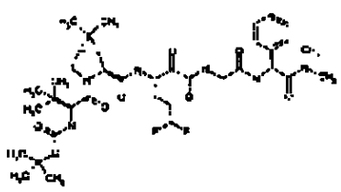
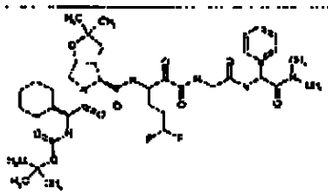
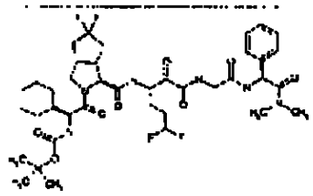
1211

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	530.62	B
	529.63	B
	738.93	A
	764.01	B
	737.95	A
	764.97	A

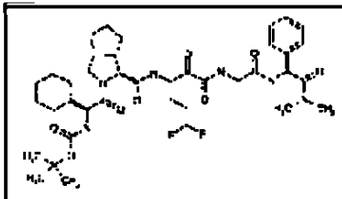
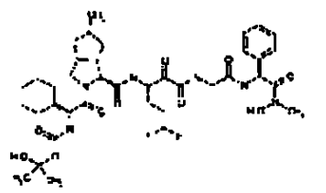
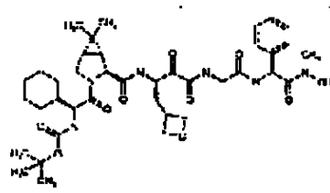
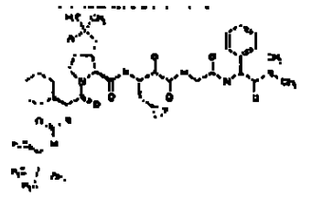
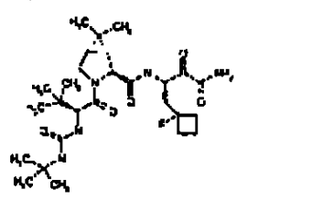
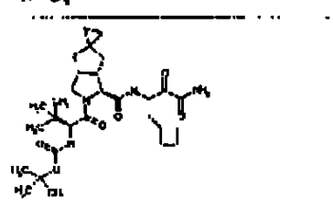
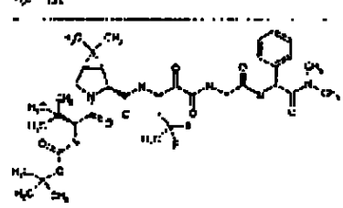
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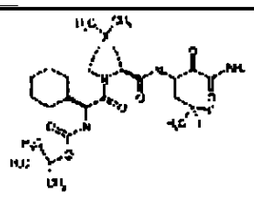
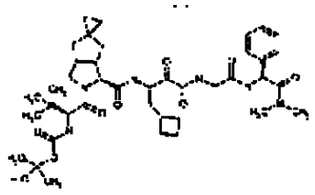
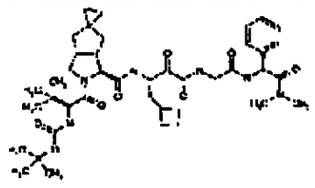
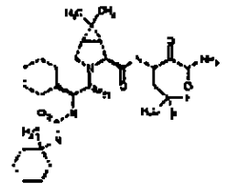
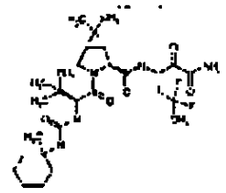
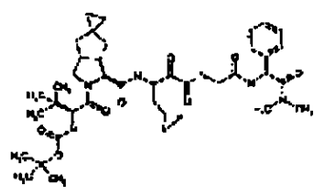
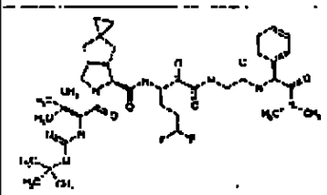
	546.71	B
	532.69	B
	764.97	A
	750.94	A
	800.95	A
	800.95	A
	786.92	A

1213
1273

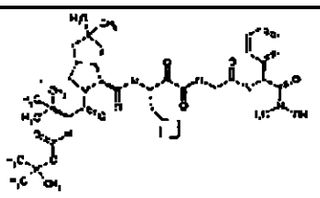
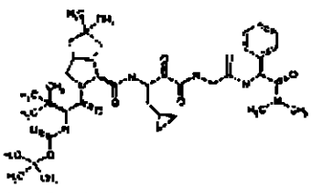
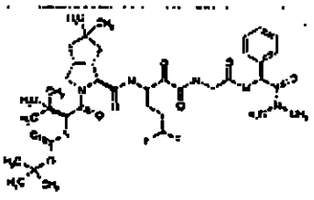
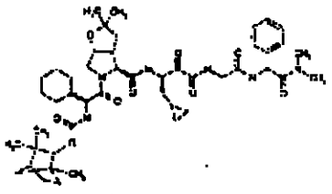
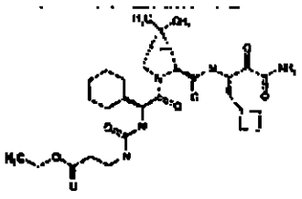
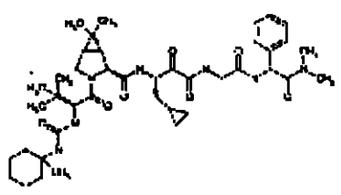
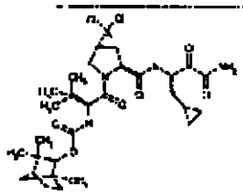
	582.69	B
	556.66	B
	566.60	B
	774.91	A
	748.88	A
	804.94	A
	810.89	A

1214

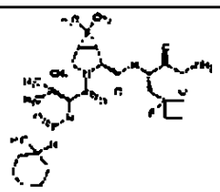
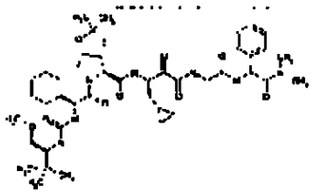
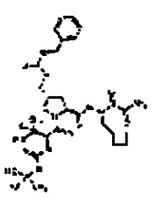
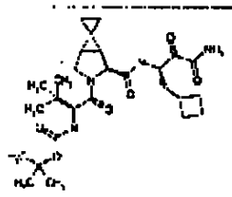
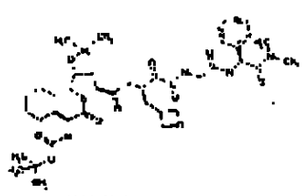
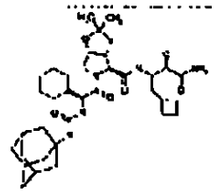
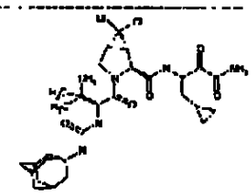
	774.91	A
	788.94	A
	766.94	A
	808.04	A
	537.68	B
	546.71	B
	748.88	B

	556.66	B
	764.97	B
	764.97	A
	595.74	B
	569.70	A
	750.94	A
	774.91	A

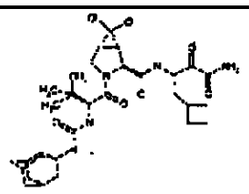
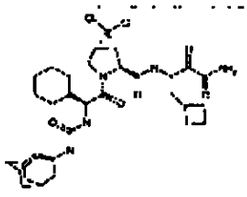
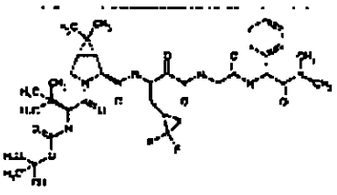
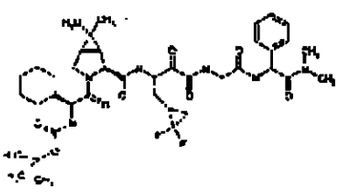
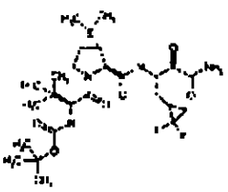
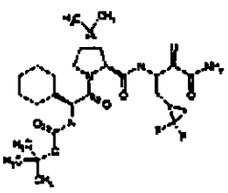
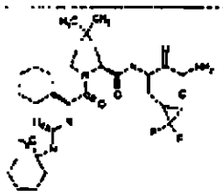
1216

	766.99	A
	752.96	A
	776.93	A
	851.10	A
	589.74	A
	763.99	A
	627.61	A

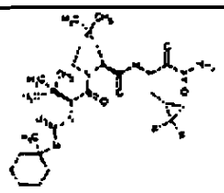
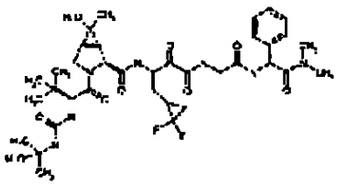
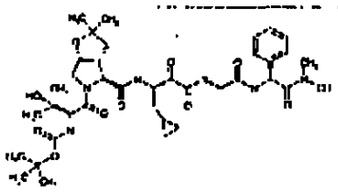
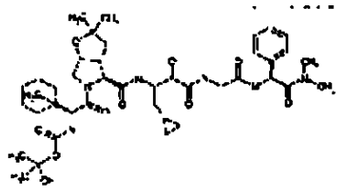
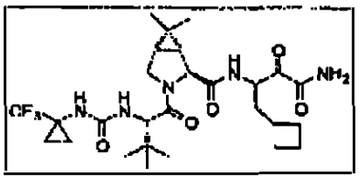
1217

	577.75	A
	838.07	A
	642.80	B
	518.66	B
	786.97	A
	653.87	B
	624.61	A

1248

	638.64	A
	664.68	A
	780.89	A
	786.92	A
	542.63	A
	568.67	A
	607.75	A

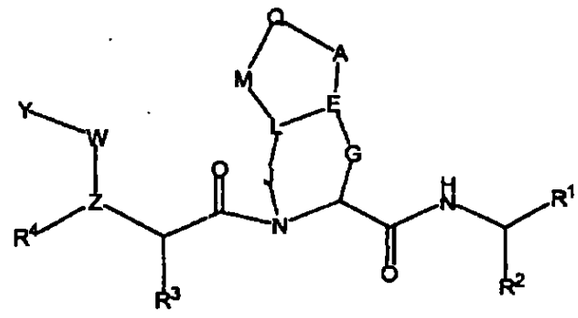
1219

	581.71	A
	759.90	A
	756.90	A
	795.00	A
	571.63	A

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo.

1. Un compuesto, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra en la Fórmula I:



Fórmula I

donde:

Y se selecciona del grupo formado por alquilo, alquil-arilo, heteroalquilo, heteroarilo, aril-heteroarilo, alquil-heteroarilo, cicloalquilo, alquiloxi, alquil-ariloxi, ariloxi, heteroariloxi, heterocicloalquiloxi, cicloalquiloxi, alquilamino, arilamino, alquil-arilamino, arilamino, heteroarilamino, cicloalquilamino y heterocicloalquilamino, con la salvedad de que Y puede estar sustituido en forma opcional con X^{11} o X^{12};

X^{11} es alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquil-alquilo, heterociclilo, heterociclilalquilo, arilo, alquilarilo, arilalquilo, heteroarilo, alquilheteroarilo, o heteroarilalquilo, con la salvedad de que X^{11} puede estar sustituido adicionalmente en forma opcional con X^{12};

X^{12} es hidroxi, alcoxi, ariloxi, tio, alquiltio, ariltio, amino, alquilamino, arilamino, alquilsulfonilo, arilsulfonilo, alquilsulfonamido, arilsulfonamido, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halógeno, ciano, o nitro, con la salvedad de que dicho alquilo, alcoxi, y arilo pueden estar sustituidos adicionalmente en forma opcional con restos seleccionados en forma independiente de X^{12};

R^1 es $-C(O)R^5$

R^5 es H, -OH, $-OR^8$, $-NR^9R^{10}$,

Z se selecciona de O, N, C(H) o C(R);

W puede estar presente o ausente, y si W está presente, W se selecciona de C(=O), C(=S), C(=N-CN), o $S(O_2)$;

Q puede estar presente o ausente, y cuando Q está presente, Q es C(H), N, P, $(CH_2)_p$, $(CHR)_p$, $(CRR')_p$, O, NR, S, o SO_2; y cuando Q está ausente, M puede estar presente o ausente; cuando Q y M están ausentes, A está ligado directamente a L;

A es O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, N(R), S, $S(O_2)$ o un enlace;

E es CH, N, CR, o un enlace doble hacia A, L o G;

G puede estar presente o ausente, y cuando G está presente, G es $(CH_2)_p$, $(CHR)_p$, o $(CRR')_p$; y cuando G está ausente, J está presente y E está conectado directamente al átomo de carbono en la Fórmula I como está ligado G;

J puede estar presente o ausente, y cuando J está presente, J es $(CH_2)_p$, $(CHR)_p$, o $(CRR')_p$, $S(O_2)$, N(H), N(R) u O; y cuando J está ausente, G está presente y E está ligado directamente a N como se muestra en la Formula I ligado a J;

L puede estar presente o ausente, y cuando L está presente, L es C(H), C(R), O, S o N(R); y cuando L está ausente, entonces M puede estar presente o

ausente; y si M está presente y L está ausente, entonces M está ligado directa e independientemente a E, y J está ligado directa e independientemente a E;

M puede estar presente o ausente, y cuando M está presente, M es O, NR, S, $S(O_2)$, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, o $(CRR')_p$;

p es un número desde 0 hasta 6; y

R, R', R^2, R^3 y R^4 pueden ser iguales o diferentes y se seleccionan independientemente del grupo formado por H; alquilo de C_1-C_{10}; alquenilo de C_2-C_{10}; cicloalquilo de C_3-C_8; heterocicloalquilo de C_3-C_8, alcoxi, ariloxi, alquiltio, ariltio, amino, amido, éster, ácido carboxílico, carbamato, urea, cetona, aldehído, ciano, nitro, halógeno; (cicloalquil)alquilo y (heterocicloalquil)alquilo, donde dicho cicloalquilo está formado por tres hasta ocho átomos de carbono, y desde cero hasta seis átomos de oxígeno, nitrógeno, azufre o fósforo, y dicho alquilo tiene desde uno hasta seis átomos de carbono; arilo; heteroarilo; alquil-arilo; y alquil-heteroarilo;

donde dichos restos alquilo, heteroalquilo, alquenilo, heteroalquenilo, arilo, heteroarilo, cicloalquilo y heterocicloalquilo pueden estar sustituidos opcionalmente y en forma apropiada por medios químicos, donde dicho término "sustituido" se refiere a una sustitución opcional y apropiada químicamente con uno o más restos seleccionados del grupo formado por alquilo, alquenilo, alquinilo, arilo, aralquilo, cicloalquilo, heterocíclico, halógeno, hidroxi, tio, alcoxi, ariloxi, alquiltio, ariltio, amino, amido, éster, ácido carboxílico, carbamato, urea, cetona, aldehído, ciano, nitro, sulfonamido, sulfóxido, sulfona, sulfonil urea, hidrazida, y hidroxamato;

además donde dicha unidad N-C-G-E-L-J-N en la Fórmula I representa tanto una estructura anular cíclica de cinco miembros como una estructura anular cíclica de seis miembros con la salvedad de que cuando dicha unidad N-C-G-E-L-J-N

representa una estructura anular cíclica de cinco miembros, o cuando la estructura anular bicíclica en la Fórmula I que comprende N, C, G, E, L, J, N, A, Q, y M representa una estructura anular cíclica de cinco miembros, entonces dicha estructura anular cíclica de cinco miembros carece de un grupo carbonilo como parte del anillo cíclico.

2. El compuesto de la reivindicación 1, en la cual R^1 es $-C(O)C(O)NR^9R^{10}$;

R9 es H;

R^{10} es H, $-R^{14}$, $-[CH(R^{1'})]_pC(O)OR^{11}$, $-[CH(R^{1'})]_pC(O)NR^{12}R^{13}$, $-[CH(R^{1'})]_pS(O_2)R^{11}$, $-[CH(R^{1'})]_pS(O_2)NR^{12}R^{13}$, $-[CH(R^{1'})]_pC(O)R^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$, o $-CH(R^{1'})C(O)N(H)CH(R^{2'})$ (R'), donde R^{14} es H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo, alquenilo, alquinilo o heteroaralquilo.

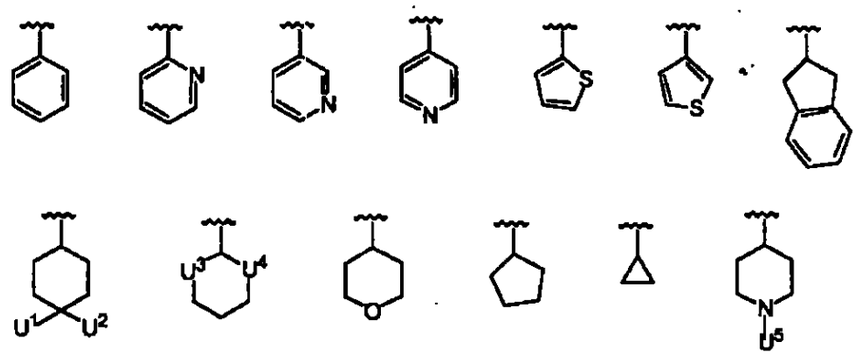
3. El compuesto de la reivindicación 2, en el cual R^{10} es H, $-R^{14}$, $-CH(R^{1'})C(O)OR^{11}$, $-CH(R^{1'})CH(R^{1'})C(O)OR^{11}$, $-CH(R^{1'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})C(O)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})S(O_2)R^{11}$, $-CH(R^{1'})CH(R^{1'})S(O_2)NR^{12}R^{13}$, $-CH(R^{1'})CH(R^{1'})C(O)R^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)OR^{11}$, $-CH(R^{1'})C(O)N(H)CH(R^{2'})C(O)NR^{12}R^{13}$, o $-CH(R^{1'})C(O)N(H)CH(R^{2'})$ (R'), donde $R^{1'}$ es H o alquilo, y $R^{2'}$ es fenilo, fenilo sustituido, fenilo sustituido con un heteroátomo, tiofenilo, cicloalquilo, piperidilo o piridilo.

4. El compuesto de la reivindicación 3, en el cual $R^{1'}$ es H.

5. El compuesto de la reivindicación 4, en el cual R^{11} es H, metilo, etilo, alilo, *ter*-butilo, bencilo, α-metilbencilo, α,α-dimetilbencilo, 1-metilciclopropilo o 1-metilciclopentilo;

R' es hidroximetilo o $-CH_2C(O)NR^{12}R^{13}$

$R^{2'}$ se selecciona en forma independiente, del grupo formado por:



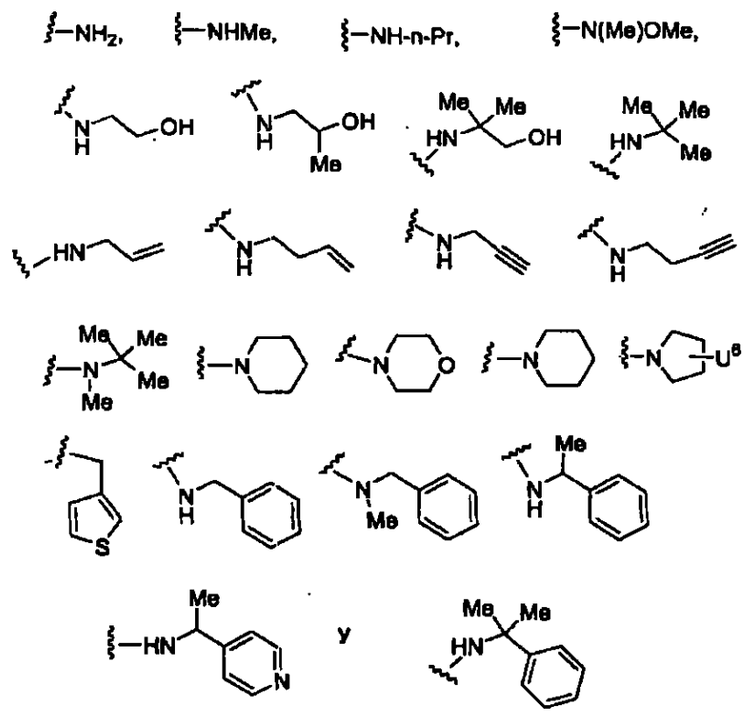
donde

U^1 y U^2 pueden ser iguales o diferentes y se seleccionan de H, F, CH_2COOH, CH_2COOMe, CH_2CONH_2, $CH_2CONHMe$, CH_2CONMe_2, azido, amino, hidroxilo, amino sustituido e hidroxilo sustituido;

U^3 y U^4 pueden ser iguales o diferentes y se seleccionan de O y S;

U^5 se selecciona del grupo formado por los restos formados por alquilsulfonilo, arilsulfonilo, heteroalquilsulfonilo, heteroarilsulfonilo, alquilcarbonilo, arilcarbonilo, heteroalquilcarbonilo, heteroarilcarbonilo, alcoxicarbonilo, ariloxicarbonilo, heteroariloxicarbonilo, alquilaminocarbonilo, arilaminocarbonilo, heteroarilaminocarbonilo o una de sus combinaciones;

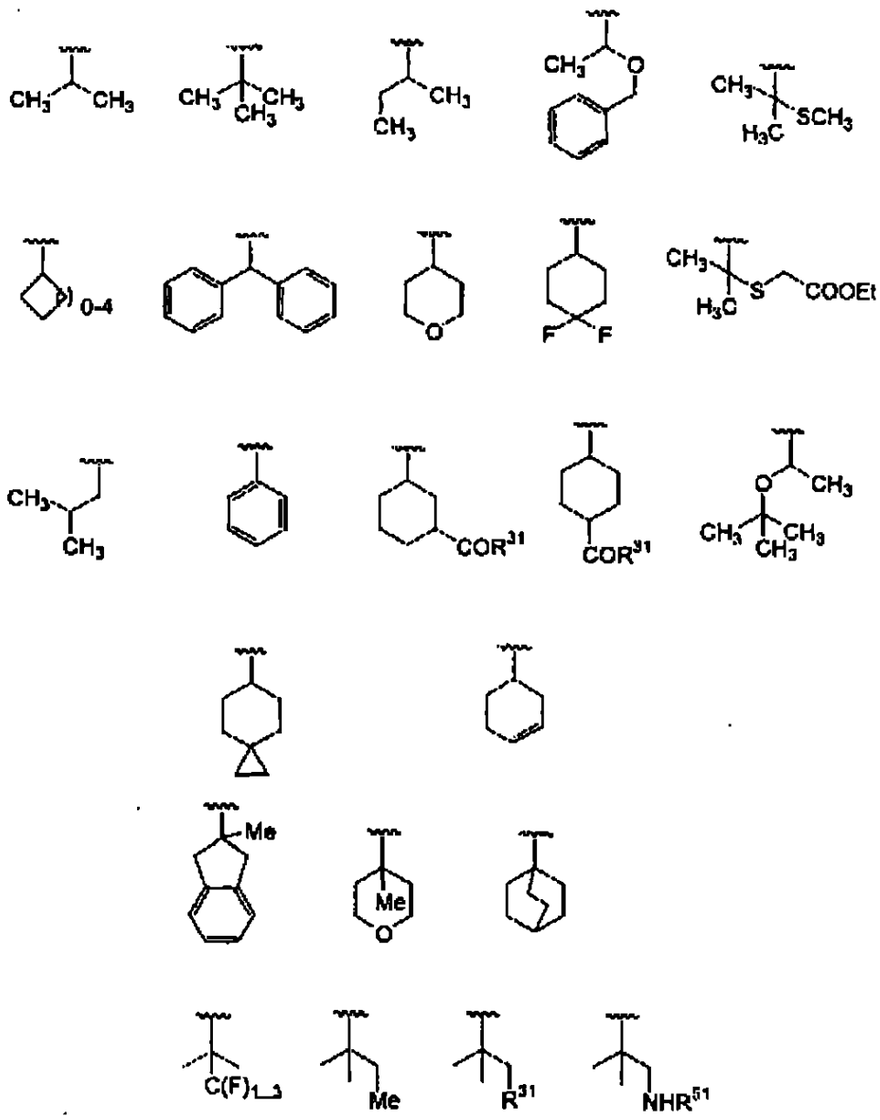
y $NR^{12}R^{13}$ se selecciona del grupo formado por:



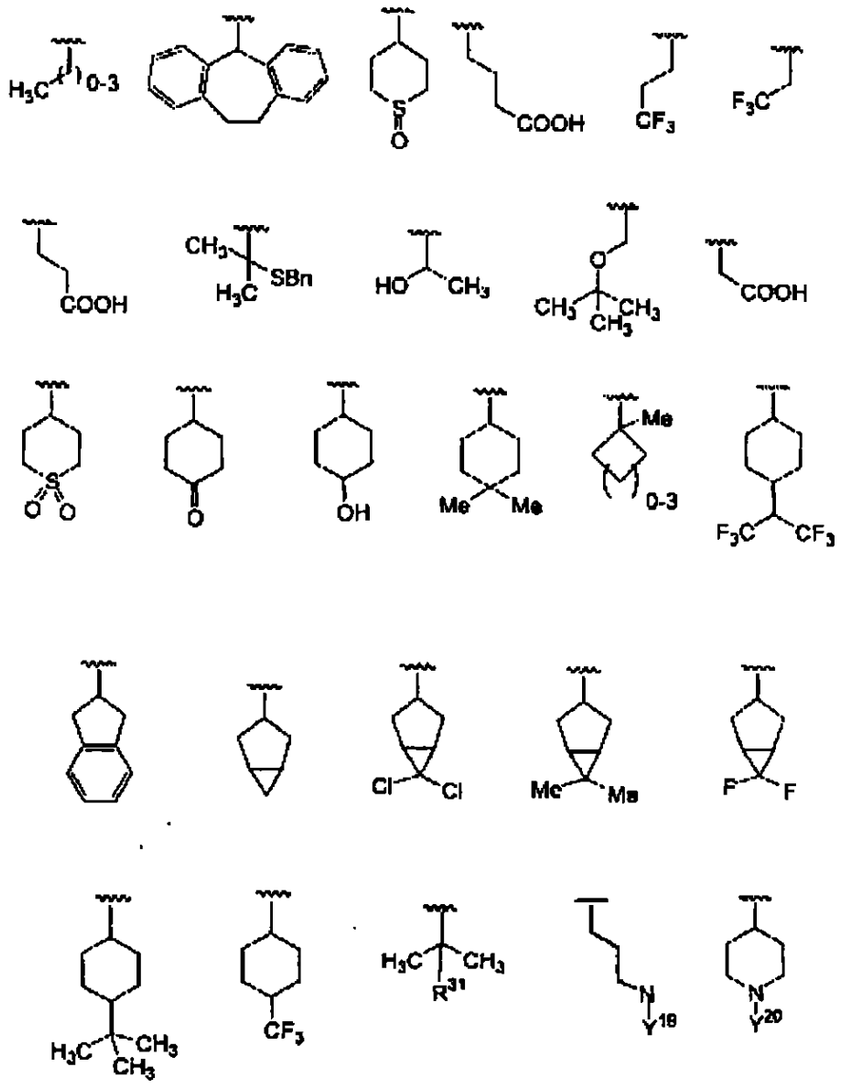
donde U^6 es H, OH, o CH_2OH; y

R^{14} se selecciona del grupo formado por: H, Me, Et, *n*-propilo, metoxi, ciclopropilo, *n*-butilo, 1-but-3-inilo, bencilo, α-metilbencilo, fenetilo, alilo, 1-but-3-enilo, OMe y ciclopropilmetilo.

6. El compuesto de la reivindicación 5, en el cual R^3 se selecciona del grupo formado por:

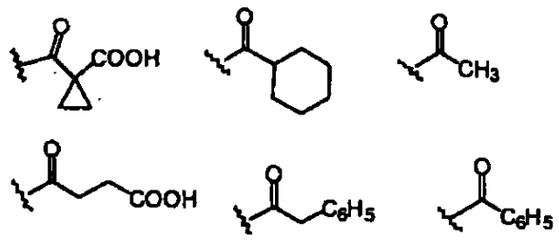


donde R^{51} = H, -$COCH_3$, -COOtBu o -CONHtBu;

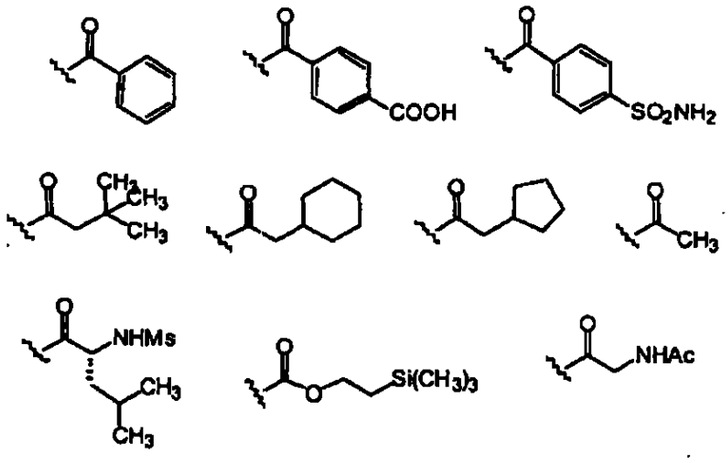


donde R^{31} = OH u OH-alquilo;

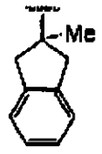
Y^{19} se selecciona de los siguientes restos:



y Y^{20} se selecciona de los siguientes restos:



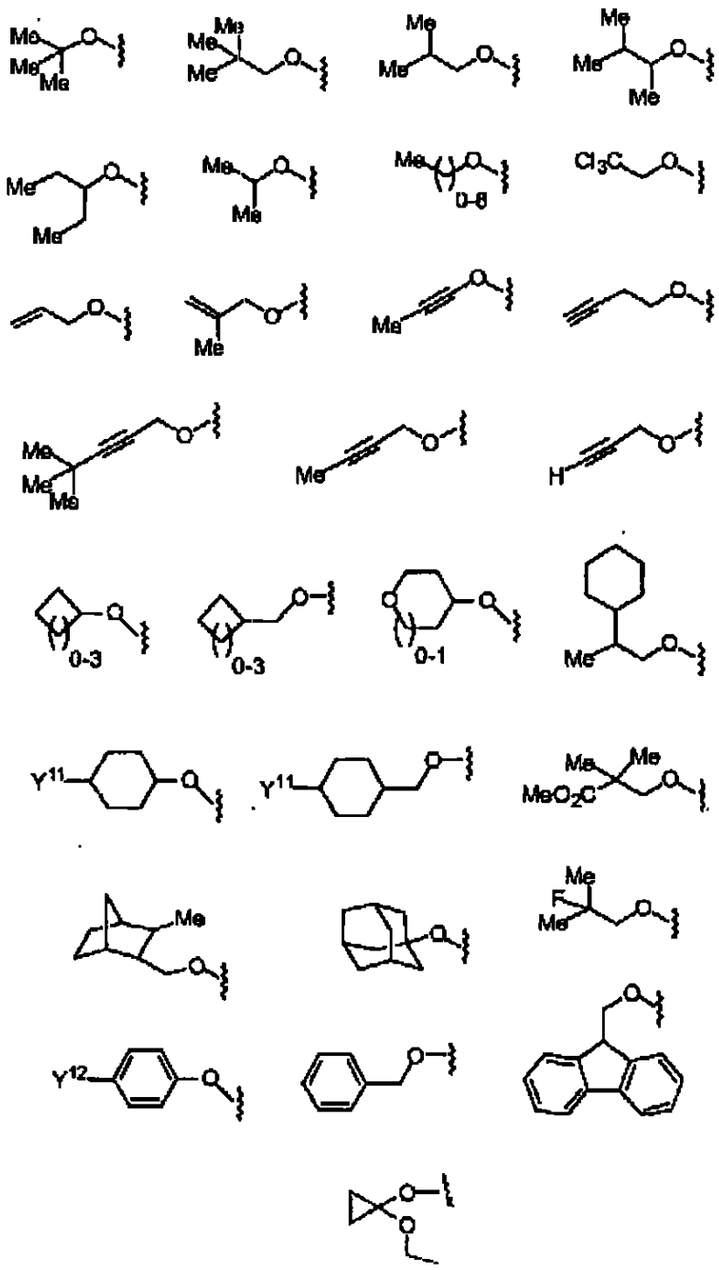
7. El compuesto de la reivindicación 6, en el cual R^3 es:

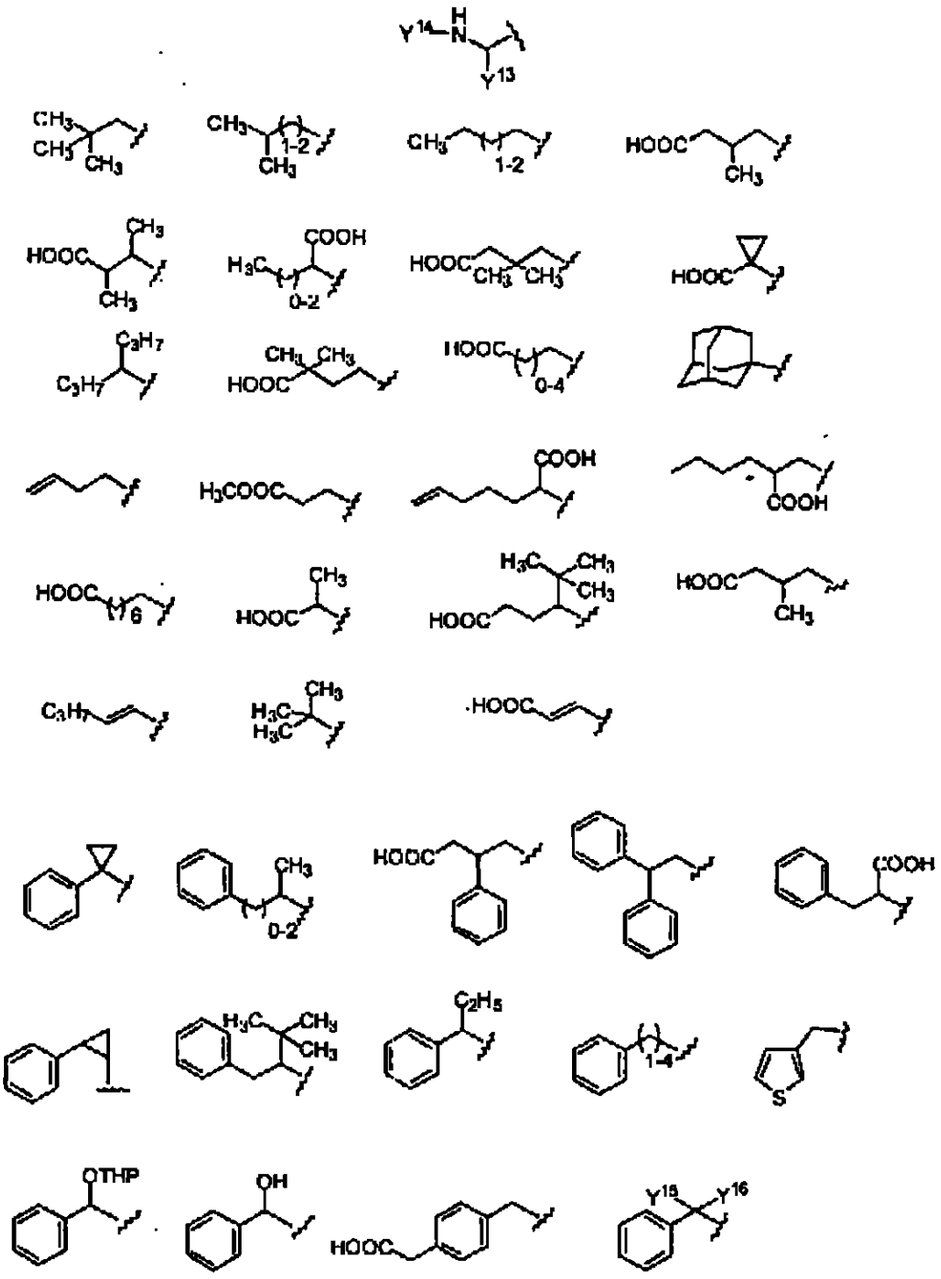


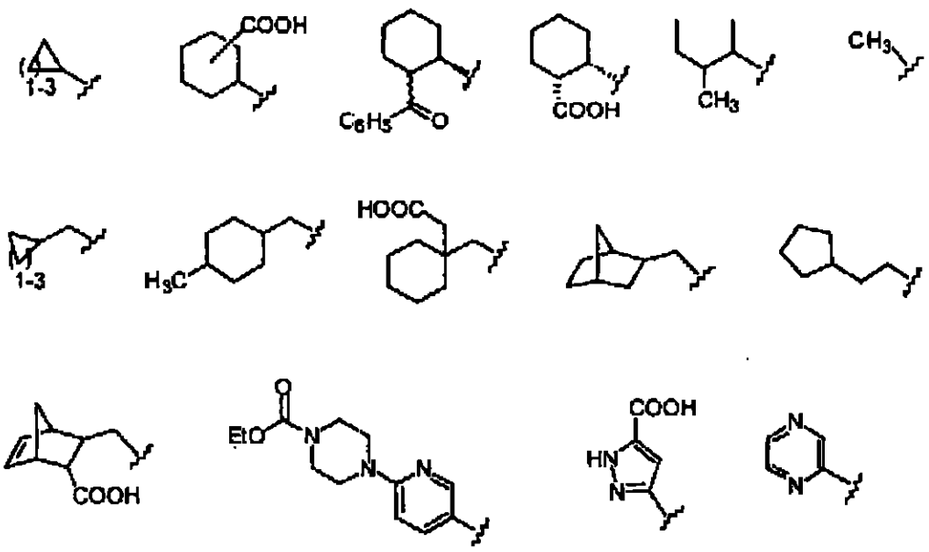
8. El compuesto de la reivindicación 6, en el cual Z es N y R^4 es H.

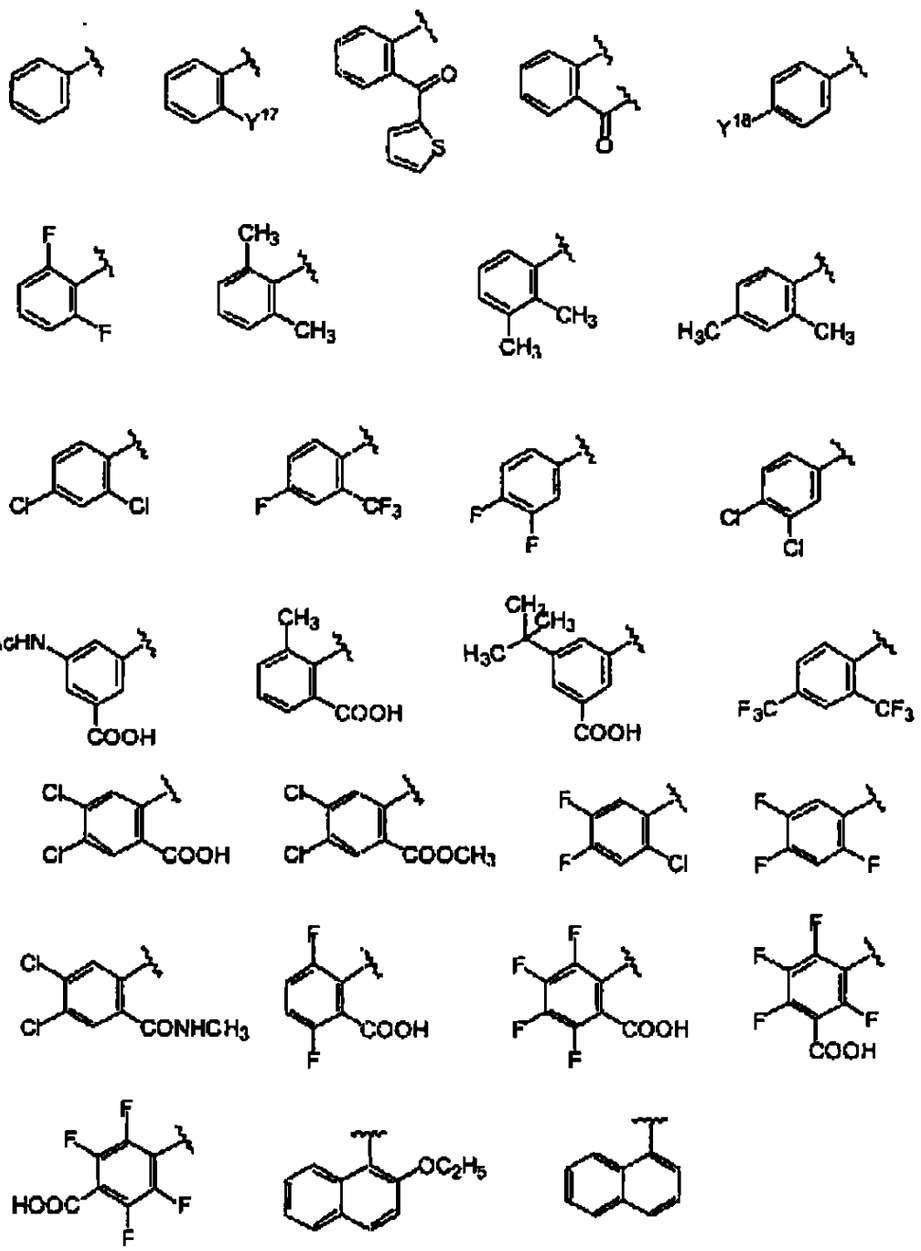
9. El compuesto de la reivindicación 8, en el cual W es C=O.

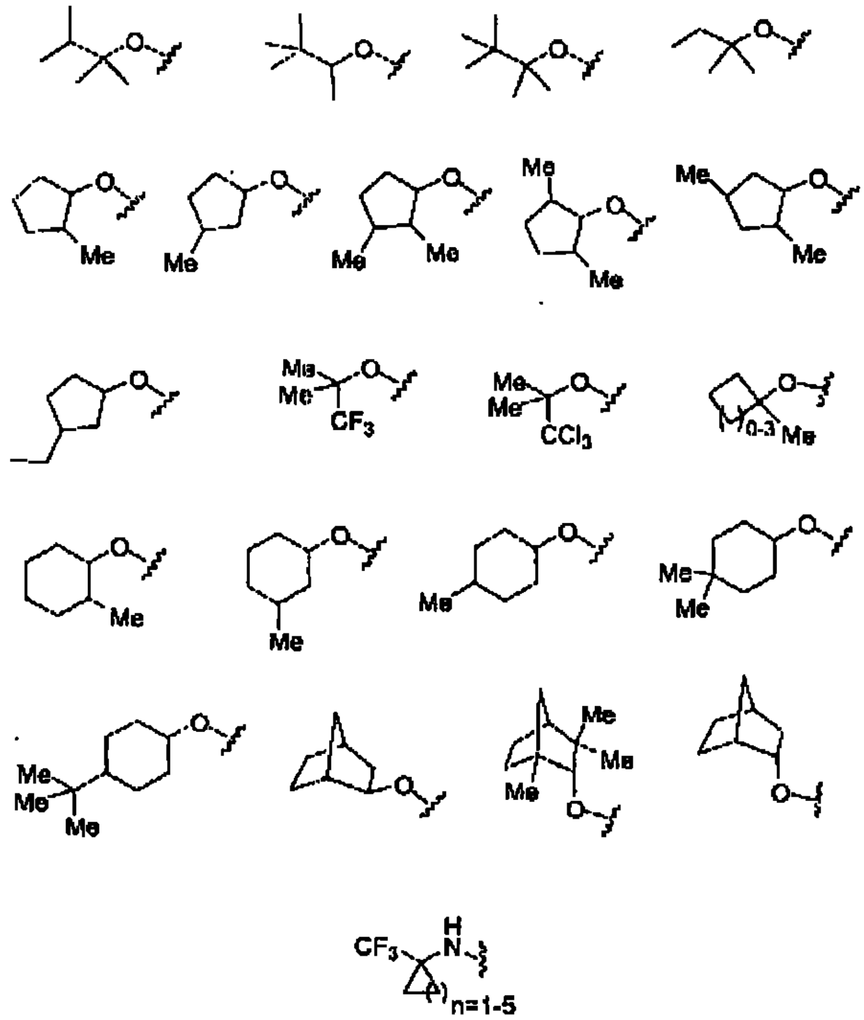
10. El compuesto de la reivindicación 9, en el cual Y se selecciona de los siguientes restos:

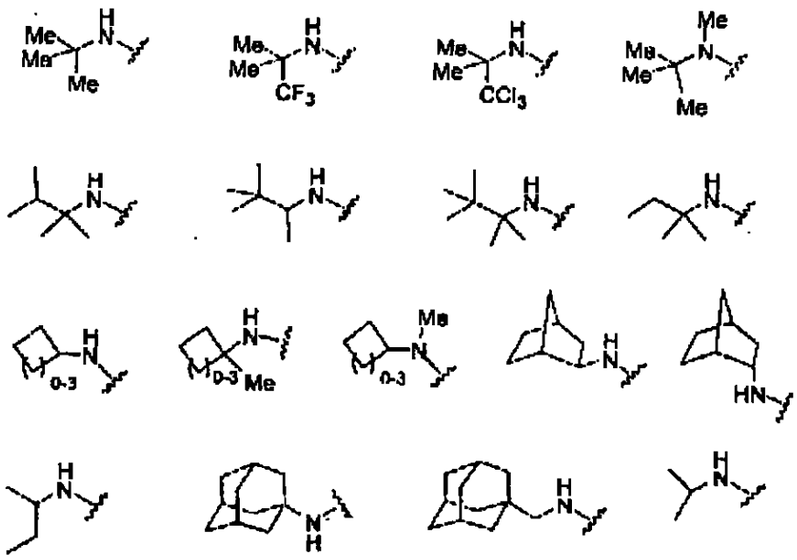

Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
0-6
Cl3C
Me
Me
Me
Me
Me
Me
Me
H
0-3
0-3
0-1
Me
Y11
Y11
Me
Me
MeO2C
Me
Me
F
Me
Y12




1-3
COOH
C6H5
O
COOH
CH3
CH3
1-3
H3C
HOOC
COOH
EtO
O
N
N
N
COOH
HN
N
N
N


Y17
O
S
O
Y18
F
F
CH3
CH3
CH3
CH3
H3C
CH3
Cl
Cl
F
CF3
F
F
Cl
Cl
AcHN
COOH
CH3
COOH
CH3
CH3
H3C
COOH
F3C
CF3
Cl
Cl
COOH
Cl
Cl
COOCH3
F
F
Cl
F
F
F
Cl
Cl
CONHCH3
F
F
COOH
F
F
F
F
F
COOH
F
F
F
F
F
HOOC
F
F
OC2H5

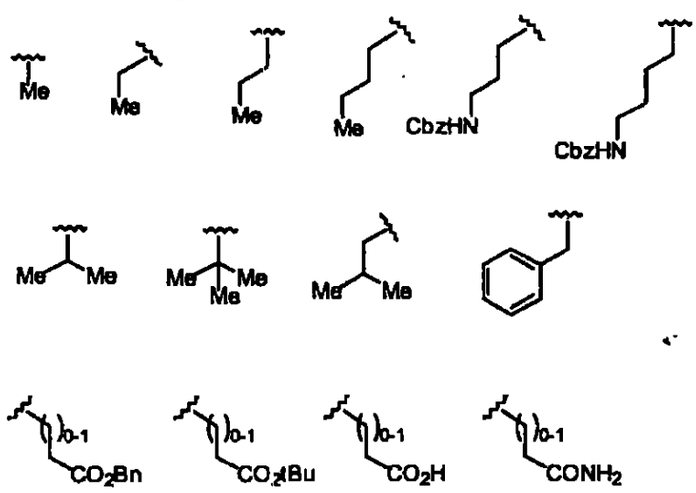




Y^{11} se selecciona de H, COOH, COOEt, OMe, Ph, OPh, NHMe, NHAc, NHPh, $CH(Me)_2$, 1-triazolilo, 1-imidazolilo, y $NHCH_2COOH$;

Y^{12} se selecciona de H, COOH, COOMe, OMe, F, Cl, o Br;

Y^{13} se selecciona de los siguientes restos:



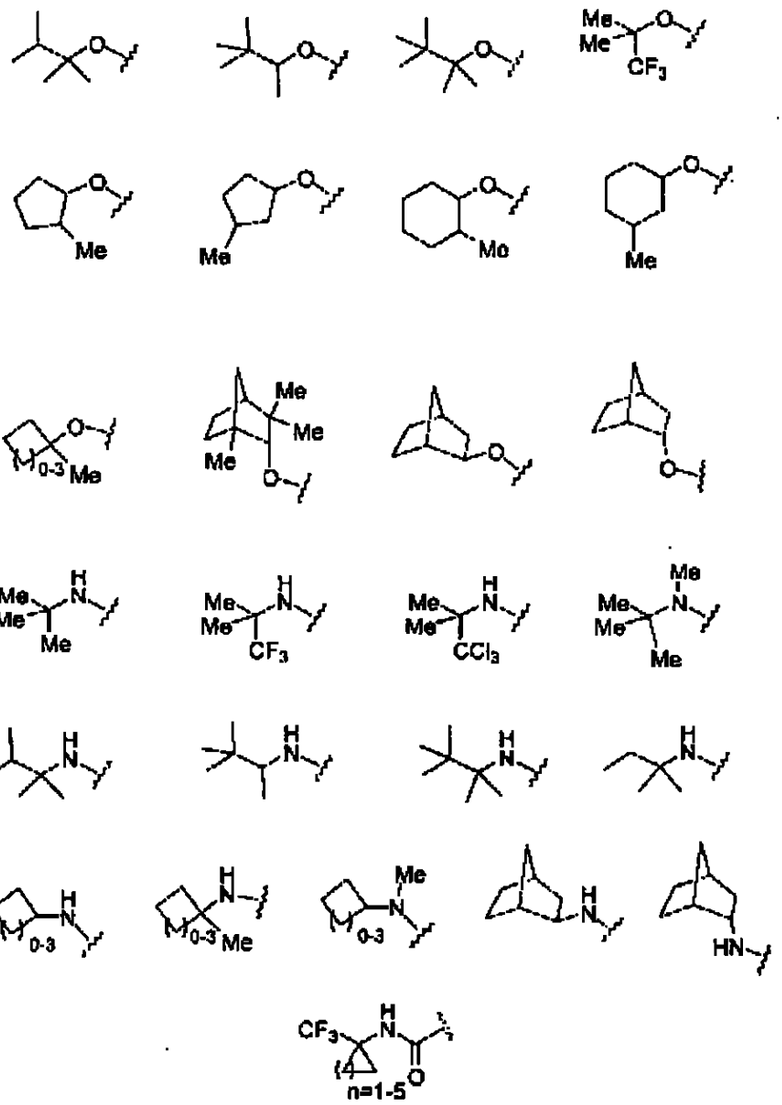
Y^{14} se selecciona de $MeS(O)_2$, Ac, Boc, iBoc, Cbz, o Alloc;

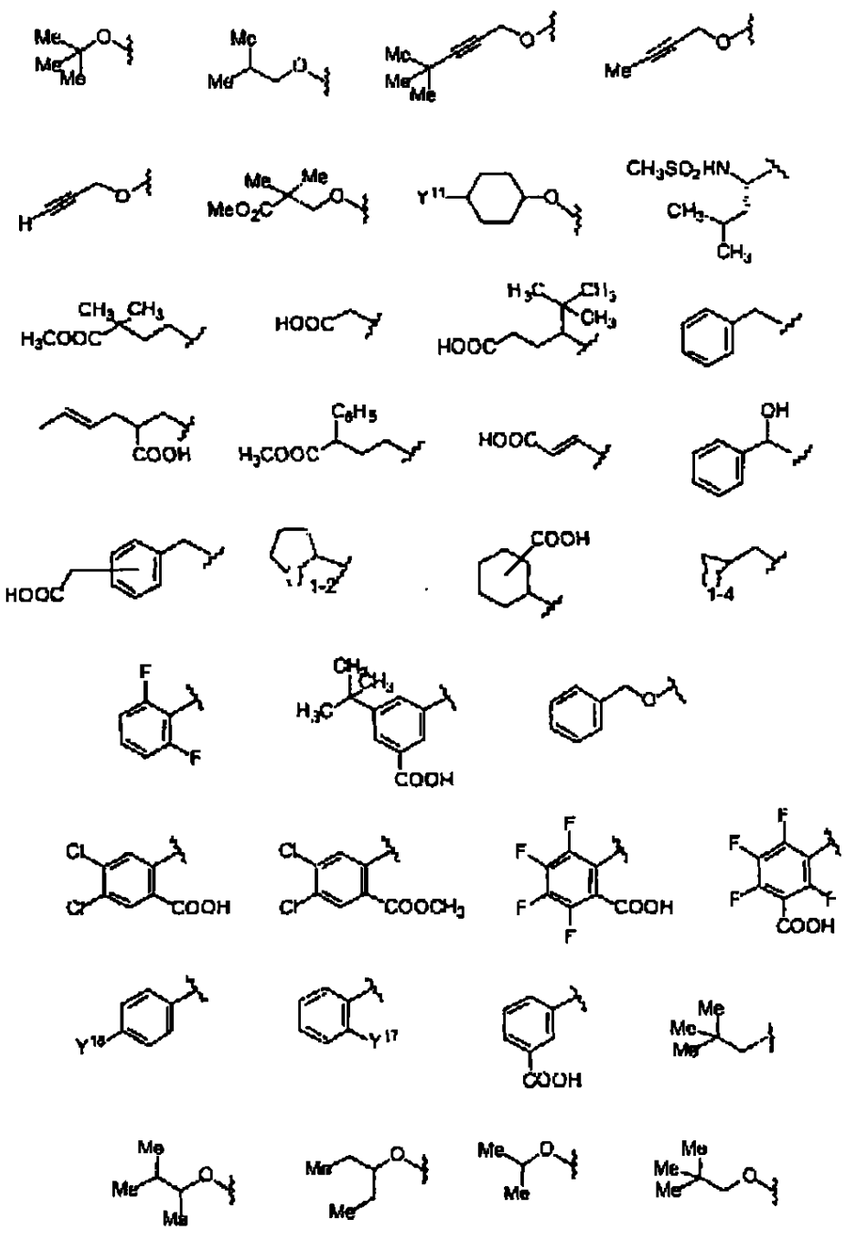
Y^{15} e Y^{16} se seleccionan en forma independiente de alquilo, arilo, heteroalquilo y heteroarilo;

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; e

Y^{18} es $-C(O)OCH_3$, $-NO_2$, $-N(CH_3)_2$, F, $-OCH_3$, $-CH_2C(O)OH$, -C(O)OH, $-S(O_2)NH_2$, o $-NHCOCH_3$.

11. El compuesto de la reivindicación 10, en el cual Y se selecciona del grupo formado por:


Me
Me
CF3
Me
Me
Me
Me
0-3
Me
Me
Me
Me
Me
Me
CF3
Me
Me
CCl3
Me
Me
Me
0-3
0-3
Me
0-3
Me
HN
CF3
n=1-5

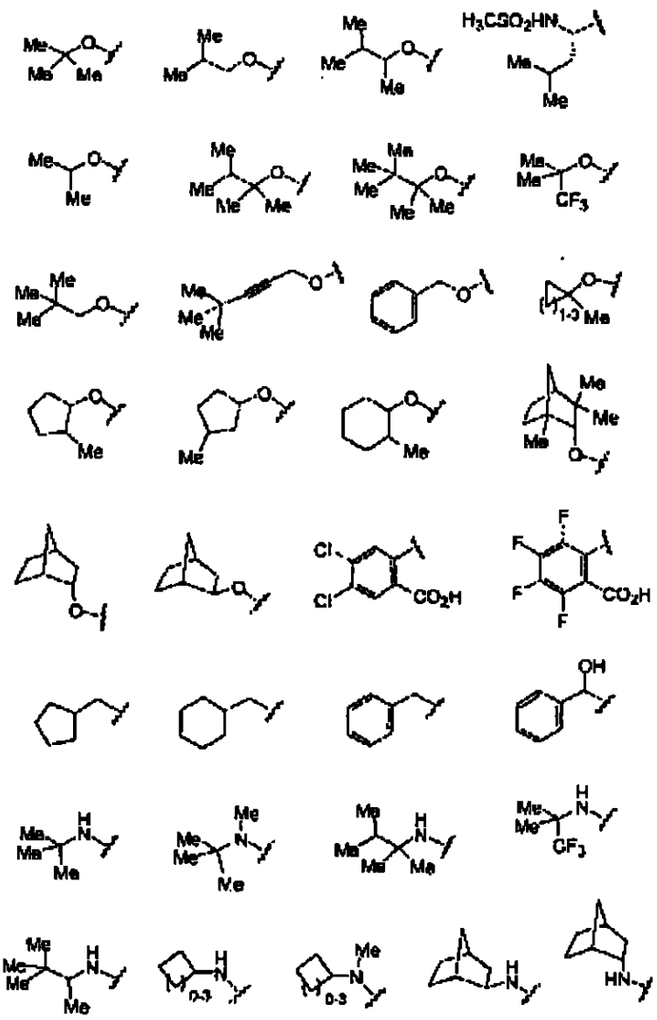


donde:

Y^{17} = CF_3, NO_2, $CONH_2$, OH, NH_2, o COOH;

Y^{18} = F, COOH.

12. El compuesto de la reivindicación 11, en el cual Y se selecciona del grupo formado por:

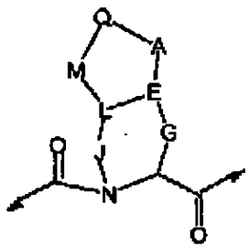


13. El compuesto de la reivindicación 12, en el cual L y M están ausentes, y J está directamente ligado a E.

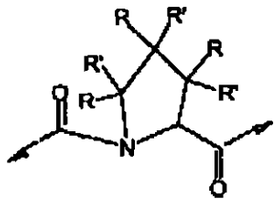
14. El compuesto de la reivindicación 12, en el cual L, J y M están ausentes y E está directamente ligado a N.

15. El compuesto de la reivindicación 12, en el cual G y M están ausentes.

16. El compuesto de la reivindicación 12, en el cual el resto:

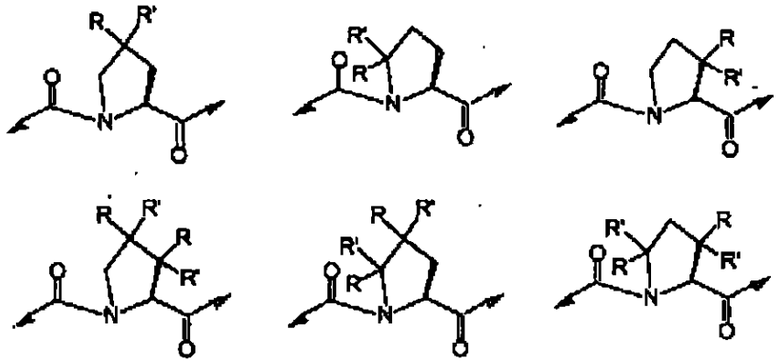


es

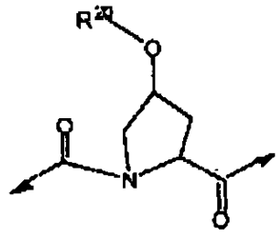


a

17. El compuesto de la reivindicación 16, en el cual la estructura a se selecciona de las siguientes estructuras:

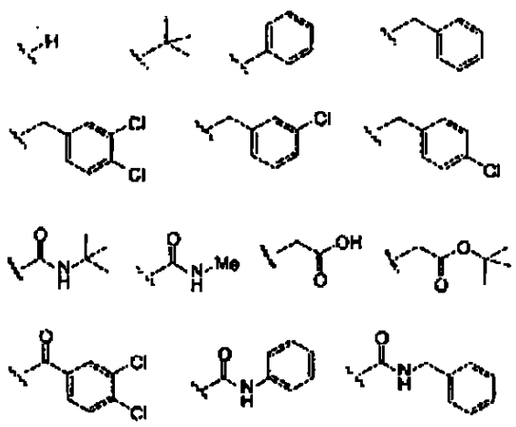


18. El compuesto de la reivindicación 16, en el cual la estructura a es:

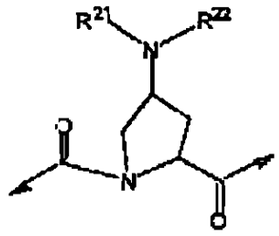


donde R^{20} se selecciona de las siguientes estructuras:

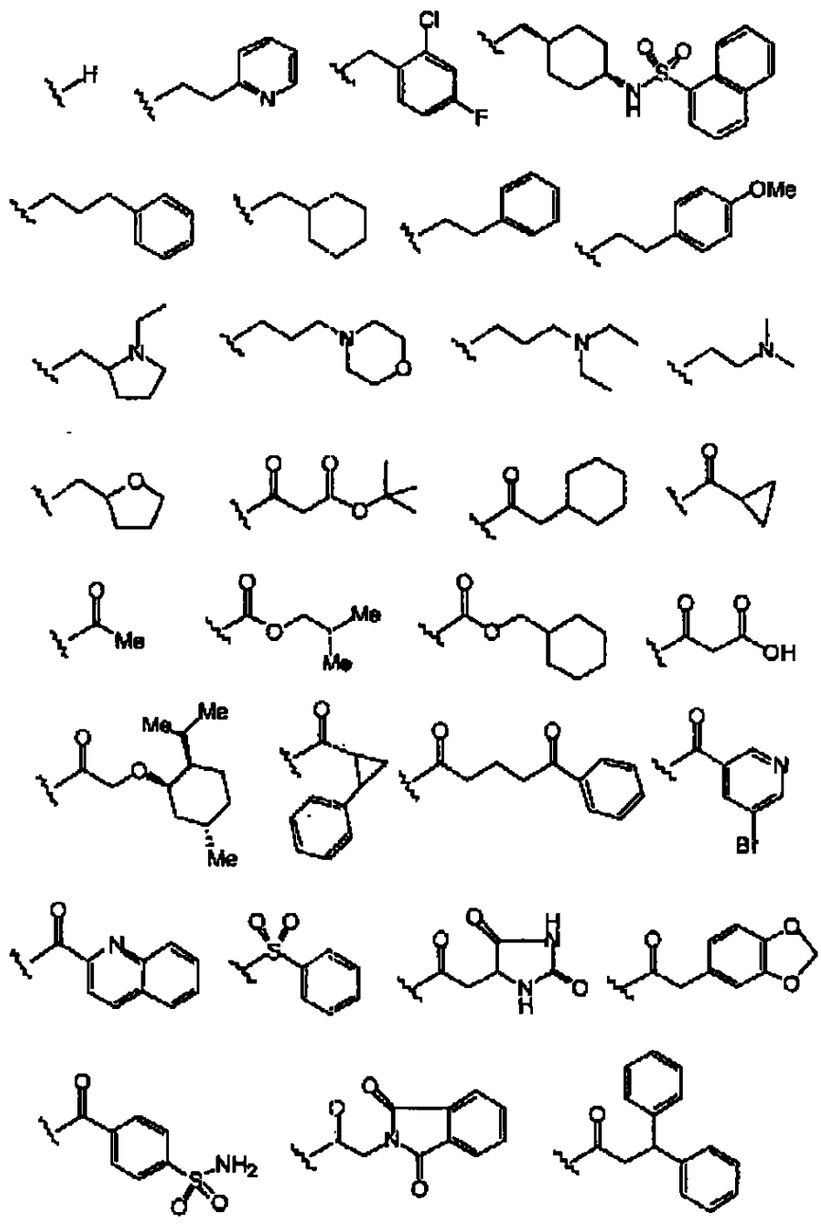
1240



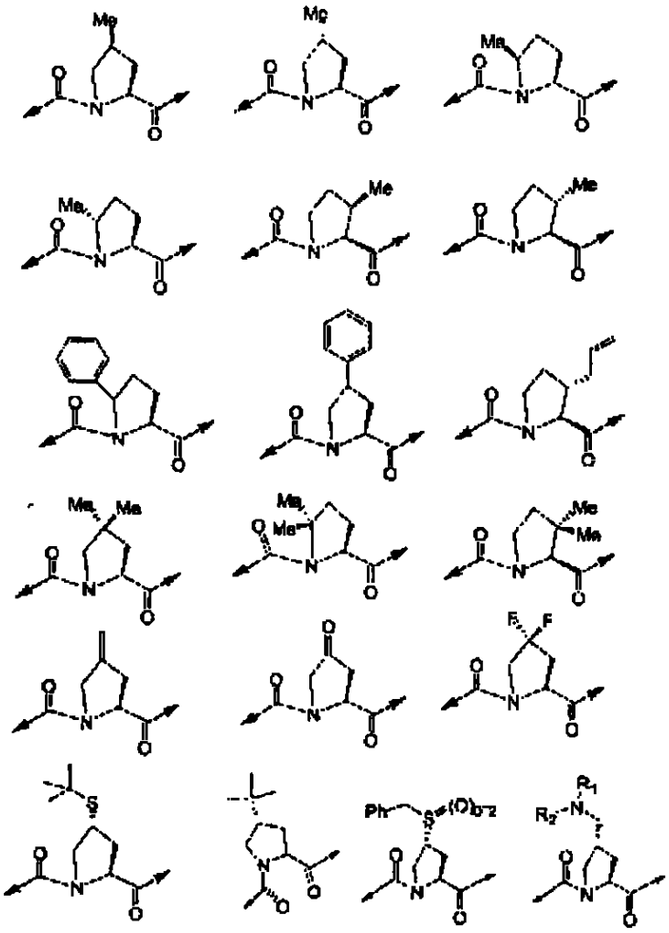
19. El compuesto de la reivindicación 16, en el cual la estructura a es:



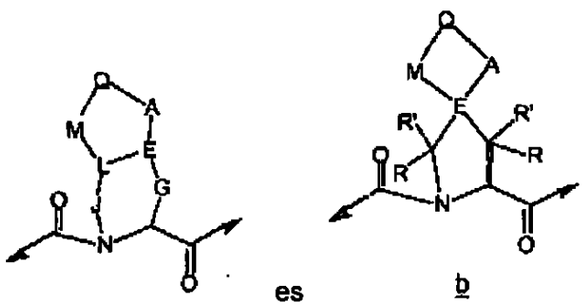
donde R^{21} y R^{22} pueden ser iguales o diferentes y se seleccionan en forma independiente del grupo formado por las siguientes estructuras:



20. El compuesto de la reivindicación 16, en el cual la estructura a se selecciona del grupo formado por las siguientes estructuras:



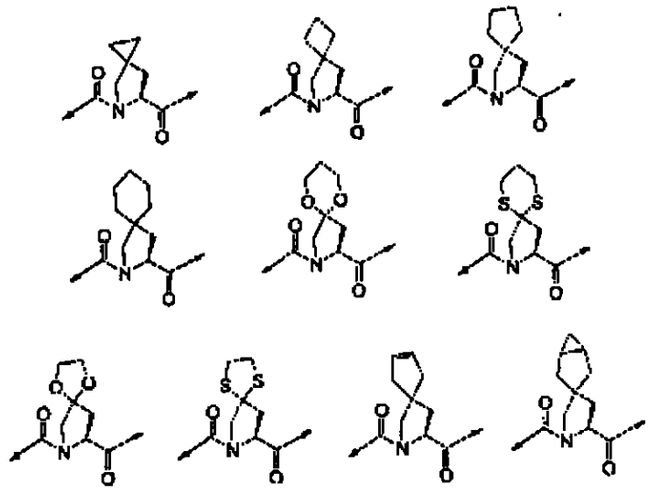
21. El compuesto de la reivindicación 12, en el cual:



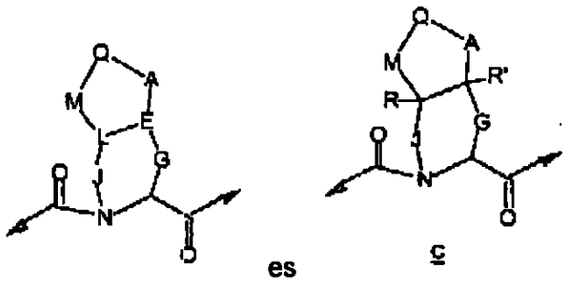
es b

donde Q puede estar presente o ausente y si Q está ausente, M, está directamente enlazado a A.

22. El compuesto de la reivindicación 21 en el cual la estructura b se selecciona de las siguientes estructuras:



23. El compuesto de la reivindicación 12, en el cual:

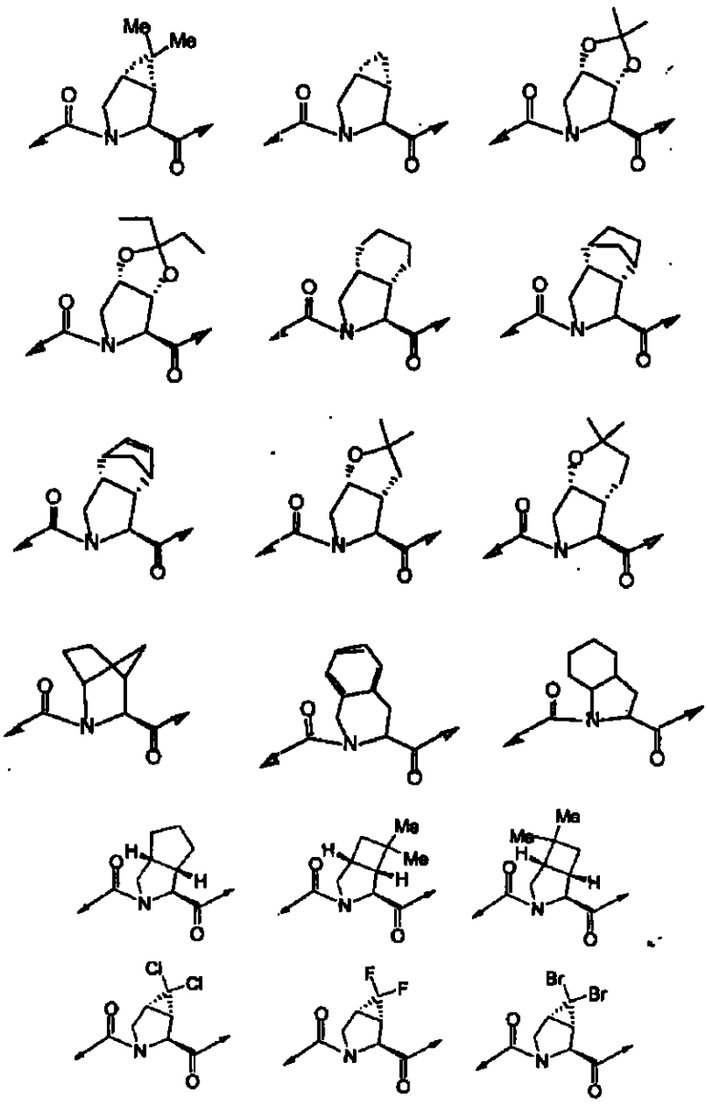


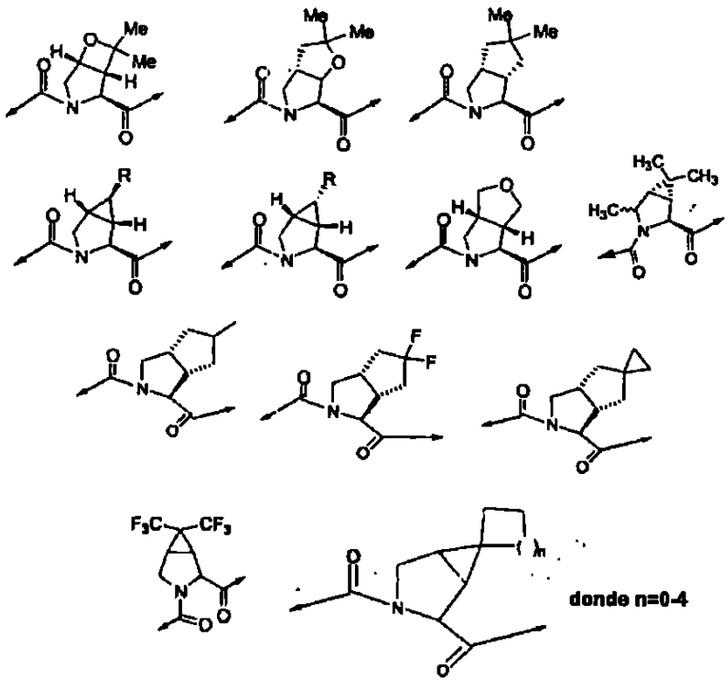
es

c

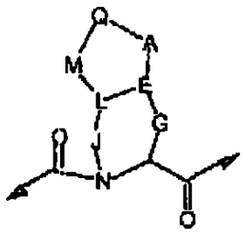
donde G y J pueden ser iguales o diferentes y se seleccionan del grupo formado por $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ y $(CRR')_p$; A y M se seleccionan en forma independiente del grupo formado por O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$; y $(CRR')_p$ y Q es CH_2, CHR, CRR', NH, NR, O, S, SO_2, NR $(CH_2)_p$, $(CHR)_p$ y $(CRR')_p$.

24. El compuesto de la reivindicación 23, en el cual la estructura c se selecciona de las siguientes estructuras:

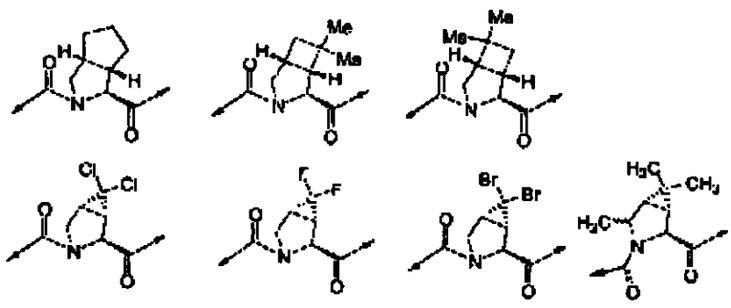


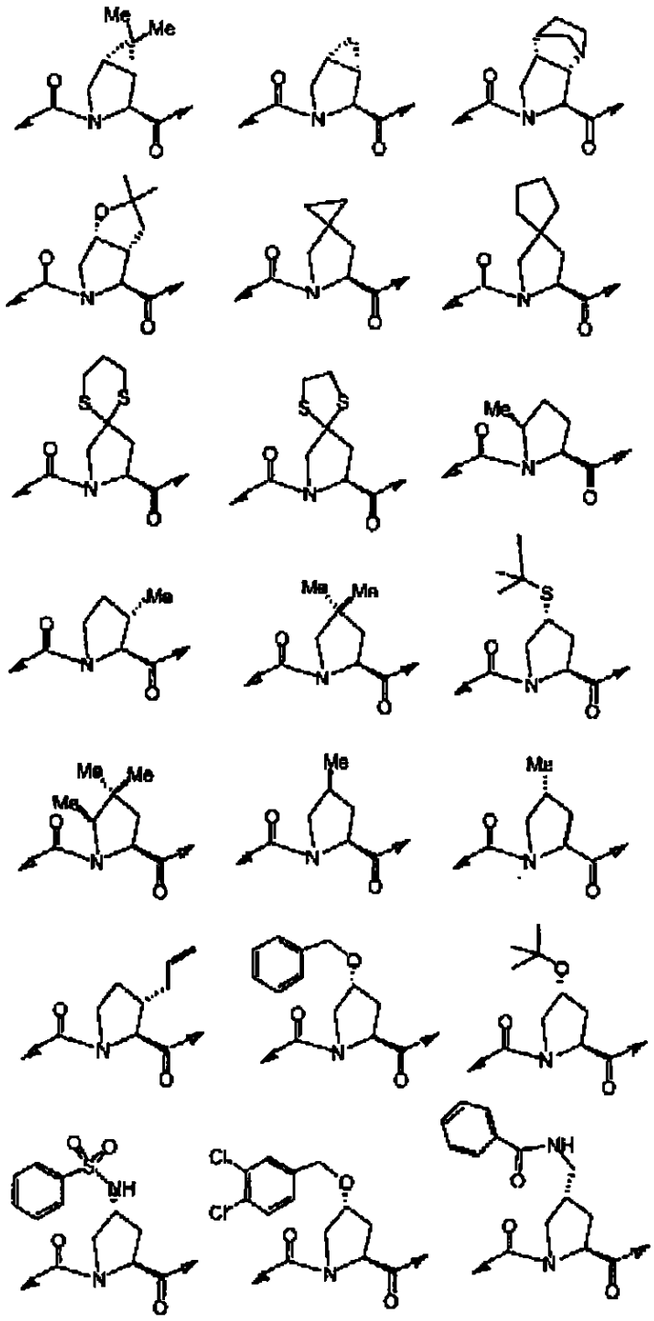


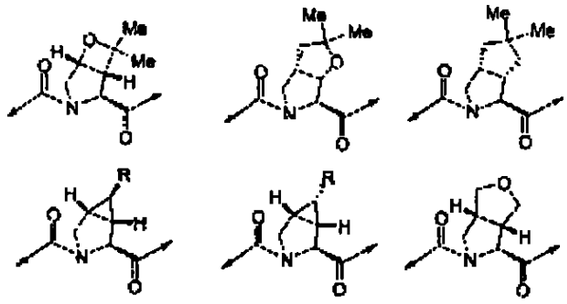
25. El compuesto de la reivindicación 12, en el cual



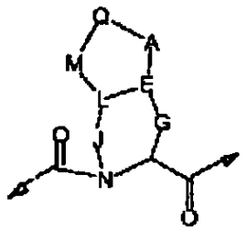
se selecciona de las siguientes estructuras:


H
H
O
N
O
Me
Me
H
H
O
N
O
Me
Me
H
H
O
N
O
Cl
Cl
O
N
O
F
F
O
N
O
Br
Br
O
N
O
H3C
CH3
H3C
O
N
O

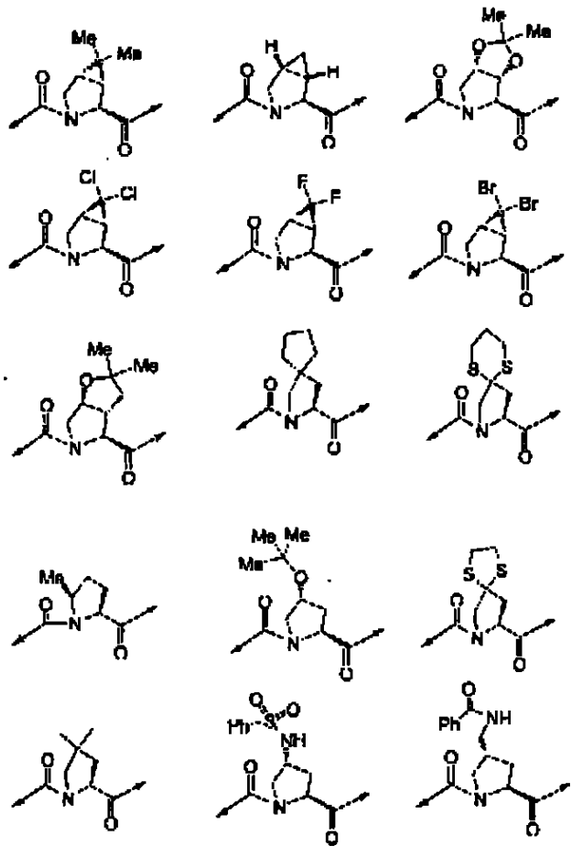




26. El compuesto de la reivindicación 25, en el cual:



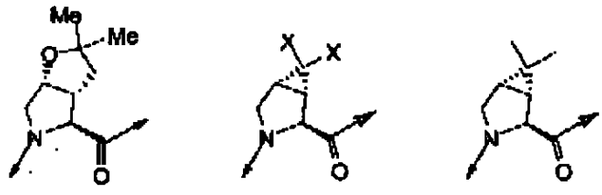
se selecciona de las siguientes estructuras:



27. El compuesto de la reivindicación 25, en el cual:

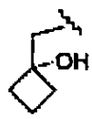


se selecciona d



X= F, Cl, Br

28. El compuesto de la reivindicación 1, en el cual R^2 es el resto:



29. Una composición farmacéutica que comprende, como ingrediente activo por lo menos un compuesto de la reivindicación 1.

30. La composición farmacéutica de la reivindicación 29, para uso en el tratamiento de trastornos asociados con el HCV.

31. La composición farmacéutica de la reivindicación 29, que comprende adicionalmente un vehículo aceptable para uso farmacéutico.

32. La composición farmacéutica de la reivindicación 31, que comprende adicionalmente por lo menos un agente antiviral.

33. La composición farmacéutica de la reivindicación 32, que comprende adicionalmente un interferón.

34. La composición farmacéutica de la reivindicación 33, en la cual dicho agente antiviral es ribavirina y dicho interferón es α-interferón o interferón pegilado.

35. Un método de tratamiento de trastornos asociados con el HCV, dicho método comprende administrar a un paciente que necesita dicho tratamiento una composición farmacéutica que comprende cantidades terapéuticamente efectivas de por lo menos un compuesto de la reivindicación 1.

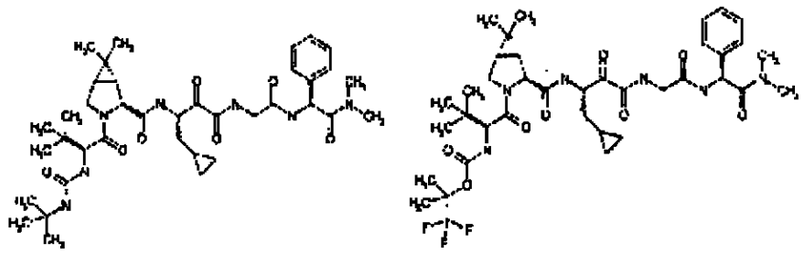
36. El método de la reivindicación 35, en el cual dicha administración es oral o subcutánea.

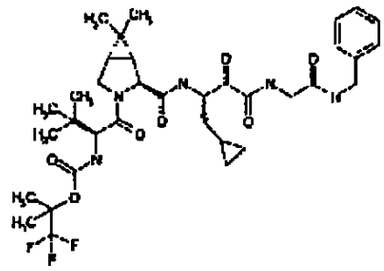
37. El uso de un compuesto de la reivindicación 1, para la fabricación de un medicamento para tratar trastornos asociados con el HCV.

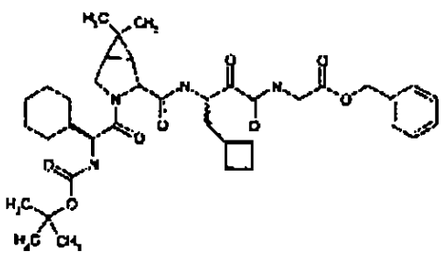
38. Un método para preparar una composición farmacéutica para el tratamiento de trastornos asociados con el HCV, dicho método comprende llevar

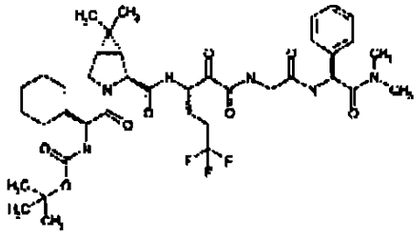
a contacto por lo menos un compuesto de la reivindicación 1, y un vehículo aceptable para uso farmacéutico.

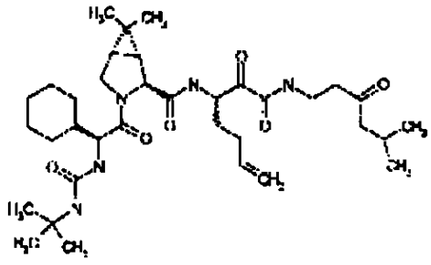
39. Un compuesto que muestra actividad de inhibición de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos y profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto se selecciona de los compuestos de las estructuras que se presentan a continuación:

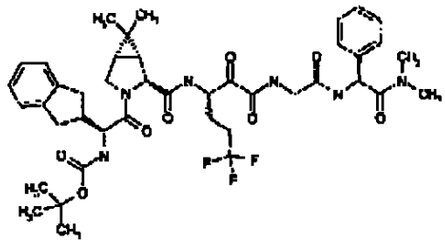


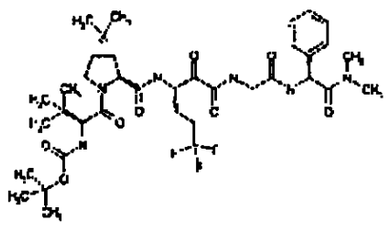


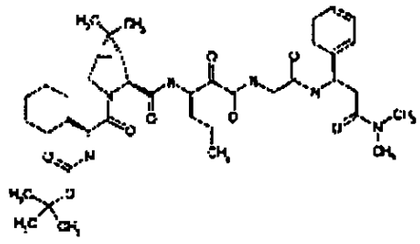


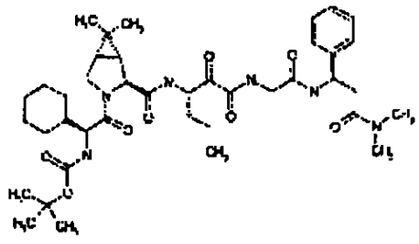


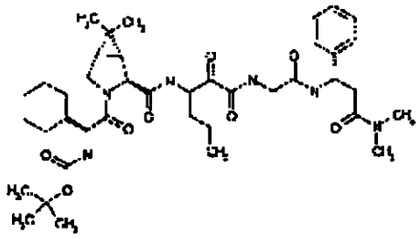


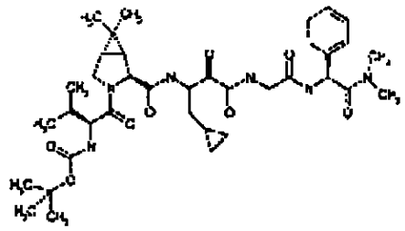


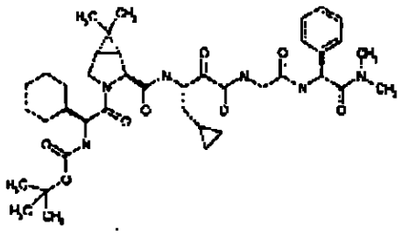


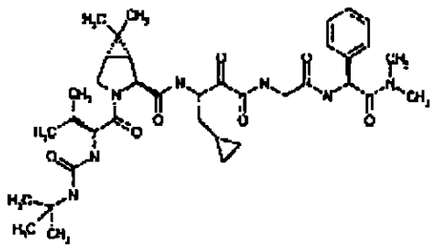


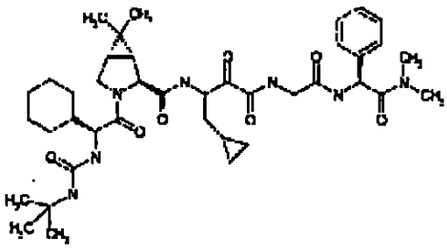


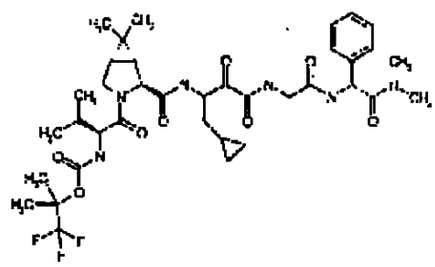


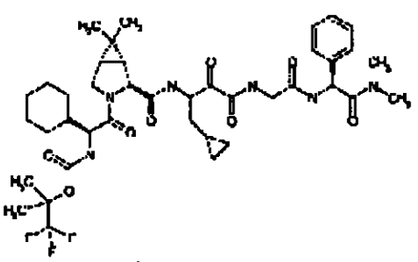


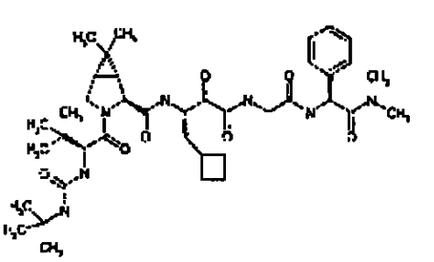


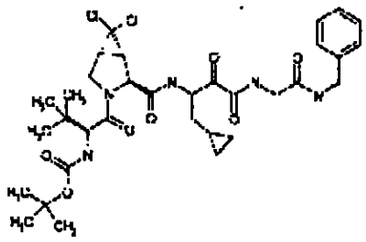


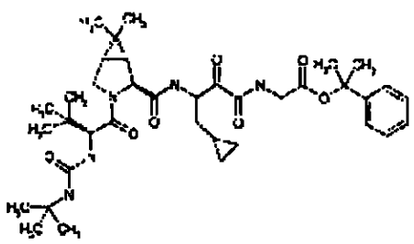


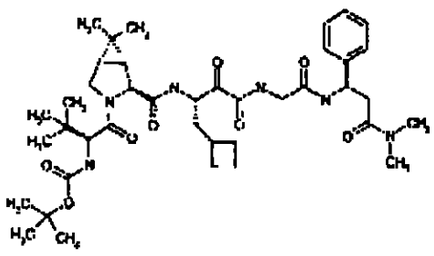


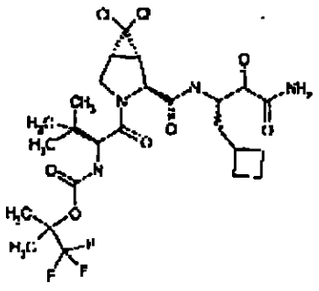


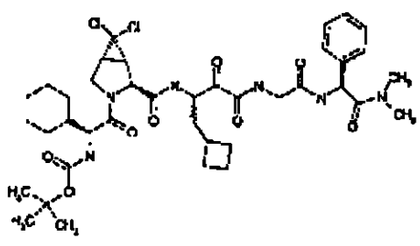


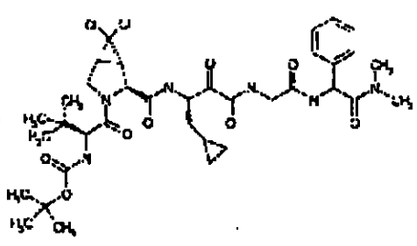


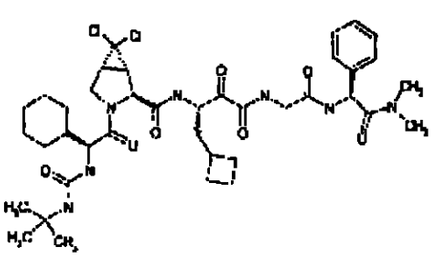


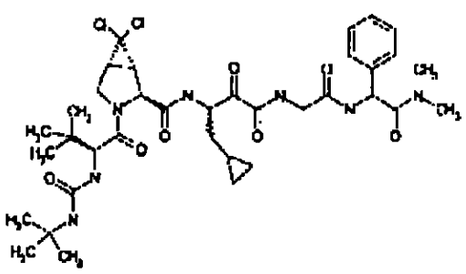


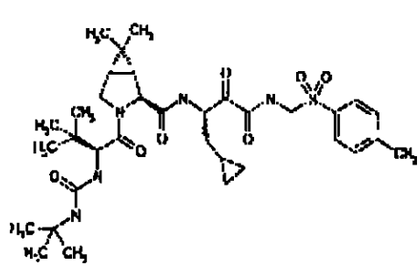


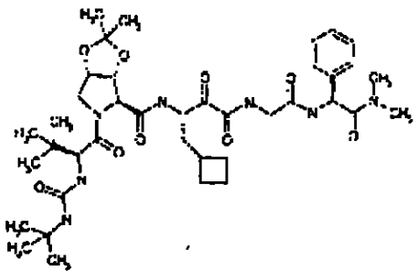


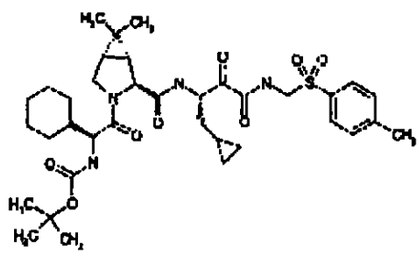


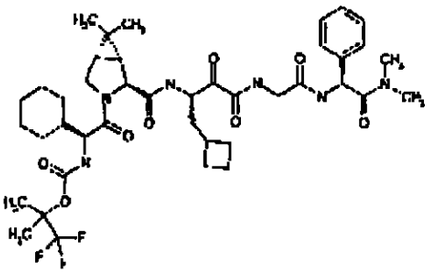


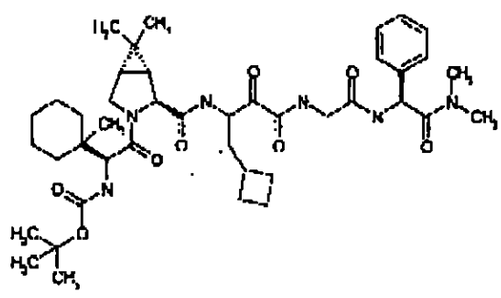


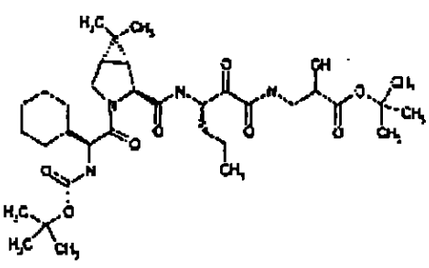


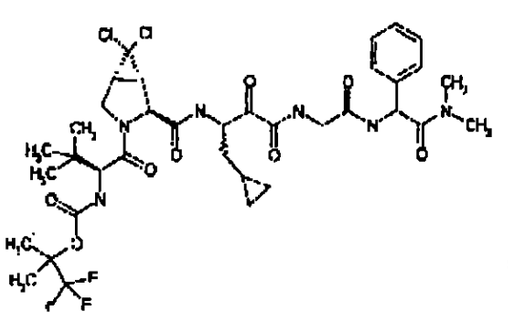


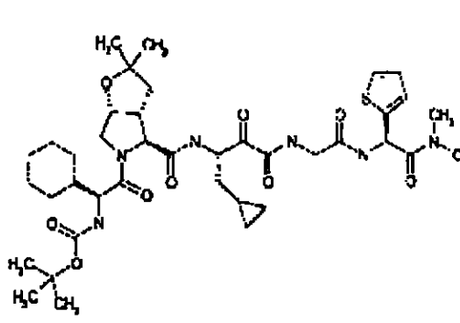


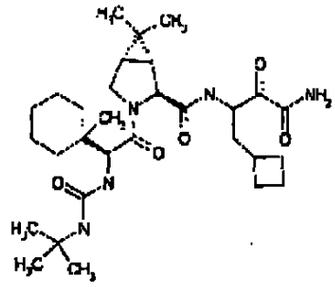


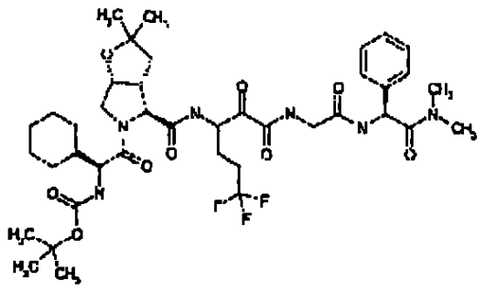


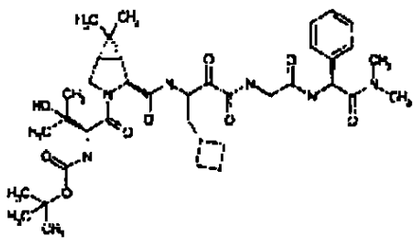


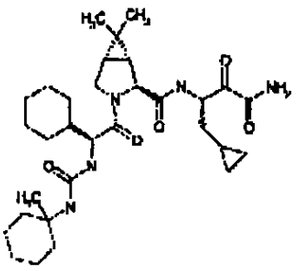


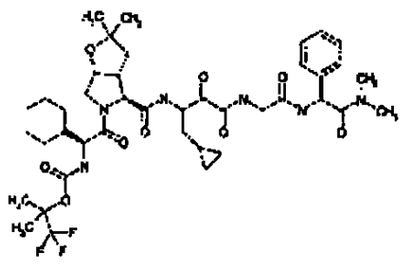


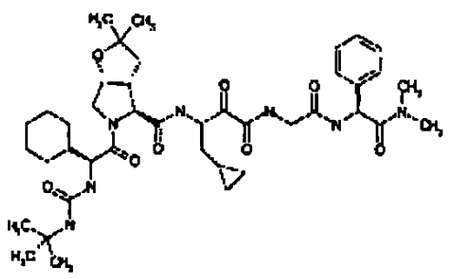


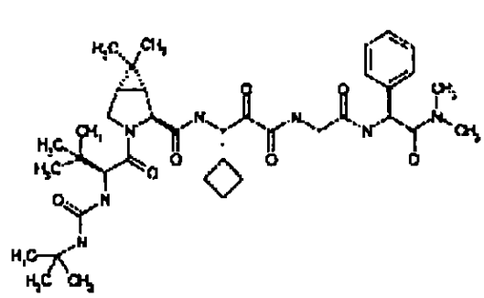


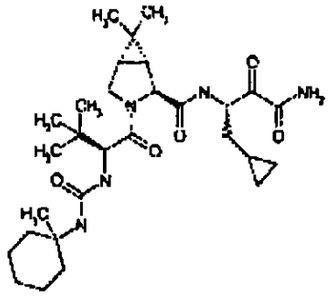


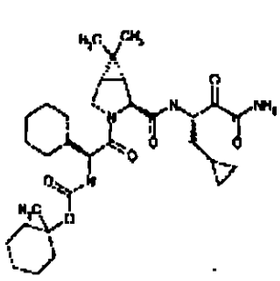


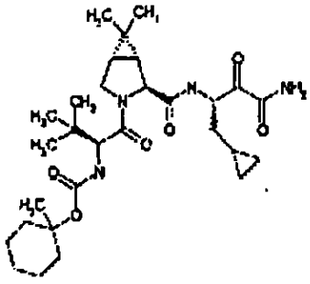


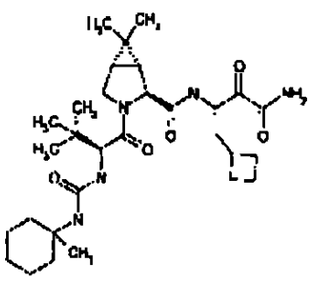


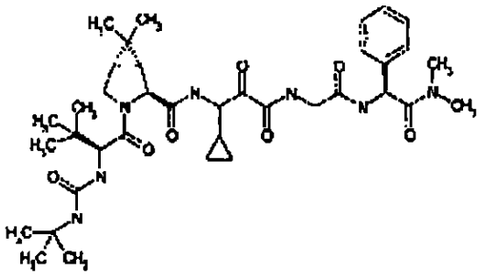


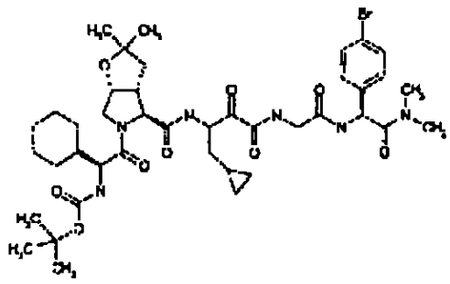


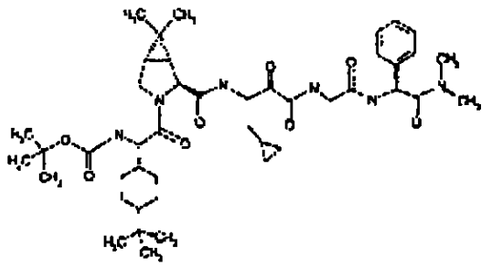


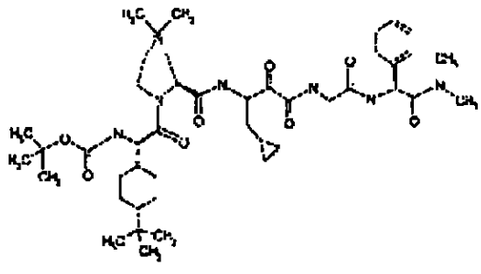


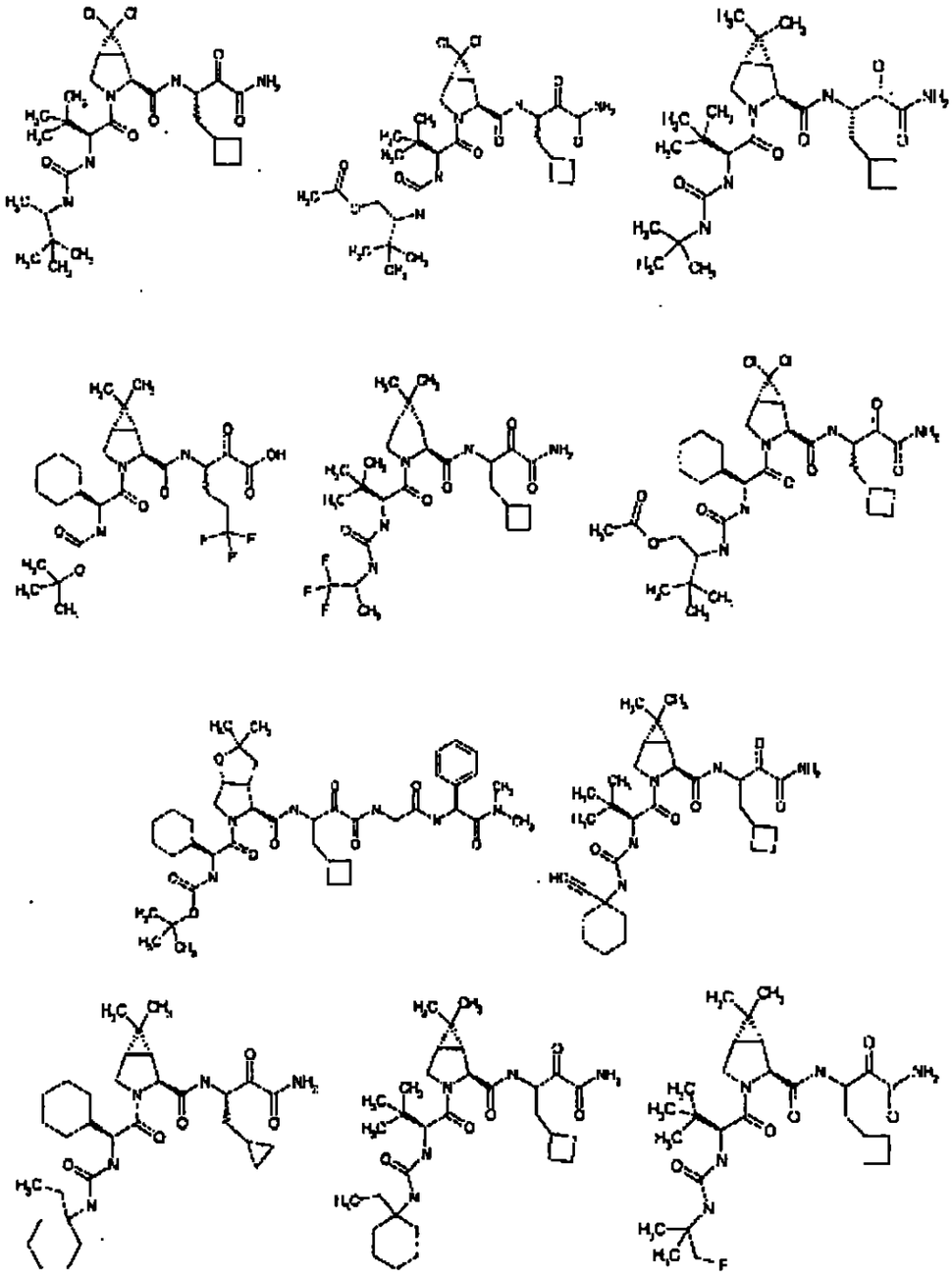




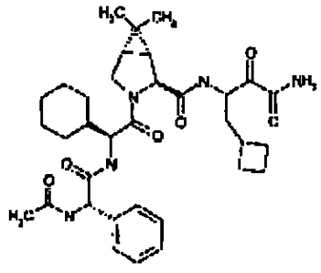


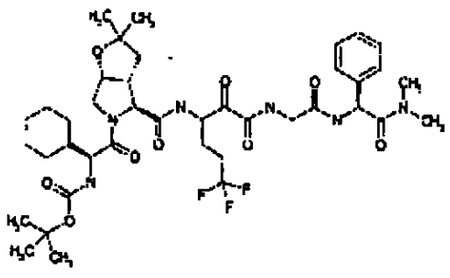


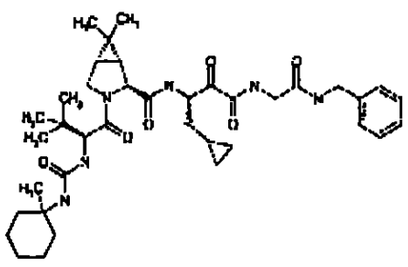


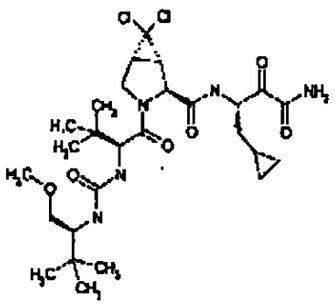


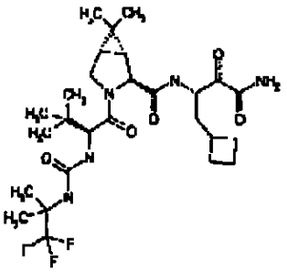
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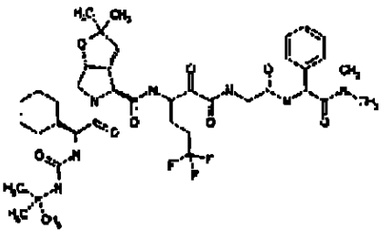


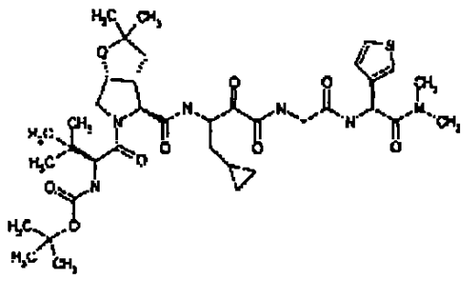


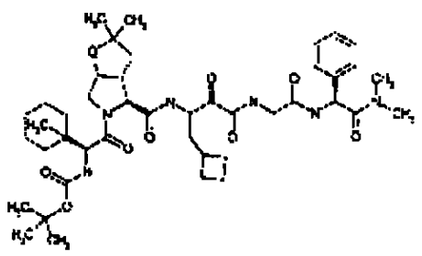




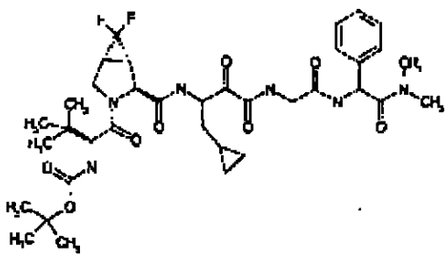


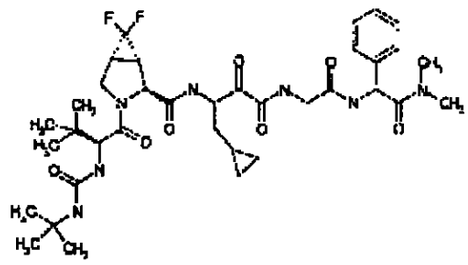


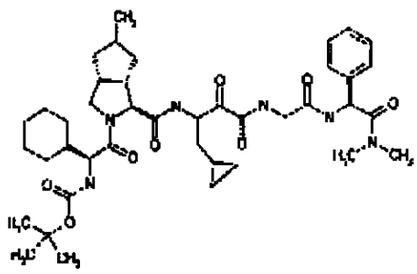


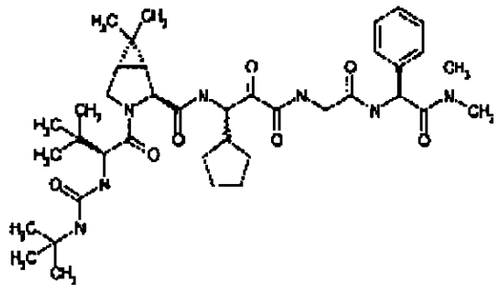


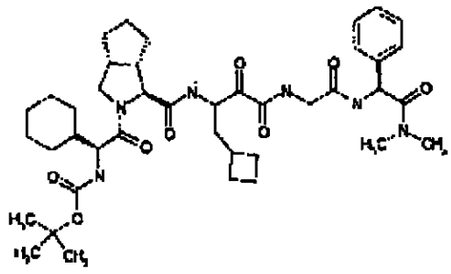
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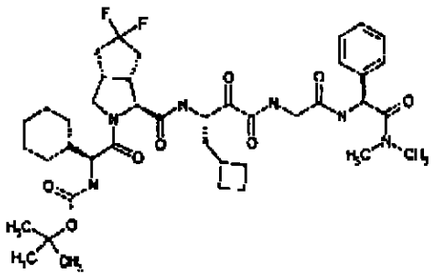


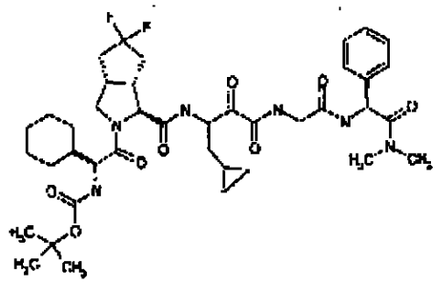


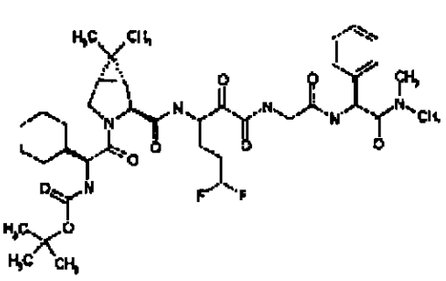


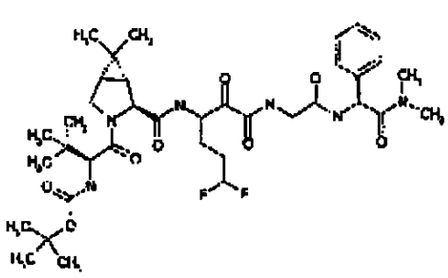


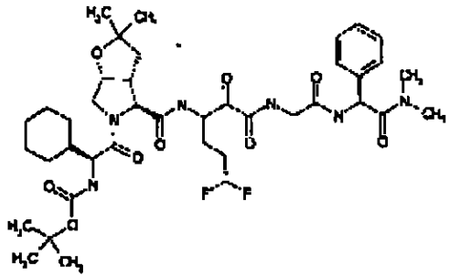


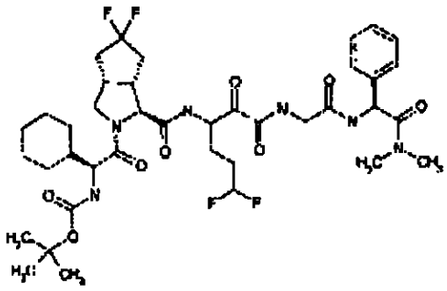


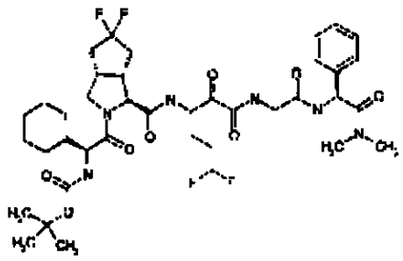


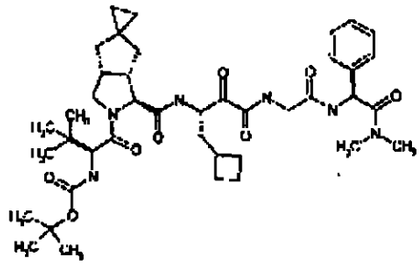


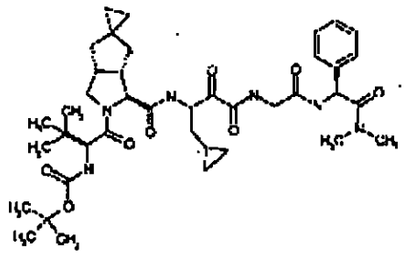


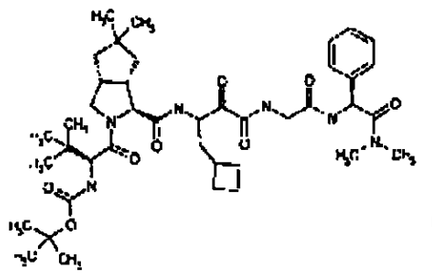


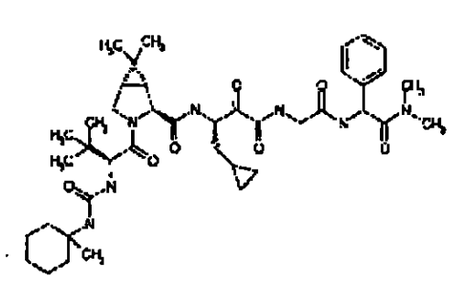


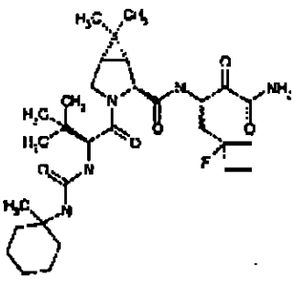


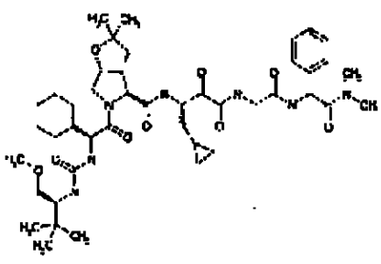


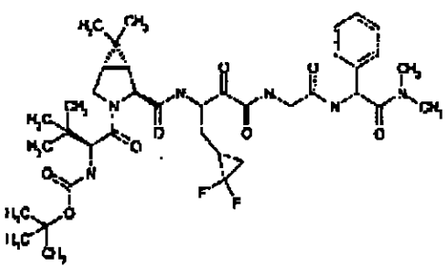


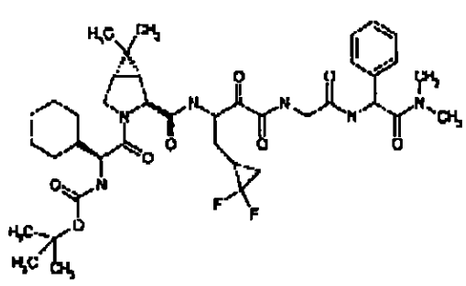


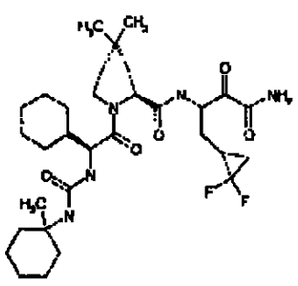


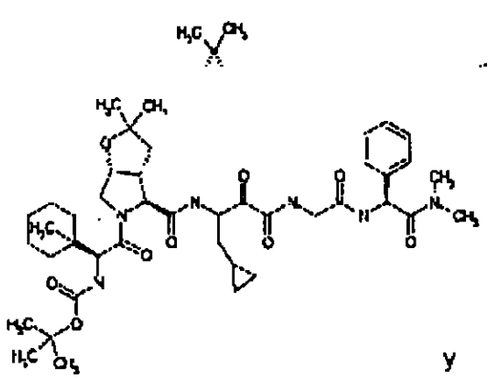


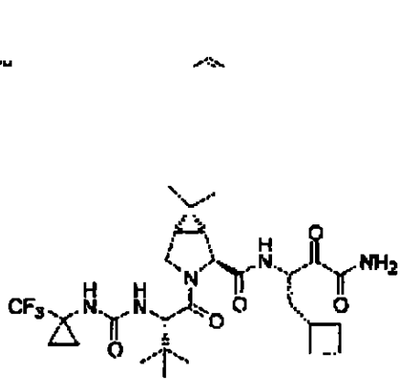












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40. Una composición farmacéutica para tratar trastornos asociados con el HCV, dicha composición comprende una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 39 y un vehículo aceptable para uso farmacéutico.

41. La composición farmacéutica de la reivindicación 40, que contiene, adicionalmente un agente antiviral.

42. La composición farmacéutica de la reivindicación 41, que contiene, adicionalmente, un interferón o un conjugado PEG-interferón alfa.

43. La composición farmacéutica de la reivindicación 42, en la cual dicho agente antiviral es ribavirina y dicho interferón es α-interferón.

44. Un método de tratamiento de un trastorno asociado con el virus de la hepatitis C, que comprende la administración de una cantidad efectiva de uno o más compuestos de la reivindicación 39.

45. Un método para modular la actividad de la proteasa del virus de la hepatitis C (HCV), que comprende el contacto de la proteasa del HCV con uno o más compuestos de la reivindicación 39.

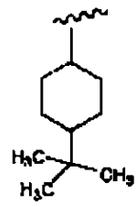
46. Un método de tratamiento, prevención o alivio de uno o más de los síntomas de la hepatitis C, que comprende la administración de una cantidad efectiva de uno o más compuestos de la reivindicación 39.

47. El método de la reivindicación 46, en el cual la proteasa del HCV es la proteasa NS3/NS4a.

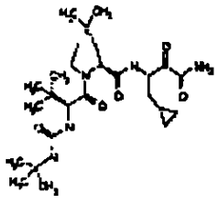
48. El método de la reivindicación 46, en el cual el compuesto o los compuestos inhiben la proteasa NS3/NS4a del HCV.

49. Un método de modular el procesamiento del polipéptido del virus de la hepatitis C (HCV), que comprende el contacto de una composición que contiene el polipéptido del HCV en condiciones en las cuales el polipéptido se procesa con uno o más compuestos de la reivindicación 39.

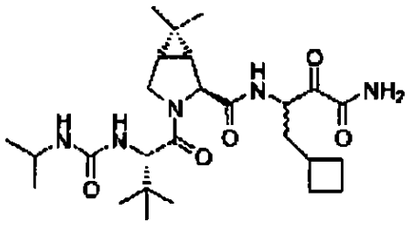
50. El compuesto de la reivindicación 6, en el cual R^3 es:



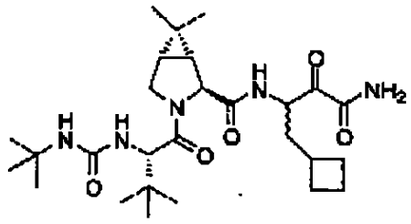
51. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:



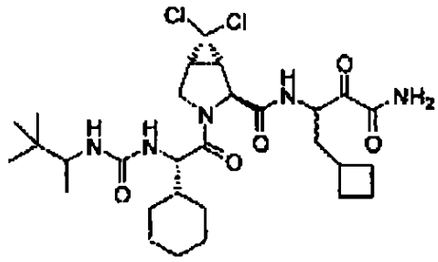
52. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:



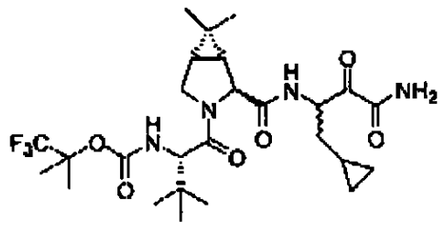
53. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:



54. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:

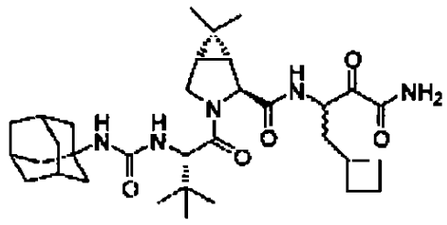


55. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:

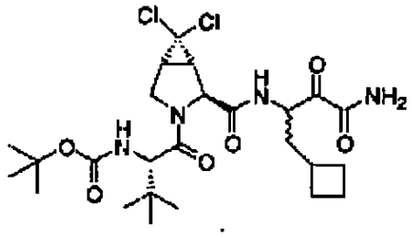


56. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso

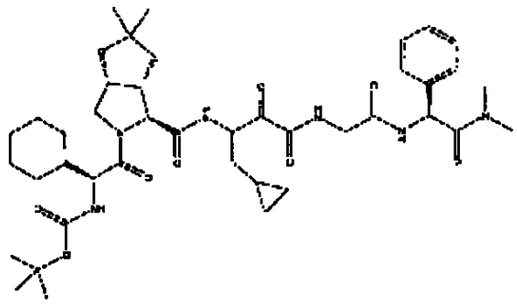
farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:



57. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:

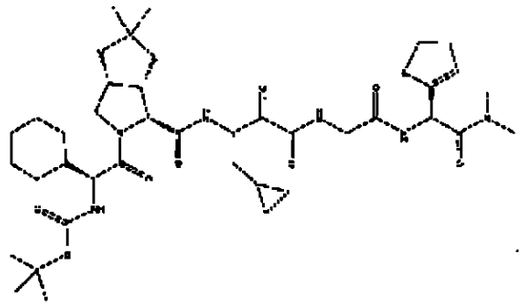


58. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:

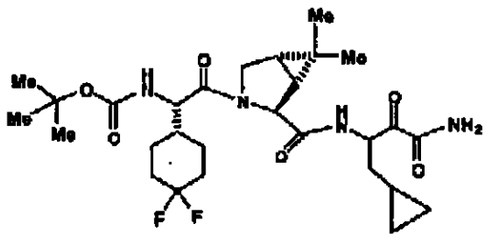


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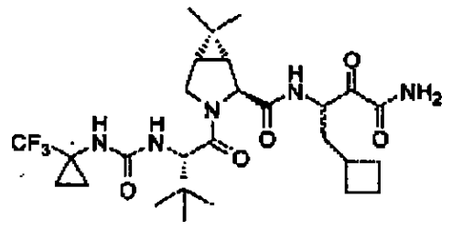
59. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:



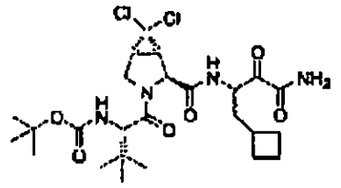
60. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:

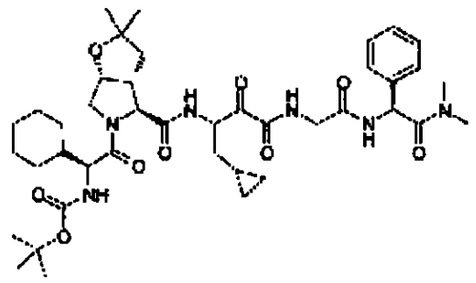


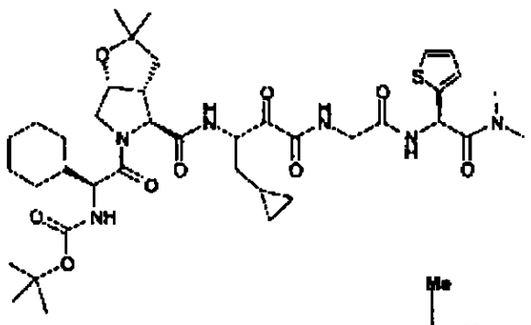
61. Un compuesto que presenta actividad inhibidora de la proteasa del HCV, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto tiene la estructura general que se muestra a continuación:

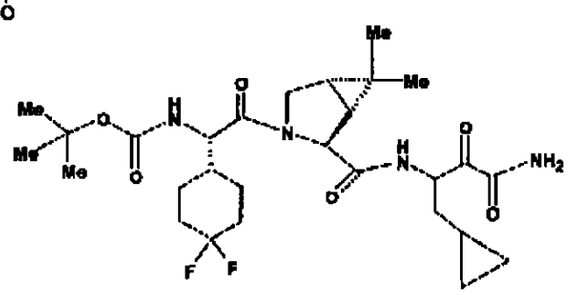


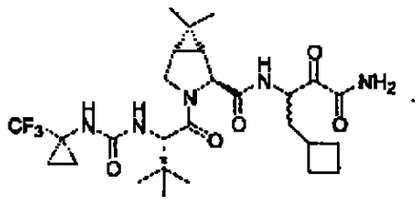
62. Una composición farmacéutica que comprende como ingrediente activo un compuesto, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto se selecciona de los siguientes:



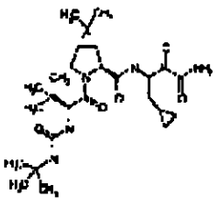


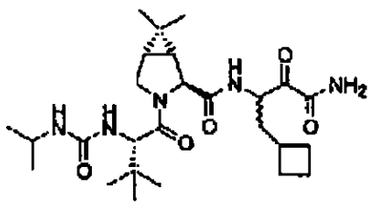


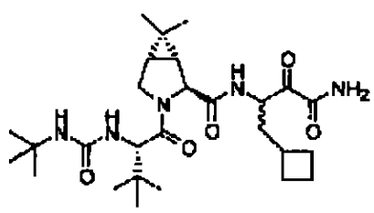


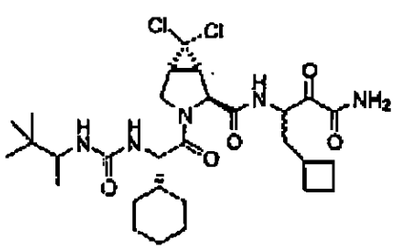

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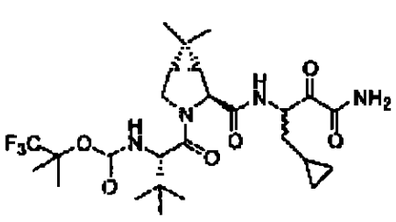
1231

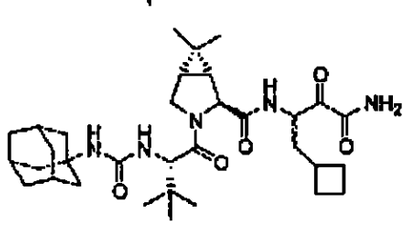










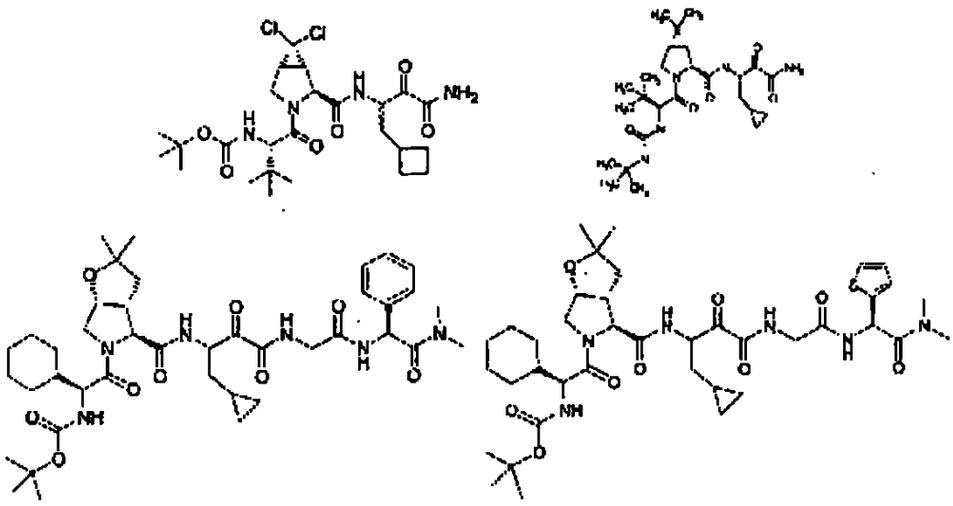


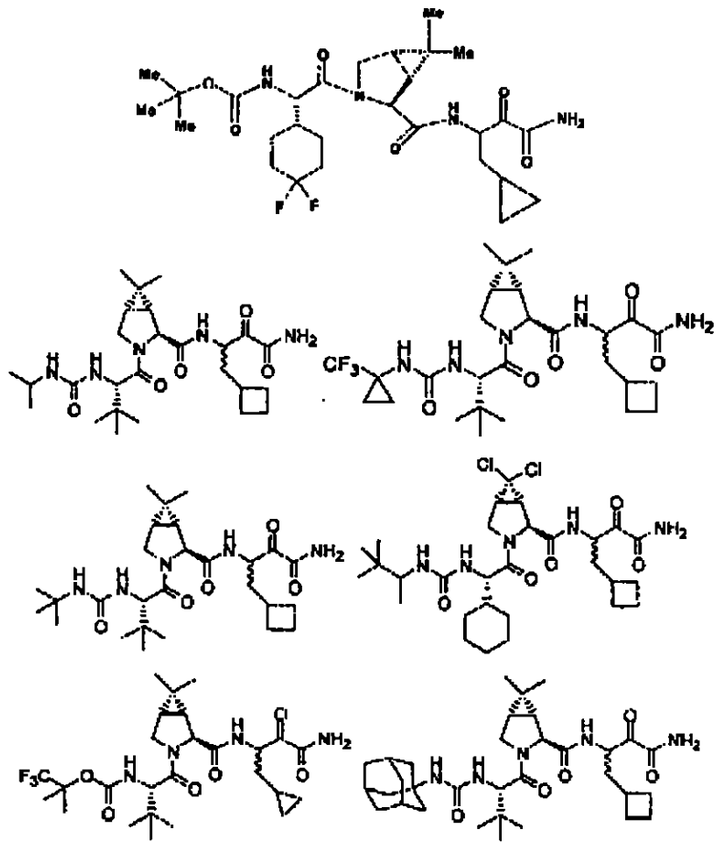
63. La composición farmacéutica de la reivindicación 62, que contiene adicionalmente un agente antiviral.

64. La composición farmacéutica de la reivindicación 63, que aún adicionalmente contiene un interferón o un conjugado PEG-interferón alfa.

65. La composición farmacéutica de la reivindicación 64, en la cual dicho agente antiviral es ribavirina y dicho interferón es α-interferón.

66. Un método de tratamiento de trastornos asociados con el HCV, dicho método comprende la administración a un paciente que necesita dicho tratamiento, una composición farmacéutica que comprende cantidades terapéuticamente efectivas de un compuesto, o los enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos o profármacos de dicho compuesto, o las sales o los solvatos aceptables para uso farmacéutico de dicho compuesto, o de dicho profármaco, dicho compuesto se selecciona de los siguientes:





p: SCHERING CORPORATION * CORVAS INTERNATIONAL, INC.

1224

Resumen de la Invención

La presente invención describe nuevos compuestos que tienen actividad inhibidora de la proteasa del HCV como también métodos para preparar dichos compuestos. En otra realización, la invención describe composiciones farmacéuticas que comprenden dichos compuestos como así también métodos para usarlos en el tratamiento de trastornos asociados con la proteasa del HCV.

PATENT COOPERATION TREATY

1275

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
COHEN, Harvey L.
LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK LLP
600 South Avenue West
Westfield, NJ 07090
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*: 15-10-2003

Applicant's or agent's file reference: SCHERI-122C

IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/01430	16/01/2003	18/01/2002

Applicant: SCHERING CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

   07/08/2003

2. This date of receipt is:

   [X] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

   [ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).

   [ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] **ATTENTION:** That date of receipt is **AFTER** the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

   [ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on: _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/
European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer
DEBEAUPUIS S
Tel. (+49-89) 2399-2483

126

OLARTE RAISBECK
13 JUL. 2004
WE ACKNOWLEDGE RECEIPT

E-Mail: eriannetti@ldlkm.com

VIA FEDERAL EXPRESS

NATIONAL PHASE PATENT APPLICATION ORDER LETTER

Senor Carlos R. Olarte
OlarteRaisbeck & Friari Ltda.
World Trade Center – Torre C
Calle 100 No. 8/55, Piso 10
Bogota, D.C. Colombia

Our File: SCHERING 3.4-122 CIP Columbia
Date: June 11, 2004

Please file a patent application in Columbia based on the international application identified below promptly after receipt of this order letter. In any event, the application must be filed by July 18, 2004 (30 months)

On the same day you receive this letter, please send us a facsimile reading: "RECEIVED SCHERING 3.4-122 CIP."
On the same day you file the application, please send us a facsimile reading: "FILED SCHERING 3.4-122 CIP."

THIS APPLICATION IS A CONTINUATION-IN-PART OF AN APPLICATION THAT IS PRESENTLY BEING PROSECUTED BY YOUR FIRM. APPLICATION NO. 03003340

INTERNATIONAL APPLICATION NO.:	PCT/US03/01430 filed 16 January 2003
APPLICANTS: **(CORVAS INTERNATIONAL, INC. HAS MERGED WITH AND INTO DENREON SAN DIEGO LLC WHO THEN ASSIGNED THEIR RIGHTS TO DENDREON CORPORATION** **(SEE PCT/IB306 – ENCLOSED)**	SCHERING CORPORATION 2000 Galloping Hill Road Kenilworth, NJ 07033-0530, USA DENDREON CORPORATION 3005 First Avenue Seattle, WA 98121, USA
TITLE:	NOVEL PEPTIDES AS NS3-SERINE PROTEASE INHIBITORS OF HEPATITIS C VIRUS
CONVENTION PRIORITY:	U.S. Appln. No. 10/052,386 filed 18 January 2002
INVENTOR(S):	See enclosed list – PLEASE USE THE ADDRESSES AS INDICATED ON THE LIST AS SOME OF THE INVENTORS HAVE RELOCATED ~~SINCE THE TIME OF FILING~~
DOCUMENTS ENCLOSED: International Application as Published Copy of PCT/IB306 Notification of Receipt of Demand Listing of Inventors CD of the application in English CD of the application in Spanish Disk containing: (1) additional new claims to be added and a paper copy of same; and (2) claim 1 as amended and a paper copy of same Copy of Examiner's Information Disclosure report, Form PTO-892, from corresponding U.S. application	**DOCUMENTS TO FOLLOW:** International Search Report (HAS NOT ISSUED TO DATE) July 13, 2004 Please acknowledge receipt Your Ref: P2004/00089

REMARKS:

1. **If any formal papers (i.e. Powers/Assignments) are required, please prepare same and forward for execution.**
2. **A copy of the assignment for the U.S. application can be provided along with the merger and assignment documents for the applicant, Dendreon.**
3. **"Additional new claims" referred to above are to be added to the claims presently in the application.**
4. **Claim 1 MUST be amended according to paper copy and disk; amendment is supported by the disclosure on pages 7-10 of PCT document; deletion also made in corresponding U.S. application.**
5. **The prior art cited by the U.S. Examiner should be made of record.**

IMPORTANT: **IN THE ABSENCE OF OUR INSTRUCTIONS, THIS APPLICATION MUST BE KEPT IN FORCE.**

LERNER, DAVID, LITTENBERG,
KRUMHOLZ & MENTLIK, LLP

International Department

OLARTE RAISBECK
13 JUL. 2004
WE ACKNOWLEDGE RECEIPT

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

3. En respuesta a la segunda observación del Examinador, me permito aportar junto al presente memorial el poder expedido por Pharmacia Corporation, cumpliendo con los requisitos de los Artículos 63 y subsiguientes del Código de Procedimiento Civil.

Atentamente,

CARLOS R. OLARTE
cc. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Documento de Cesión.
Poder.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
IN01159K1		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 03/01430	16/01/2003	18/01/2002
Applicant		
SCHERING CORPORATION		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

RELACION DE TRANSPORTES DE JUNIO 4 A JULIO 6 No.28

JUNIO 04.

SIC Vs OFICINA	1.000
OFICINA Vs SIC	1.000

JUNIO 7.

SIC Vs OFICINA	1.000
OFICINA Vs SIC	7.000

JUNIO 8.

SIC Vs OFICINA	1.000
OFICINA Vs BANCO POPULAR	1.000
BANCO POPULAR Vs OFICINA	1.000

JUNIO 9.

SIC Vs OFICINA	1.000

JUNIO 10.

SIC Vs OFICINA	1.000
OFICINA Vs NOTARIA Vs SIC	8.000

JUNIO 11.

SIC Vs OFICINA	1.000
OFICINA Vs SIC	7.000

JUNIO 16.

SIC Vs OFICINA	1.000

JUNIO 17.

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OFICINA Vs NOTARIA	1.000
NOTARIA Vs SIC	1.000

JUNIO 18.

SIC Vs OFICINA	1.000
OFICINA Vs SIC	1.000

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/01430

1278

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/062 C07K5/065 A61K38/55

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)
IPC 7 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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/40262 A (DU PONT PHARM CO) 7 June 2001 (2001-06-07) claims; table 5	1-66
P,X	WO 02/08244 A (SCHERING CORP ; CORVAS INT INC (US)) 31 January 2002 (2002-01-31) claims	1-66
X	WO 01/74768 A (VERTEX PHARMA ; COURT JOHN (US); MALLEY ETHAN O (US); PERNI ROBERT (US) 11 October 2001 (2001-10-11) claims; tables	1-66

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

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 2004	07/07/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fuhr, C

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OFICINA Vs SIC	1.000
JUNIO 25.	
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NOTARIA Vs SIC	1.000
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JUNIO 28.	
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SIC Vs ICA	1.000
ICA Vs BANCO POPULAR	1.000
BANCO POPULAR Vs OFICINA	1.000
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ICA Vs OFICINA	1.000
JULIO 02.	
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NOTARIA Vs SIC	1.000
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ICA Vs BANCAFE	1.000
BANCAFE Vs ICA	1.000
ICA Vs OFICINA	1.000
JULIO 6.	
SIC Vs OFICINA	1.000

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 35,36 and 44-49 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.

Continuation of Box I.2

The International Search Authority considered the term prodrug used in claims 1, 39, 51-62 and 66 and in all claims being dependet or relating to these claims, to be vague and unclear and thus leaveing the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear (Article 6 PCT). The search has therefore been restricted to the subject matter of claims 1-66 excluding the term 'prodrug'.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

TOTAL	**63.000**

Cordialmente,

FREDERICK H. TORRES.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/01430

Box I Observations where certain claims were found unsearchable (Continuation of item 1 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 35,36 and 44-49 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. [X] 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:

see FURTHER INFORMATION sheet PCT/ISA/210

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 II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Industria y Comercio
SUPERINTENDENCIA

Radicación No. 03059814

30 JUL 2004

Por la cual se impone una sanción

EL SUPERINTENDENTE DELEGADO PARA LA PROTECCIÓN DEL CONSUMIDOR

En ejercicio de sus facultades legales, en especial las que se le confieren en los decretos 2153 de 1992, 3466 de 1982, 2269 de 1993, y

CONSIDERANDO

PRIMERO. Que los artículos 7 y 8 del decreto 2269 de 1993 disponen que los productos o servicios sometidos al cumplimiento de una norma técnica colombiana oficial obligatoria, en adelante NTCOO, o Reglamento Técnico en adelante RT, deben cumplir con éstos independientemente que se produzcan en Colombia o se importen y, previamente a su comercialización, los fabricantes y/o los importadores deberán demostrar el cumplimiento del Reglamento Técnico a través de certificado de conformidad expedido por un organismo de certificación acreditado o reconocido. Dichos certificados deberán entregarse al comprador o distribuidor, por parte del fabricante o importador.

SEGUNDO. Que mediante resolución No. 0322 de 2002 emanada del Ministerio de Desarrollo Económico, ahora Ministerio de Comercio, Industria y Turismo, expidió el Reglamento Técnico RTC-002 MDE para acristalamientos de seguridad

CALLER ID LIST

Jul. 06 2004 06:20PM

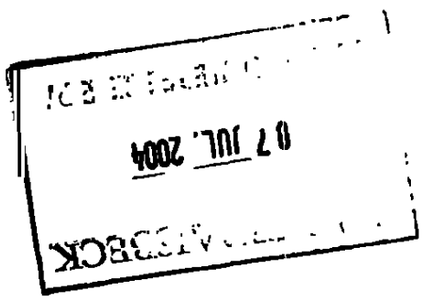
YOUR LOGO : OLARTERAISBECK
YOUR FAX NO. : 571+6017799

NO.	NAME	TELEPHONE NUMBER	TIME OF CALL	ANSWER	STATUS
01	NO NAME RCVD	1-621-0006	Jul. 06 06:19PM	FAX	!
02	NO NAME RCVD	1-349-2669	Jul. 06 04:26PM	FAX	!
03	NO NAME RCVD	1-909-9500	Jul. 06 03:45PM	FAX	!
04	NO NAME RCVD	1-201-5454	Jul. 02 04:41PM	FAX	!
05	NO NAME RCVD	1-283-7490	Jul. 02 11:55AM	FAX	!
06	NO NAME RCVD	1-601-9511	Jul. 02 10:54AM	FAX	!
07	NO NAME RCVD	1-909-9500	Jul. 02 04:44AM	FAX	!
08	NO NAME RCVD	1-219-1013	Jul. 01 05:49PM	FAX	!
09	NO NAME RCVD	1-909-9500	Jul. 01 01:47PM	FAX	!
10	NO NAME RCVD	1-638-2660	Jul. 01 01:04PM	FAX	!
11	NO NAME RCVD	1-346-6488	Jun. 30 06:44PM	FAX	!
12	NO NAME RCVD	1-346-6488	Jun. 30 06:33PM	FAX	!
13	NO NAME RCVD	1-323-9000	Jun. 30 10:37AM	FAX	!
14	OVERSEAS	1-909-9500	Jun. 29 06:51PM	FAX	!
15	PRIVATE	PRIVATE CALLER	Jun. 29 06:50PM	FAX	!
16	PRIVATE	PRIVATE CALLER	Jun. 29 06:48PM	FAX	!
17	PRIVATE	PRIVATE CALLER	Jun. 29 06:47PM	FAX	!
18	NO NAME RCVD	1-625-8480	Jun. 29 11:58AM	FAX	!
19	NO NAME RCVD	1-710-8425	Jun. 29 10:20AM	FAX	!
20	NO NAME RCVD	1-245-6073	Jun. 28 05:22PM	FAX	!
21	NO NAME RCVD	1-404-8999	Jun. 28 04:59PM	FAX	!
22	NO NAME RCVD	1-601-9978	Jun. 28 12:55PM	FAX	!
23	NO NAME RCVD	1-672-6100	Jun. 28 11:59AM	FAX	!
24	NO NAME RCVD	1-489-5004	Jun. 25 03:17PM	FAX	!
25	NO NAME RCVD	1-530-3750	Jun. 25 03:15PM	FAX	!
26	NO NAME RCVD	1-571-0626	Jun. 25 12:01PM	FAX	!
27	NO NAME RCVD	1-218-4956	Jun. 25 11:39AM	FAX	!
28	NO NAME RCVD	1-651-4420	Jun. 25 10:12AM	FAX	!
29	NO NAME RCVD	1-909-9500	Jun. 25 10:11AM	FAX	!
30	NO NAME RCVD	1-909-9500	Jun. 25 10:08AM	FAX	!

! : YOU HAVE NOT CONFIRMED THE CALLER'S INFORMATION YET.
* : YOU CALLED BACK.
(SPACE): YOU CONFIRMED BY USING '+' OR '-' RECEIVING FAX AND RECEIVING VOICE.

TO TURN OFF THE AUTO-CALLER LIST, PRESS 'MENU' #26.
THEN SELECT OFF BY USING '+' OR '-'.

FOR FAX ADVANTAGE ASSISTANCE, PLEASE CALL 1-800-HELP-FAX (435-7329).



INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 03/01430

1281

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0140262 A	07-06-2001	AU 2055301 A	12-06-2001
		CA 2390349 A1	07-06-2001
		EP 1252178 A1	30-10-2002
		JP 2003526634 T	09-09-2003
		WO 0140262 A1	07-06-2001
		US 2002123468 A1	05-09-2002
WO 0208244 A	31-01-2002	AU 7698801 A	05-02-2002
		BR 0112540 A	24-06-2003
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		NO 20030272 A	21-03-2003
		SK 752003 A3	05-08-2003
		WO 0208244 A2	31-01-2002
WO 0174768 A	11-10-2001	AU 5116501 A	15-10-2001
		CA 2405043 A1	11-10-2001
		EP 1268519 A2	02-01-2003
		JP 2003529583 T	07-10-2003
		WO 0174768 A2	11-10-2001
		US 2003236242 A1	25-12-2003

❖Cinco empresas de calzado conformación comercializadora en Cúcuta
❖Surtigás es una empresa distribuidora perteneciente al Grupo Promigás

Movida empresarial

Gas

Sobredemandados bonos por $60 000 millones de Surtigás

Centrión las emisión es de bonos de las compañías del sector privado. En efecto, una de las empresas que también llevó cabo una operación de este tipo fue Surtigás, empresa distribuidora de gas perteneciente al Grupo Promigás S.A. La empresa efectuó una emisión de bonos ordinarios por un valor de 60.000 millones de pesos. Según se conoció, la emisión fue calificada con AA+ por la firma evaluadora de riesgo Duff & Phelps de Colombia. La subasta fue sobredemandada, colocándose a un plazo de 7 años con un rendimiento equivalente a la inflació más 7.4 por ciento.

Publicidad

Euro RSCG Worldwide renueva su estructura de comunicación

Con el propósito de continuar con su cobida de cowerlinx en una empresa de comunicaciones de marketing integrado líder Euro RSCG Wechtelde presenta en Colombia, al igual que en el resto del mundo, una nueva estructura de comunicaciones. Se trata de Euro RSCG 4D, la nueva marca de la agencia que comprende servicios alternativos de marketing y esencia digital. Esta estructura surge en Colombia de la fusión de las empresas The Sales Machine, servicios de marketing y Euro RSCG Interaction, y en el mundo de la fusión con las agencias que se unieron al grupo en septiembre de 2003 como resultado de la reorganización de Havas, tales como Euro RSCG Skybridge, EHS Brann, Brann Worldwide y MKS.

Aerolíneas

American Airlines presenta balance de tercera frecuencia

La aerolínea American Airlines informó que en tres semanas de operación, el cerce velo clarlo Bogotá-Miami-Bogotá mostró resultados positivos con una ocupación del 81 por ciento. La equilibración de la frecuencia de vuelos entre las dos ciudades por parte de AA ha permitido l transporte de 153 pasajeros en promedio por día, adicionales al servicio que le aerolínea venía prestando anteriormente. "Estos resultados, que reflejo el dinamismo del mercado y la respuesta de los viajeros, nosotros nuestro sciento al ampliar nuestras operaciones en el país señaló José María Giraldo, director de la empresa en Colombia.



José María Giraldo director AA para Colombia

Negocios

Crearan una comercializadora y agencia de desarrollo en Cúcuta

Cotorce empresas de los sectores calzado y confin se unieron y

FARMACÉUTICO El laboratorio Procaps se ha visto afectado

Millonaria disputa enfrenta a Gynopharm contra Merck

Un mercado valorado en cerca de tres millones de dólares al año, pues que se calcula más por su firmas, dado el aumento de la expectativa de vida Colombia, parece ser la razón fundamental por la que las farmacéuticas Merck Sharp and Dohme (MSD) y Gynopharm se encuentran inmersas en una nueva guerra comercial.

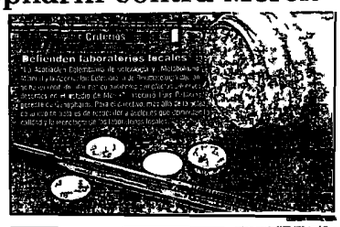
Hace dos años y media el laboratorio Gynopharm lanzó en Colombia Nexium, un medicamento para tratar la osteoporosis que entró competir con el líder del mercado en prescripciones, Pantoran, de la multinacional Merck Sharp and Dohme.

De este dicapio para acá, la venta de estos productos ha tenido vaivenes muy marcados. Actualmente Nexium lidera el mercado de la osteoporosis en prescripción, con una participación de 12 por ciento y Pantoran con el 1 por ciento, según investigaciones especializadas.

Ambas empresas están hoy enfrascadas en una guerra comercial que ha implicado el anuncio público de estudios sobre drogas de el consumo de la competencia, hasta denuncias por competencia desleal.

A mediados de abril pasado, Merck reveló los resultados de un estud realizado en Estados Unidos donde se advirtió de los riesgos para pacientes y en el que se indicó que Nexium no es eficaz y aumenta la posibilidad de dependencia.

La afirmación, realizada por directivos de la multinacional nivel local, generó de inmediatas reacciones en Gynopharm, pues cuestionaba la calidad de su producto ustedes puede en vida de poder al laboratorio colombiano



Criterios

Defienden laboratorios locales



Ambas empresas están enfrascadas en una guerra comercial que ha implicado anuncio públicos de estudios sobre drogas de el consumo de la competencia, hasta denuncias por competencia desleal.

	Merck S.A.	Gynopharm S.A.
Ventas	$8.326,8	$ 942,8
Pastas	$ 269,2	$ 53,7
Participación	3a 4a	ABC
Imp. Nacional	100,0%	11,3%

Los Peñaloza, quien argumentó que dicha estación no corresponde al lugar más que una oficina pequeña, con personal desleal, esos grupos farmacéuticos que conocen el documento no se tomaron y tomaron por inducir error el consumidor".

Ante esa situación, anfaciaron Procaps dijo que era vital la Superintendencia estudie el hecho competencia desleal, se tomen contundentemente las sanciones que a bultadas la ley.

portunidad de Industria y Comercio, la cual estuvo asesorada por una serie de investigaciones que muestran una versión diferente del comportamiento de ventas planteado por Merck.

Pruebas

Gynopharm le solicitó la Universidad Nacional que se pronuncie sobre la sigmoidefinición del documento emitido por MSD y el experto dictaminación afirmó que el estudio se remonta ser sólo una hipótesis.

"Existen pertinencias é acuerdo con los autores en que es sólo una hipótesis de trabajo.

salen que la USP (United States Pharmacopeia) en 1975 y en consiglass inicial ja la prueba de disolución como método válido para la valoración de un medicamento, teniendo empleado por el tiempo para valorar "disolución", señaló l documento de la Universidad

Para las investigaciones no pronos old, pues en Colombia el índice organismo autorizado para llevar cabo este tipo de investigaciones es el Instituto Nacional de Vigilancia de los Medicamentos y los Alimentos (Invima).

Así lo ha manifestado en varias oportunidades el director de la ofed, Julio Cées Mancipio español que este de la información conocida, por cuanta pesas se tomaron muestras para hacer los estudiosos pertinentes. Al respecto, se llegó la conclusión de que el medicamento de Gynopharm cumplía con el estándar establecido y que la muestra de conformidad de aprovechamiento que podía que la muestra es aceptable.

Adicionalmente, hubo dos criterios científicos nivel local que se pronunciaron frente al

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN — **MODELO DE UTILIDAD**	( )	( )
Indicacion de que se solicita la concesion de una patente	( )	( )
Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
Descripción de la invención.	( )	( )
Dibujos de ser estos pertinentes.	( )	( )
Comprobante de Pago de las tasas establecidas.	( )	( )
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 grafica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicacion de que solicita el registro de un Esquema de trazado	( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )

Firma Responsable

SUPERINDUSTRIA Y COMERCIO
Radicacion 04068146 00000000 Folios 1281
Fecha (AMD) 2004-07 16 17 41 52
Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia 2020 DIVISION DE NUEVAS CREACIONES

Fecha

1283

Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá D C

Doctor(a)
CARLOS R. OLARTE
Apoderado

Oficio N° 07405

ASUNTO:

Radicación N°	04-68146
Solicitud internacional	PCT/US03/01430
Fecha inicio fase nacional	18/08/2004
Trámite	011
Evento	379
Actuación	416
Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).
- Los dibujos adjuntos no son legibles ó copiables para trámites posteriores de publicación y título.
- El solicitante debe presentar un nuevo título, que permita identificar la materia de la cual trata la solicitud, ya que el relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente (Regla 4.3 PCT, Art. 27, 27 Decisión 486, Circular Única 5.2.9).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha,
06 AGO. 2004
202044

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
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