03/3340

Industria y Comercio

SUPERINTENDENCIA

INVENTARIO

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT.

SOLICITUD

PATENTE DE INVENCIÓN

03/3340

21. **EXPEDIENTE No.**

54. **TÍTULO** NUEVOS PEPTIDOS COMO ENHIBDORES DE PROTEASA SERINA- NS3 DEL VIRUS DE LA HEPATITIS C.

51. **CLASIFICACIÓN INTERNACIONAL**

71. **SOLICITANTE** SCHERING CORPORATION; CORVAS INTERNATIONAL, INC.

DOMICILIO

74. **APODERADO**

37/ 80/

22. **BOGOTÁ, D. C.,** Rocha 20

(FORMA P-10)

21. EXPEDIENTE Nº 03-3340

54. TÍTULO Nuevos Peptidos Como Inhibidores De Proteasa Serina - NS3 Del Virus De La Hepatitis C.

51. CLASIFICACIÓN INTERNACIONAL A61K 31/4375

71. SOLICITANTE Schering Corporation Corucs International, Inc.

DOMICILIO

74. APODERADO Carlos R. Olarte.

22. BOGOTÁ, D. C.

62

PETITORIO

(1)

I

Industria y Comercio
SUPERINTENDENCIA

03 003340 00

SUPERINTENDENCIA Y COMERCIO
Radicacion : 03003340 00000000 Folios: 1018
Fecha (AMD): 2003-01-20 17:36:18
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

(1) **SOLICITUD DE :**

[X]	Patente de Invención	[ ]	Patente de Modelo de Utilidad
[ ]	Capítulo I.	[X]	Capítulo II.

(2) SOLICITANTE (71)

Nombre: SCHERING CORPORATION; CORVAS INTERNATIONAL, INC.
Dirección: 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530 E.U.A. 3030 Science Park Road San Diego, CA 92121 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: New Jersey, Estados Unidos de América.
Teléfono: Fax:
E-Mail

IDENTIFICACION
C.C. [ ] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número

(3) REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: Avda 82 No. 10-62 Piso 6
Teléfono: 634-1500 Fax: 376-2211
E-Mail: patents.bogota@bakernet.com

IDENTIFICACION
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número 79.782.747 Btá TP 74.295

(4) INVENTOR (ES) (72)

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

(5) PCT (85)

Solicitud Internacional No. PCT/US01/22678 Fecha Julio 19, 2001
Publicación Internacional No. WO 02/08244 Fecha Enero 31, 2002

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

(7) Clasificación Internacional (51) A61K 31/4375

(8) Prioridad

SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Julio 21, 2000	60/220,108

(9) Comprobante de pago No. 63,149; 1,692. **Fecha** 09-23-02; 01-10-03.

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

(10) **ANEXOS**

2

- [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 inventor al solicitante o a su causante
- [ ] Declaraciones
- [X] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [X] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA
- [ ] De ser el caso, copia del contrato de acceso
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- [ ] De ser el caso, certificado de depósito del material biológico
- [ ] Arte final 12 x 12
- [X] 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.
- [ ] Otros: Búsqueda Internacional,

(11) **FIGURA CARATERISTICA**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:

C.C. 79.782.747 de Btá T.P. 74295

Instrucciones para la presentación de los anexos, ver reverso de esta página

Case No. IN01159K

Attachment "A"

Saksena, Anil K., citizen of the United States of America, residing at 53 Beverley Road, Upper Montclair, New Jersey 07059, U.S.A.

Girijavallabhan, Viyyoor Moopil, citizen of the United States of America, residing at 10 Maplewood Drive, Parsippany, New Jersey 07054, U.S.A.

Lovey, Raymond G., citizen of the United States of America, residing at 65 Woodside Avenue, West Caldwell, New Jersey 07006, U.S.A.

Jao, Edwin E., citizen of the United States of America, residing at 20 Crosswood Way, Warren, New Jersey 07059, U.S.A.

Bennett, Frank, citizen of the United Kingdom, residing at 419 Draco Road, Piscataway, New Jersey 08854, U.S.A.

McCormick, Jinping L., citizen of the United States of America, residing at 5 Pace Drive, Edison, New Jersey 08820, U.S.A.

Wang, Haiyan, citizen of Peoples Republic of China, residing at 5 Cubberly Court, Cranbury, New Jersey 08512, U.S.A.

Pike, Russell E., citizen of the United States of America, residing at RD #1, 31 Florence Street, Stanhope, New Jersey 07874, U.S.A.

Bogen, Stephane L., citizen of France, residing at 13 Dahlia Road, Somerset, New Jersey 08873, U.S.A.

Chan, Tin-Yau, citizen of Hong Kong, residing at 26 Barlow Road, Edison, New Jersey 08817, U.S.A.

Liu, Yi-Tsung, citizen of the United States of America, residing at 34 Alexandria Road, Morris Township, New Jersey 07960, U.S.A.

Zhu, Zhaoning, citizen of Peoples Republic of China, residing at 34 Stonehedge Drive, East Windsor, New Jersey 08520, U.S.A.

Njoroge, F. George, citizen of Kenya, residing at 11 Softwood Way, Warren, New Jersey 07059, U.S.A.

Arasappan, Ashok, citizen of India, residing at 18 Larsen Court, Bridgewater, New Jersey 08807, U.S.A.

Parekh, Tejal N., citizen of India, residing at 1885 Ednamary Way, Unit C, Mountain View, California 94040, U.S.A.

Ganguly, Ashit K., citizen of the United States of America, residing at 96 Cooper Avenue, Upper Montclair, New Jersey 07043, U.S.A.

Chen, Kevin X., citizen of the United States of America, residing at 44 Gill Lane, Apt. 1D, Iselin, New Jersey 08830, U.S.A.

Venkatraman, Srikanth, citizen of India, residing at 35 Roanoke Street, Woodbridge, New Jersey 07095, U.S.A.

Vaccaro, Henry A., citizen of the United States of America, residing at 123 Somerset Avenue, South Plainfield, New Jersey 07080, U.S.A.

Pinto, Patrick A., citizen of the United States of America, residing at 34 Battle Ridge Road, Morris Plains, New Jersey 07950, U.S.A.

Santhanam, Bama, citizen of India, residing at 10 Somerset Avenue, Bridgewater, New Jersey 08807, U.S.A.

Wu, Wanli, citizen of the Peoples Republic of China, residing at 452 Horizon Drive, Edison, New Jersey 08817, U.S.A.

Hendrata, Siska, citizen of the United States of America, residing at 15 Flintlock Terrace, Rockaway, New Jersey 07866, U.S.A.

Huang, Yuhua, citizen of the Peoples Republic of China, residing at 760 Boulevard, Westfield, New Jersey 07090, U.S.A.

Kemp, Scott Jeffrey, citizen of the United States of America, residing at 7873 Avenida Navidad #263, San Diego, California 92122, U.S.A.

Levy, Odile Esther, citizen of the United States of America, residing at 5304 Ruette de Mer, San Diego, California 92130, U.S.A.

Lim-Wilby, Marguerita, citizen of Malaysia, residing at 6333 Castejon Drive, La Jolla, California 92037, U.S.A.

Tamura, Susan Y., citizen of the United States of America, residing at 9166 Bedel Court, San Diego, California 92129, U.S.A.

R 6

Industria y Comercio

SUPERINTENDENCIA

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03003340 00000000 Folios: 1018
Fecha (AMD): 2003-01-20 17:36:18
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 02 - 63,149
FECHA : SEPTIEMBRE 23 DE 2002

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JULIAN ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	050-00110-6	3135146	23/09/2002	38,825,000.00

***** 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	378,000.00
			TOTAL : $	378,000.00

SON: TRESCIENTOS SETENTA Y OCHO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

Industria y Comercio

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
*Radicacion : 03003340 00000000 Folios: 1018
Fecha (AMD): 2003-01-20 17:36:18
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

CIA

RECIBO OFICIAL DE CAJA : 03 - 1,692
FECHA : ENERO 10 DE 2003

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JULIAN ANDRES VARGAS	CONSIGNACION	BANCO POPULAR	050-00110-6	8285310	10/01/2003	15,979,000.00

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

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-09 OTROS SERVICIOS DE PROPIEDAD I	998	VALOR COMPLEMENTO TARIFA A#O ANTR	22,000.00
			TOTAL : $	22,000.00

SON: VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

8

Traducción Oficial No. 02-899

Efectuada el día 20 de agosto de 2002, de un documento escrito en Inglés, al cual para su identificación se le estampa el sello de María del Pilar Iglesias, Traductora e Intérprete Oficial por Resolución No. 819 del 15 de abril de 1971 expedida por el Ministerio de Justicia de la República de Colombia.

Traducción de las autenticaciones notariales y subsiguientes correspondientes a un Poder otorgado por **SCHERING CORPORATION** a CARLOS REINALDO OLARTE Y/O ALVARO CORREA ORDOÑEZ, documento éste que viene en español y se explica por sí solo.

La firma y cargo de Edward H. Mazer como Funcionario Autorizado de la compañía arriba citada fueron debidamente certificados por el Notario Público Norma Gallina del Estado de Nueva Jersey, según consta en la Certificación Notarial, que también viene en español y que fue firmada por dicho Notario el 2 de agosto de 2002, quien tuvo a la vista la Escritura de Constitución de la Compañía reformada el 4 de abril de 1996 y el Certificado de Constitución actualizado al 16 de junio de 1997.

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.

09 DIC 2002

BOGOTA, D.C.

ALMA NAVARRO DE [illegible]
NOTARIA ONCE (11)

[illegible] Iglesias
TRADUCTORA E INTERPRETE OFICIAL
Resolución No. 819 Minjusticia

9

APOSTILLA

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

1. País: Estados Unidos de América

   El presente documento público

2. Fue firmado por Norma Gallina

3. Que actuó en su calidad de Notario Público del Estado de Nueva Jersey.

4. Lleva el sello del mencionado Notario Público

   Se certificó

5. En Trenton, Nueva Jersey 6. El 9 de agosto de 2002

7. Por parte de John E McCormac, CPA, Tesorero de Nueva Jersey.

8. Bajo el Número A156329.

9. Sello del Estado de Nueva Jersey

10. Firmado por John E McCormac

Es traducción fiel y completa efectuada por:

María del Pilar Iglesias
C.C.41.339.183 de Bogotá

COMO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA.
09 DIC 2002
BOGOTA, D.C. - COLOMBIA
NELMA NAVARRO DE BAUTISTA
NOTARIA ONCE (11)

María del Pilar Iglesias
C. C. 41.339.183 de Bogotá
Intérprete Oficial según Resolución No. 819 de
15 de Abril de 1971 del Ministerio de Justicia

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
NORMA GALLINA

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

4. BEARS THE SEAL/STAMP OF:
NORMA GALLINA, NOTARY

CERTIFIED

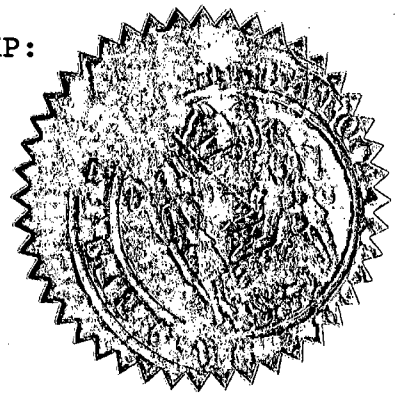
5. AT TRENTON, NEW JERSEY

6. THE 9TH DAY OF AUGUST 2002

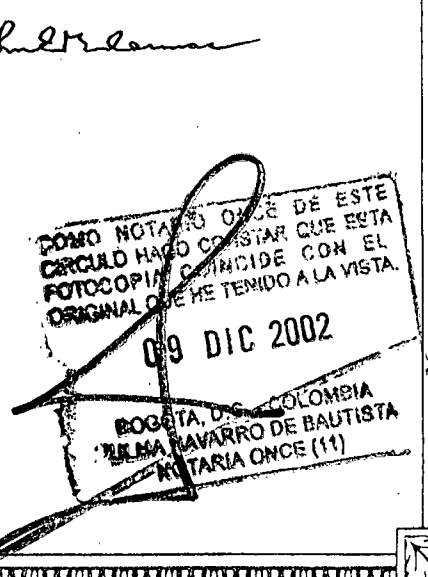
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A156329

9. SEAL/STAMP:



10. SIGNATURE



RAISBECK, LARA, RODRIGUEZ & RUEDA
MEMBERS OF THE FIRM
BAKER & McKENZIE
ATTORNEYS AT LAW

AV 82 No. 10-62, 6TH FLOOR
BOGOTA, D.C. COLOMBIA
TELEPHONE (57-1) 634-1500
FACSIMILE (57-1) 376-2211
NIT 860.068.840-3
OFFICE.BOGOTA@BAKERNET.COM
WWW.BAKERNET.COM

11

POWER OF ATTORNEY

The undersigned.

SCHERING CORPORATION

located in
2000 Galloping Hill Road
Kenilworth, New Jersey 07033
United States of America

declares that it hereby grants to

CARLOS REINALDO OLARTE AND/OR

ALVARO CORREA ORDOÑEZ

a full and sufficient power of attorney to apply to the proper national officers and authorities for the issue of:

Patents of Invention, Patents for Utility Models, Industrial Design Registrations, mergers, changes of name, assignments, filing and prosecution of oppositions, changes of address.

to which end it empowers them to take all steps necessary before said authorities for the objects stated, to file petitions, prepare descriptions, make protests, declarations, appeals and objections, pay imposts, apply for certifications, receive documents and securities, abandon applications and collect refunds. To the said mandatories sufficient power is granted hereby to receive notifications for and 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 patents, and to do everything that may be required, before administrative or judicial officers of any class giving them likewise power to substitute these presents and revoke such substitutions if necessary.

Done and subscribed in
Kenilworth, New Jersey, USA

On the 2nd day of August

2002

(Signature)
Edward H. Mazer
Duly Authorized Officer

PODER

La abajo firmada.

SCHERING CORPORATION

domiciliada en
2000 Galloping Hill Road
Kenilworth, New Jersey 07033
Estados Unidos de America

declara por el presente otorgar a

CARLOS REINALDO OLARTE Y/O

ALVARO CORREA ORDOÑEZ

poder especial amplio y bastante para recabar de las oficinas y autoridades nacionales que correspondan, la obtención de :
Patentes de Invención, Patentes de Modelo de Utilidad, Registro de Diseños Industriales, fusiones, cambios de nombre, cesiones, presentación y trámite de oposiciones, cambios de dirección.

a cuyo efecto los faculta para dar ante dichas autoridades, todos los pasos necesarios al objeto indicado, elevar solicitudes, formular descripciones , protestas, declaraciones, apelaciones y reclamos, oblar impuestos, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede a los expresados mandatarios 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 las patentes se presentaren y hacer cuanto fuere necesario, ante las autoridades administrativas o judiciales de cualquier orden, dándoles asimismo facultad para sustituir el presente y en caso necesario revocar dichas sustituciones.

Dado y firmado en _____

A los ____ días del mes de _____

2002

ANTE NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE ME FUE PRESENTADO A LA VISTA.
09 DIC 2002
BOGOTA, D.C. COLOMBIA
NOTARIA ONCE (11)

RAISBECK, LARA, RODRIGUEZ & RUEDA
MEMBERS OF THE FIRM
BAKER & McKENZIE
ATTORNEYS AT LAW

AV 82 No. 10-62, 6TH FLOOR
BOGOTA, D.C. COLOMBIA
TELEPHONE (57-1) 634-1500
FACSIMILE (57-1) 376-2211
NIT 860.068.840-3
OFFICE.BOGOTA@BAKERNET.COM
WWW.BAKERNET.COM

12

NOTARIAL CERTIFICATION

On this 2nd day of August

2002, the undersigned Notary

CERTIFIES

1. That Edward H. Mazer

of legal age and domiciled in Millburn, New Jersey United States of America

set his hand on the foregoing document.

2. That the grantor is to me personally know and that he/she has legal capacity to execute the instrument.

3. That the grantor has executed the foregoing document as

Duly Authorized Officer

of the judicial person

4. That the judicial person

SCHERING CORPORATION

having its home office in 2000 Galloping Hill Road, Kenilworth, New Jersey 07033, USA

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:

Certificate of Incorporation, as amended, dated April 4, 1996
Certificate of Restated Incorporation filed June 16, 1997

Norma Gallina
Notary Public

NORMA GALLINA
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires June 27, 2005

CERTIFICACION NOTARIAL

A los _____ dias del mes de _____

de 2002, el suscrito Notario

DA FE

1. Que _____

mayor y domiciliado en _____

suscribió de su puño y letra el documento que antecede.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

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

_____

de la persona jurídica

_____

4. Que la persona jurídica

_____

con sede en _____

_____

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se ha otorgado el poder está comprendido entre los que constituyen su objeto social.

5. Que el otorgante tiene efectivamente la representación que ostenta, y que esta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono especificamente con expresión de sus fechas y de su origen o procedencia:

_____

_____

_____

El Notario Público

DESPACHO NOTARIO ONCE DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
09 DIC 2002
BOGOTA, D.C. - COLOMBIA
NOTARIA ONCE

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 January 2002 (31.01.2002)

PCT

(10) International Publication Number
WO 02/08244 A2

(51) International Patent Classification[7]: C07K

(21) International Application Number: PCT/US01/22678

(22) International Filing Date: 19 July 2001 (19.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/220,108 21 July 2000 (21.07.2000) US

(71) Applicants: **SCHERING CORPORATION** [US/US]; Patent Department - K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). **CORVAS INTERNATIONAL, INC.** [US/US]; 3030 Science Park Road, San Diego, CA 92121 (US).

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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, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations 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*
— *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.

WO 02/08244 A2

(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.

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.

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.

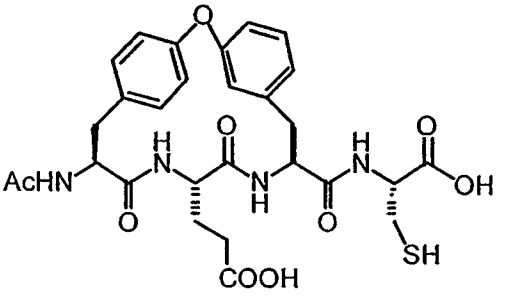
Inhibitors of HCV protease that have been reported include antioxidants (see, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (see, International Patent Application Publication No. WO 98/17679, Landro et al. (1997) Biochem. 36:9340-9348, Ingallinella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

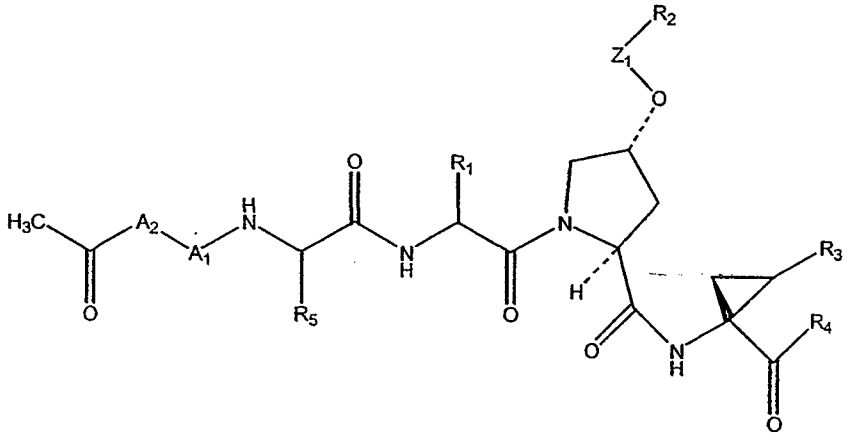
HCV has been implicated in cirrhosis of the liver and in induction of hepatocellular carcinoma. The prognosis for patients suffering from HCV infection is currently poor. HCV infection is more difficult to treat than other forms of hepatitis due to the lack of immunity or remission associated with HCV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

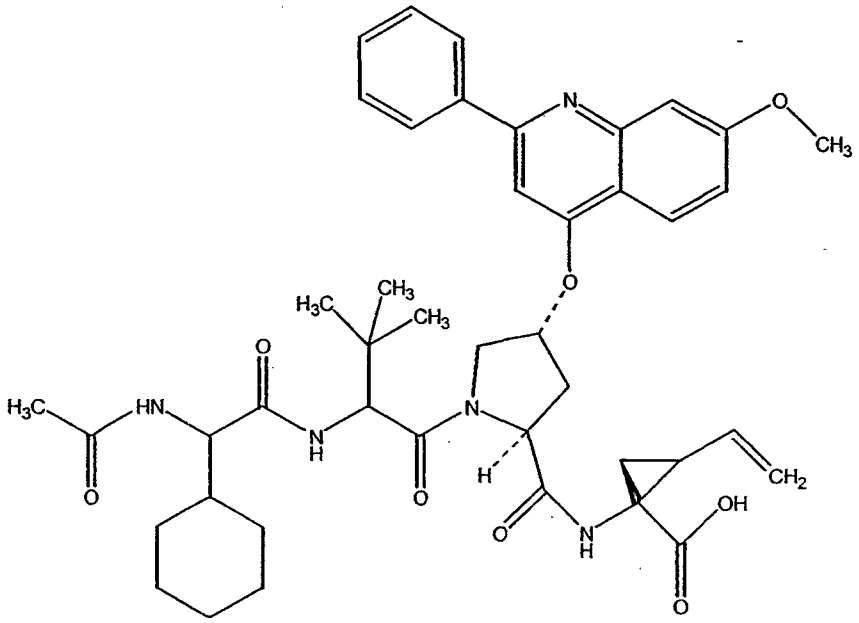


Reference is also made to W. Han *et al, Bioorganic & Medicinal Chem. Lett,* (2000) 10, 711-713, which describes the preparation of certain α-ketoamides, α-ketoesters and α-diketones containing allyl and ethyl functionalities.

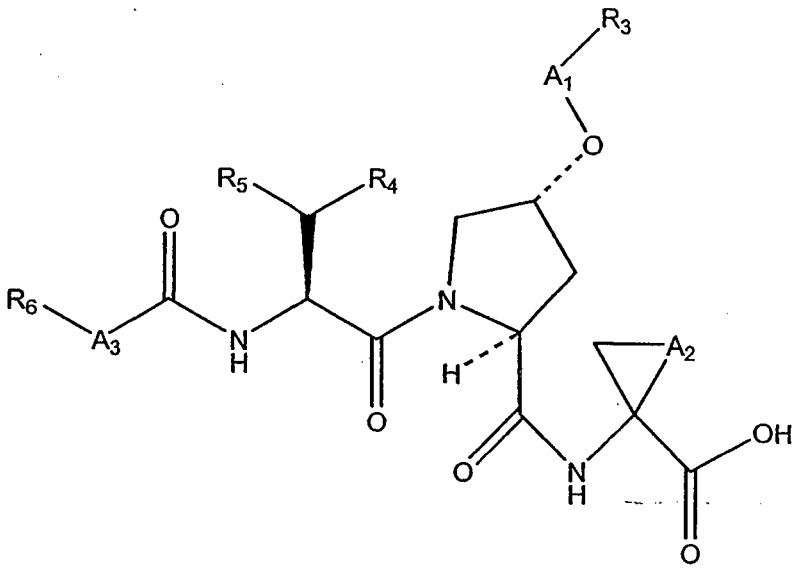
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



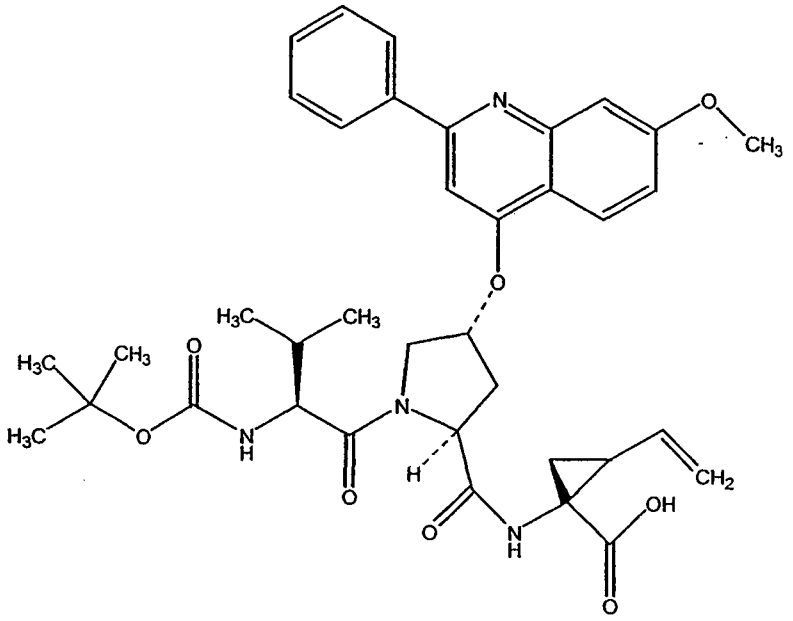
where the various elements are defined therein. An illustrative compound of that series is:



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.

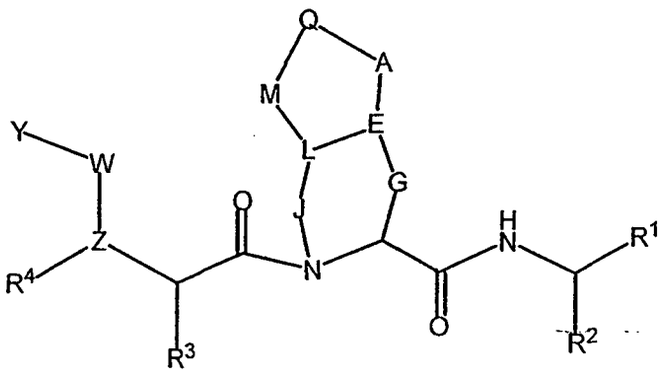
A still further object of the present invention is to provide methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

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, including enantiomers, stereoisomers, rotamers, tautomers, racemates and prodrug of said compound, and 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 the following moieties: 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 COR^5 or $B(OR)_2$, wherein R^5 is H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, or COR^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, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pCOR^{11}$, $[CH(R^{1'})]_pCH(OH)R^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COOR^{11}$ and $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})CONR^{12}R^{13}$, 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, CH or CR;

W may be present or absent, and if W is present, W is selected from C=O, C=S, C(=N-CN), or SO_2;

Q may be present or absent, and when Q is present, Q is CH, 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, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_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 $(CRR')_p$, SO_2, NH, NR 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 CH, CR, O, S or NR; 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, SO_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 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 represents a five-membered or 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:

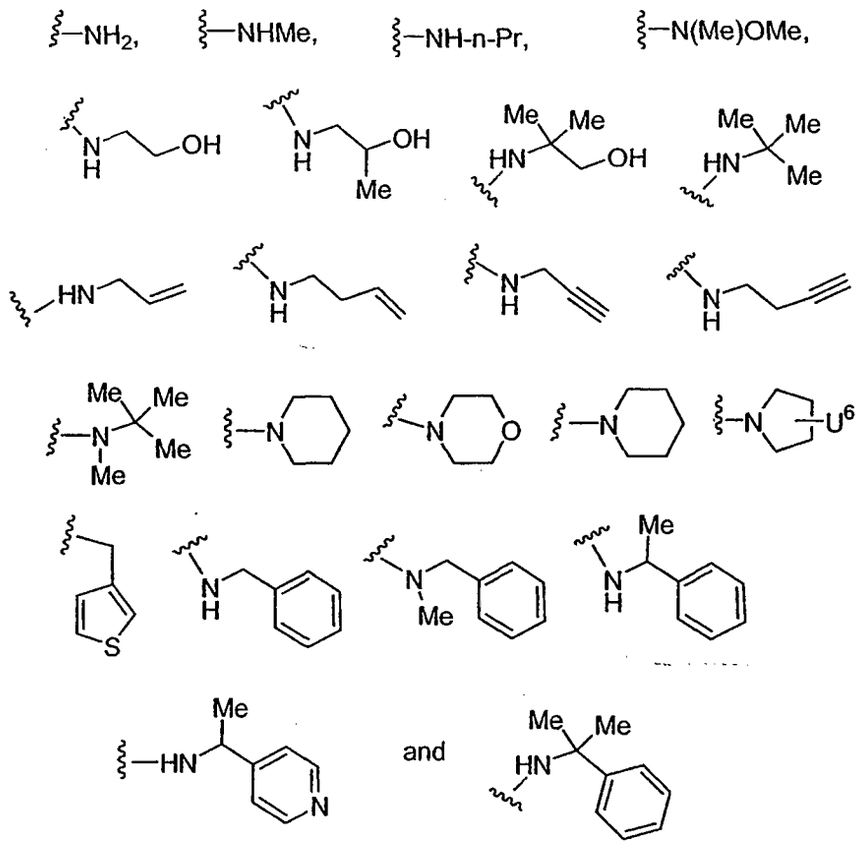
Preferred definition for R^1 is COR^5 with R^5 being H, OH, $COOR^8$ or $CONR^9R^{10}$, where R^8, R^9 and R^{10} are defined above. Still preferred moiety for R^1 is $COCONR^9R^{10}$, where R^9 is H; and R^{10} is H, R^{14}, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pSO_2N\ R^{12}R^{13}$, $[CH(R^{1'})]_pCOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})\ CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, 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}, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})SO_2R^{11}$, $CH(R^{1'})CH(R^{1'})SO_2N\ R^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})COR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})\ CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, 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 $CH_2CONR^{12}R^{13}$ where

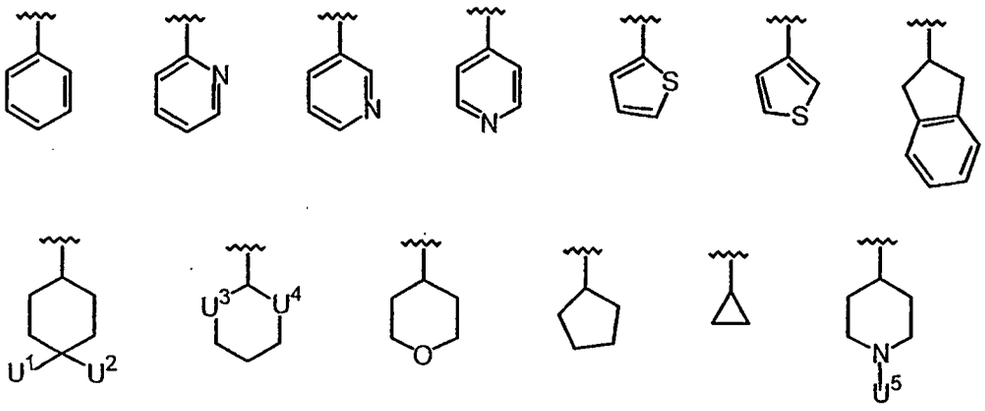
$NR^{12}R^{13}$ is selected from the group consisting of:



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, cyclopropylmethyl;

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



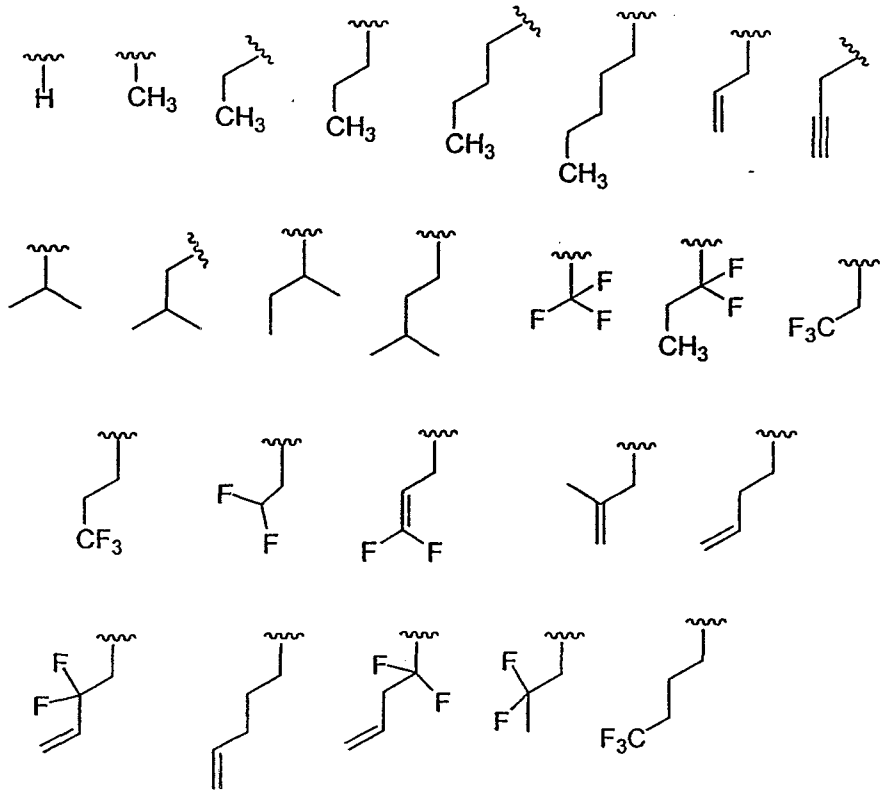
wherein:

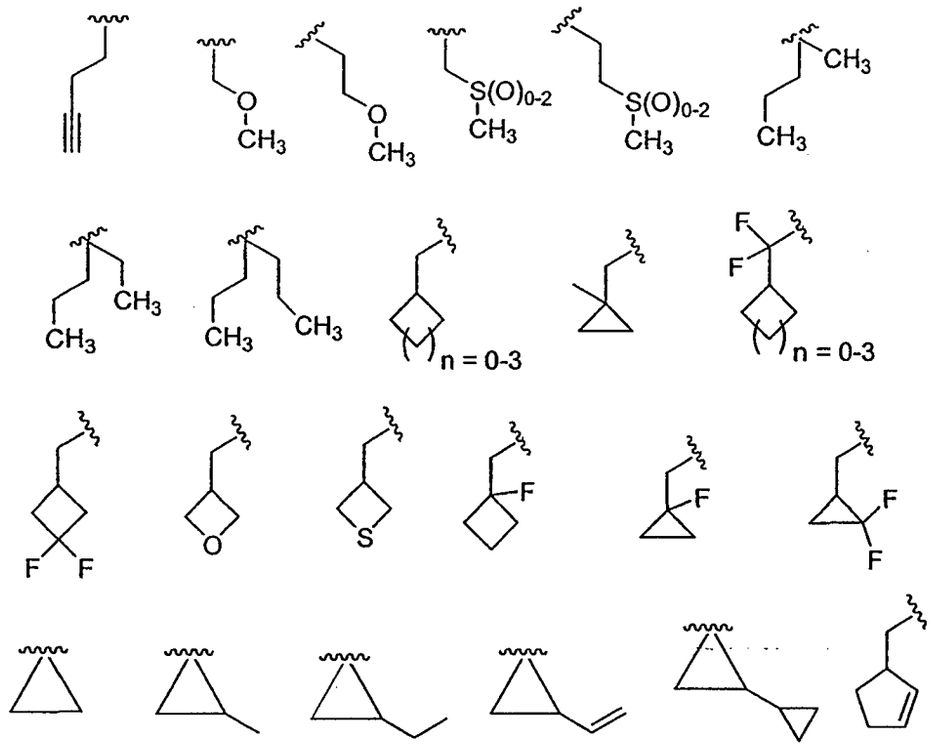
U^1 and U^2 maybe same or different and are selected from H, F, CH_2COOH, CH_2COOMe, CH_2CONH_2, $CH_2CONHMe$, CH_2CONMe_2, azido, amino, hydroxyl, substituted amino, substituted hydroxyl;

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

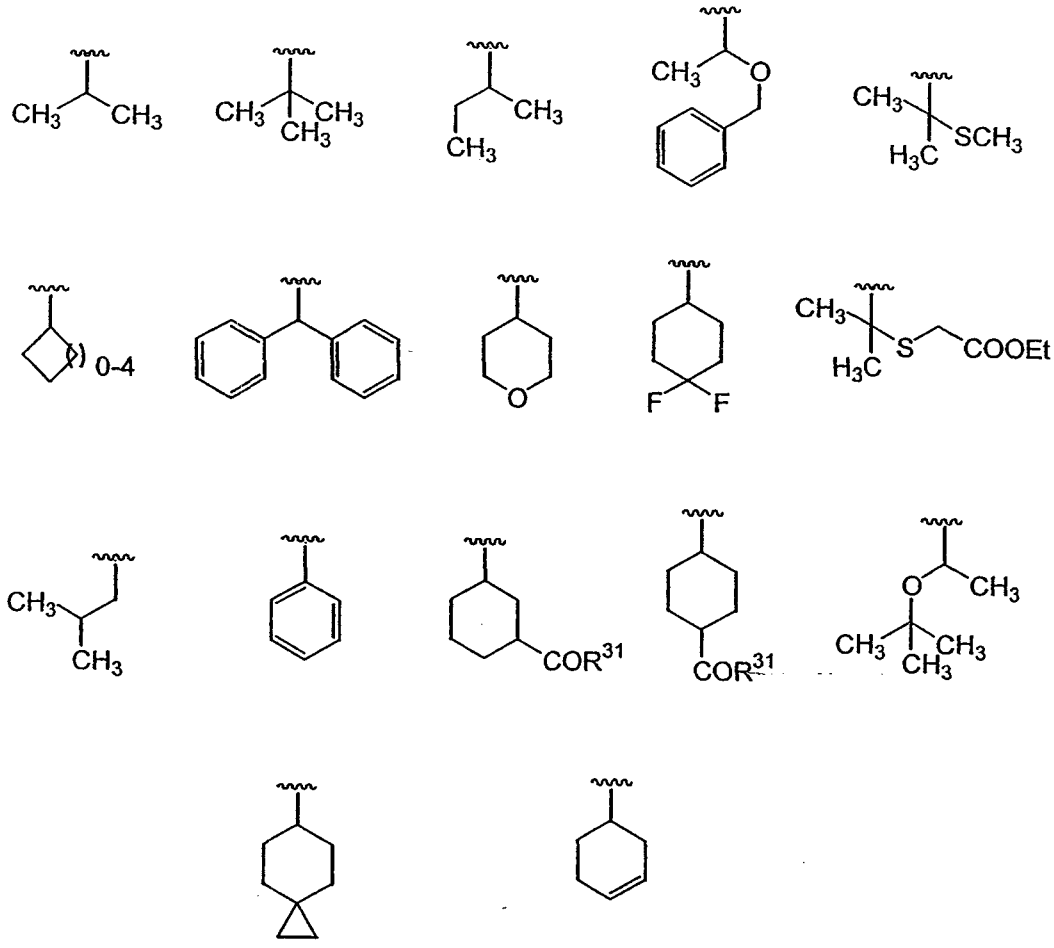
U^5 is selected from the moieties consisting of alkyl sulfonyl, aryl sulfonyl, heteroalkyl sulfonyl, heteroaryl sulfonyl, alkyl carbonyl, aryl carbonyl, heteroalkyl carbonyl, heteroaryl carbonyl, alkoxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkylaminocarbonyl, arylaminocarbonyl, heteroarylaminocarbonyl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

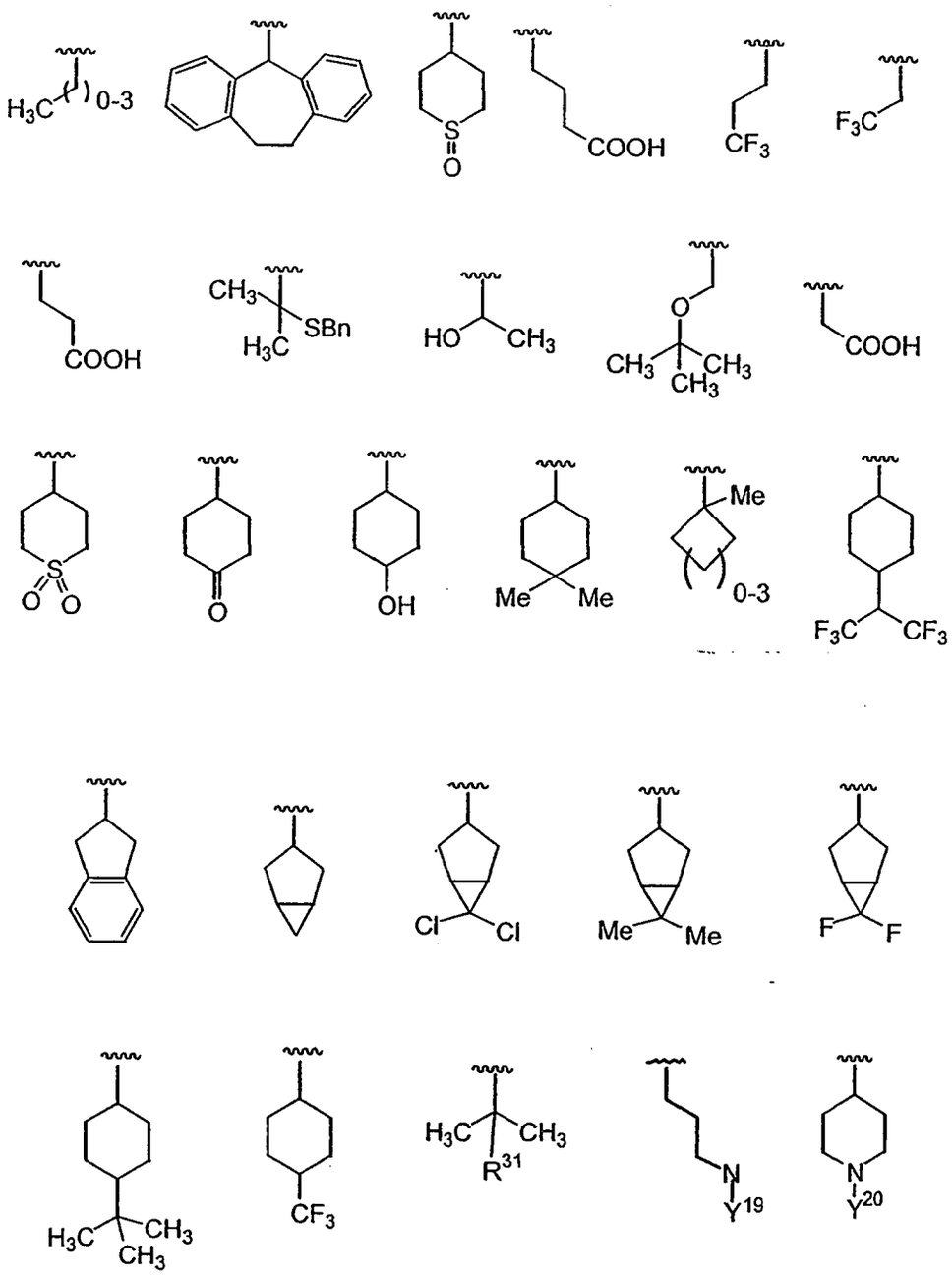
Preferred moieties for R^2 are:





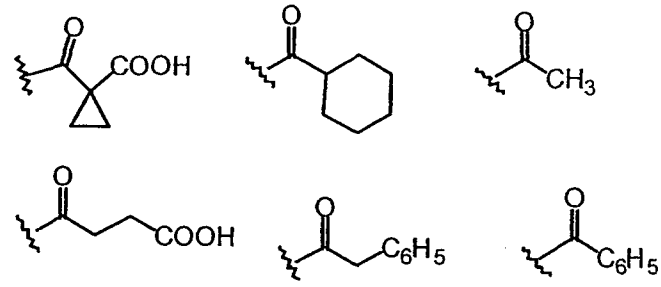
Preferred moieties for R^3 are:


CH3
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

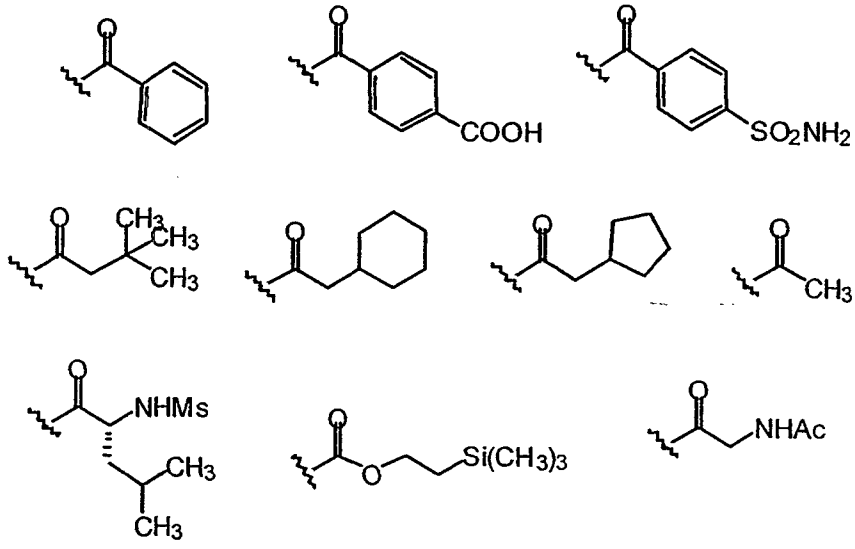


wherein R^{31} = OH or O-alkyl;

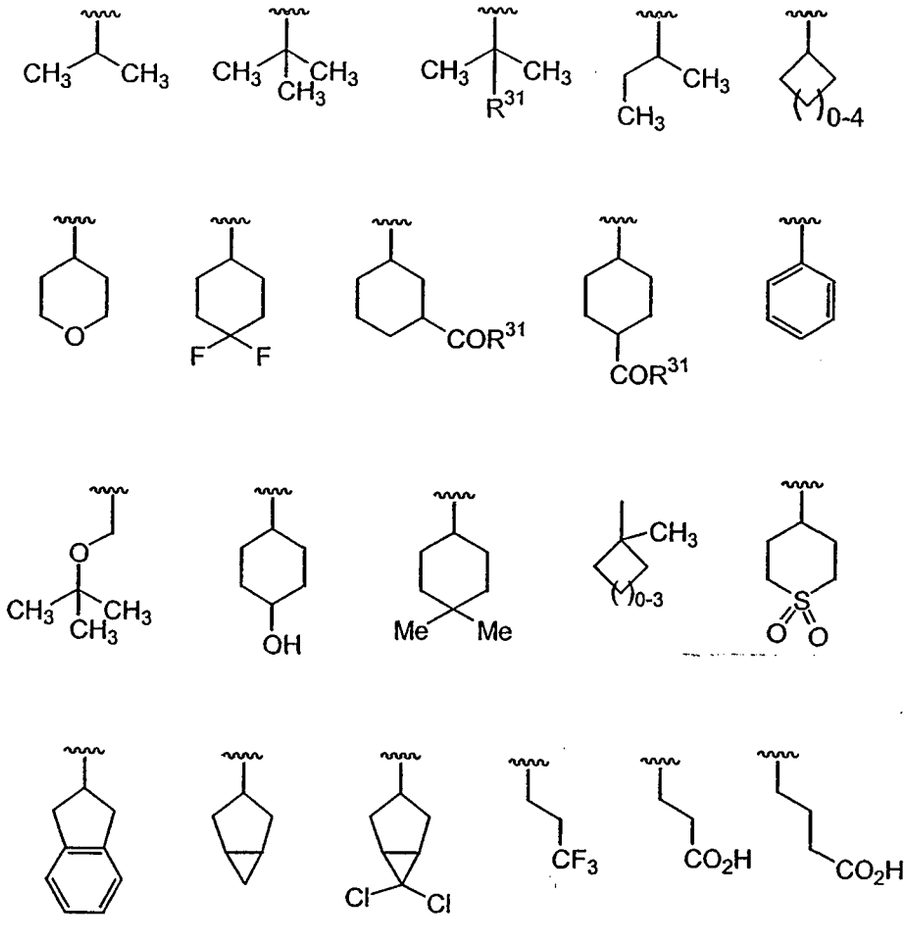
Y^{19} is selected from the following moieties:



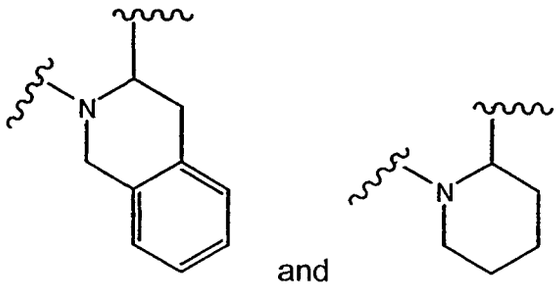
and Y^{20} is selected from the following moieties:



Most preferred moieties for R^3 are:

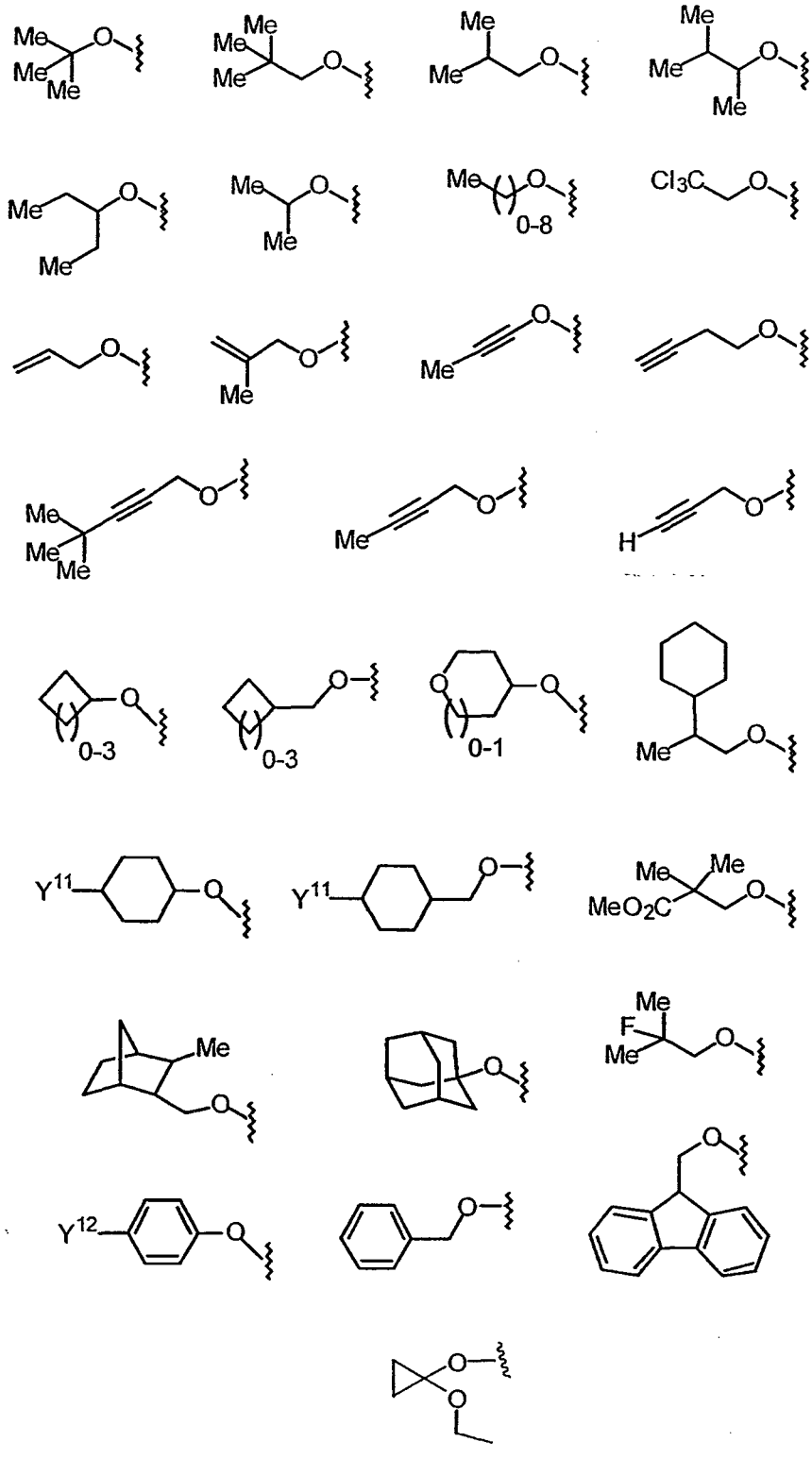


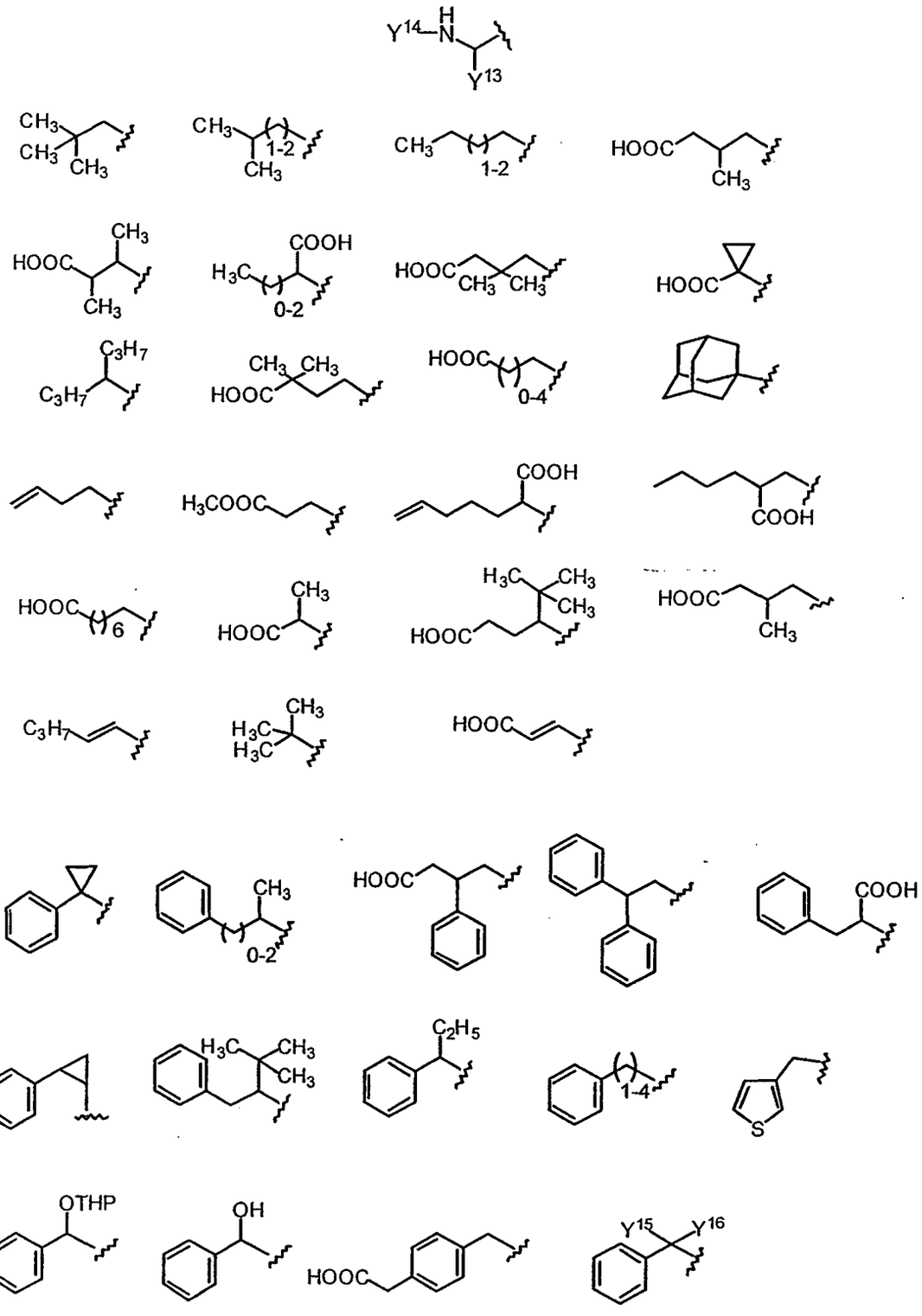
Some other preferred moieties are: for Z it is N, for R^4 it is H, and for W it is C=O. Additionally, the moiety Z-C-R^3 in Formula I, with R^4 being absent, may be represented by the following structures:

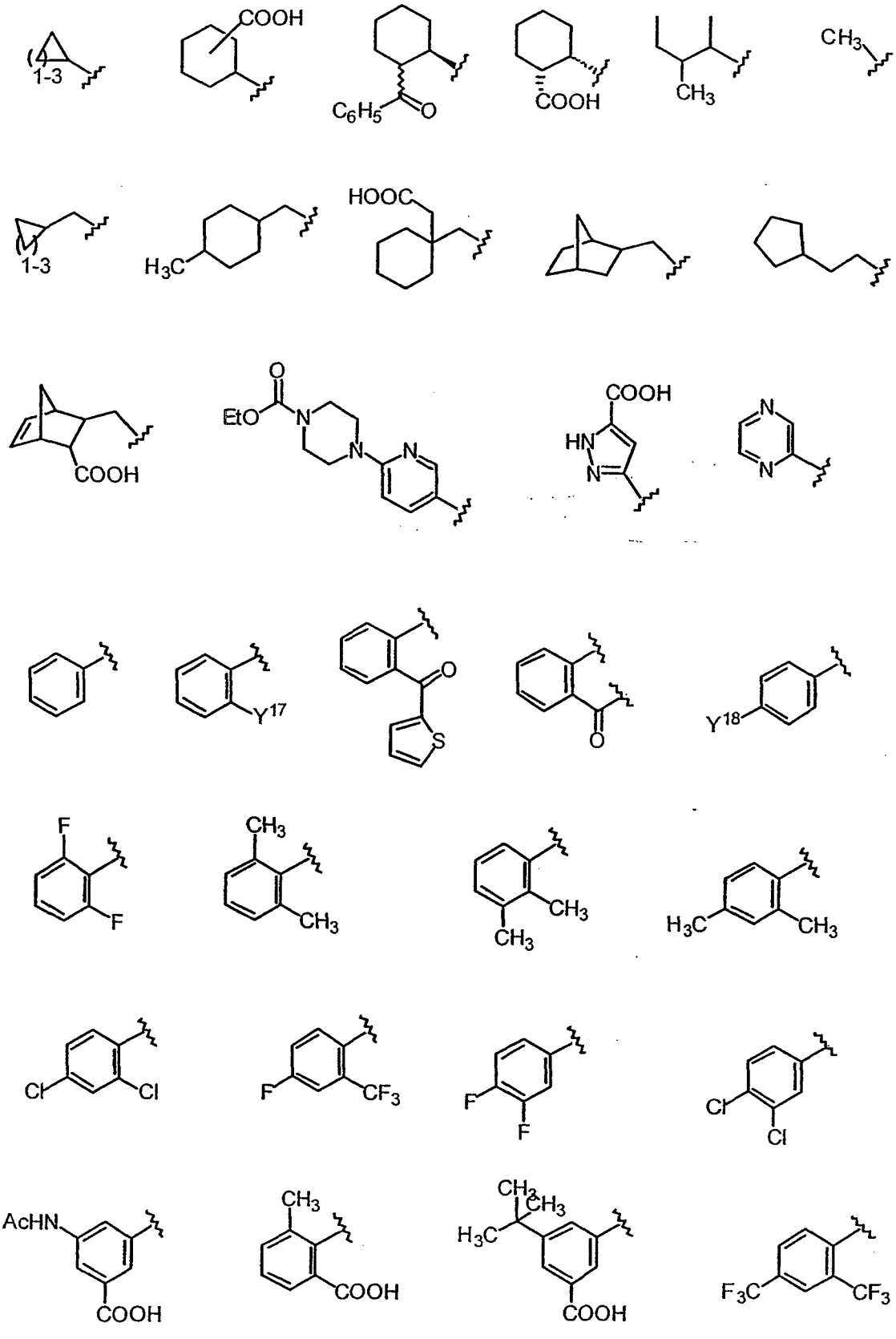


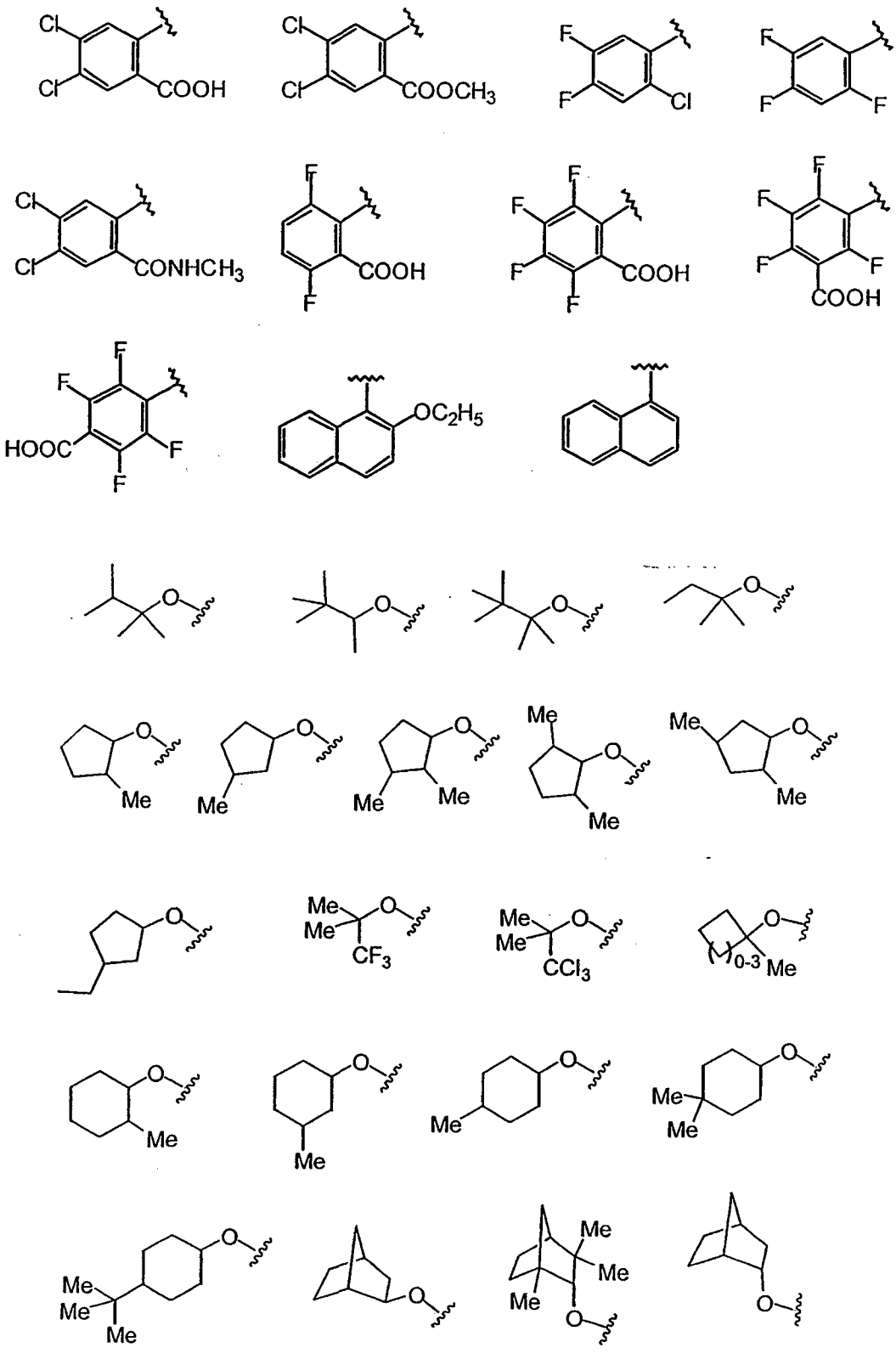
and

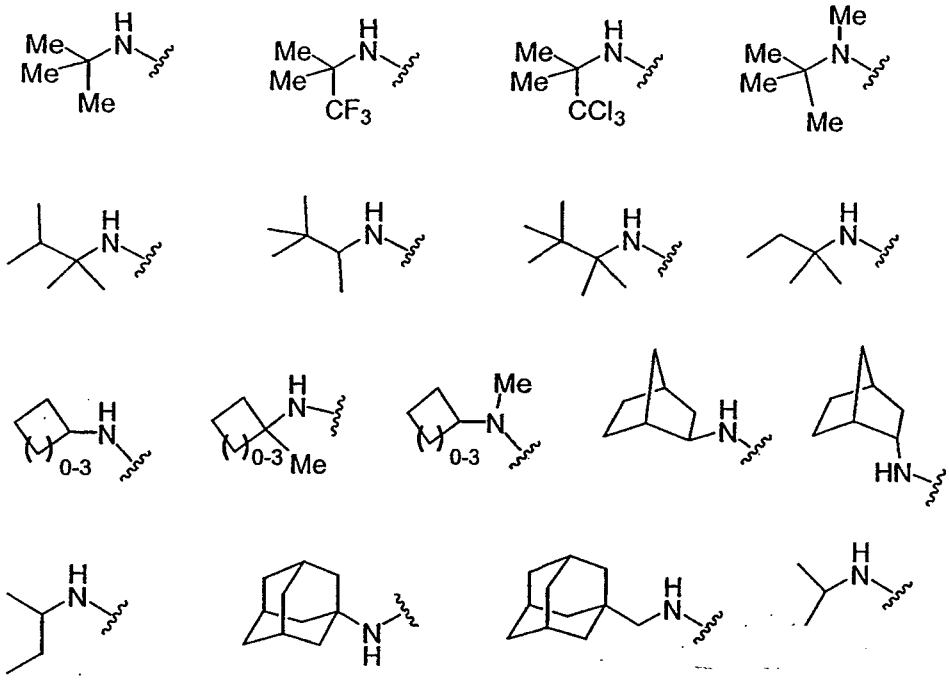
Preferred moieties for Y are:




Y14
H
N
Y13
CH3
CH3
CH3
1-2
HOOC
COOH
0-2
C3H7
0-4
6
OTHP
OH
Y15
Y16
C2H5
1-4
S


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
COOH
F
F
F
F
COOH
F
F
HOOC
F
F
OC2H5
O
Me
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
Me
Me
Me
O

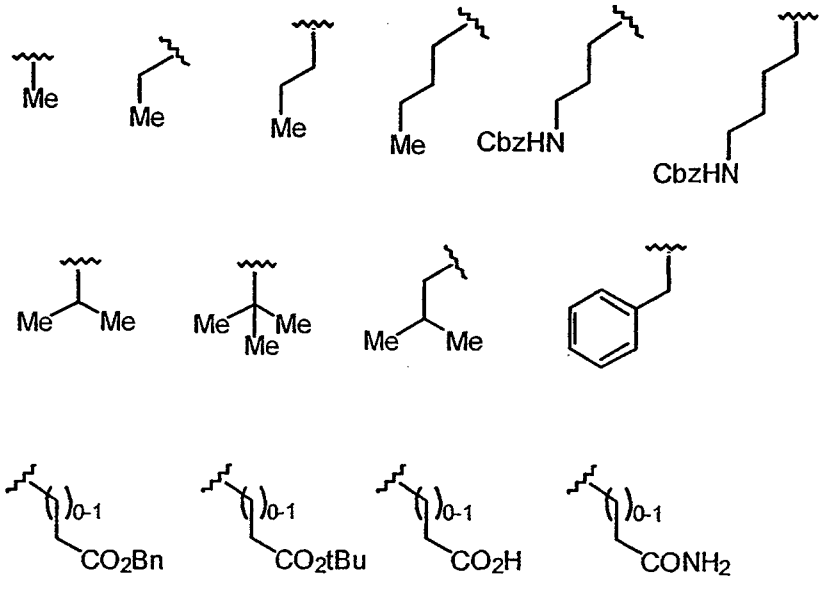


wherein:

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:



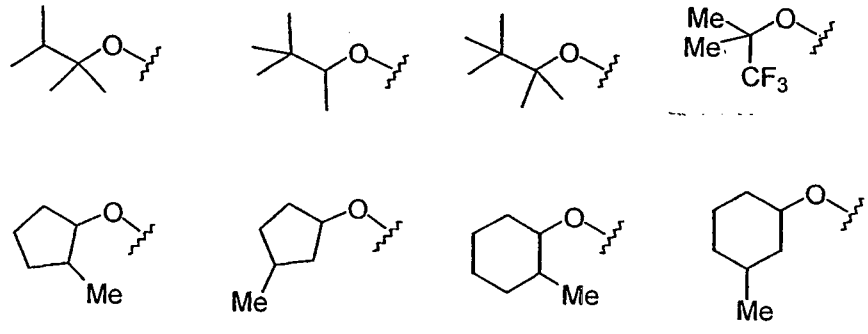
Y^{14} is selected from $MeSO_2$, Ac, Boc, iBoc, Cbz, or Alloc;

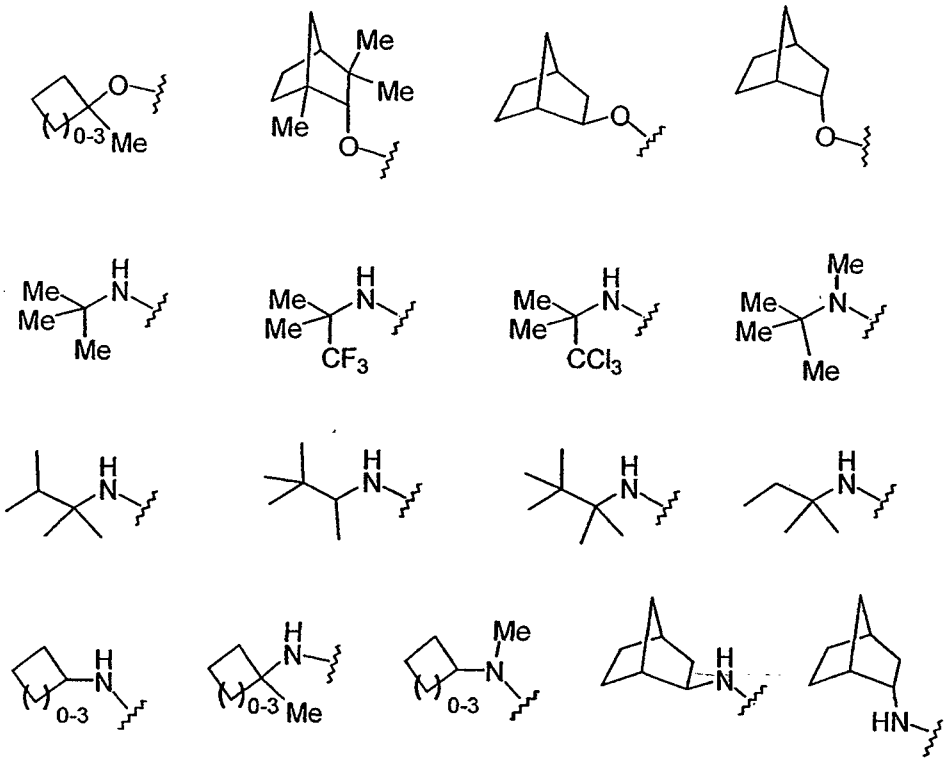
Y^{15} and Y^{16} are independently selected from alkyl, aryl, heteroalkyl, and heteroaryl;

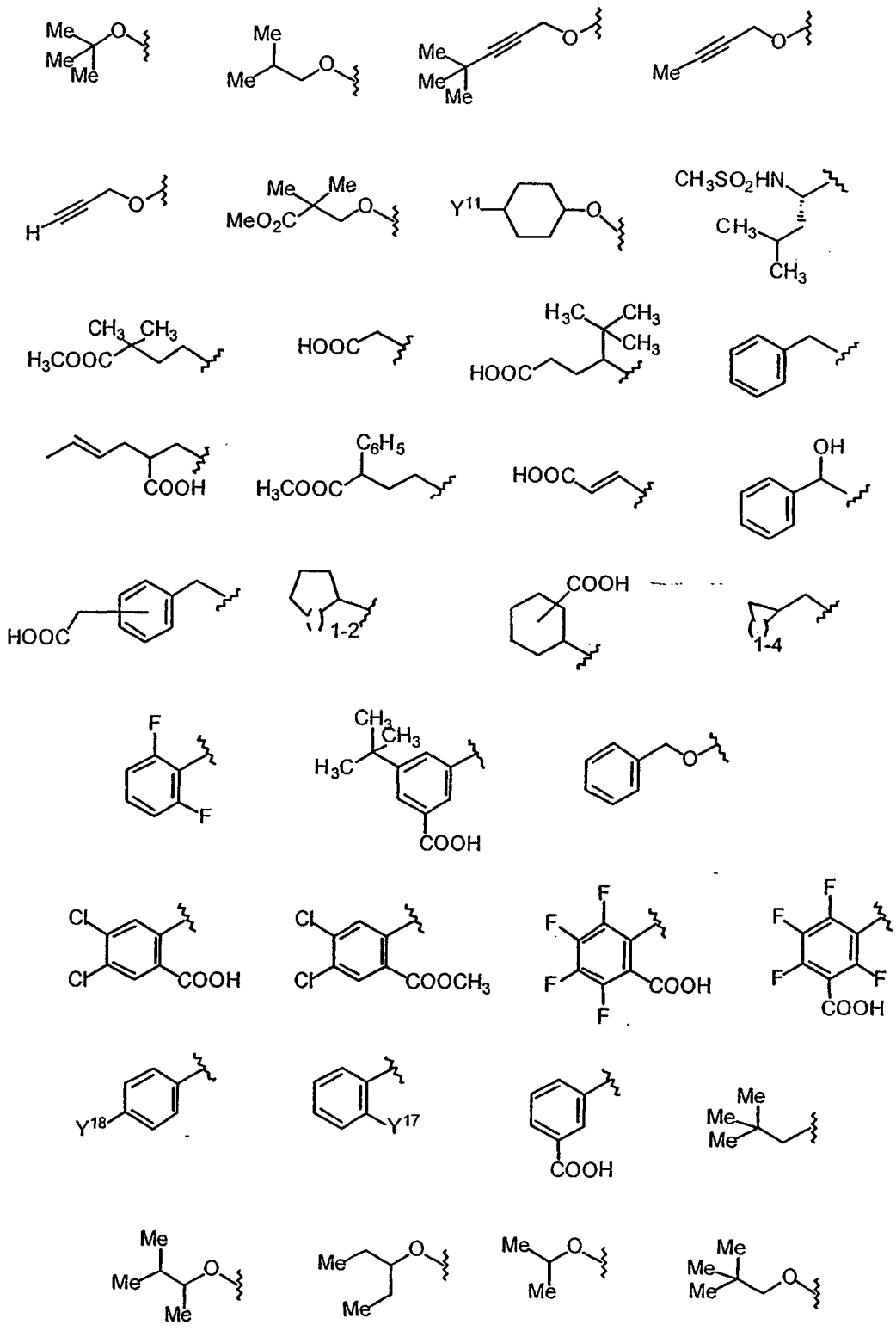
Y^{17} is CF_3, NO_2, $CONH_2$, OH, $COOCH_3$, OCH_3, OC_6H_5, C_6H_5, COC_6H_5, NH_2, or COOH; and

Y^{18} is $COOCH_3$, NO_2, $N(CH_3)_2$, F, OCH_3, CH_2COOH, COOH, SO_2NH_2, or $NHCOCH_3$.

Y may be more preferably represented by:

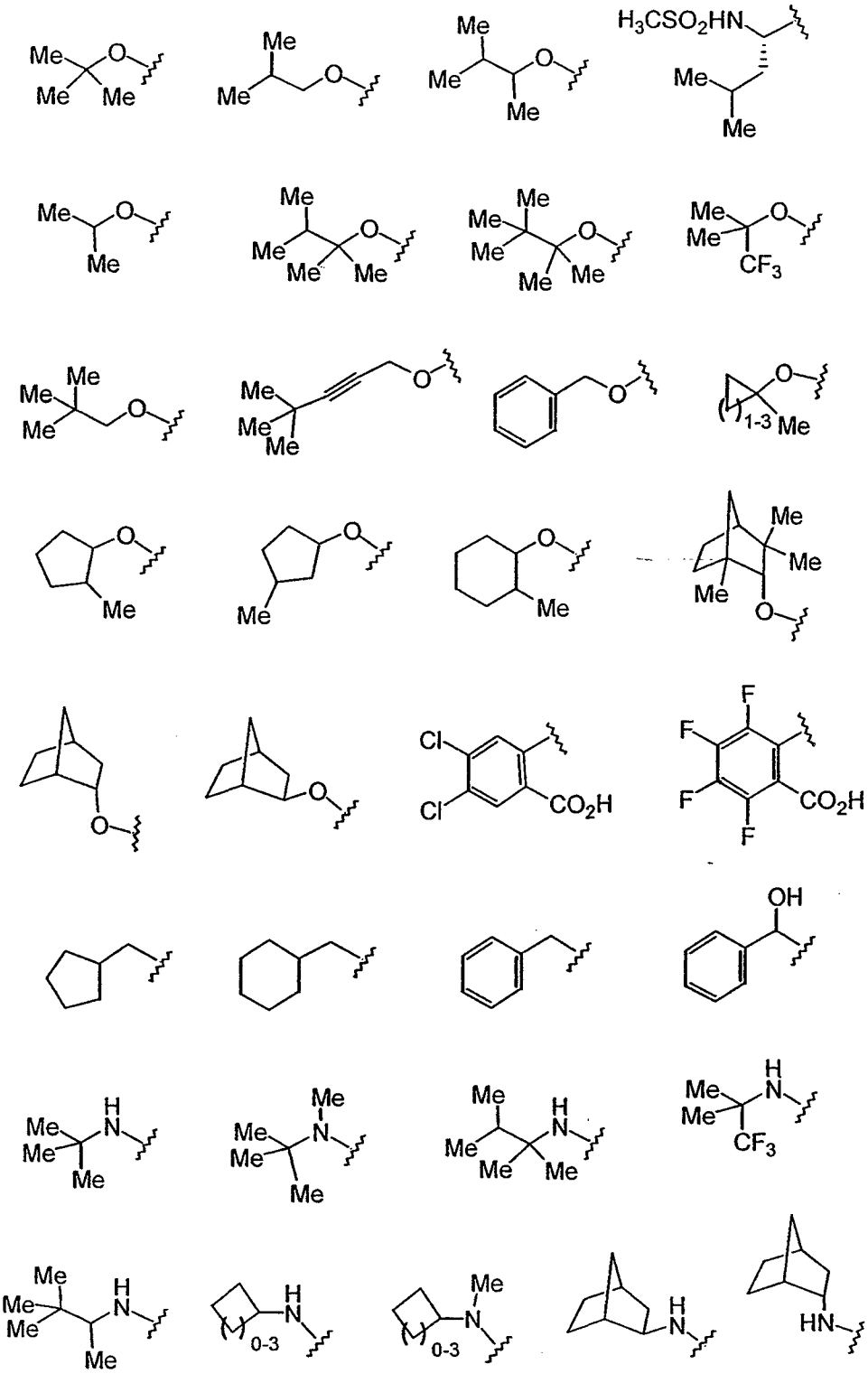



O
0-3
Me
Me
Me
Me
O
O
O
H
N
Me
Me
Me
H
N
Me
Me
CF3
H
N
Me
Me
CCl3
Me
N
Me
Me
Me
H
N
H
N
H
N
H
N
H
N
0-3
H
N
0-3
Me
Me
N
0-3
H
N
H
N

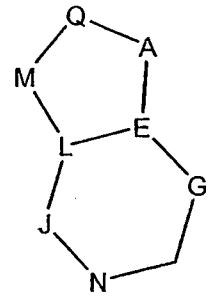


wherein:
Y^{17} = CF_3, NO_2, $CONH_2$, OH, NH_2, or COOH;
Y^{18}= F, COOH,

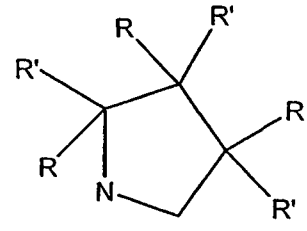
Still more preferred moieties for Y are:



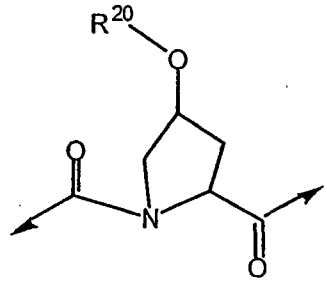
As shown in Formula I, the unit:



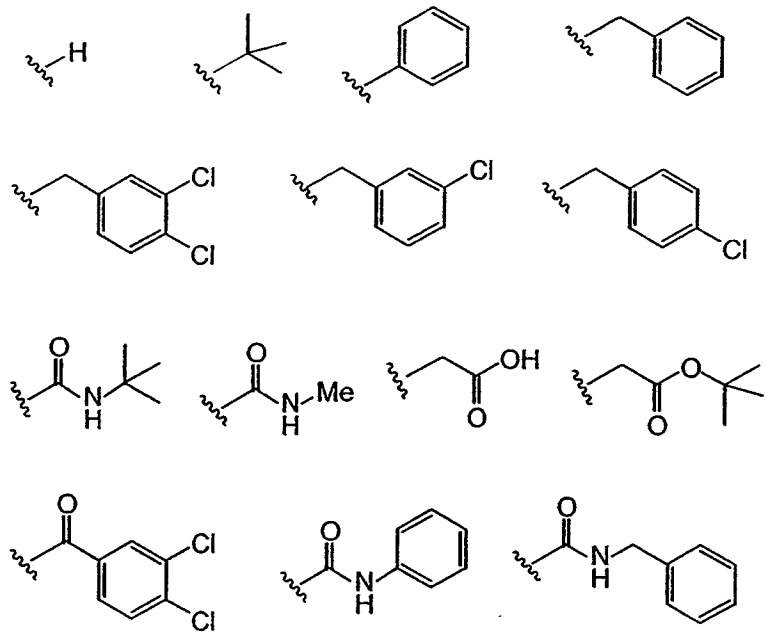
represents a cyclic ring structure, which may be a five-membered or six-membered ring structure. When that cyclic ring represents a five-membered ring, it is a requirement of this invention that that five-membered cyclic ring does not contain a carbonyl group as part of the cyclic ring structure. Preferably,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



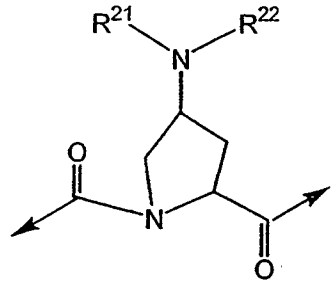
wherein R and R' are defined above. Preferred representations for that five-membered cyclic ring structure is:



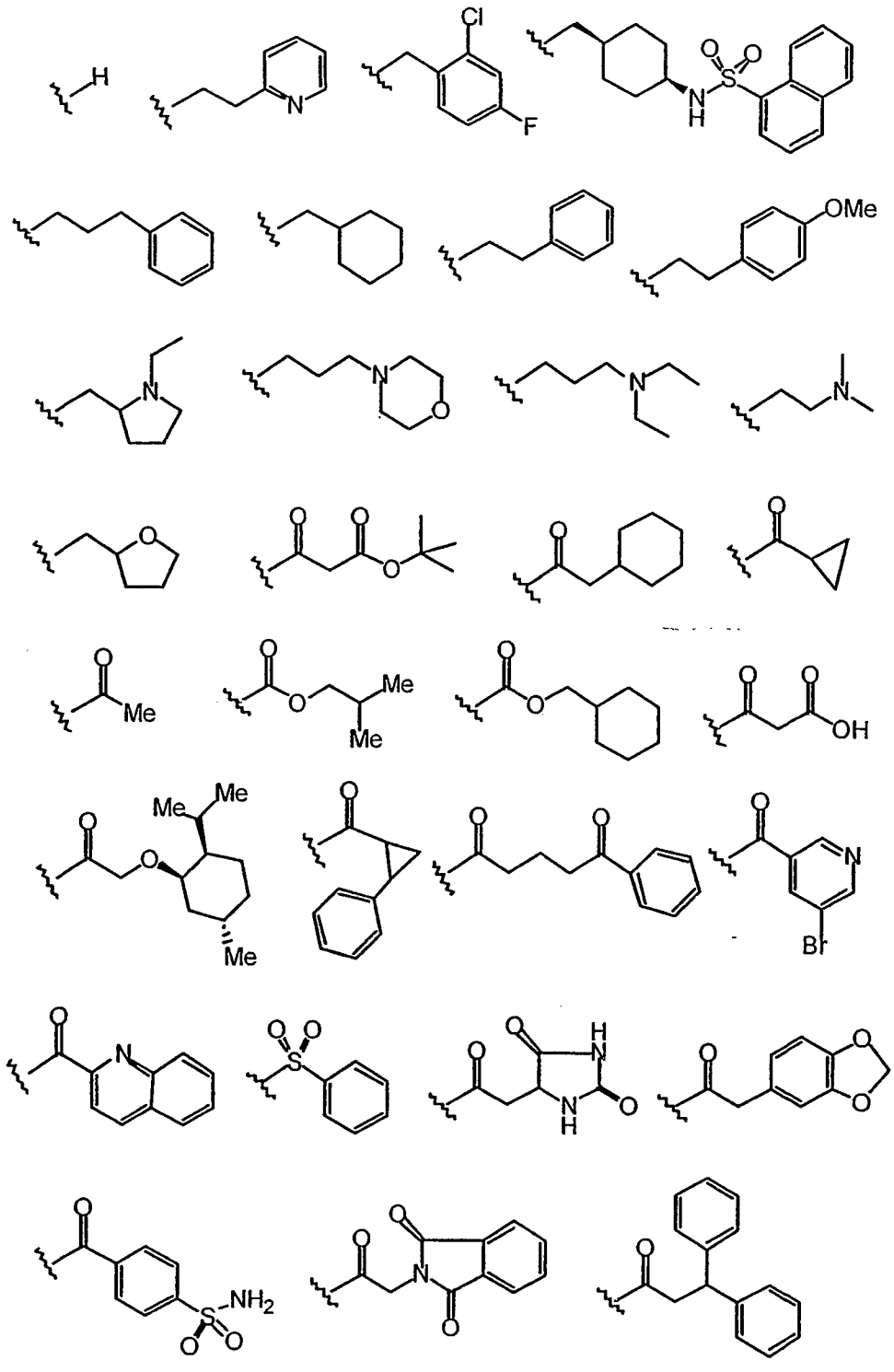
where R^{20} is selected from the following moieties:



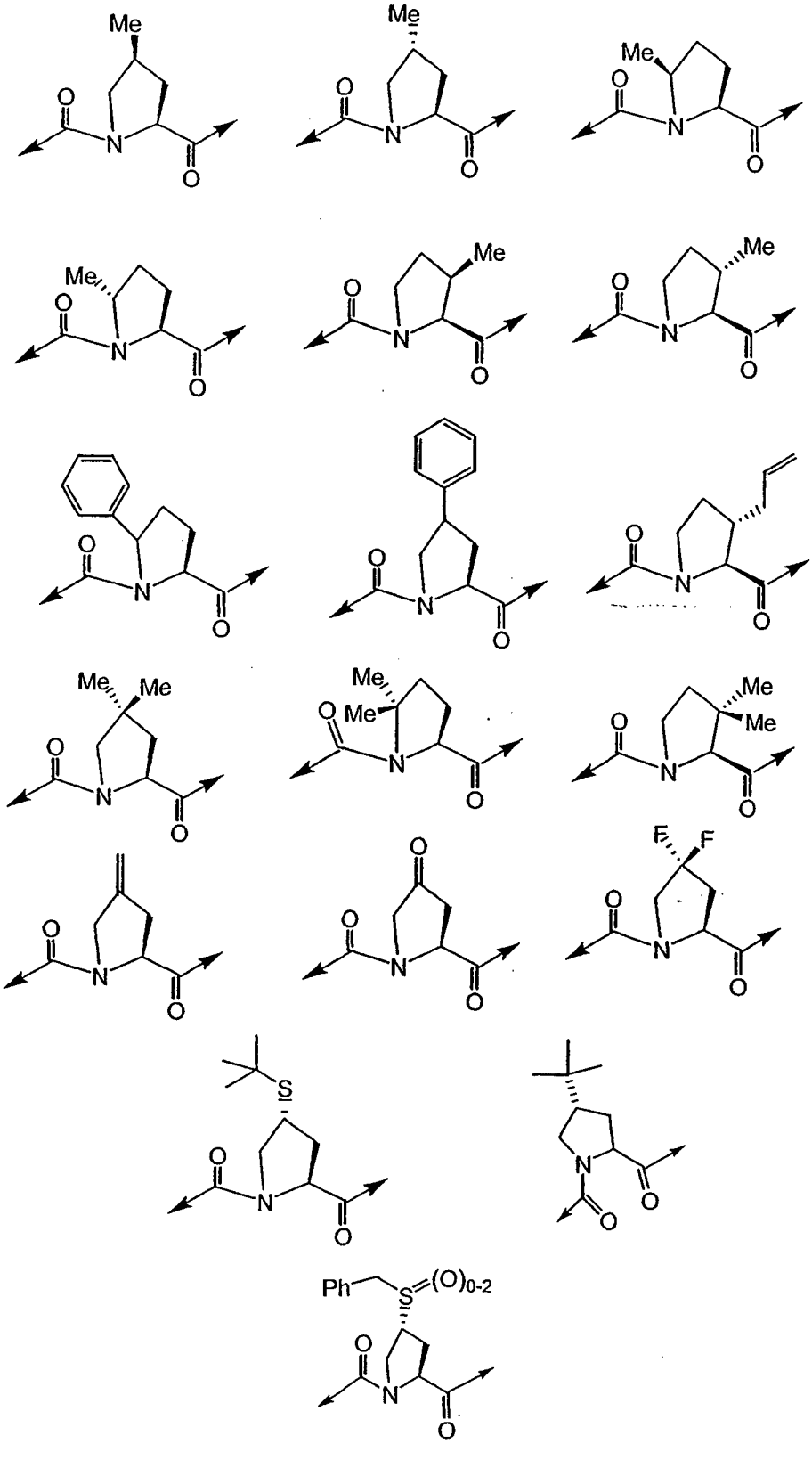
Furthermore, that five-membered ring, along with its adjacent two exocyclic carbonyls, may be represented as follows:



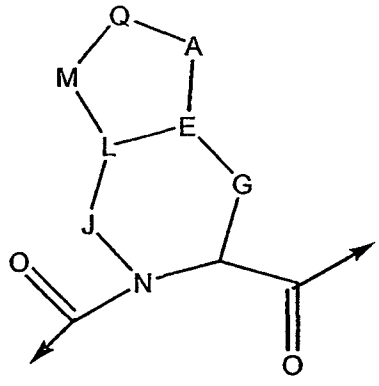
in which case, R^{21} and R^{22} may be the same or different and are independently selected from the following moieties:



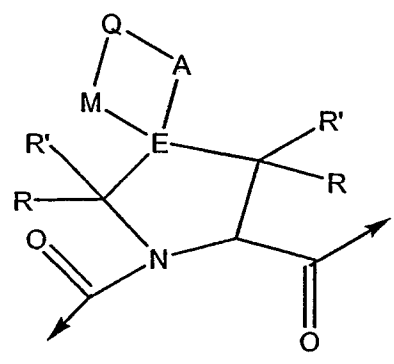
Some preferred illustrations for the five-membered ring structure:


Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
F
F
S
Ph
S
(O)0-2

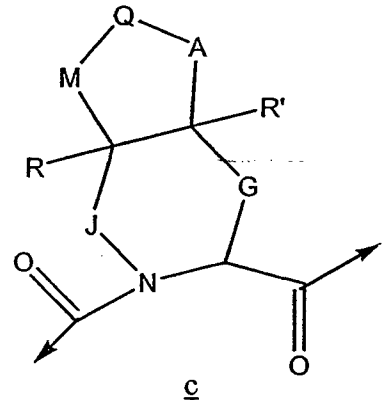
Additionally, the unit:



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

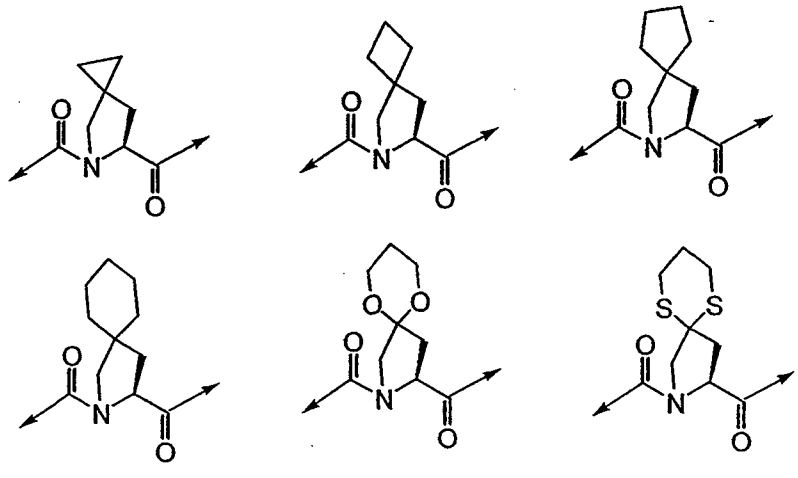


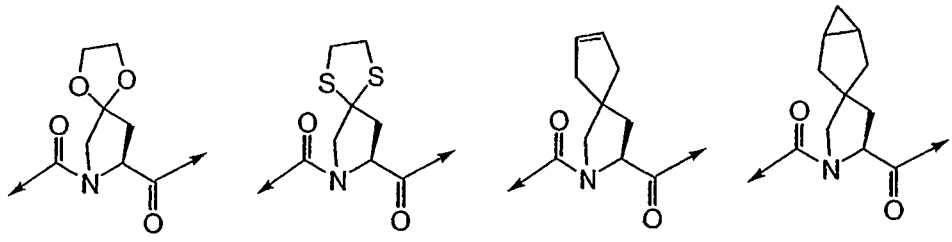
b



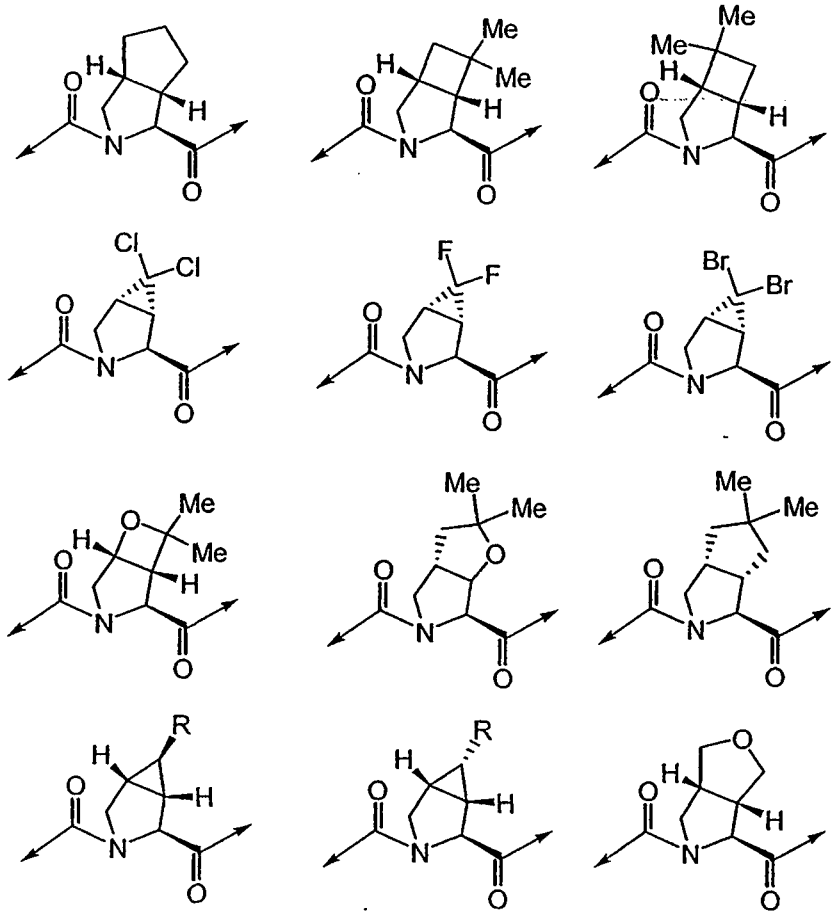
c

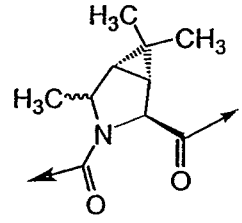
Preferred definitions for b are:

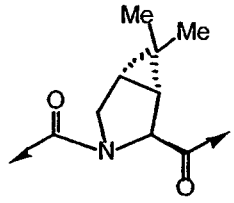


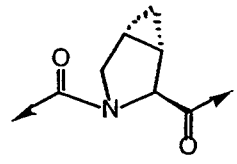


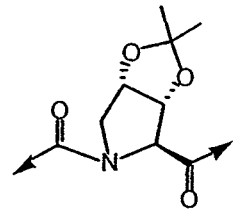
In c, G and J are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; A and M are independently selected from the group consisting of O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; and Q is CH_2, CHR, CRR', NH, NR, O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, and $(CRR')_p$. Preferred definitions for c are:

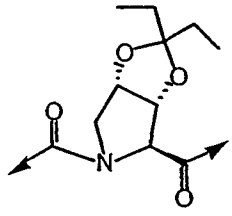


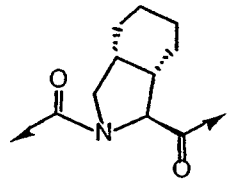


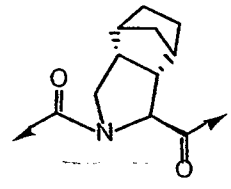


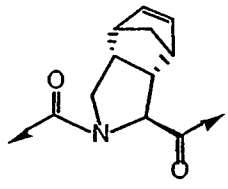


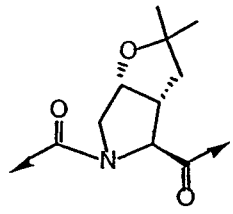


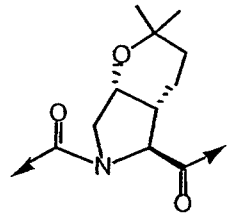


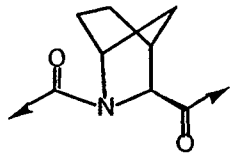


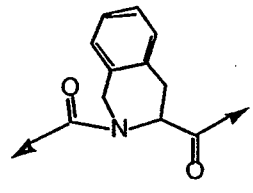


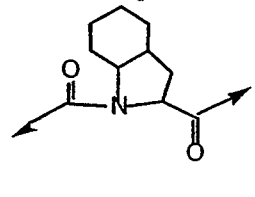




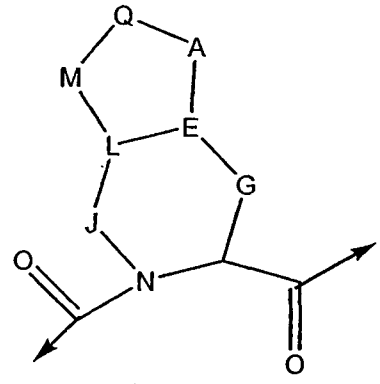




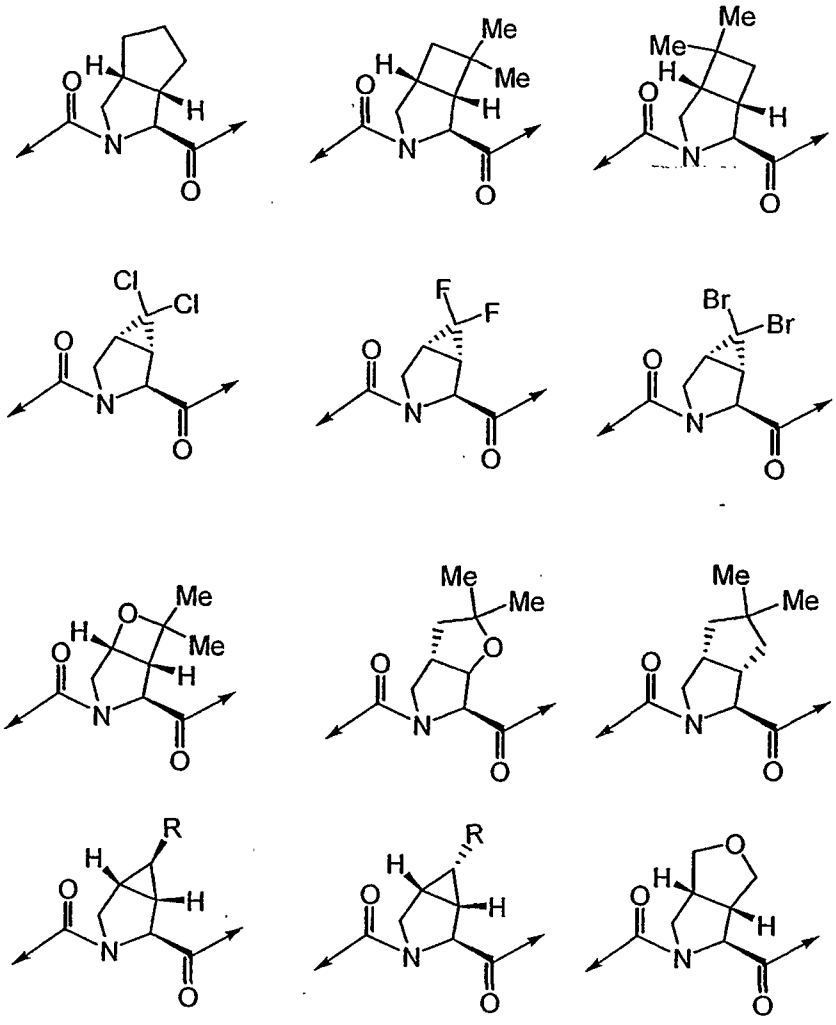


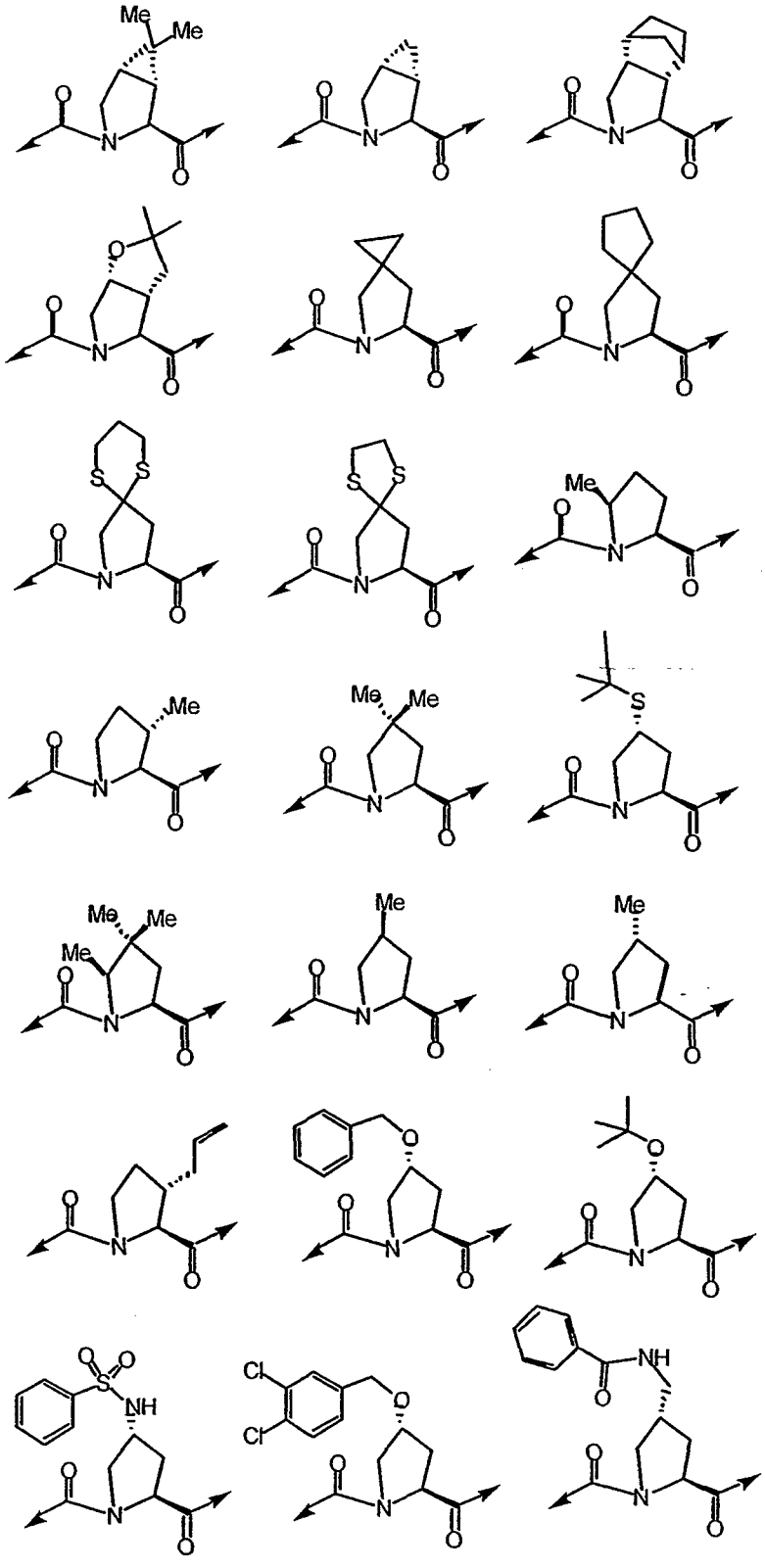


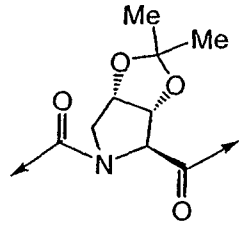
When the cyclic ring structure is depicted as:



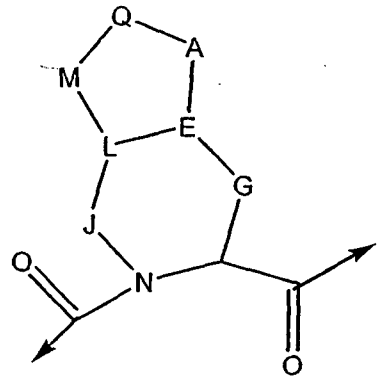
its most preferred illustrations are as follows:



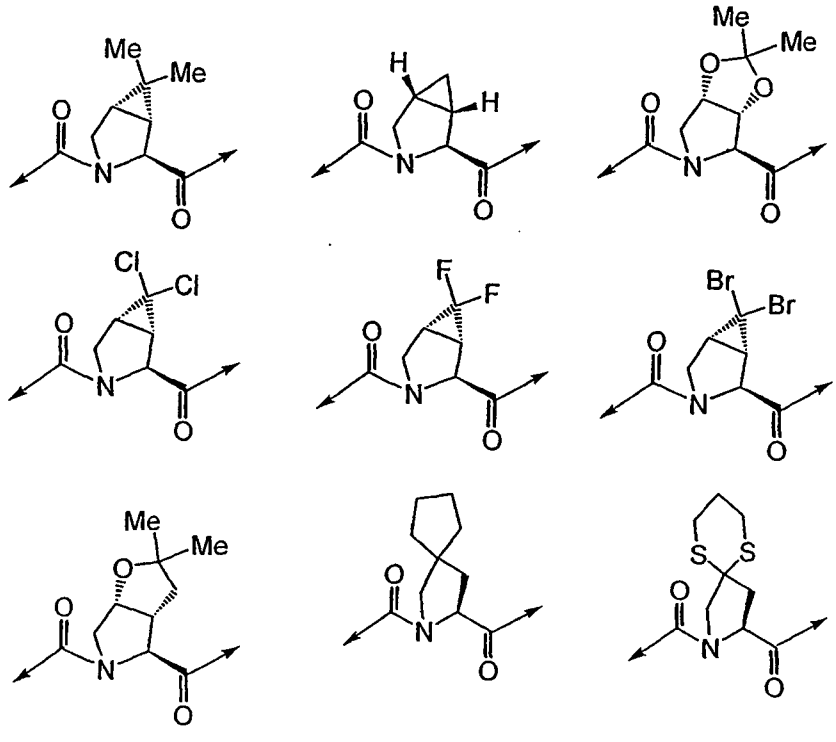

Me
Me
O
N
O
S
S
NH
Cl
Cl

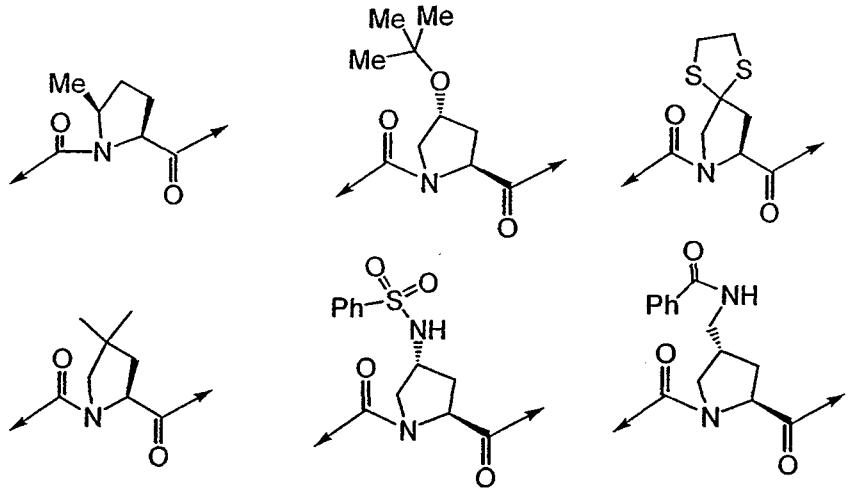


Some of the still preferred moieties for the unit:



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 addiitonal 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

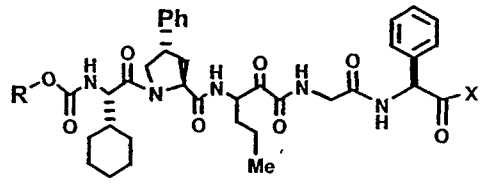
302	C
303	B
304	C
305	C
306	C
307	B
308	B
309	C
310	C
311	C
312	C
313	B
314	A
315	B
316	B
317	A
318	A
319	A
320	A
321	C
322	C
323	C
324	C
325	A
326	A
327	C
328	B
329	B
330	A
331	A
332	A
333	B
334	B
335	B
336	A
337	A
338	C
339	A
340	C
341	C
342	C
343	A
344	C
345	C

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

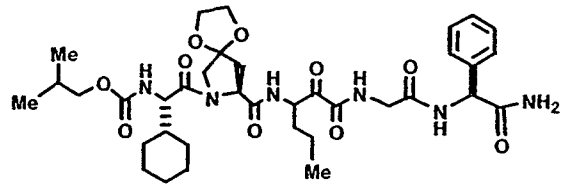
HCV continuous assay Ki* range:

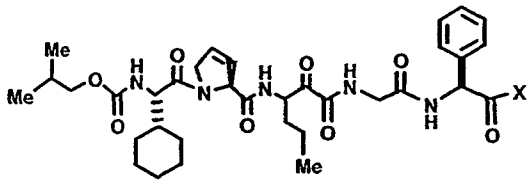
Category A = 1-100 nM; Category B = 101-1,000 nM; Category C >1000 nM.

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.

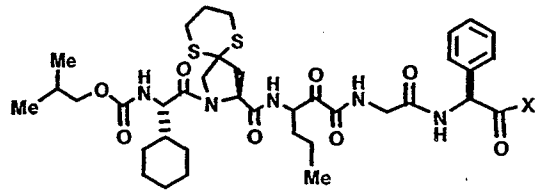


(R = t-butyl, X = NH_2)
(R = Isobutyl, X = NH_2)
(R = t-butyl, X = OH)
(R = Trichloroethyl, X = OH)

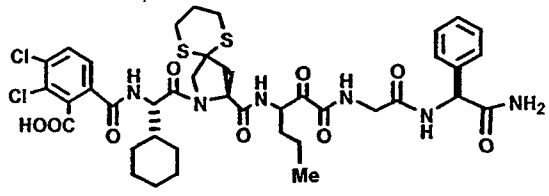


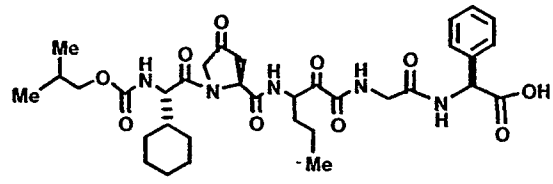


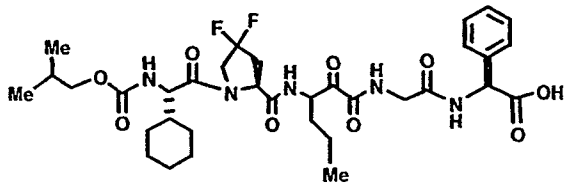
(X = O^tBu)
(X = OH)

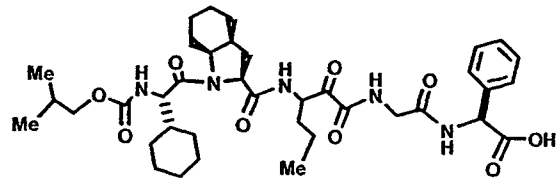


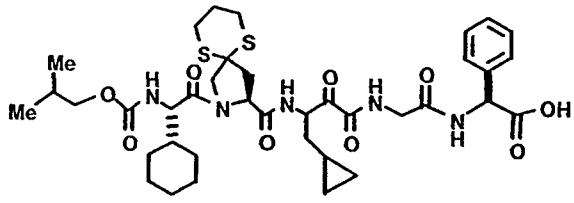
(X = OH)
(X = O^tBu)
(X = NH_2)
(X = NHMe)
(X = NMe_2)

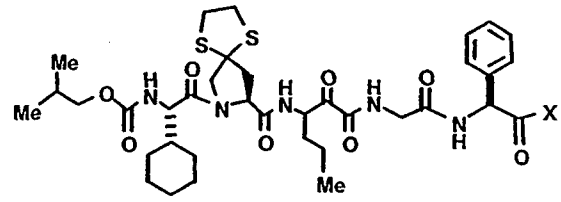




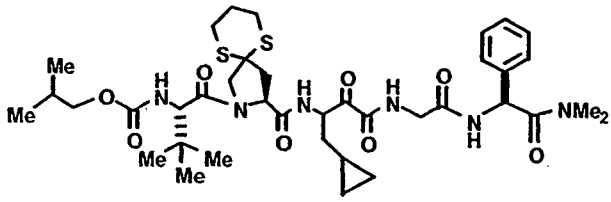


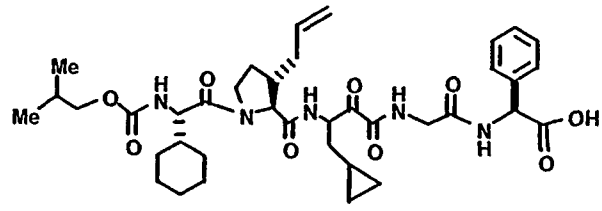


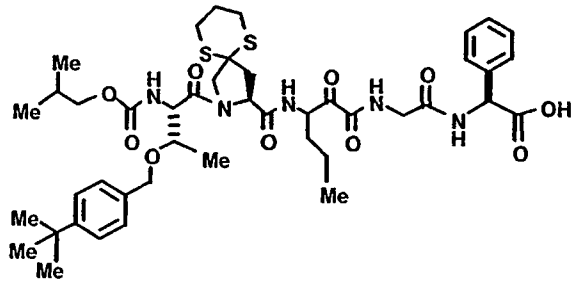


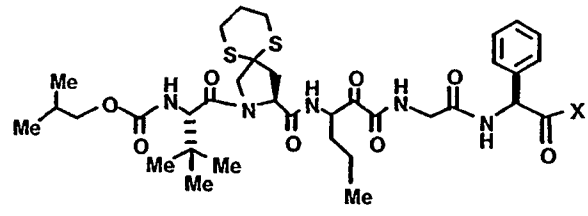


(X = NH_2)
(X = NMe_2)
(X = NHMe)
(X = OH)

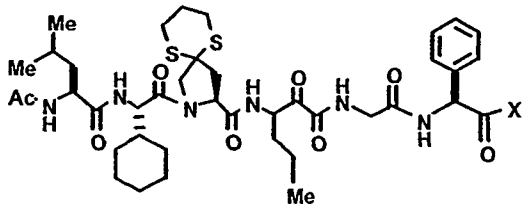




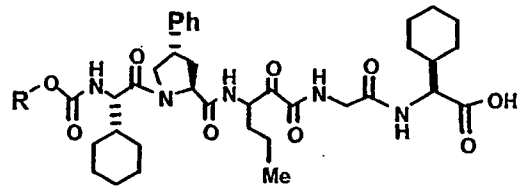




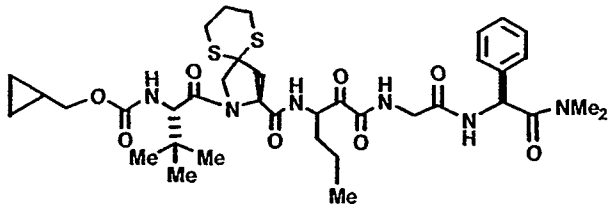
(X = O^tBu)
(X = OH)
(X = NH_2)
(X = NMe_2)

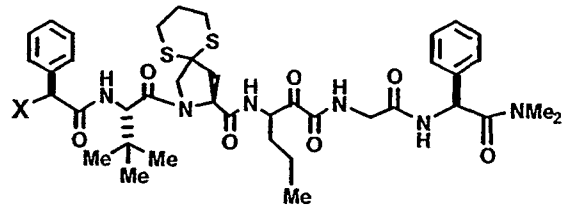


(X = O^tBu)
(X = OH)
(X = NH_2)
(X = NMe_2)
(X = NMeOMe)

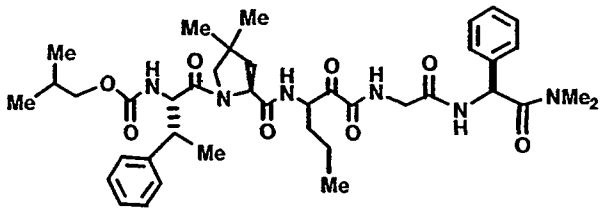


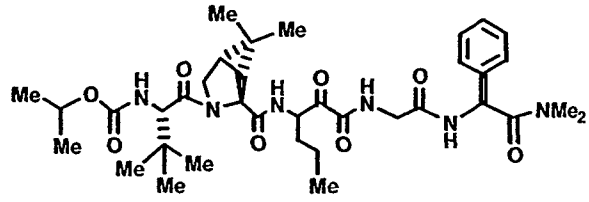
(R = t-butyl)
(R = Isobutyl)

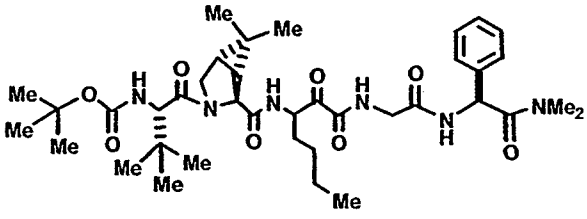


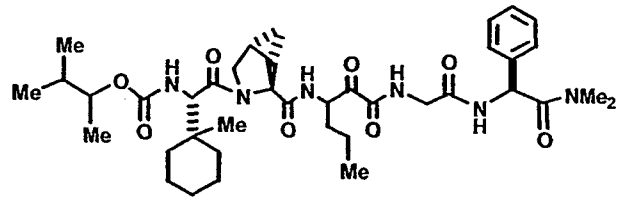


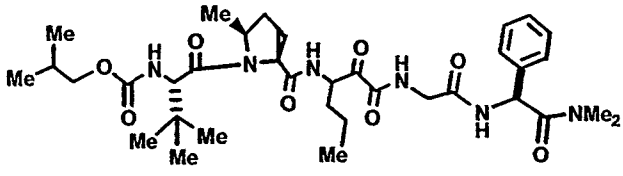
(X = Me, Y = CH_2Me)
(X = OAc, Y = Me)

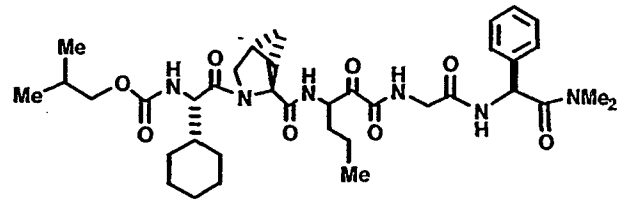


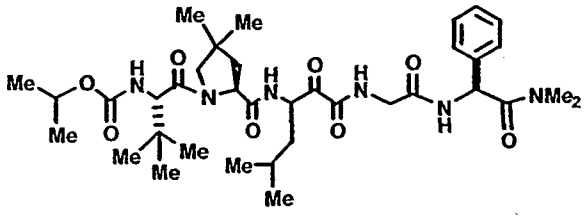


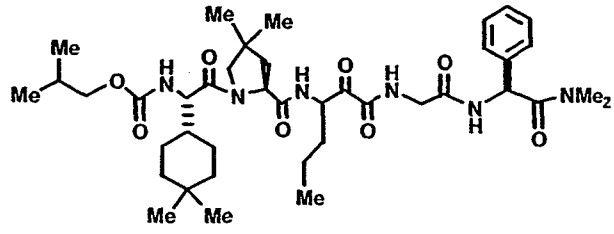


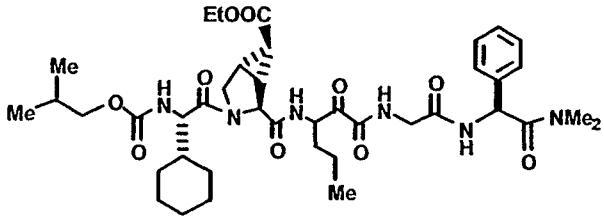


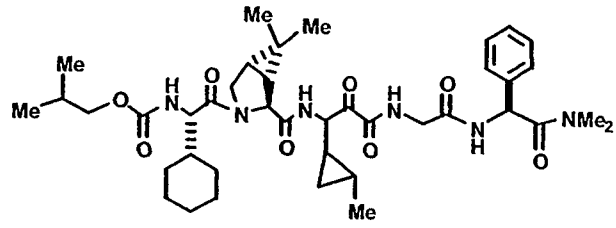


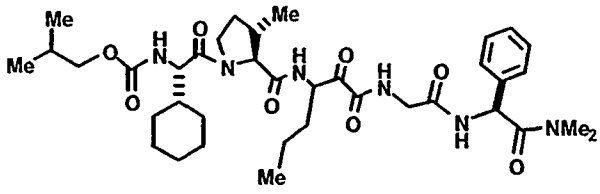


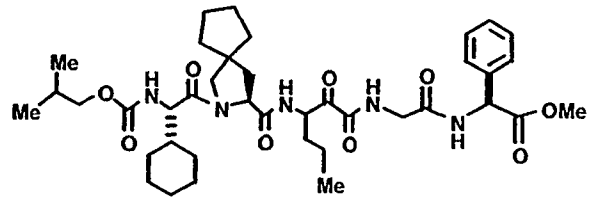


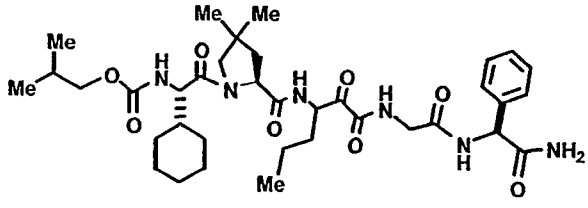


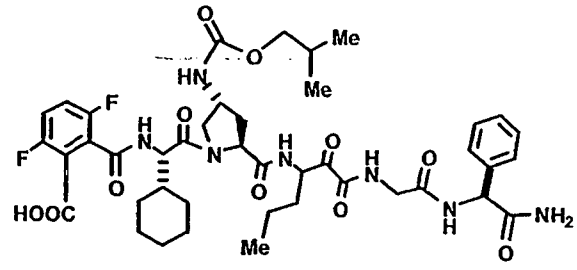


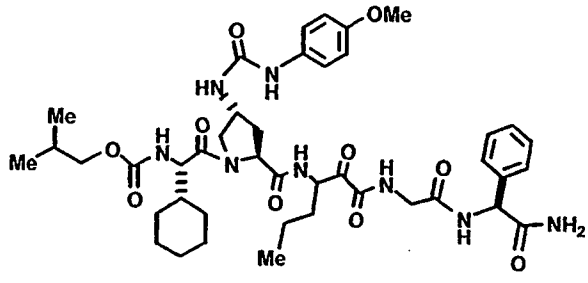


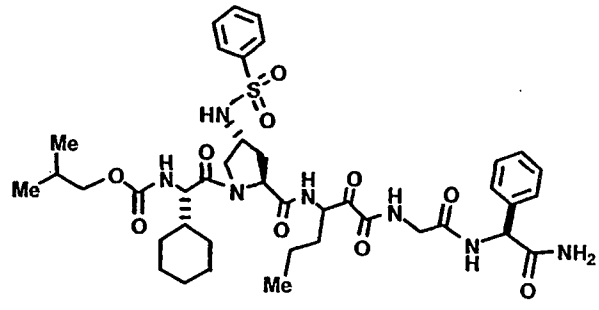


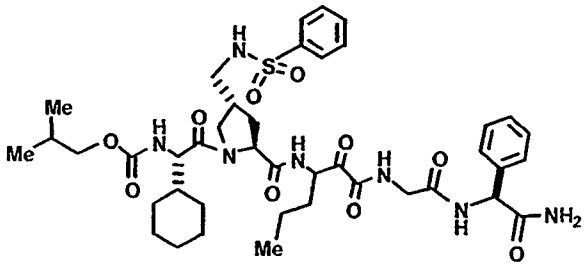


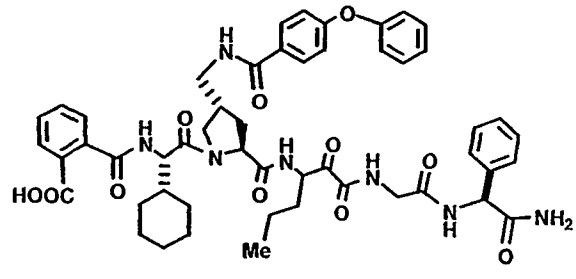


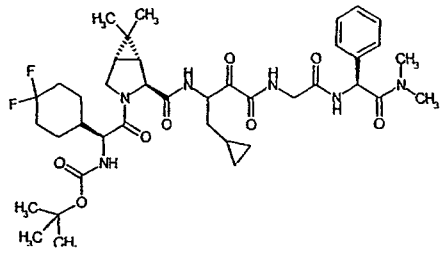


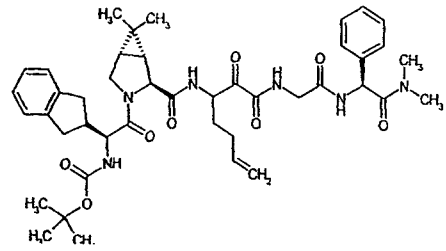


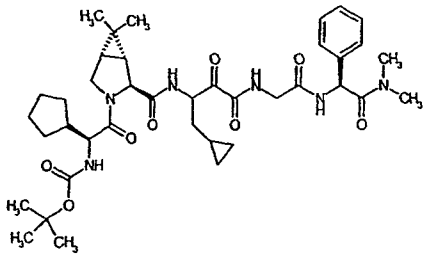


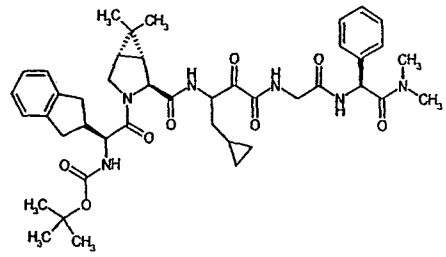


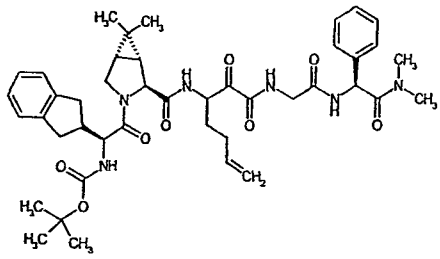


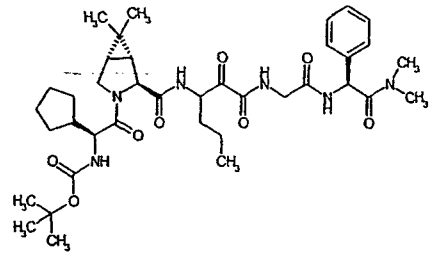


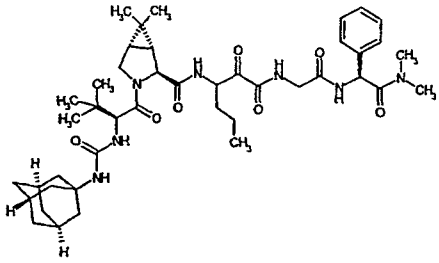


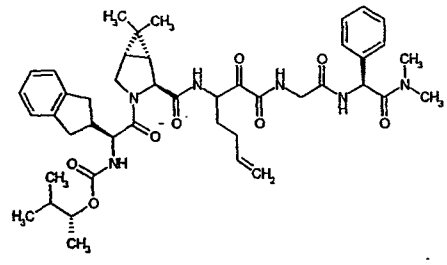


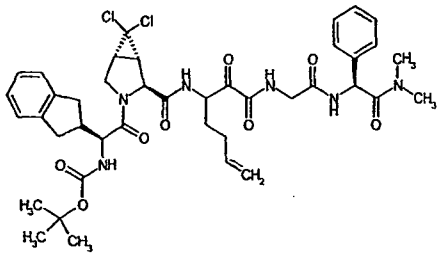


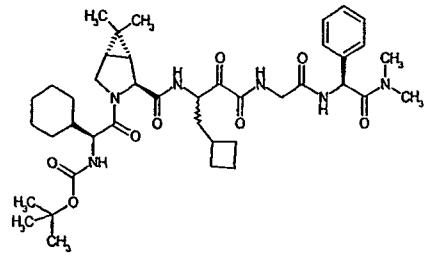


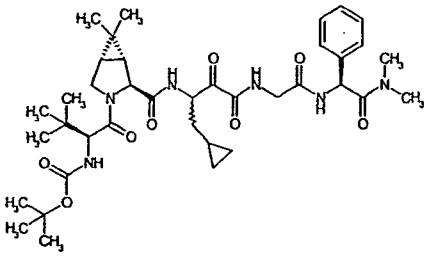


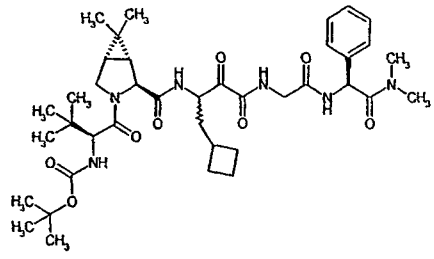


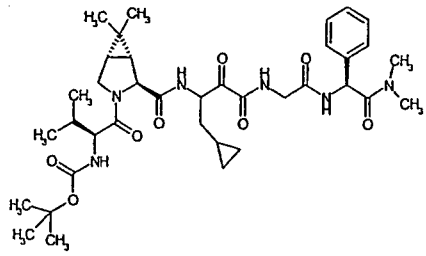


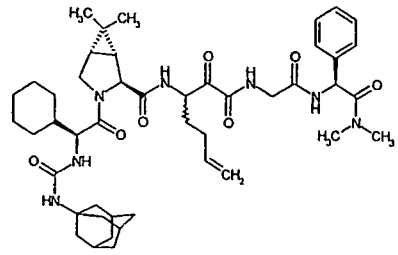


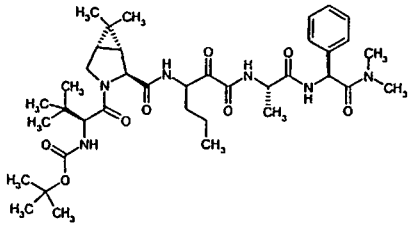


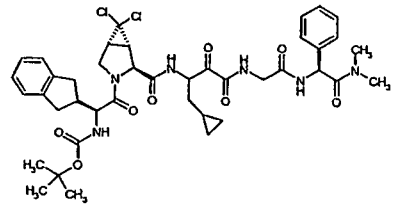


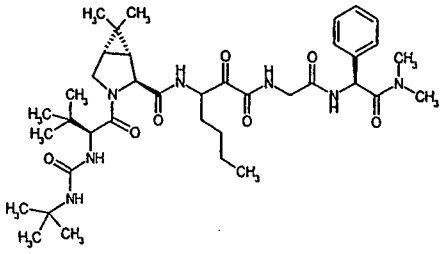


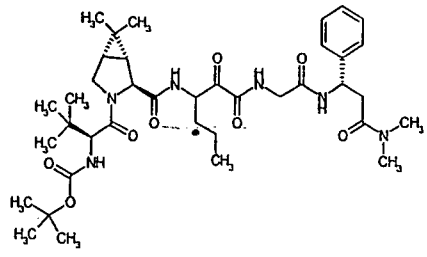


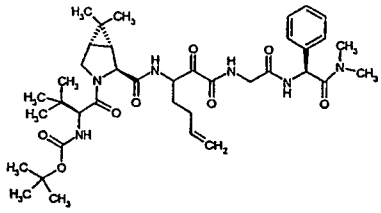


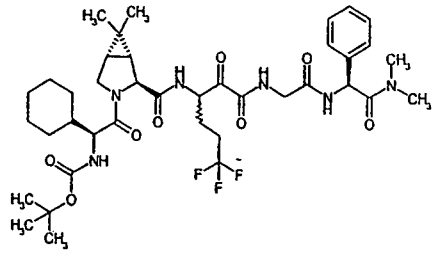


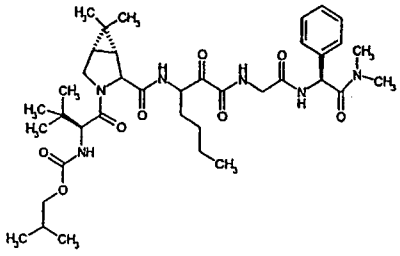


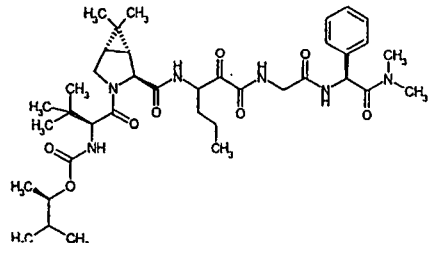


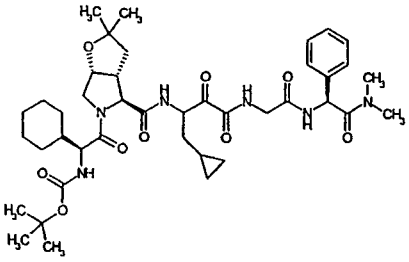


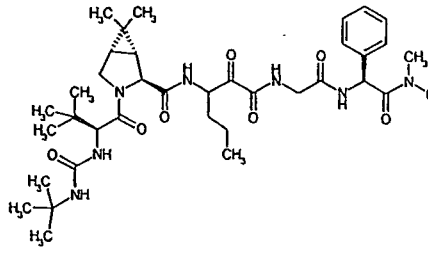






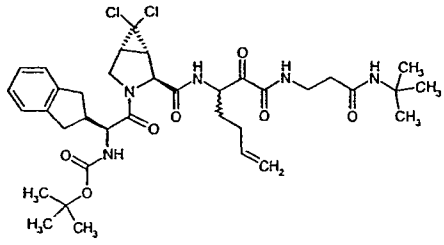


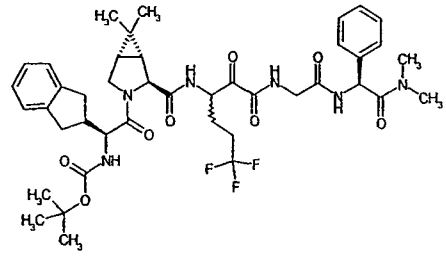


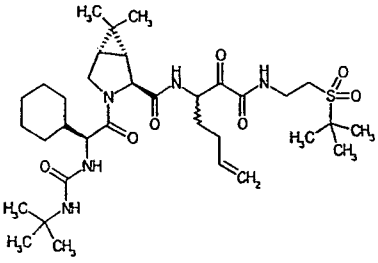


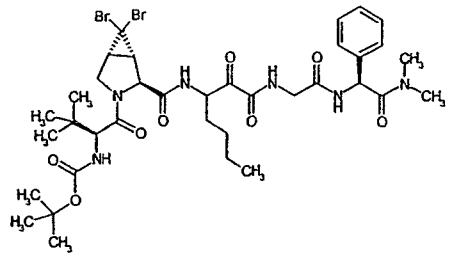


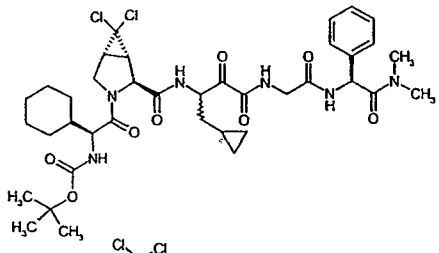


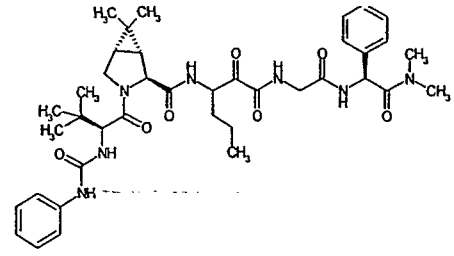


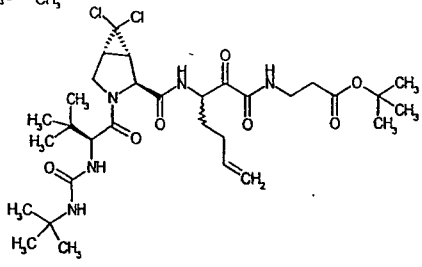


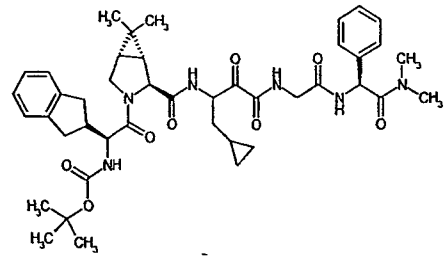


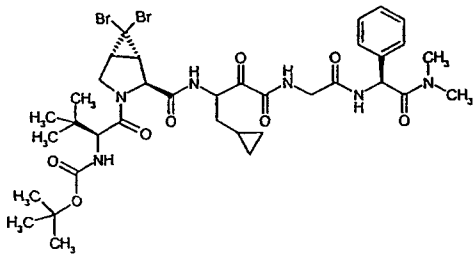


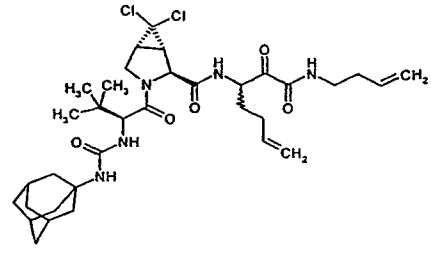


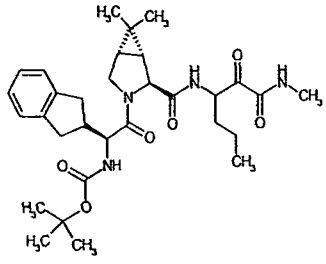


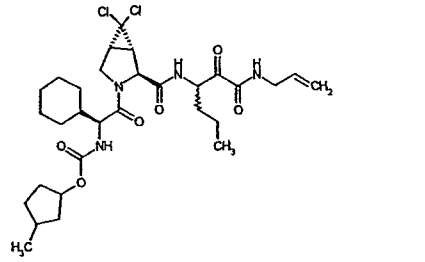


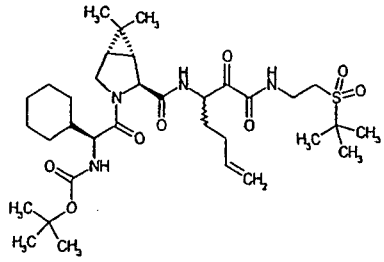


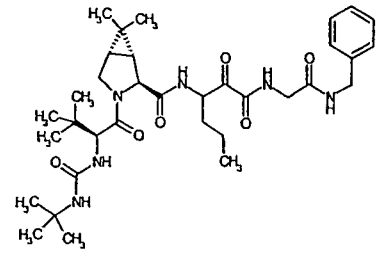


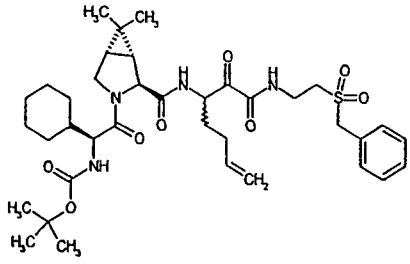


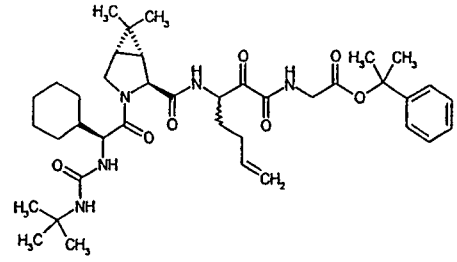


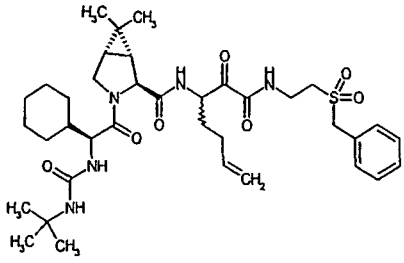


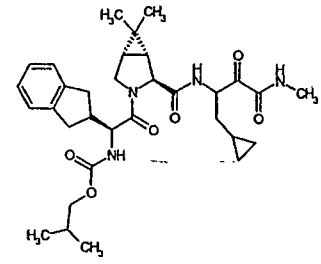


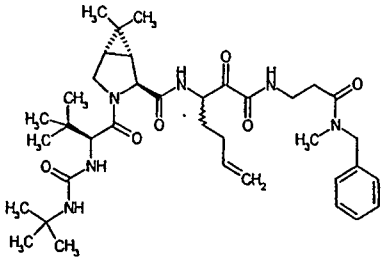


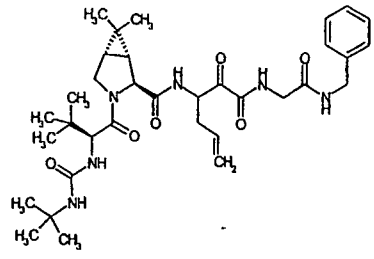


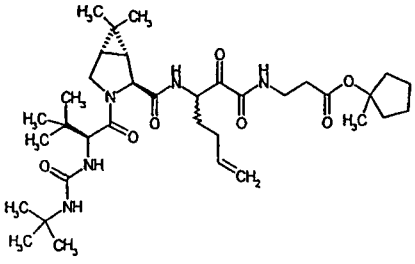


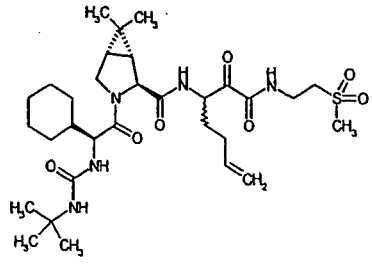


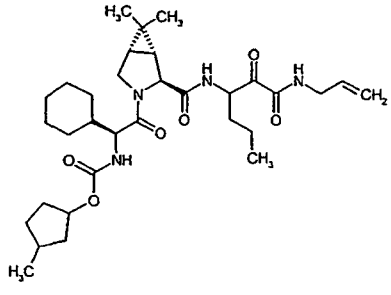


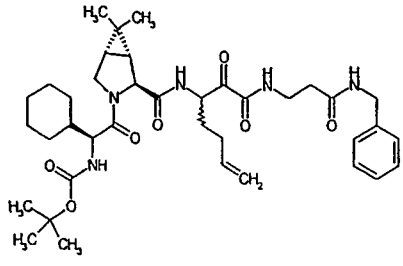


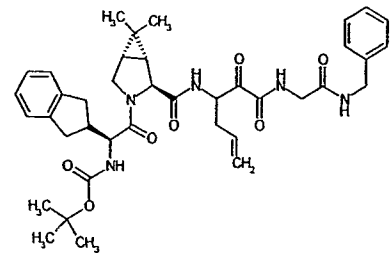


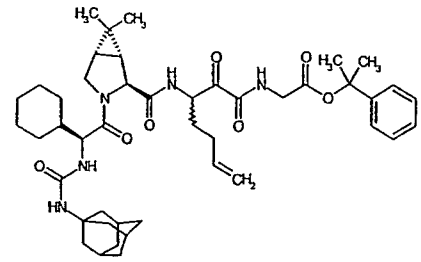


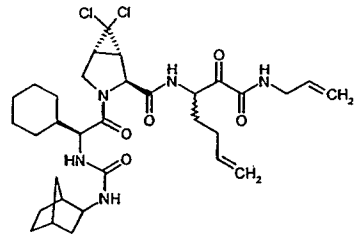


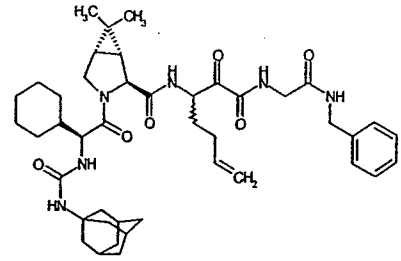


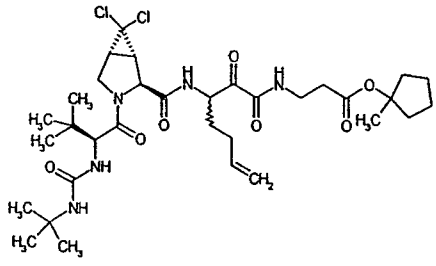


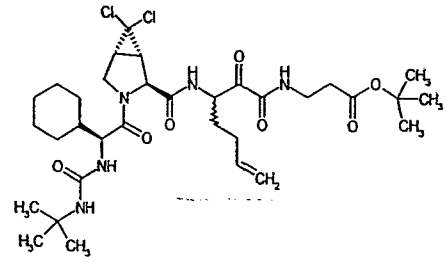


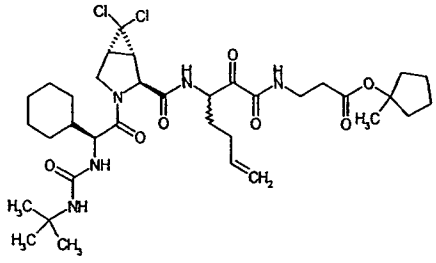


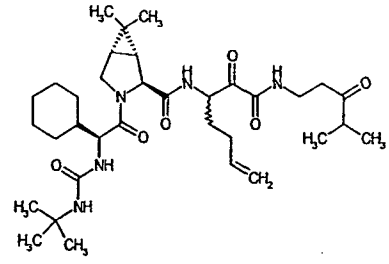


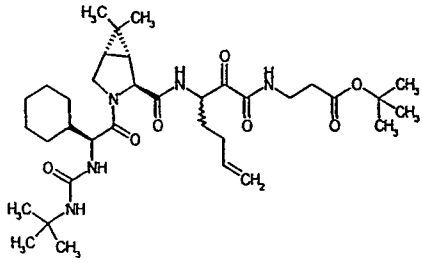


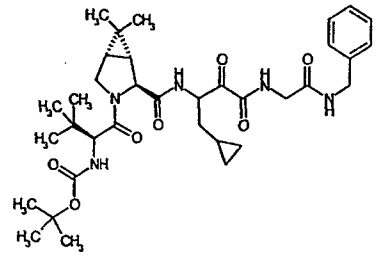


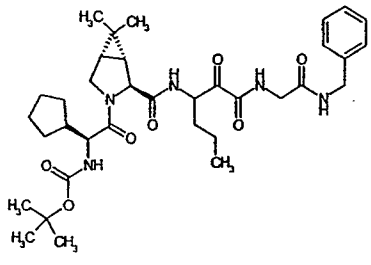


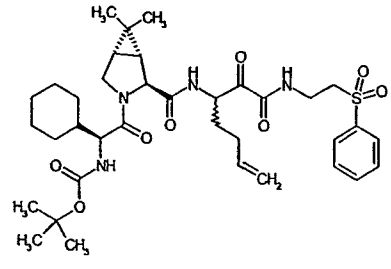


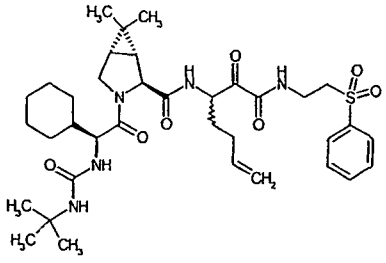


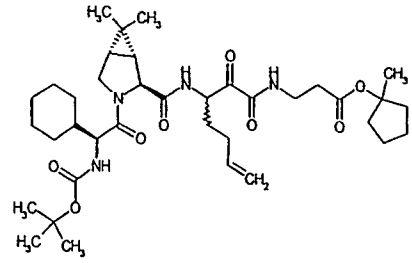


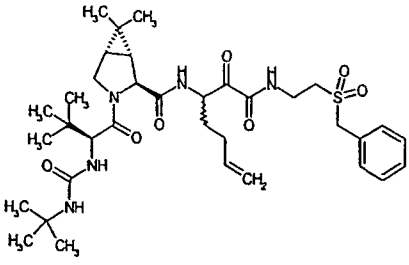


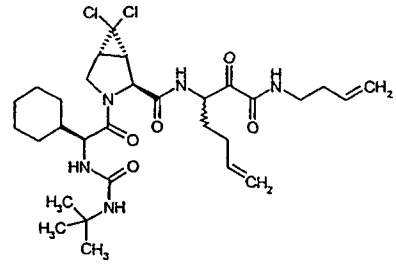


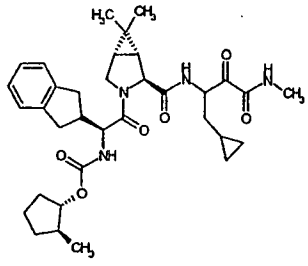


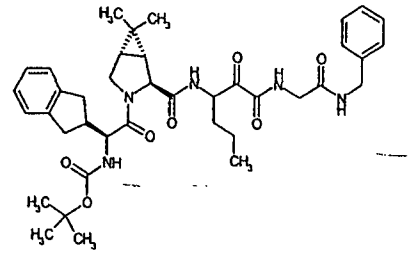


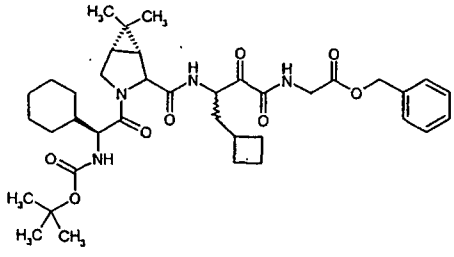


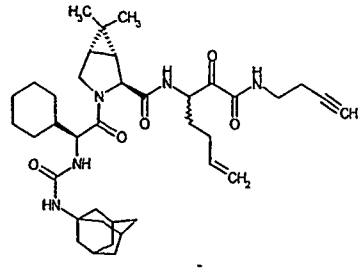


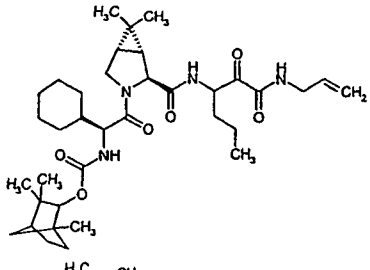


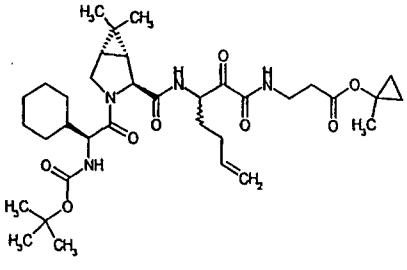


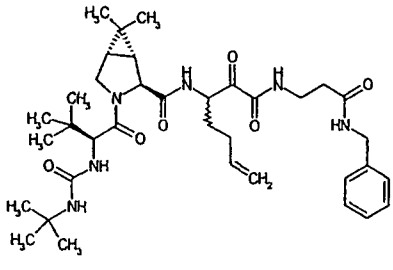


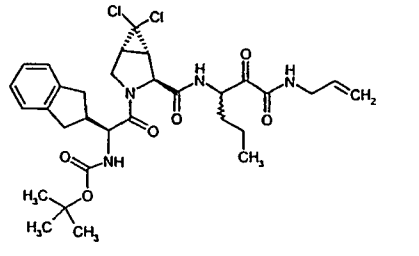


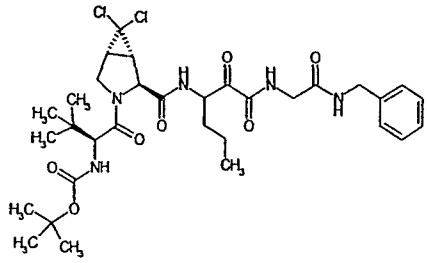


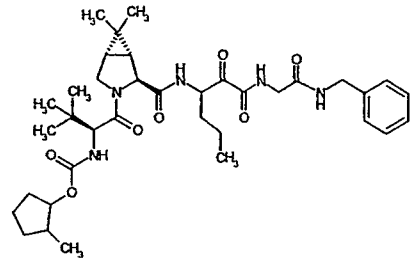


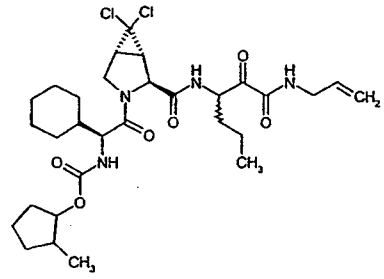


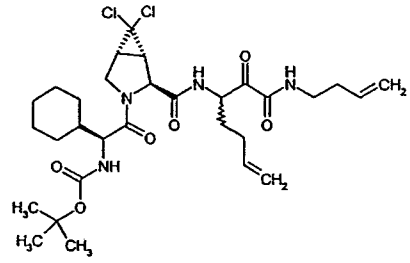


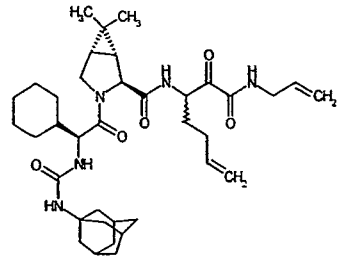


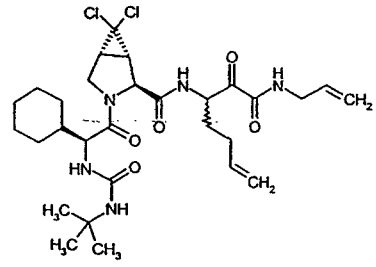


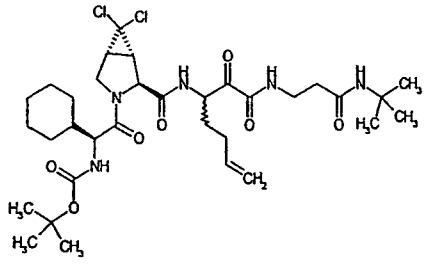


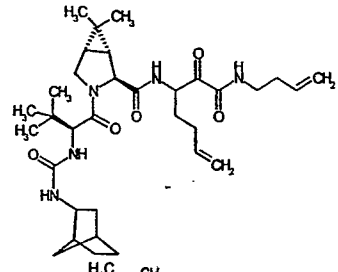


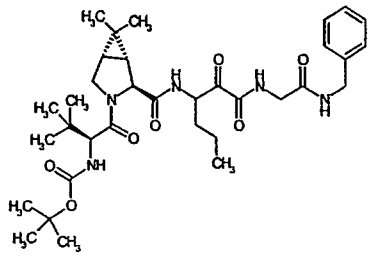


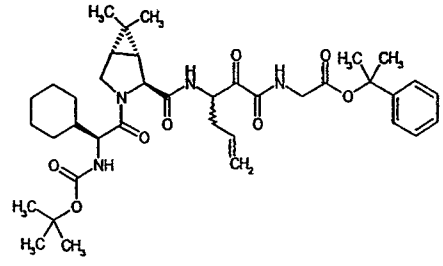


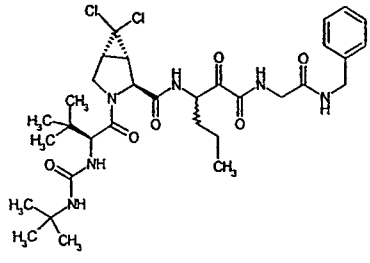


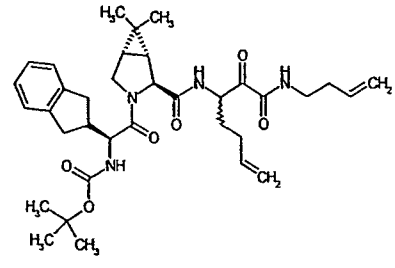


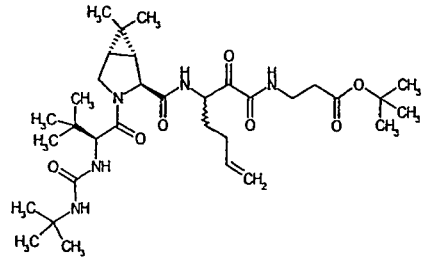


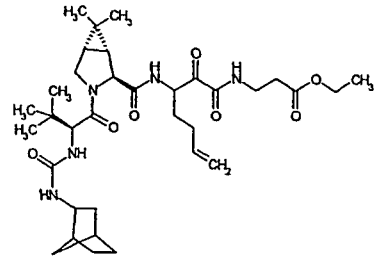


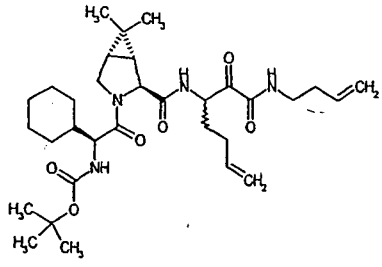


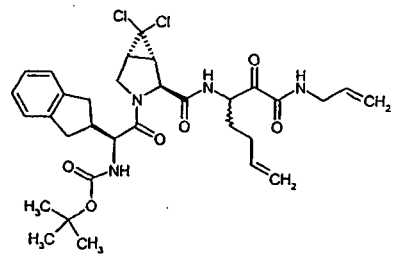


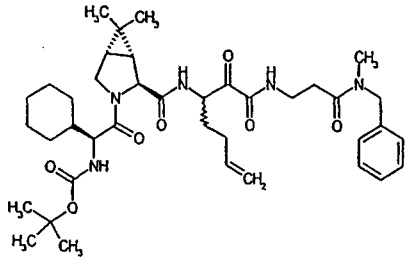


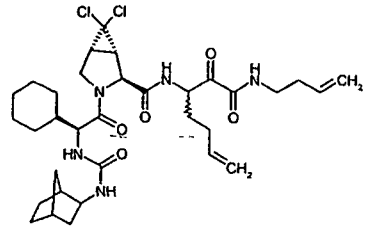


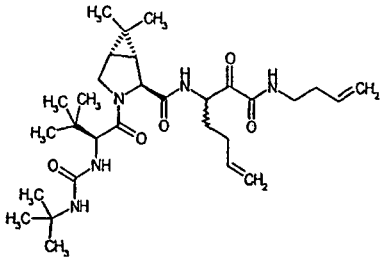


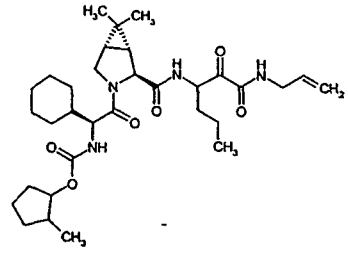


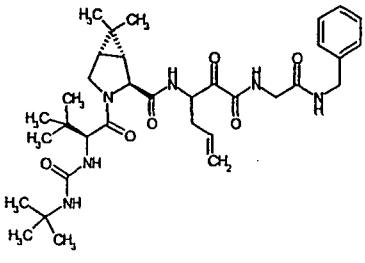


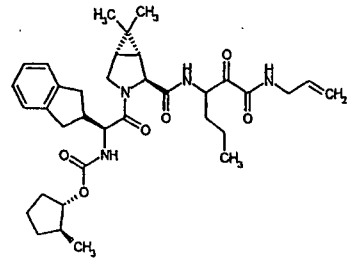


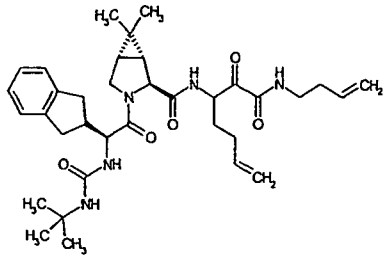


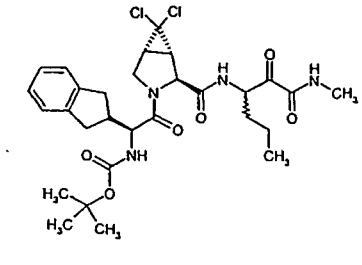


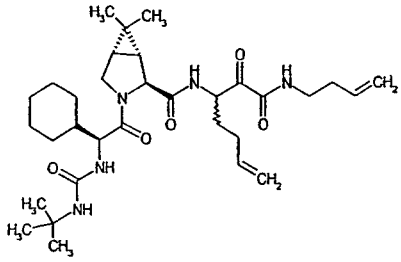


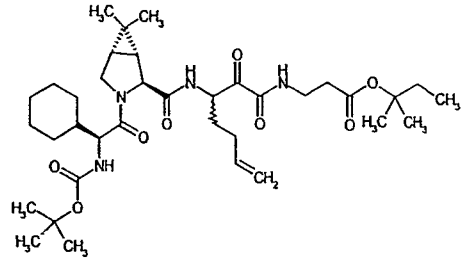


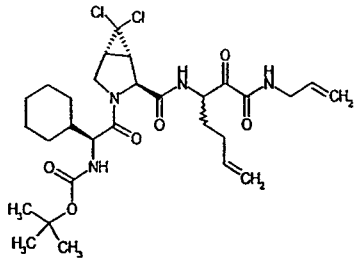


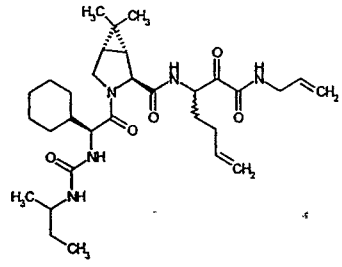


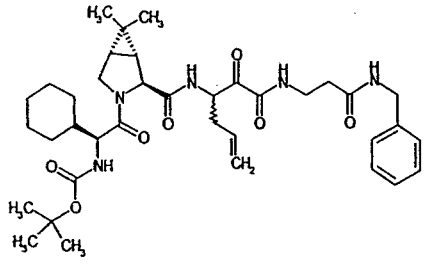


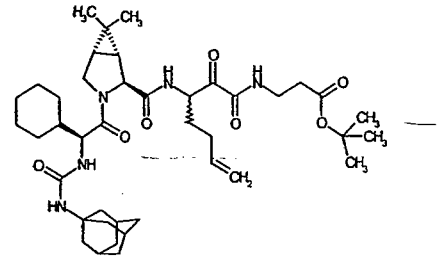


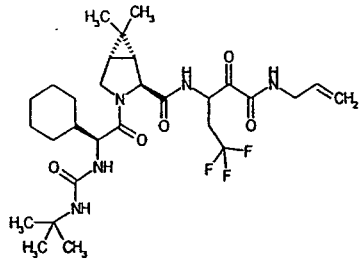


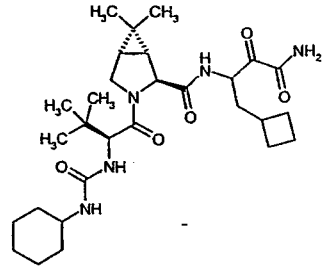


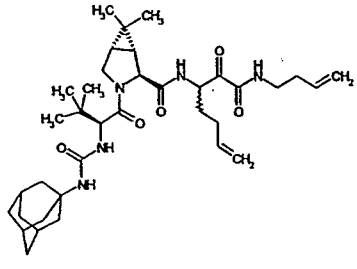


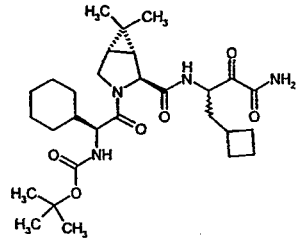


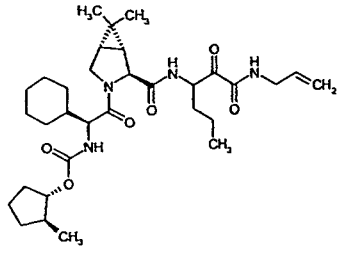


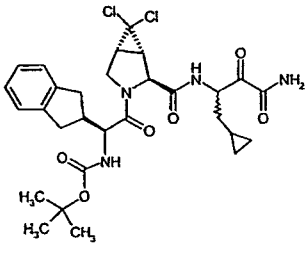


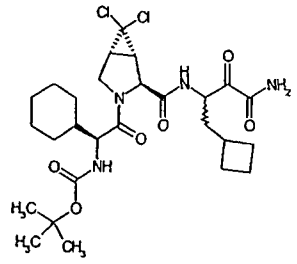


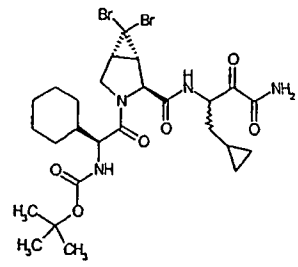


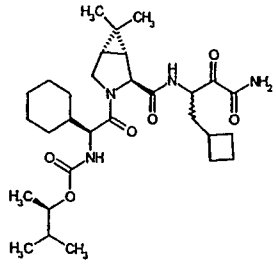


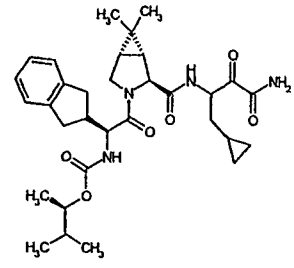


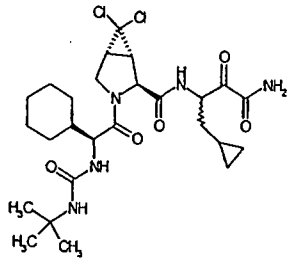


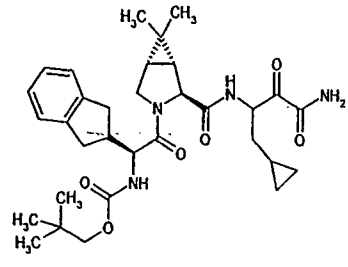


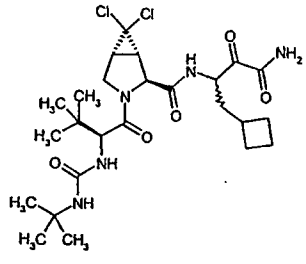


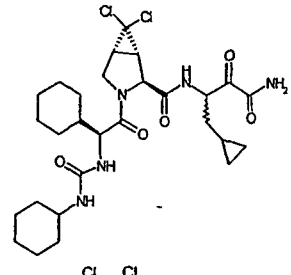


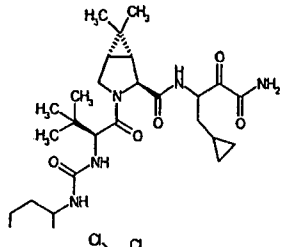


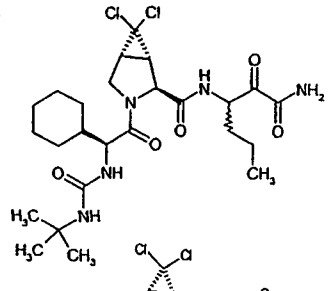


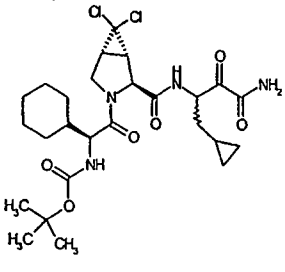


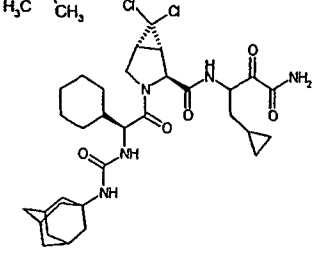


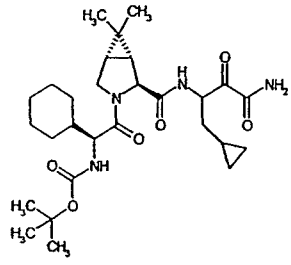


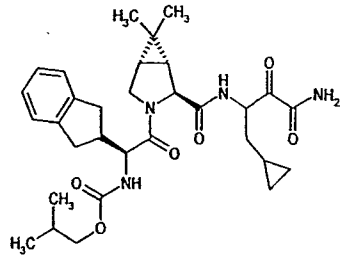


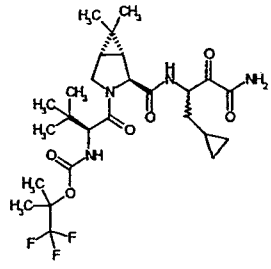


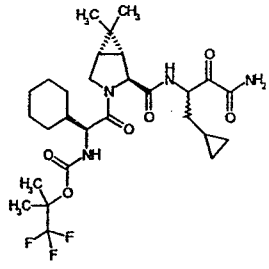


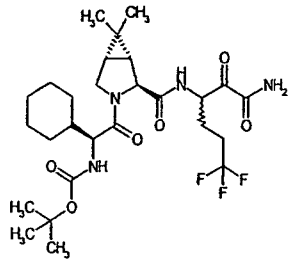


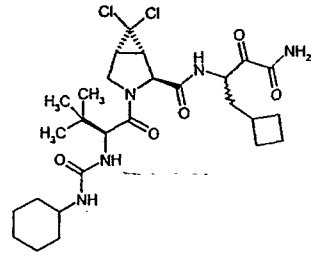


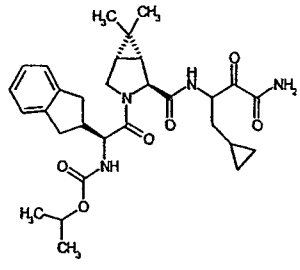


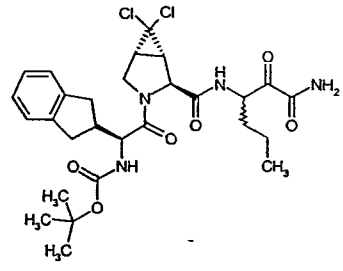


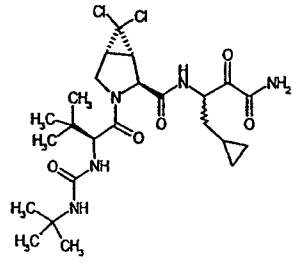


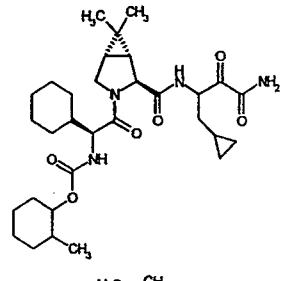


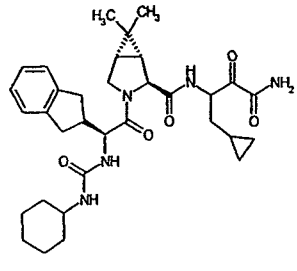


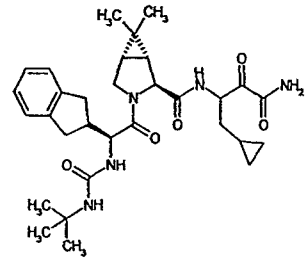


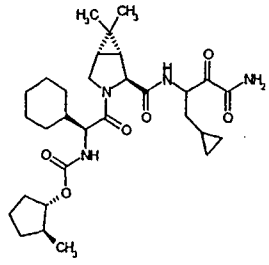


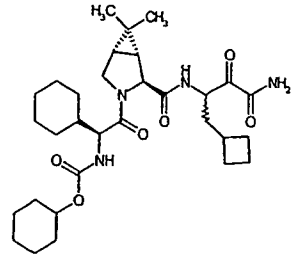


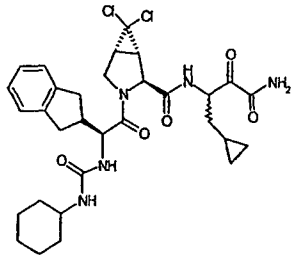


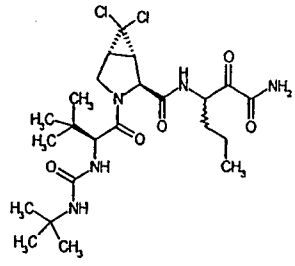


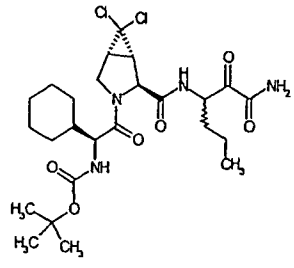


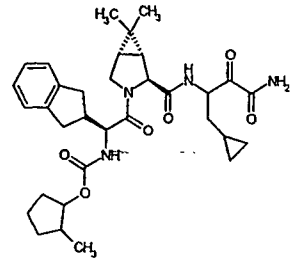


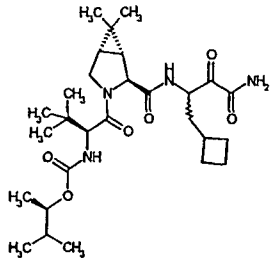


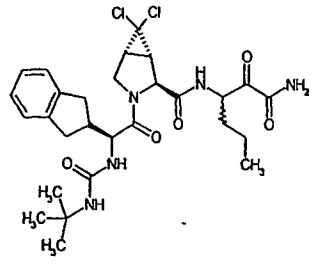


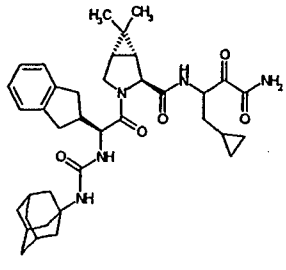


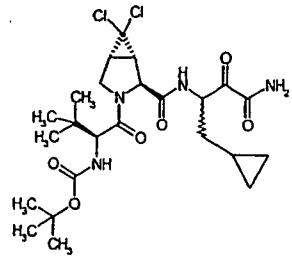


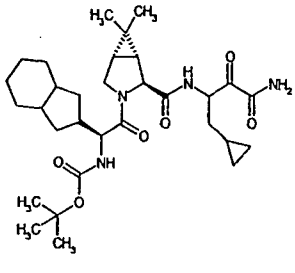


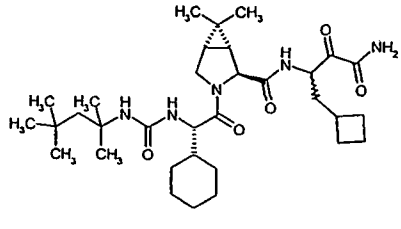


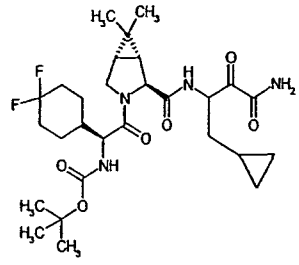


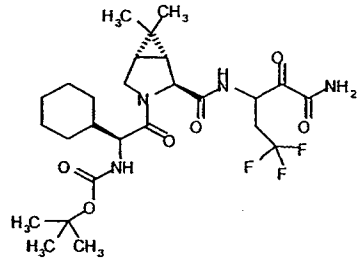


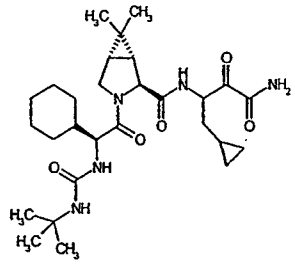


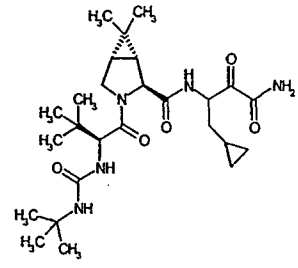


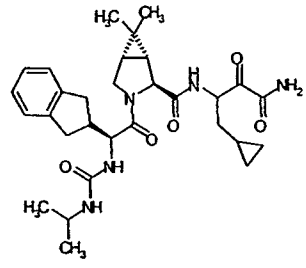


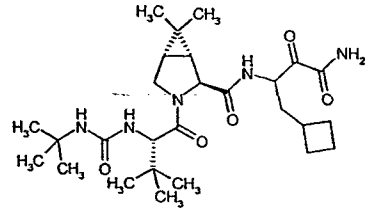


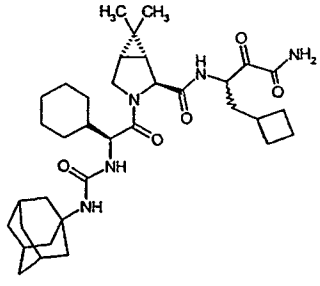


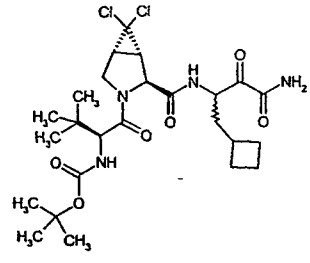


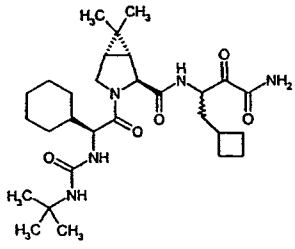


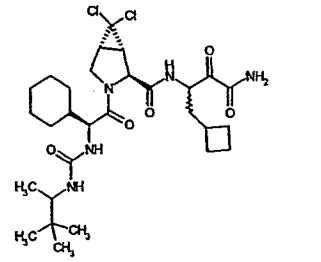


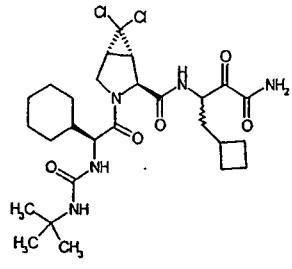


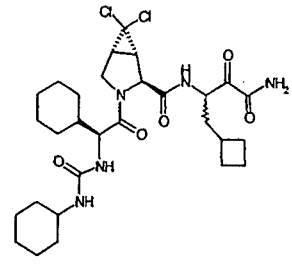


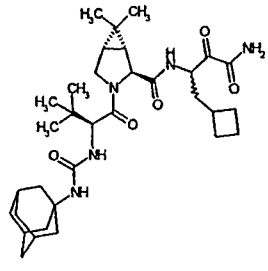


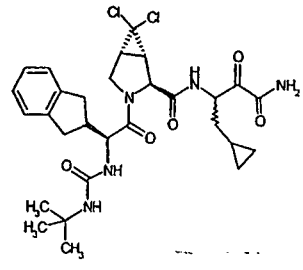


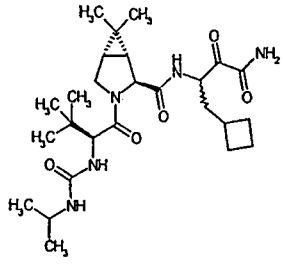


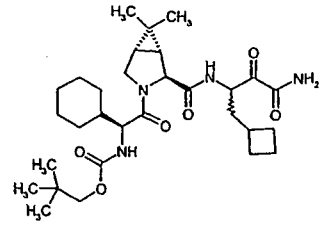


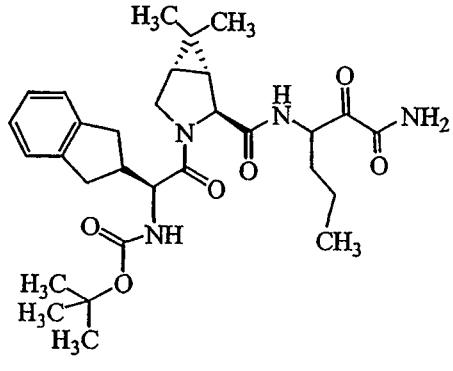


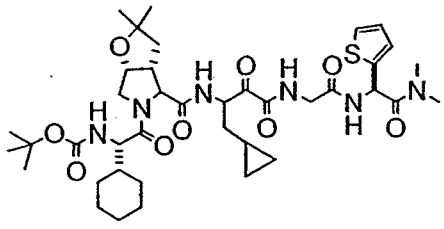


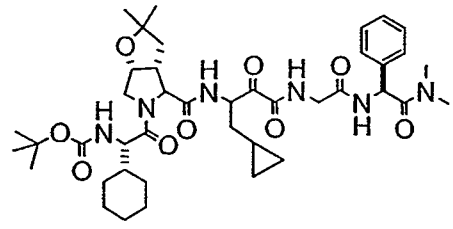


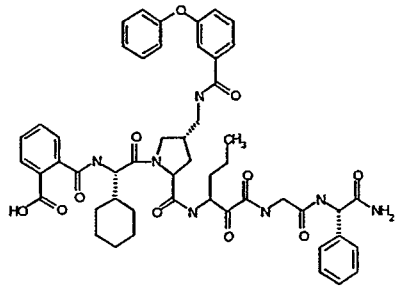


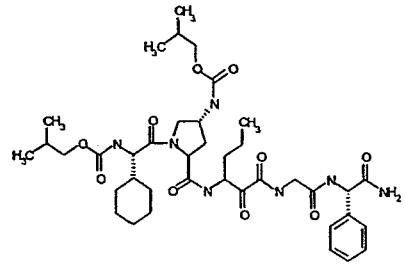


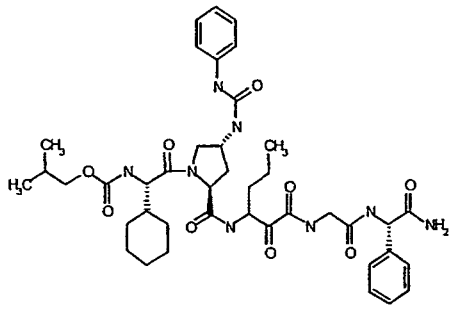


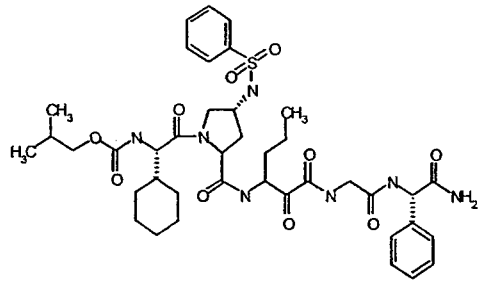


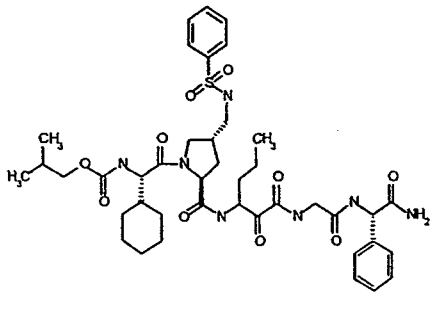


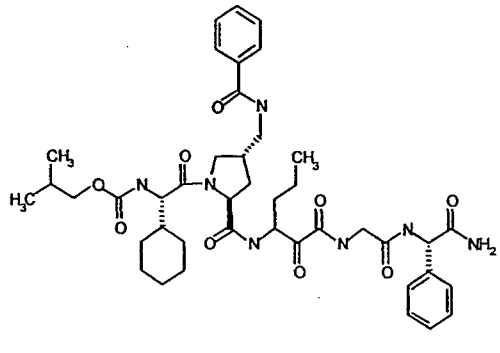


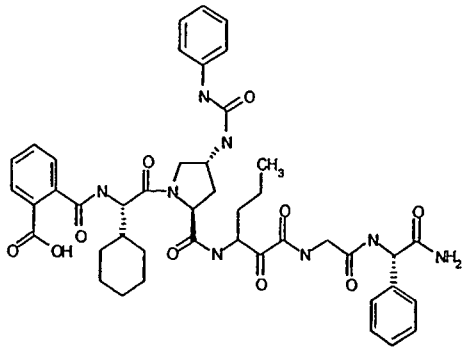


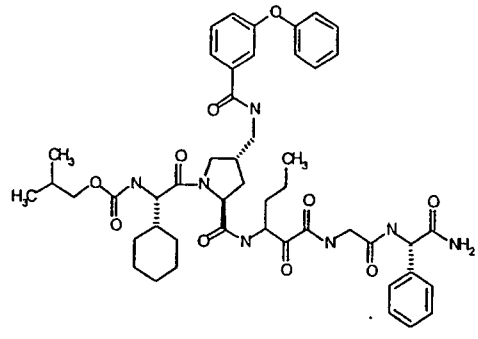


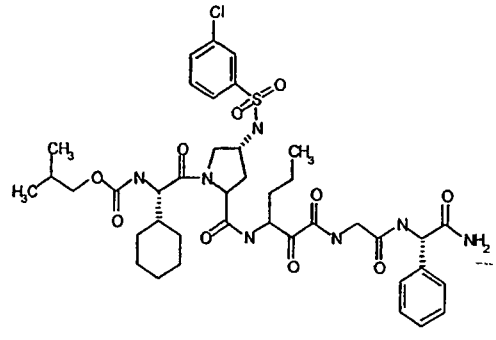


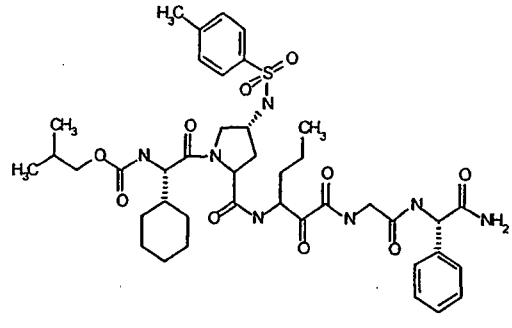


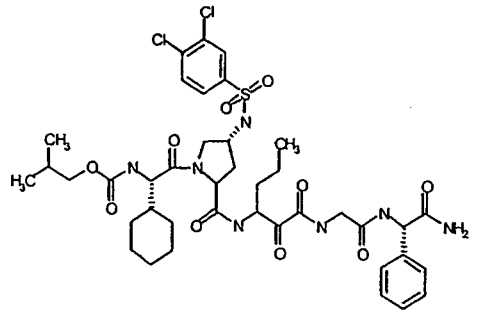


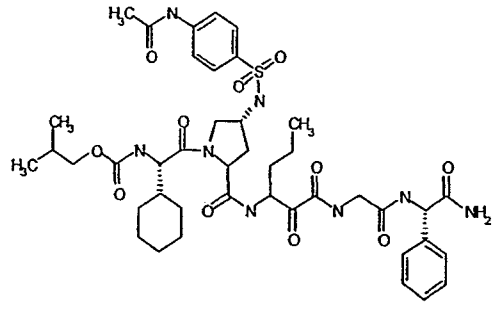


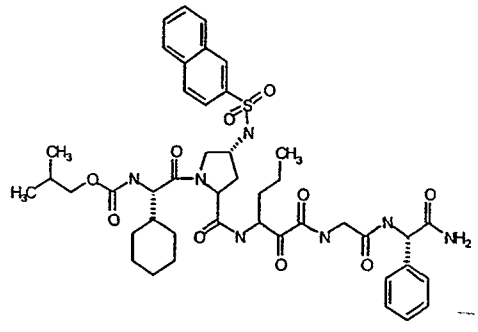


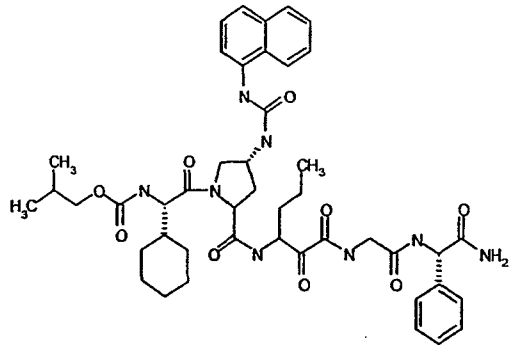




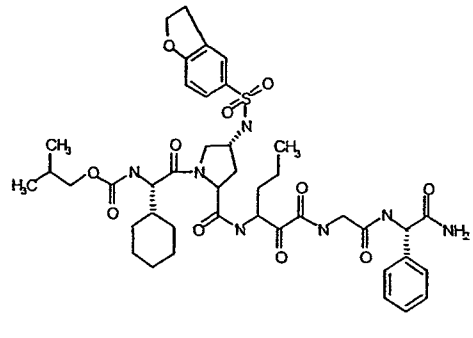


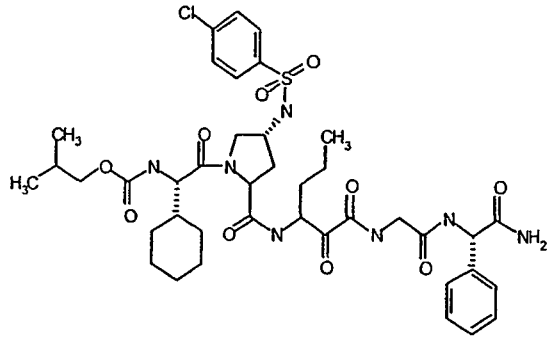


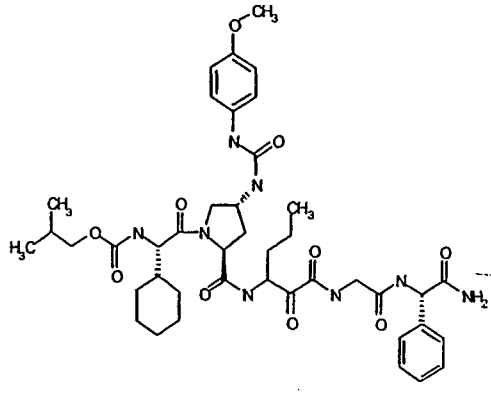


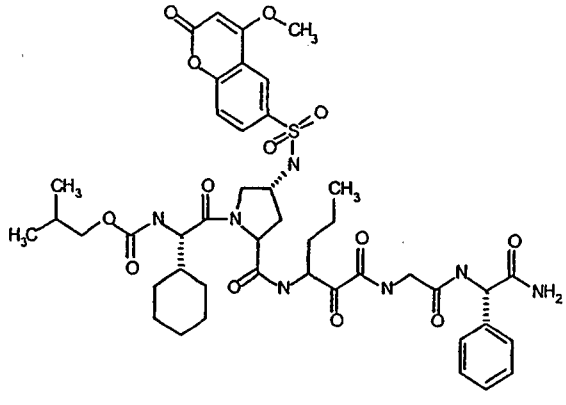


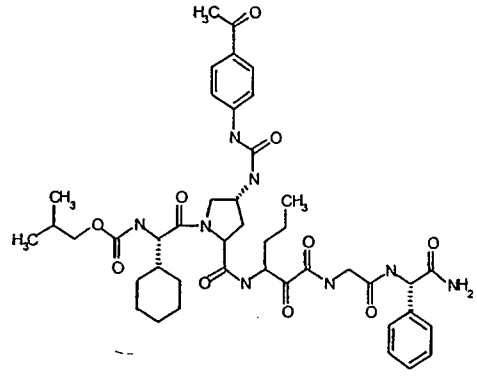
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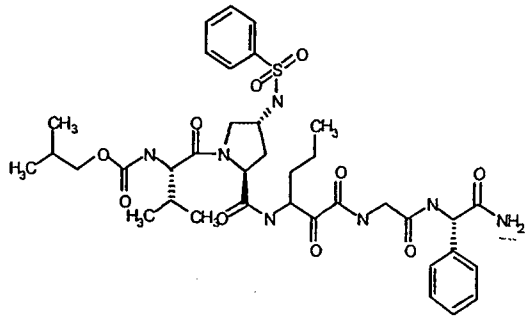


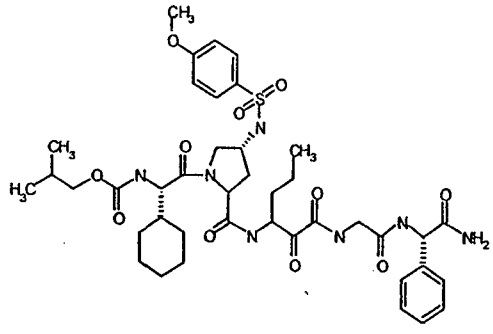


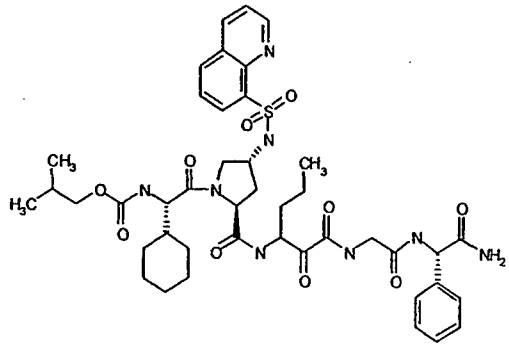


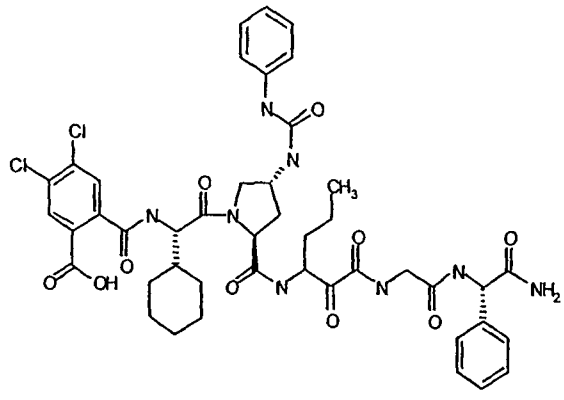


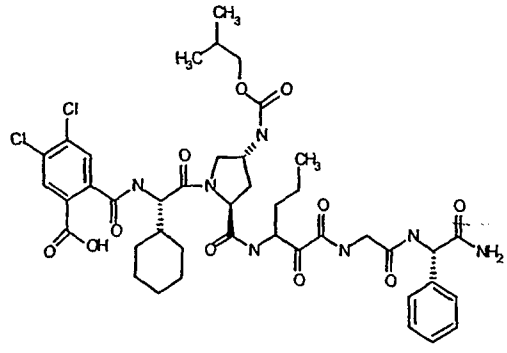


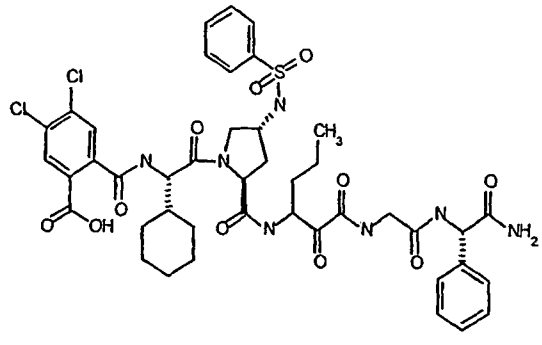


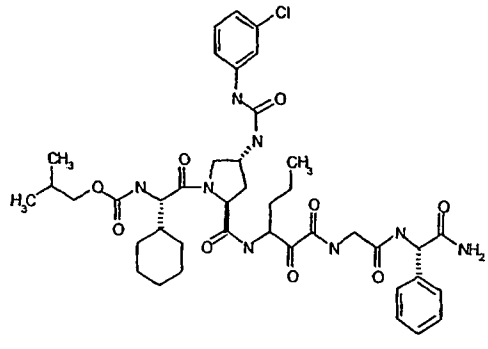


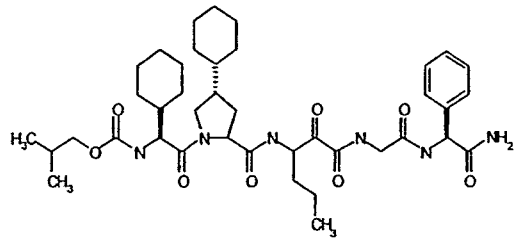


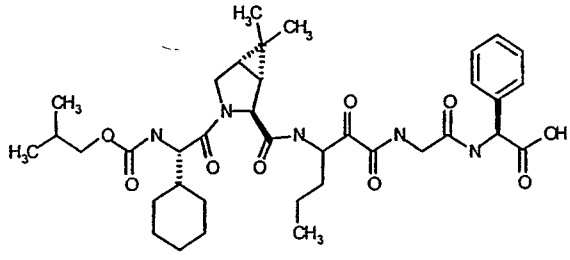


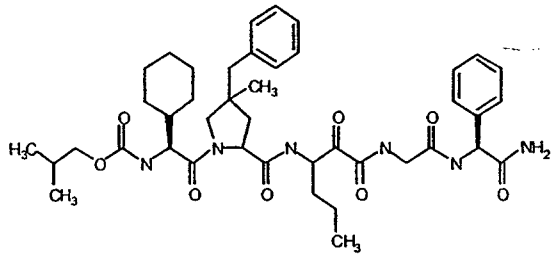


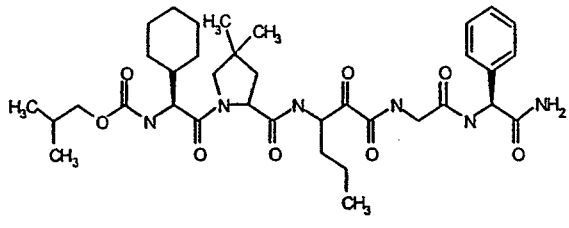


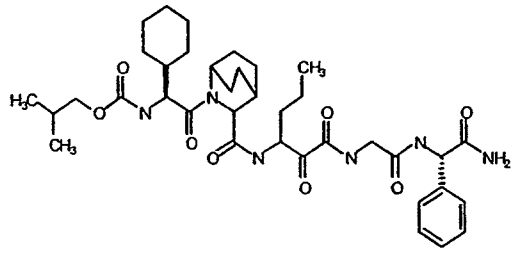




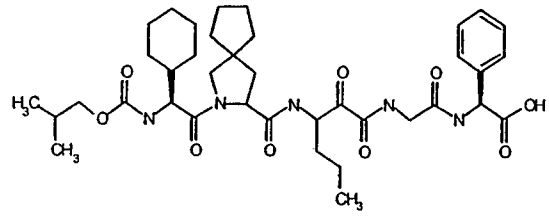


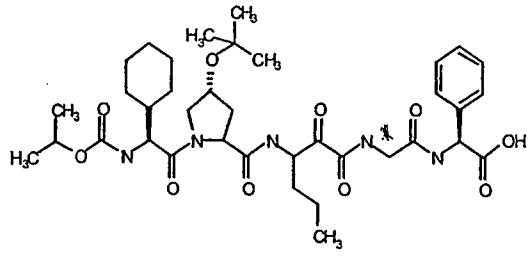


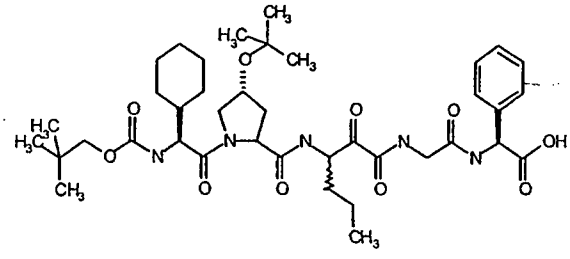


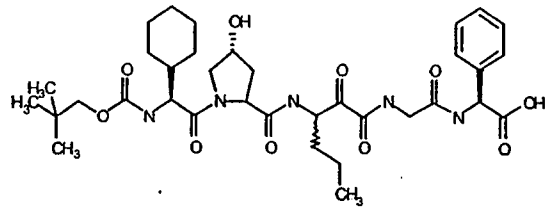


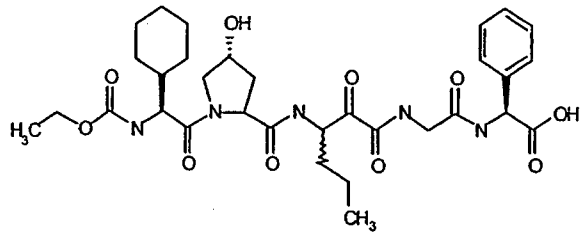
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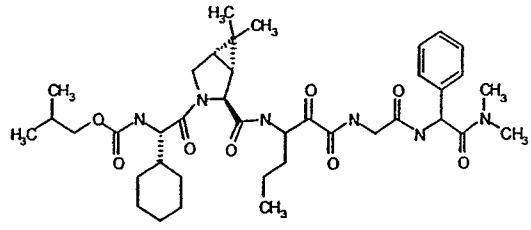


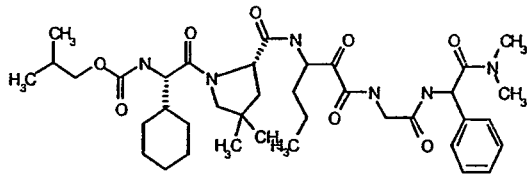


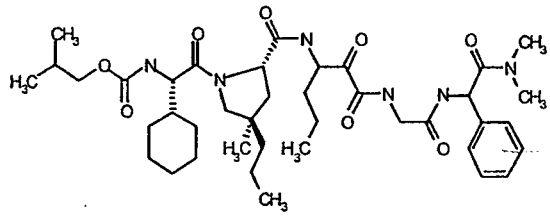


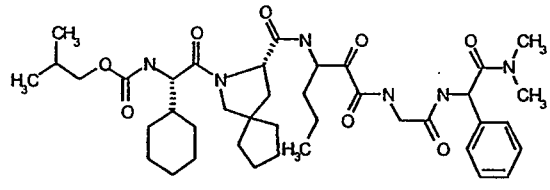


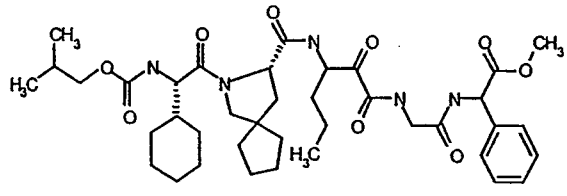
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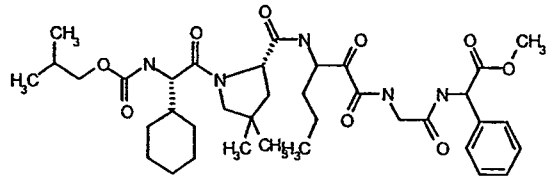




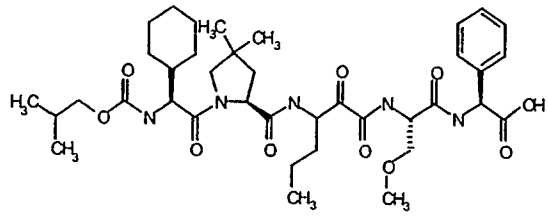


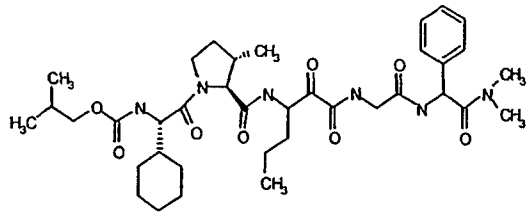


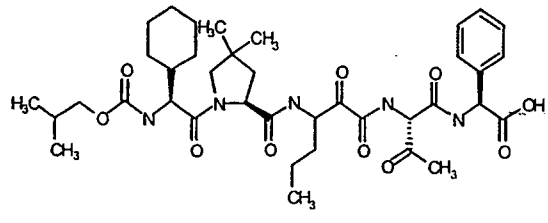


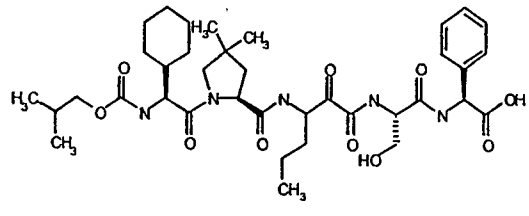


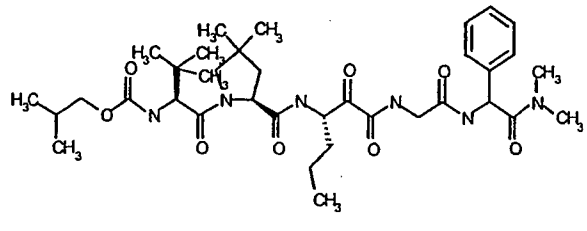
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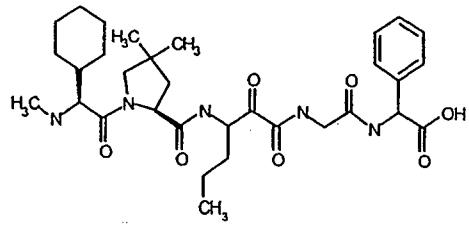


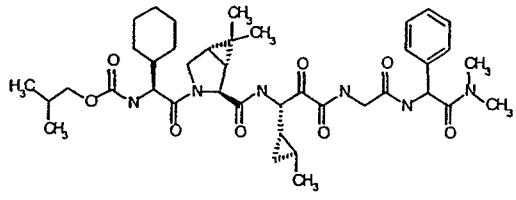


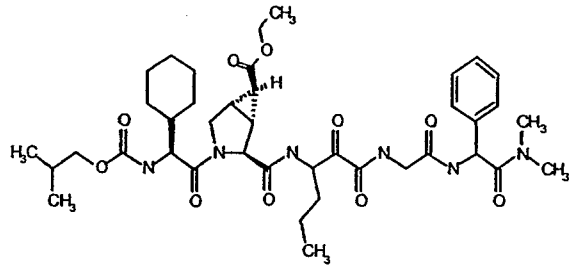


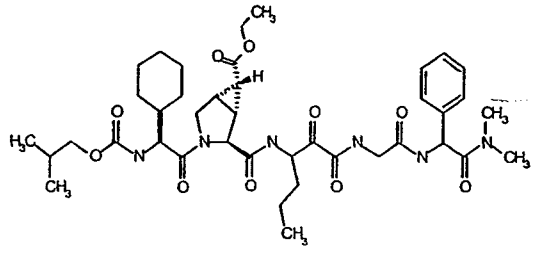


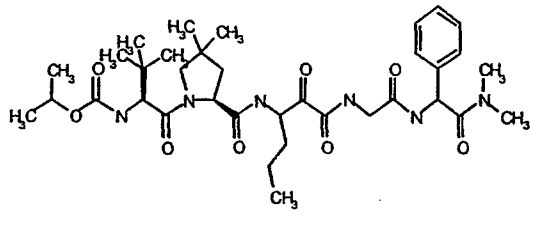


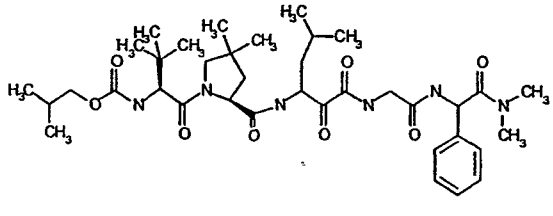


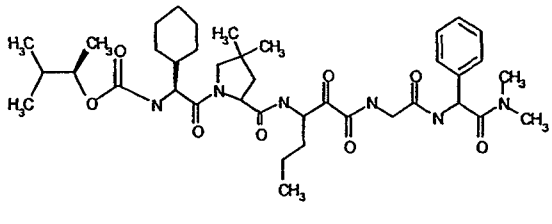


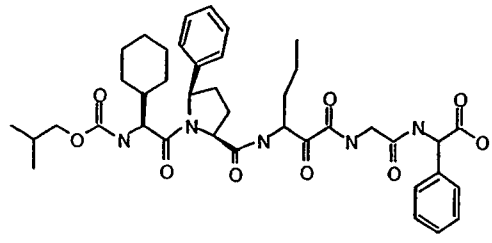


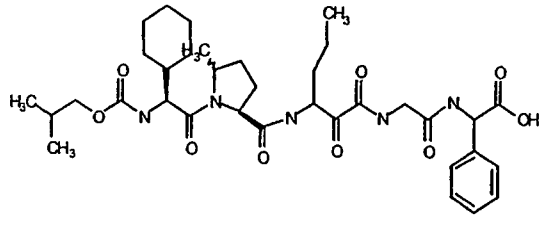


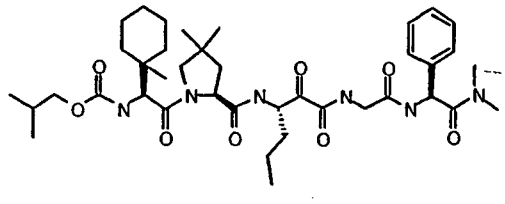


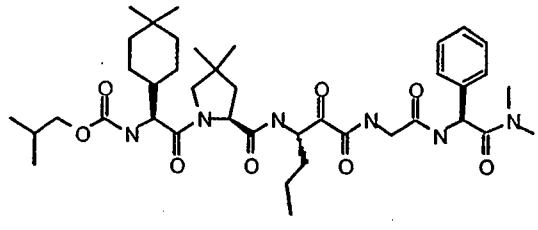


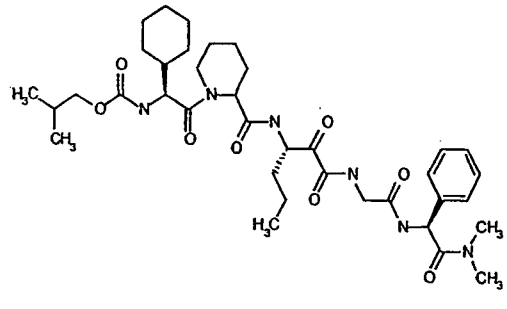




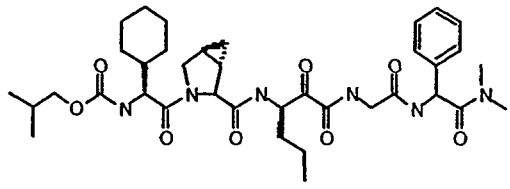


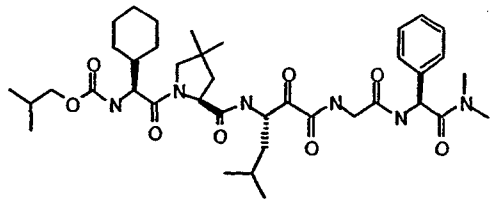


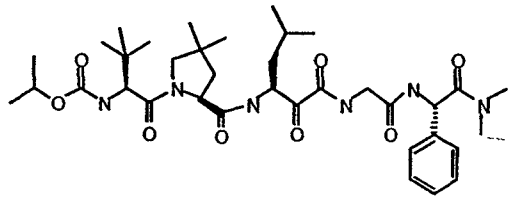


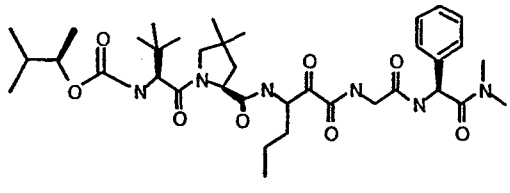


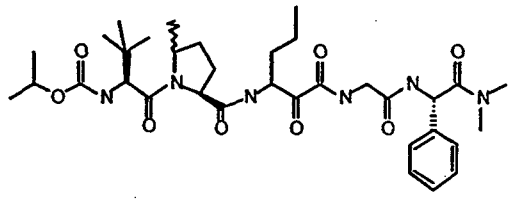
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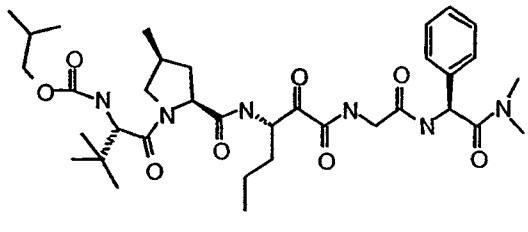


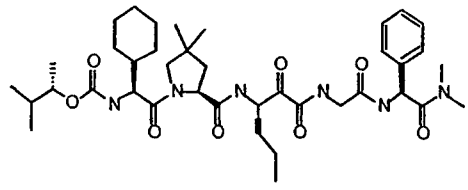


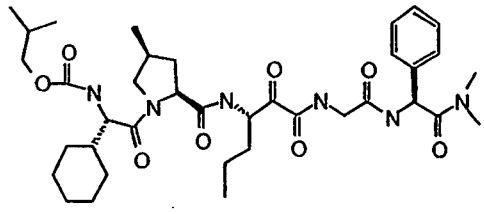


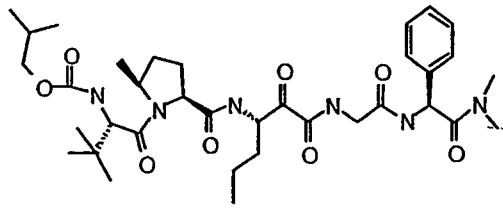


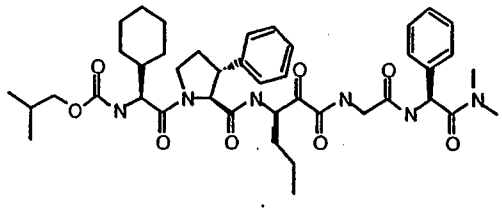


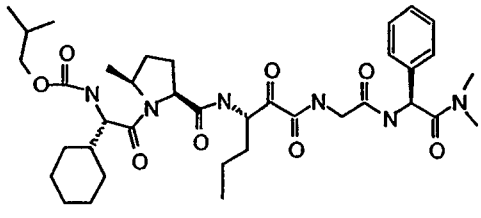


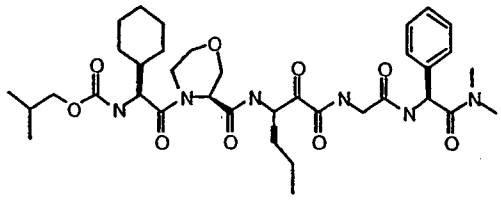


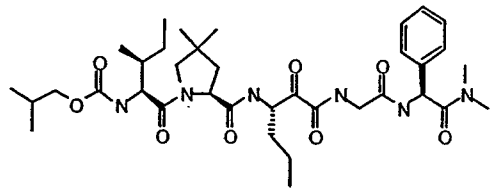


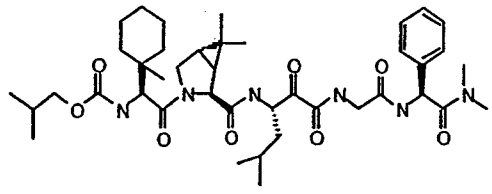


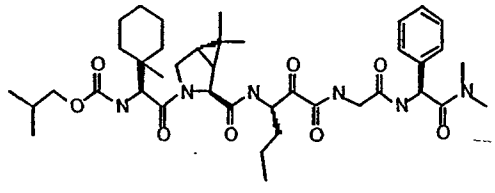


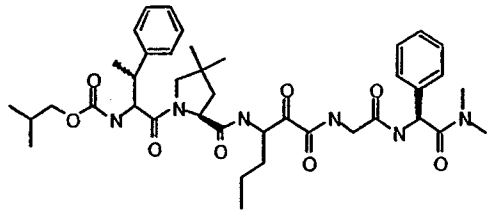


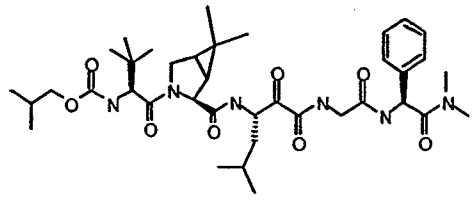




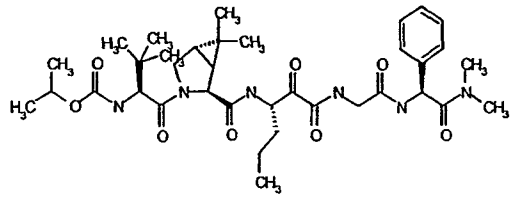


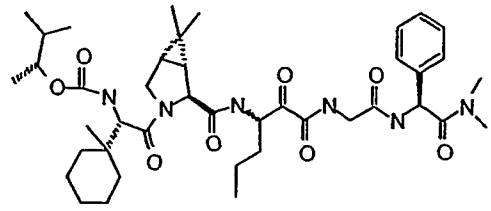


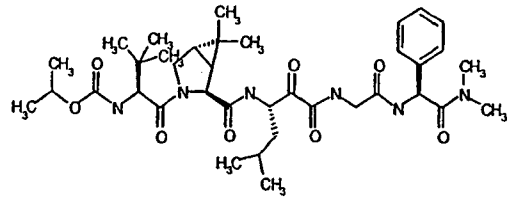


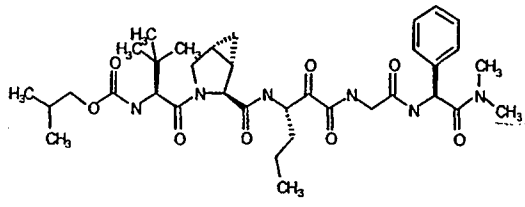


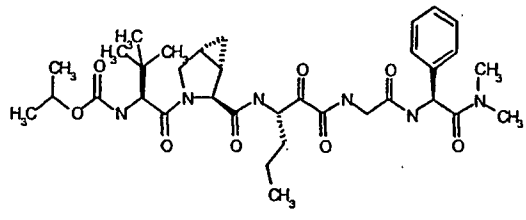
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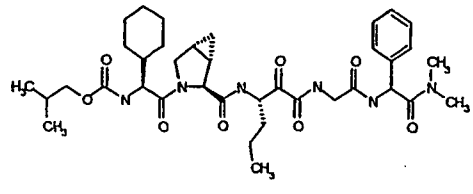


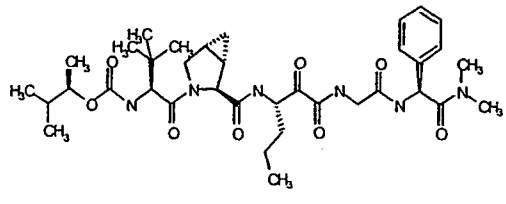


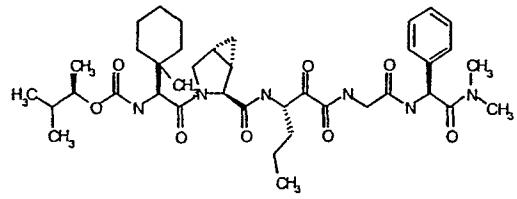












Depending upon their structure, the compounds of the invention may form pharmaceutically acceptable salts with organic or inorganic acids, or organic or inorganic bases. Examples of suitable acids for such salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, 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

^tBu 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

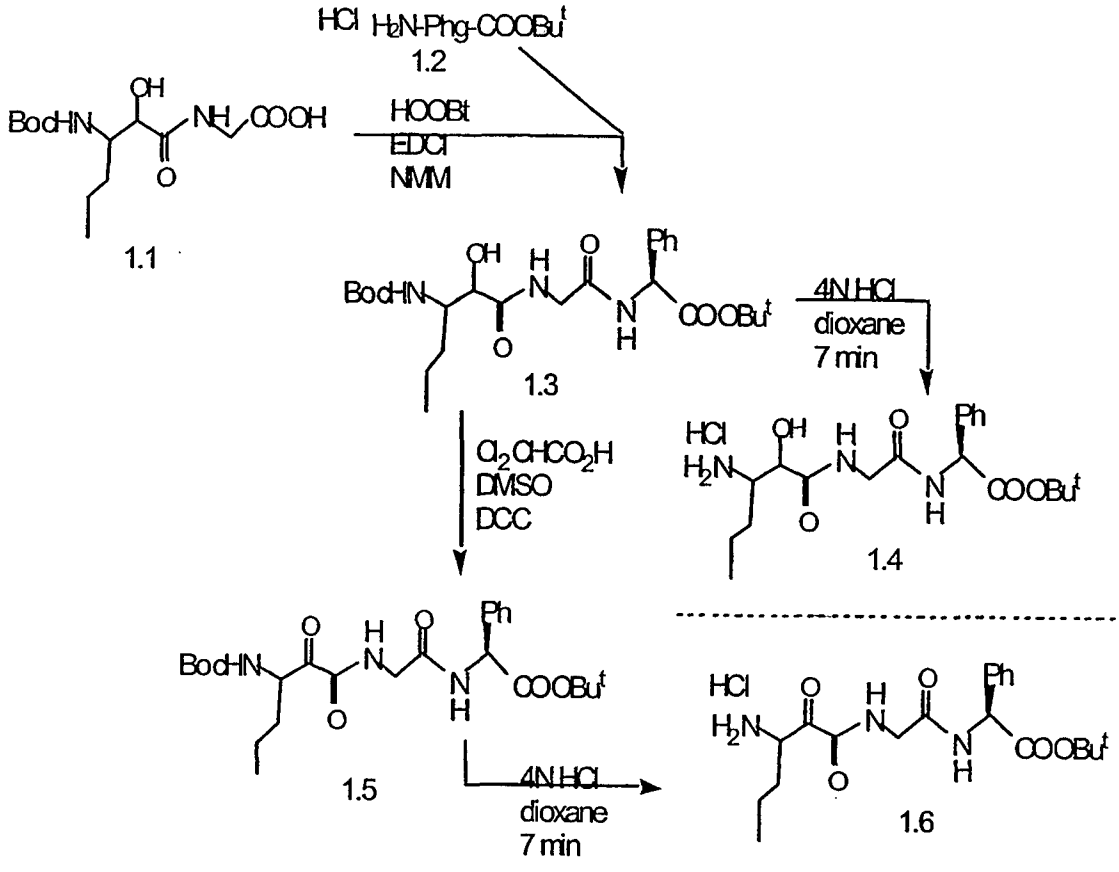
DMAP: 4-N,N-Dimethylaminopyridine

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

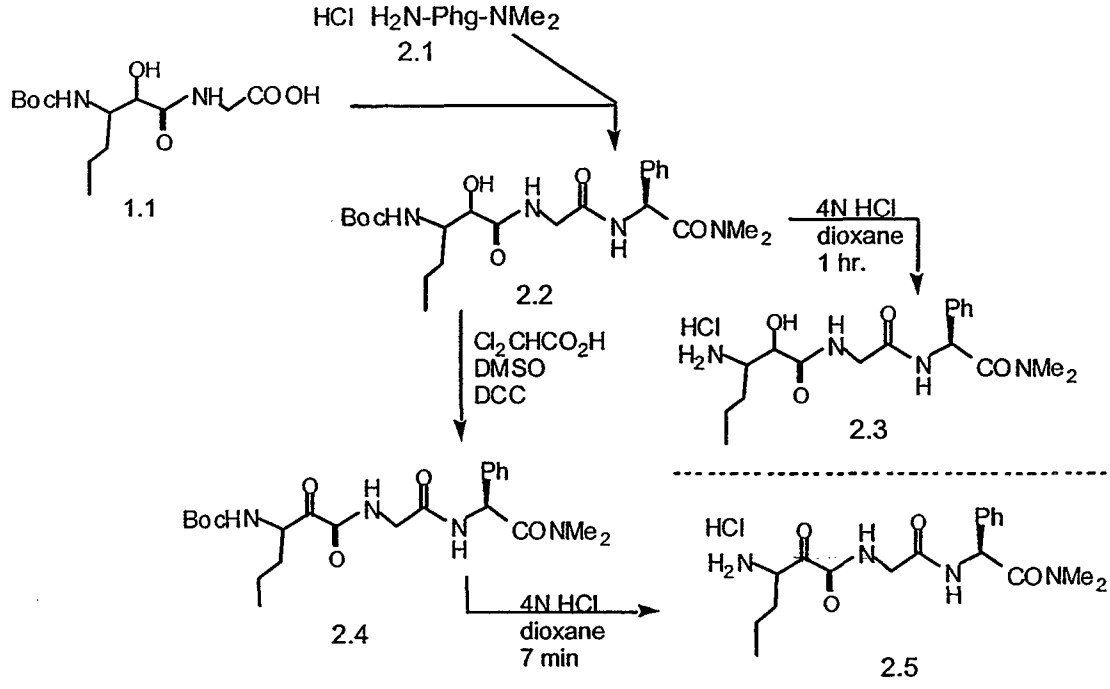
General Preparative Schemes:

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

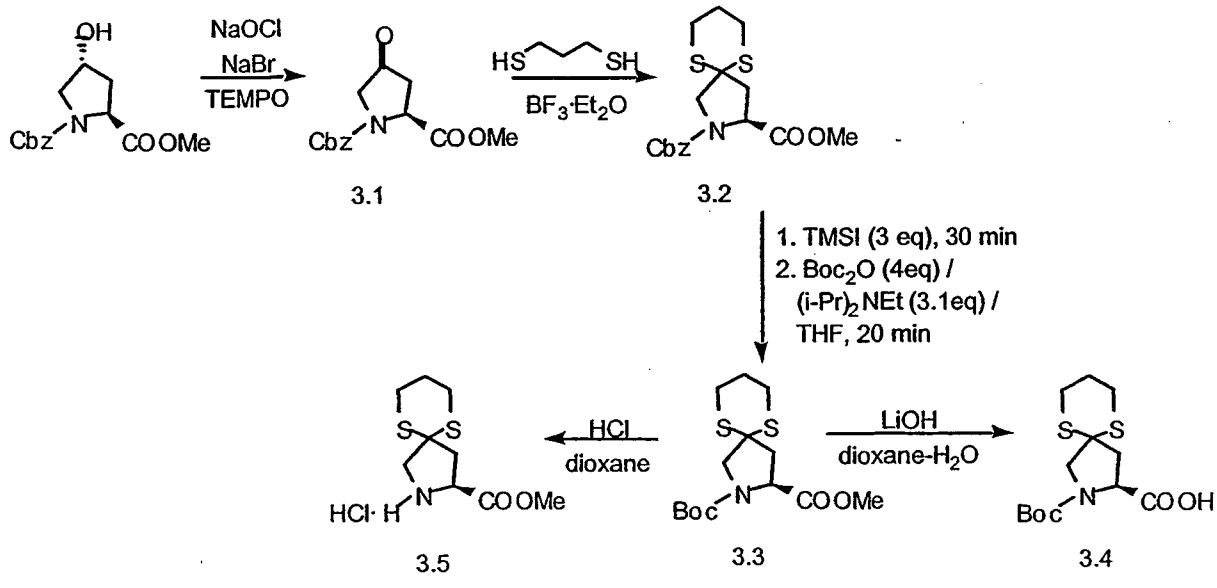
SCHEME 1


HCl H2N-Phg-COOBut
1.2
HOOBt
EDCI
NMM
BocHN
OH
NH
COOH
O
1.1
BocHN
OH
H
N
O
N
H
Ph
COOBut
1.3
4N HCl
dioxane
7 min
HCl
H2N
OH
H
N
O
N
H
Ph
COOBut
1.4
Cl2CHCO2H
DMSO
DCC
BocHN
O
H
N
O
N
H
Ph
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N
O
N
H
Ph
COOBut
1.6

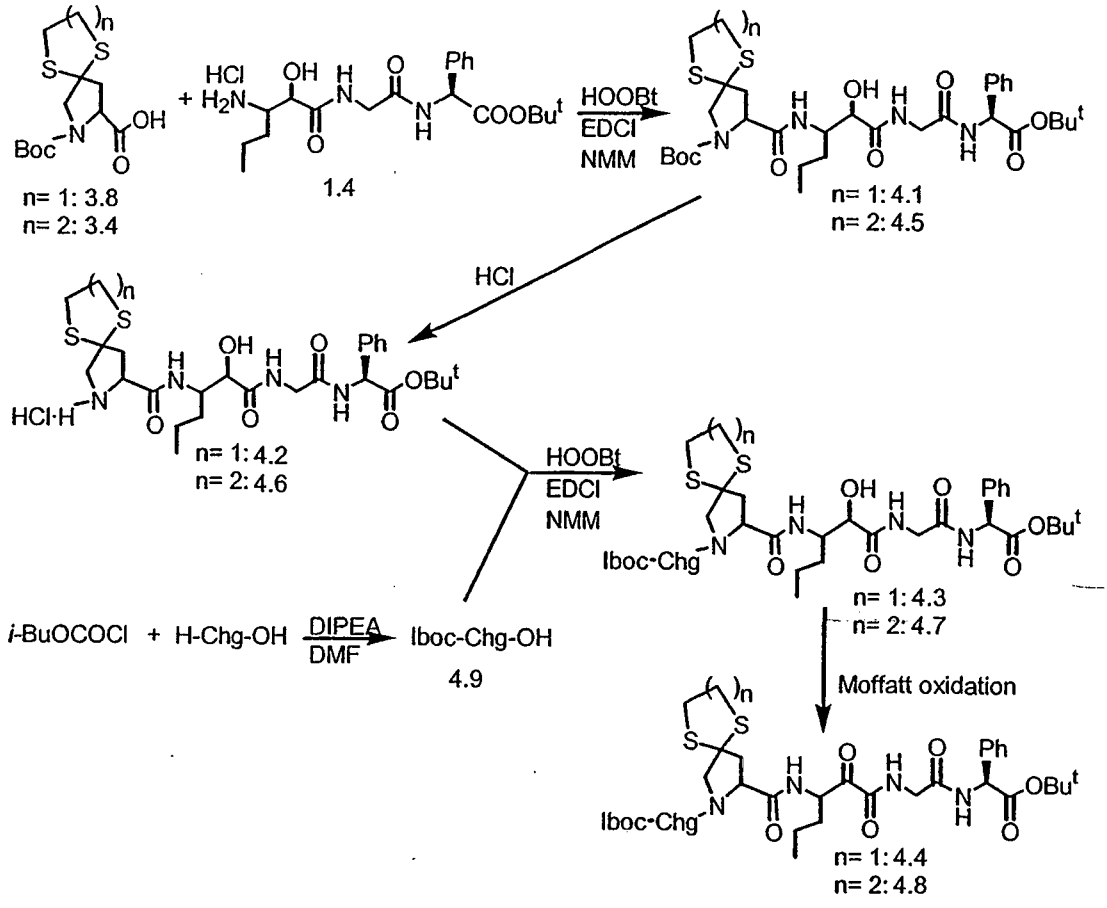
SCHEME 2



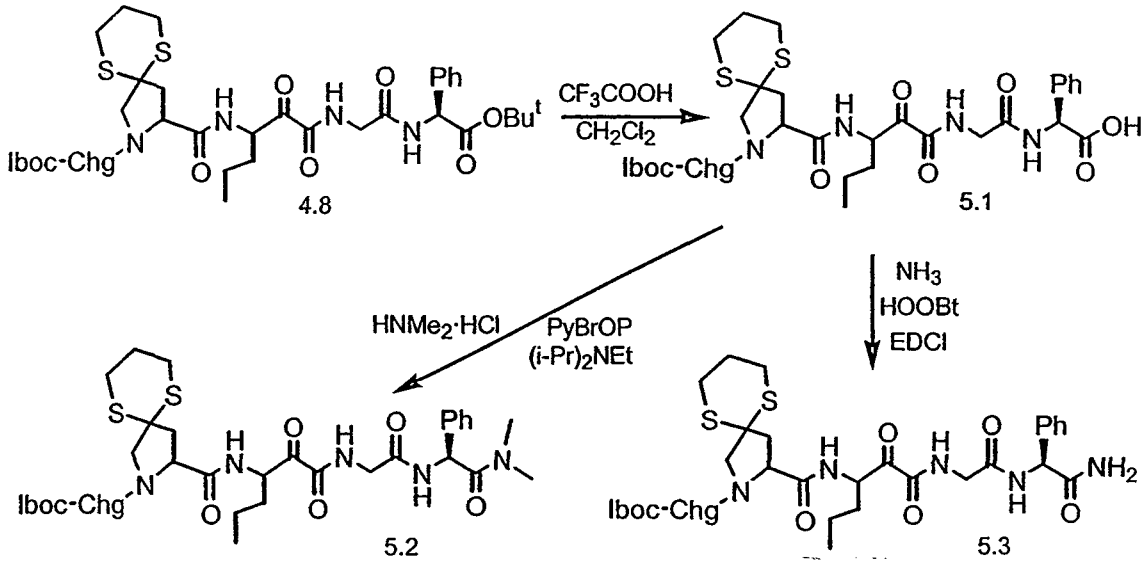
SCHEME 3



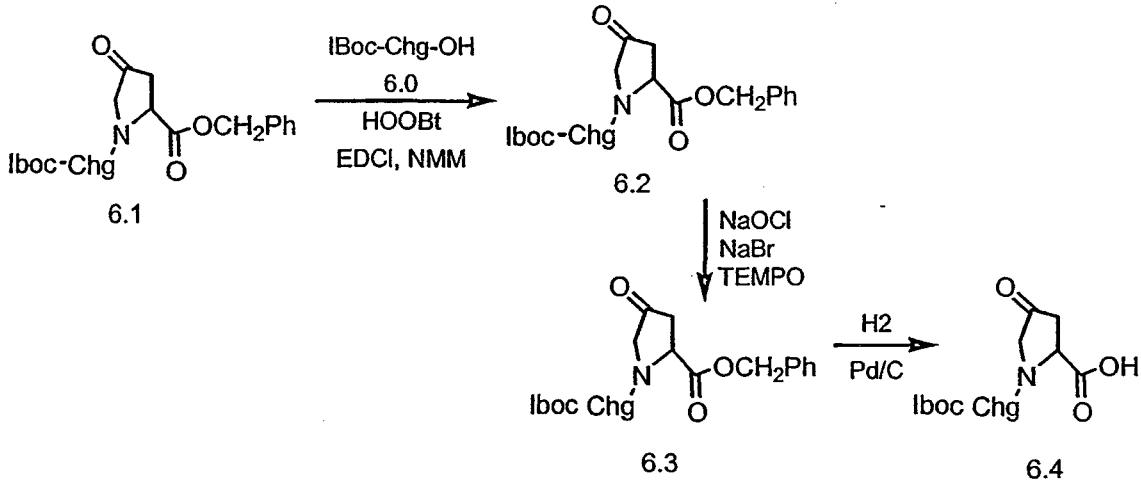
SCHEME 4


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
Iboc-Chg
n= 1: 4.3
n= 2: 4.7
Moffatt oxidation
n= 1: 4.4
n= 2: 4.8
i-BuOCOCl + H-Chg-OH
DIPEA
DMF
Iboc-Chg-OH
4.9

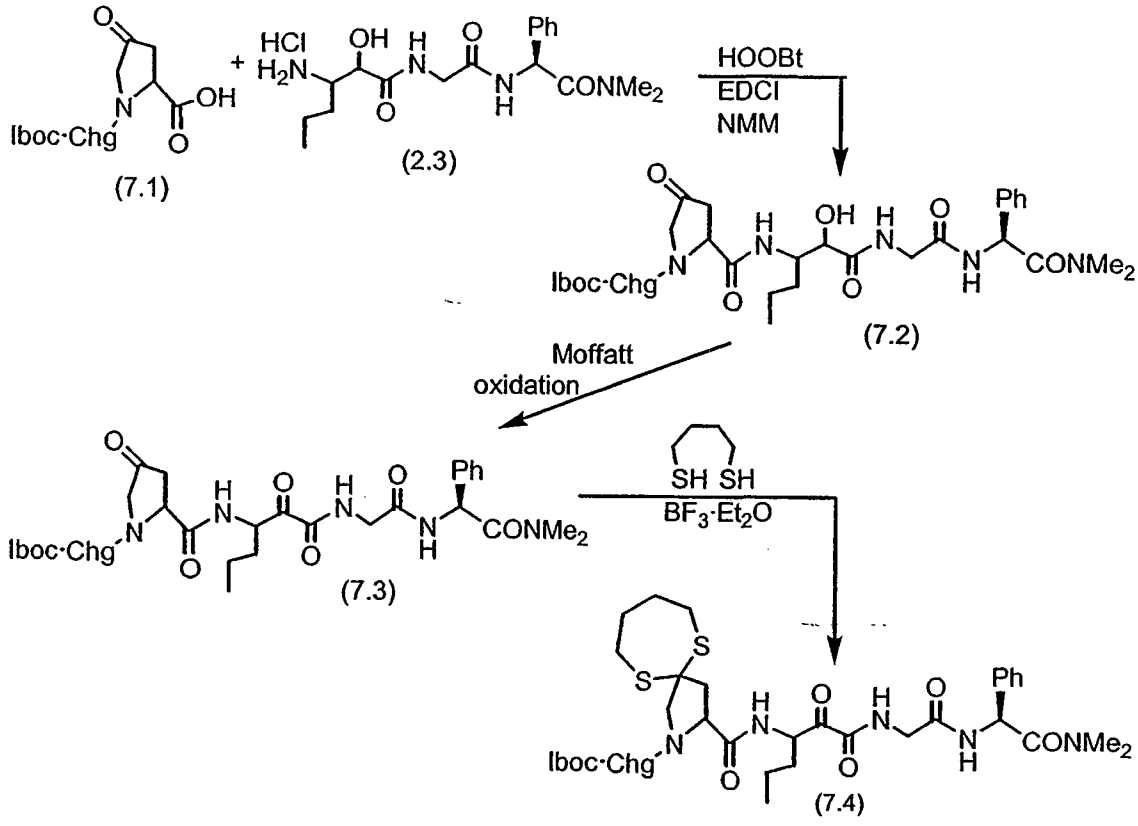
SCHEME 5



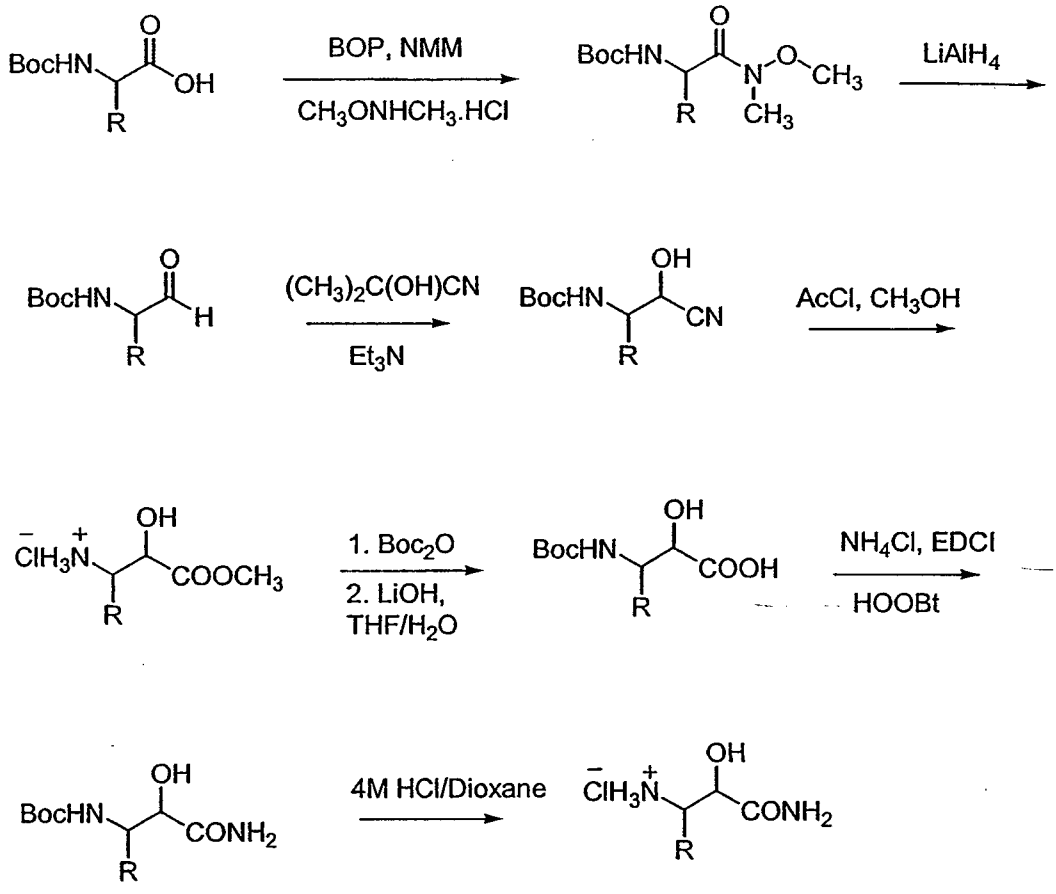
SCHEME 6



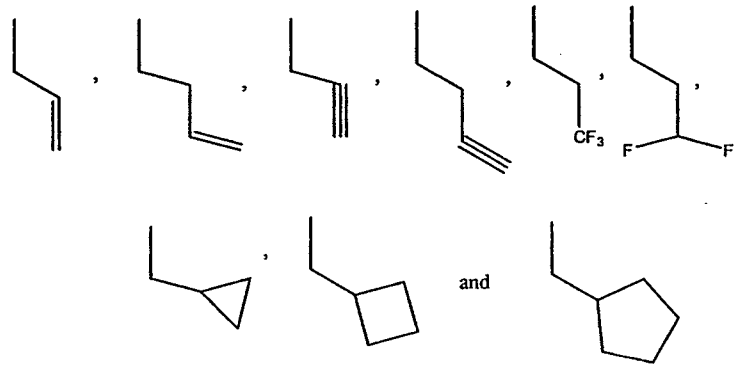
SCHEME 7


Iboc-Chg
(7.1)
HCl H2N
OH
Ph
CONMe2
(2.3)
HOOBt
EDCI
NMM
(7.2)
Moffatt
oxidation
(7.3)
SH SH
BF3·Et2O
(7.4)

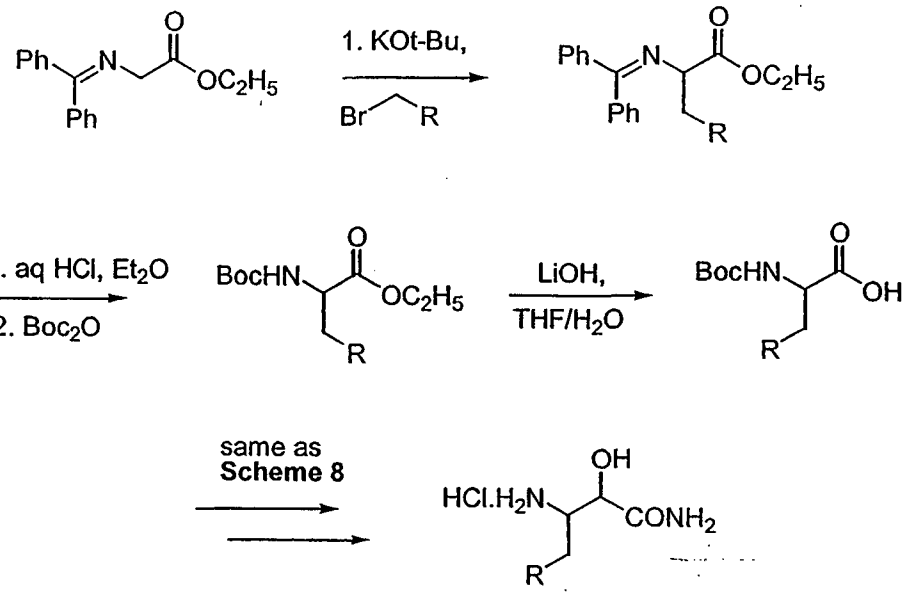
SCHEME 8

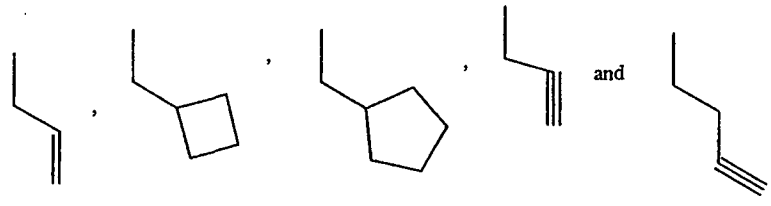


where R =

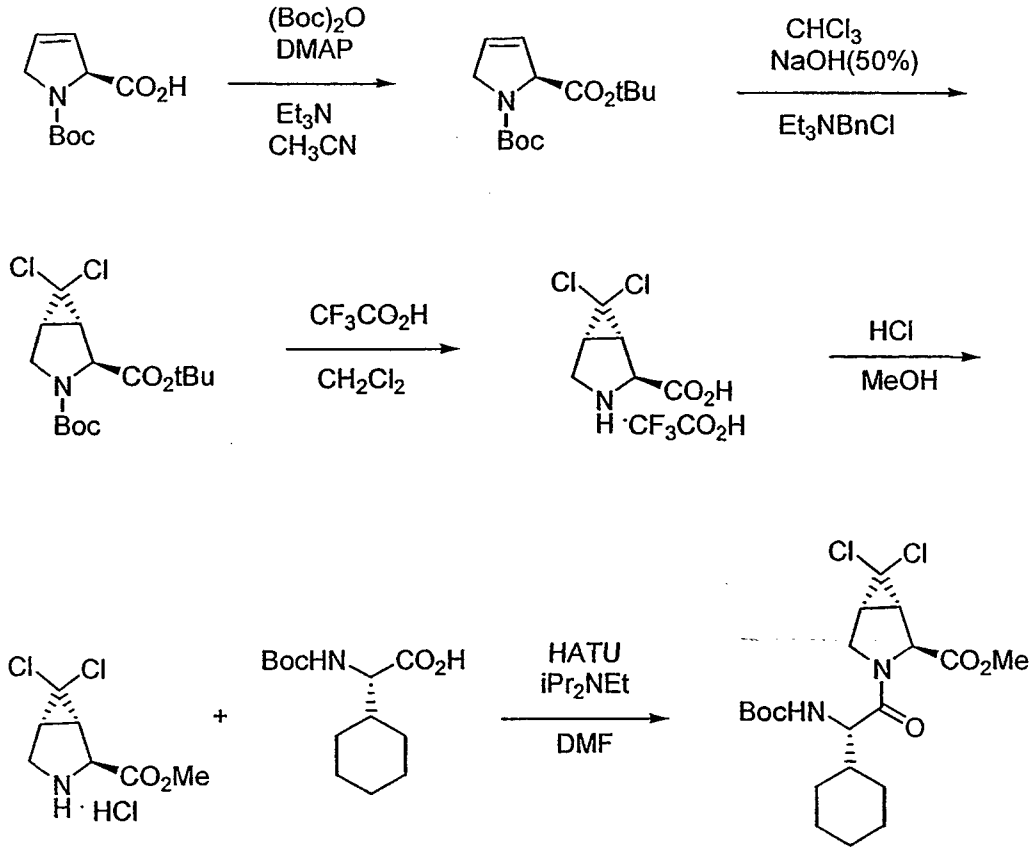


SCHEME 9

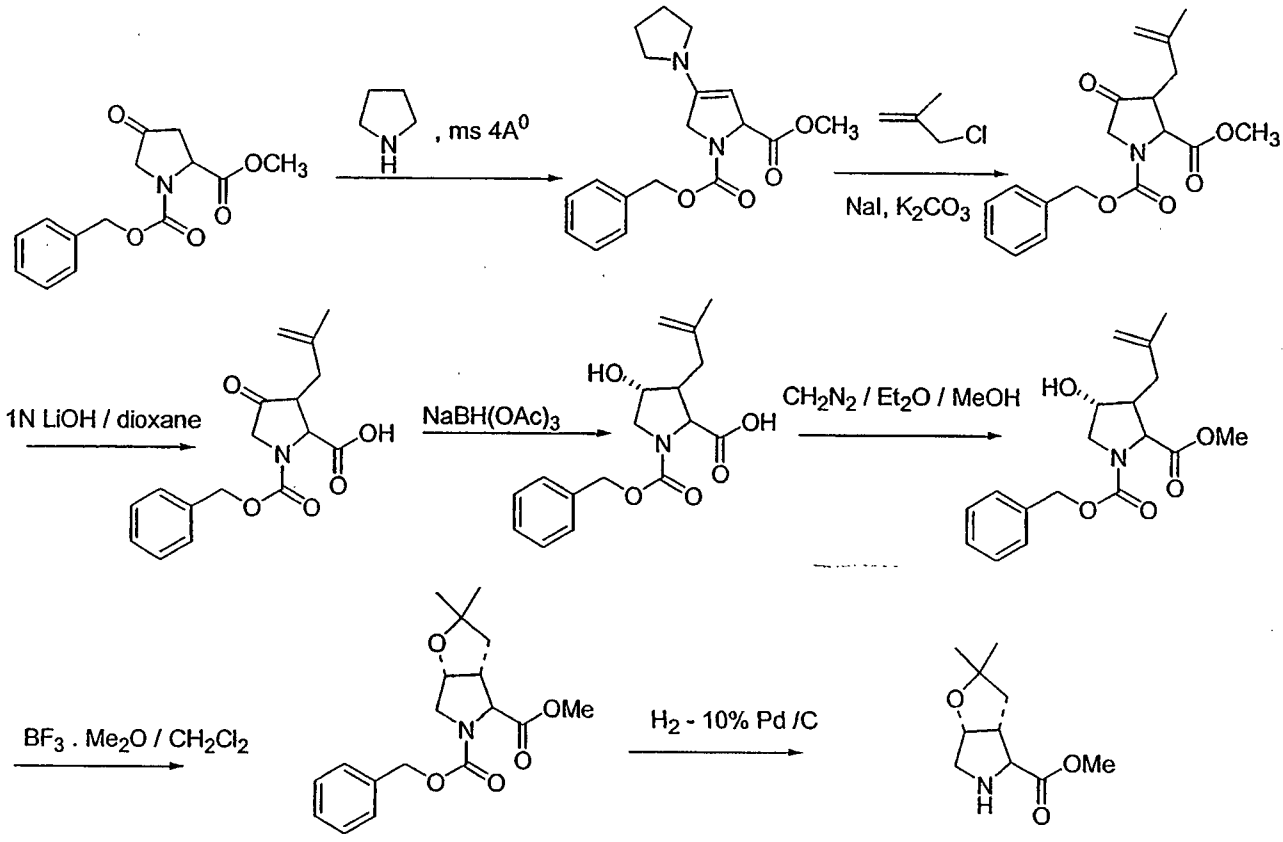


where R =  and

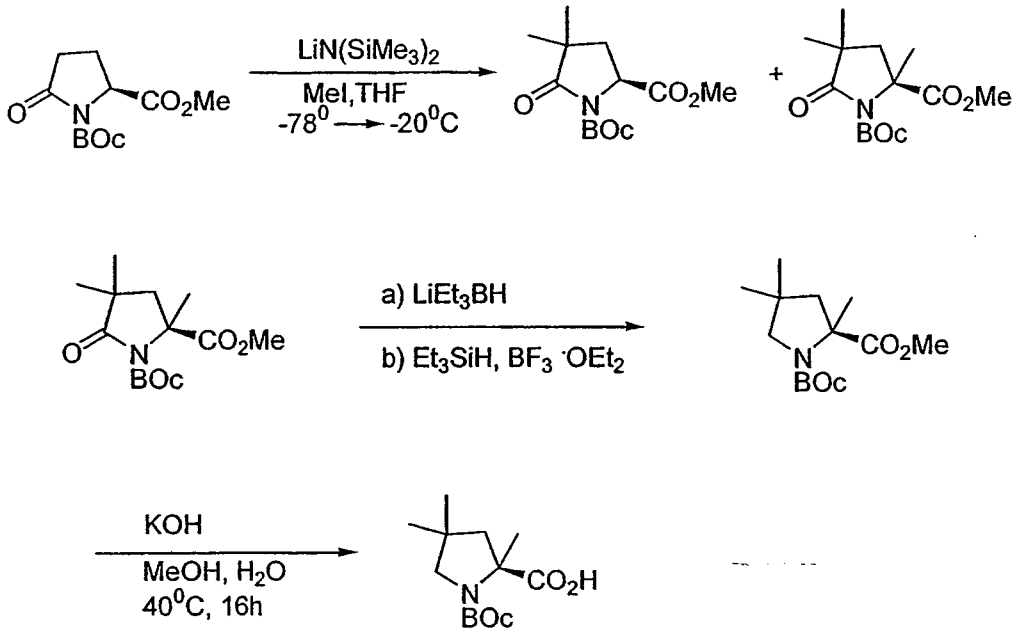
SCHEME 10


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

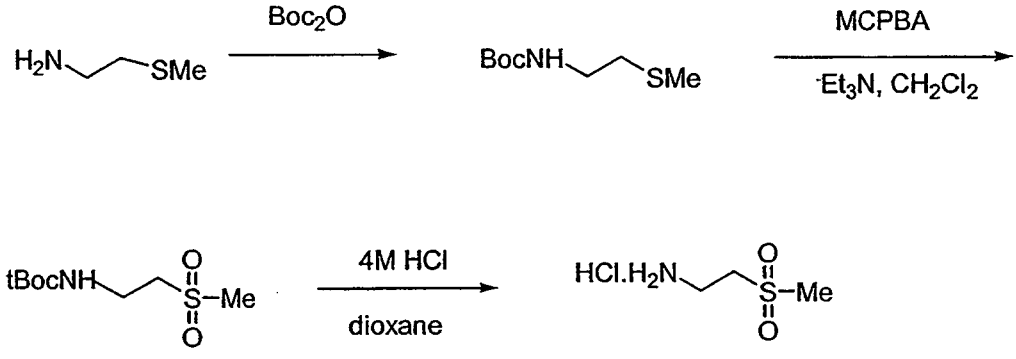
SCHEME 11


, ms 4A0
NaI, K2CO3
1N LiOH / dioxane
NaBH(OAc)3
CH2N2 / Et2O / MeOH
BF3 . Me2O / CH2Cl2
H2 - 10% Pd /C

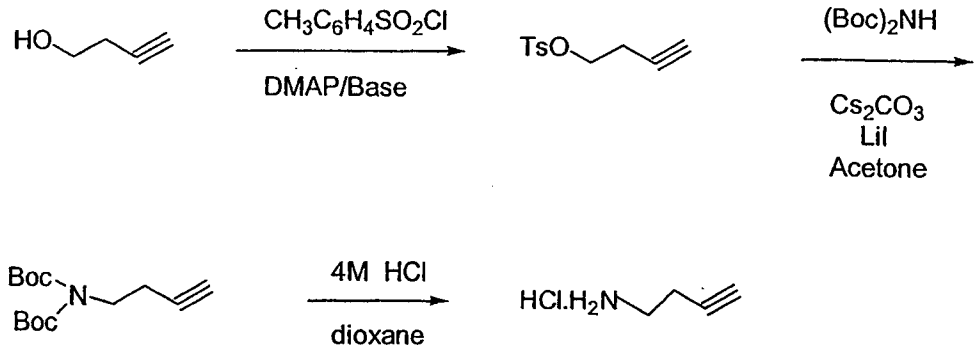
SCHEME 12



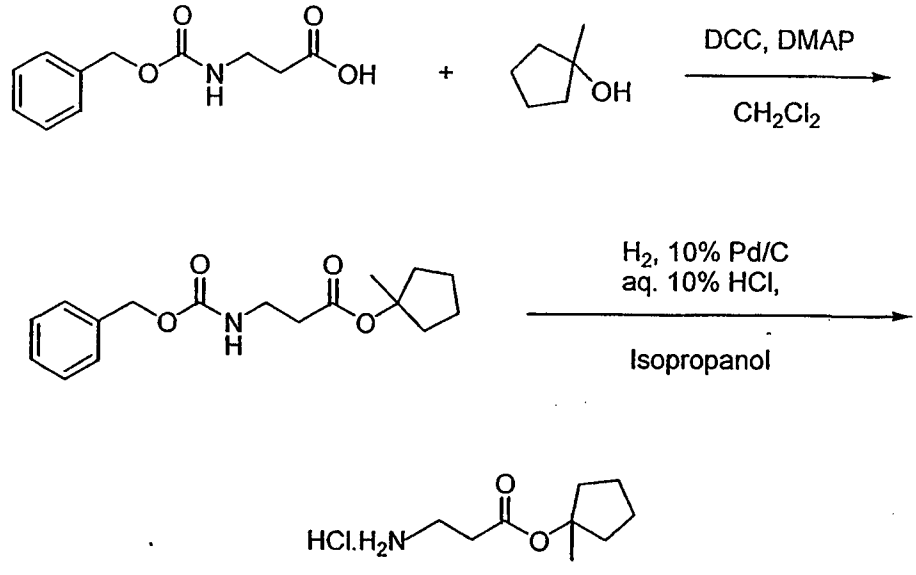
SCHEME 13



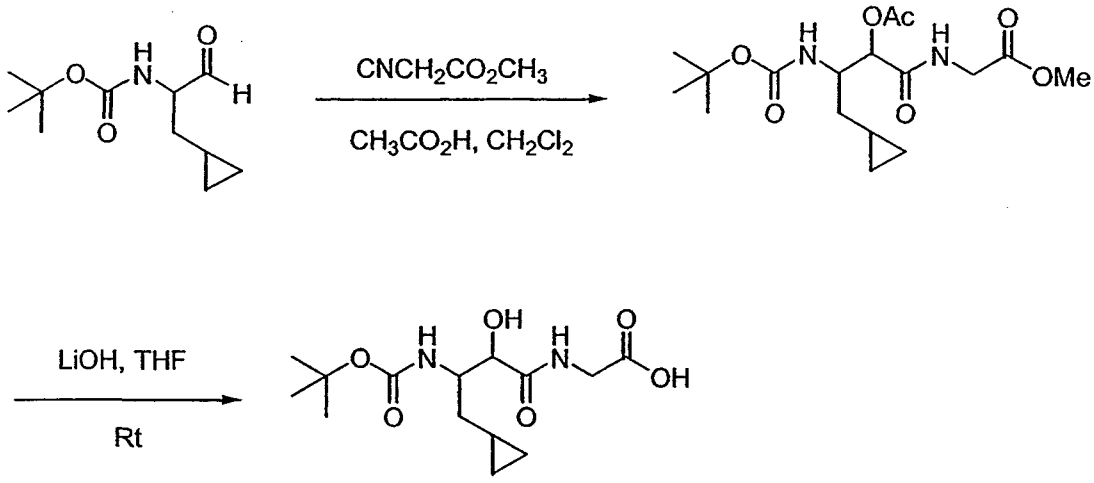
SCHEME 14



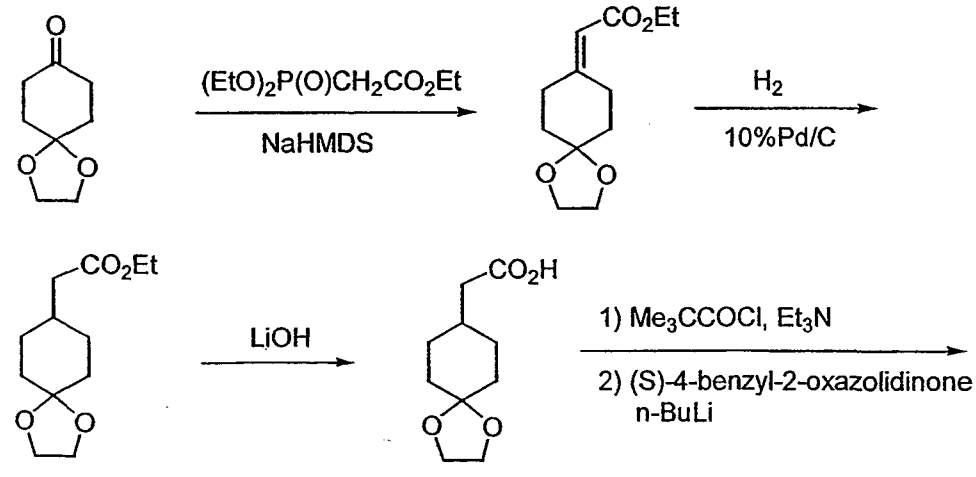
SCHEME 15

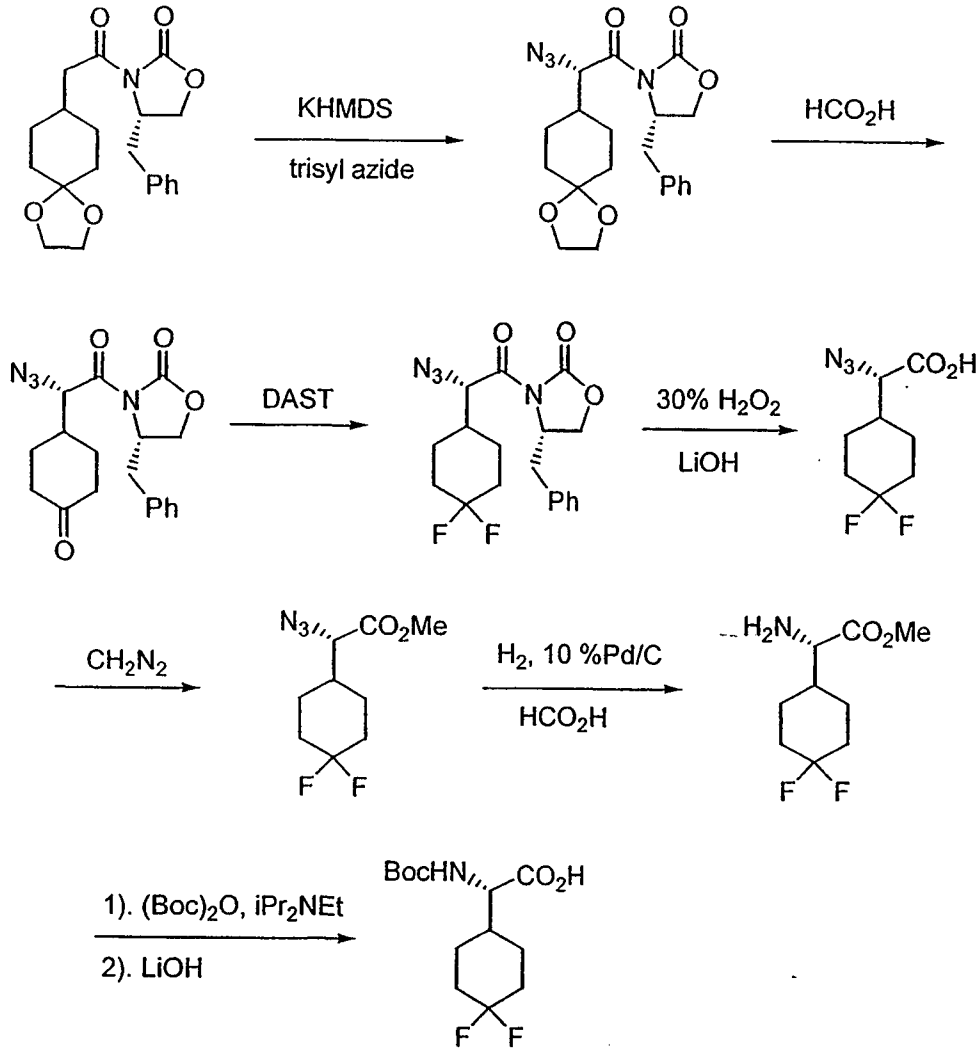


SCHEME 16

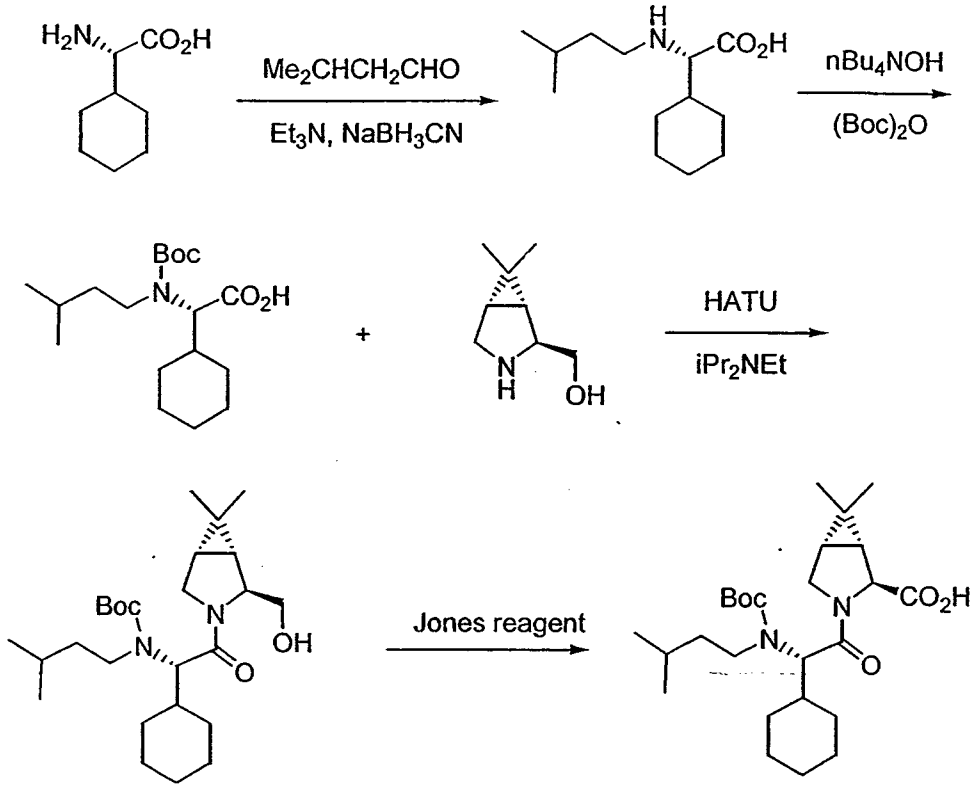


SCHEME 17

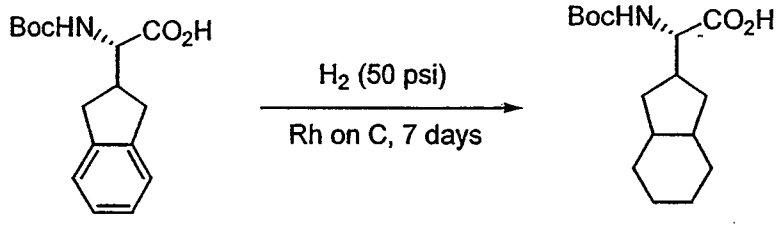



KHMDS
trisyl azide
HCO2H
DAST
30% H2O2
LiOH
CH2N2
H2, 10 %Pd/C
HCO2H
1). (Boc)2O, iPr2NEt
2). LiOH

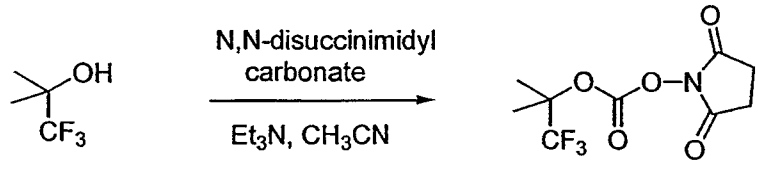
SCHEME 18



SCHEME 19



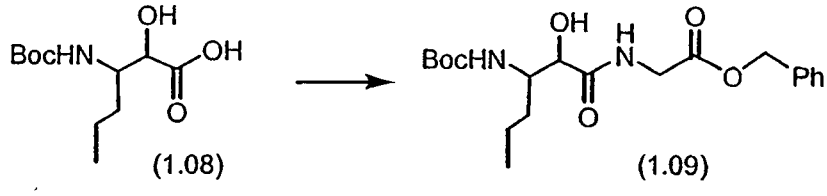
SCHEME 20



Preparation of Intermediates:

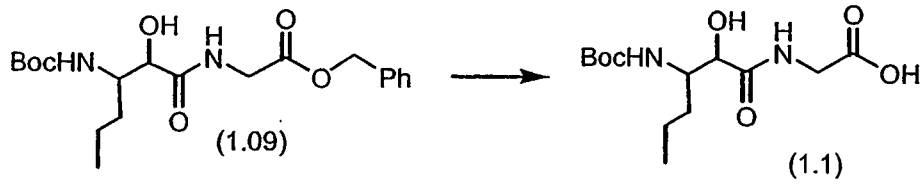
Preparative Example 1

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)

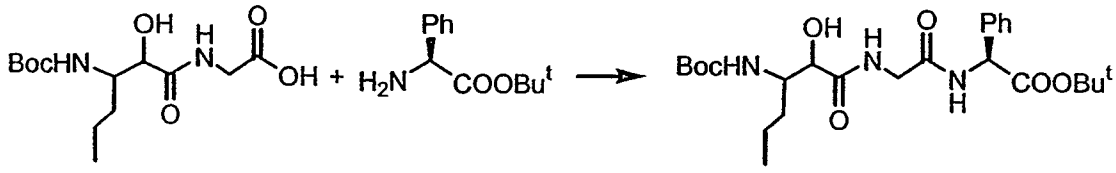


A solution of Compound (1.09) (7.00 g, 17.8 mmol) in absolute ethanol (300 mL) was stirred at room temperature under a hydrogen atmosphere in the presence of Pd-C (300 mg, 10%). The reaction progress was monitored by tlc. After 2 h, the mixture was filtered through a celite pad and the resulting solution

was concentrated in vacuo to give Compound (1.1) (5.40 g, quantitative). LRMS *m/z* MH^+= 305.1.

Preparative Example 2

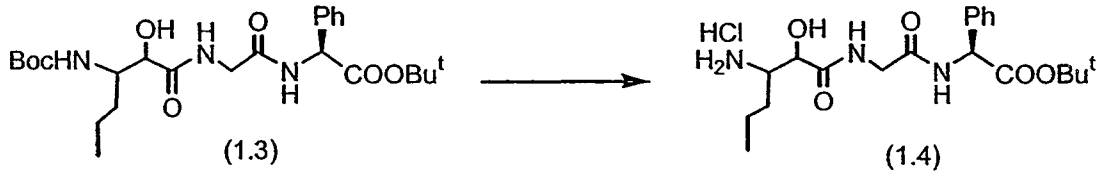
Step A Compound (1.3)



(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)

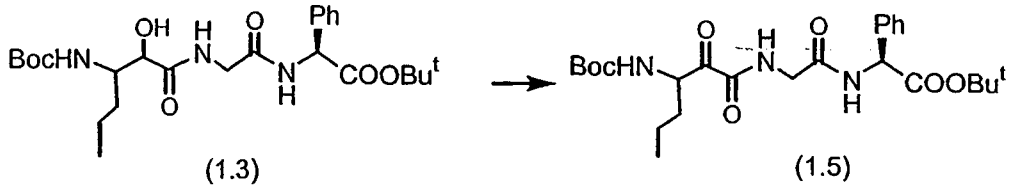


(1.3) (1.4)

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)

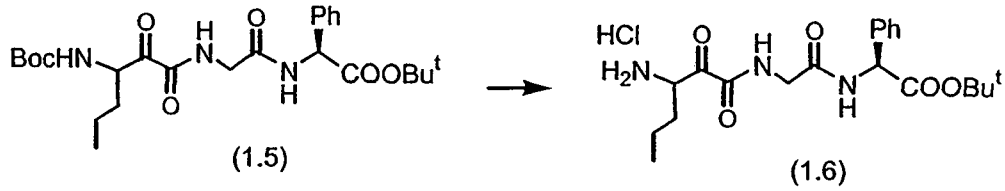


(1.3) (1.5)

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)

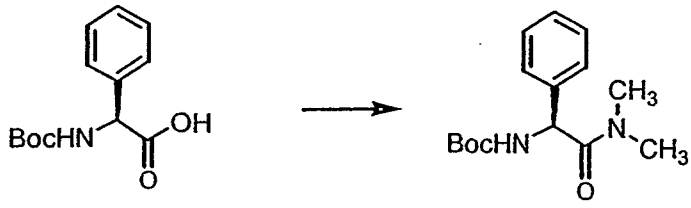


(1.5) (1.6)

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

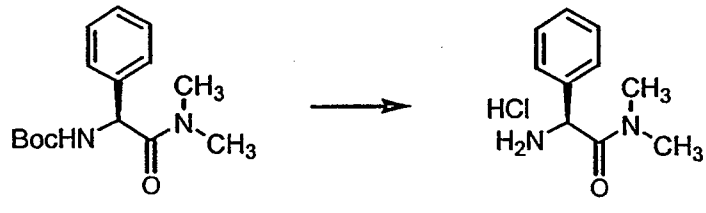
Step A Compound (2.09)



(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)

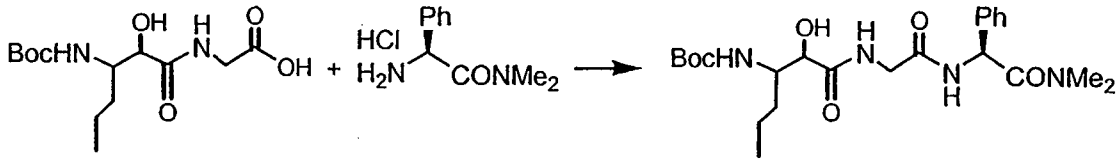


(2.09) (2.1)

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

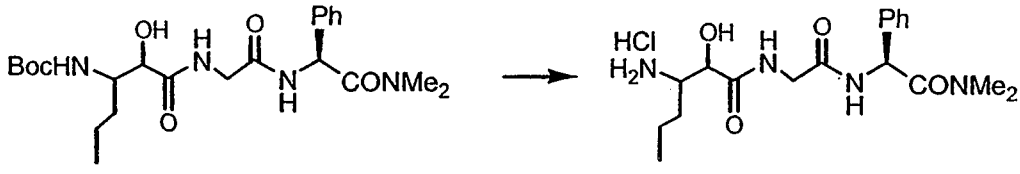
Step A Compound (2.2)



(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)

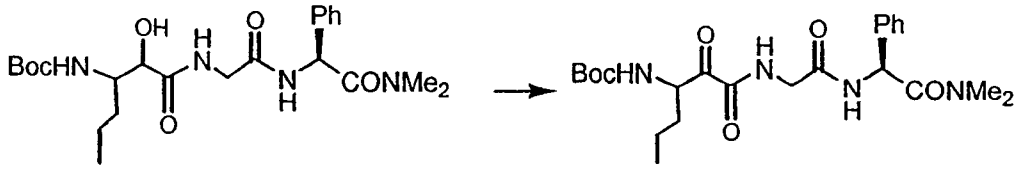


(2.2) (2.3)

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

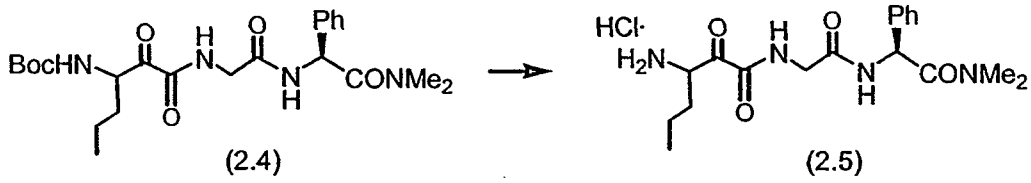
Step A Compound (2.4)



(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)

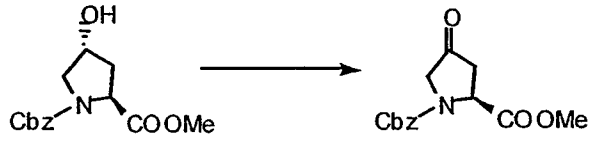


(2.4) (2.5)

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

Preparative Example 8

Step A Compound (3.1)

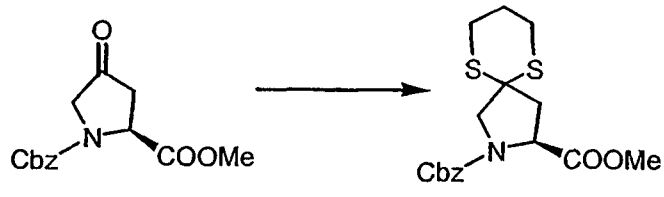


(3.01) (3.1)

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).

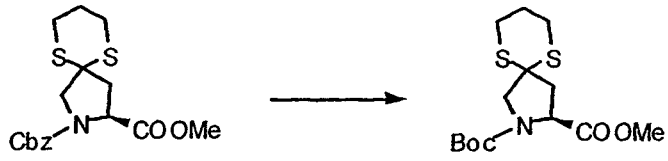


(3.1) (3.2)

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.

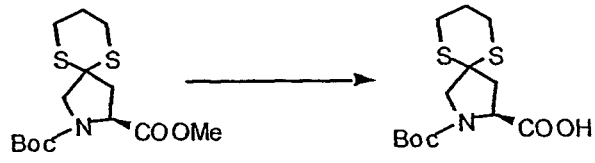
Step C Compound (3.3)



(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.

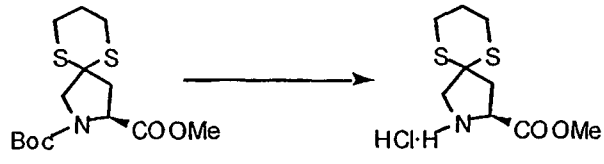
Step D Compound (3.4)



(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).

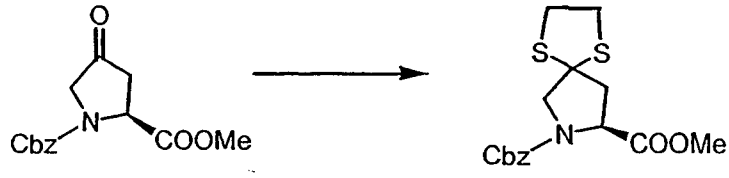


(3.3) (3.5)

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

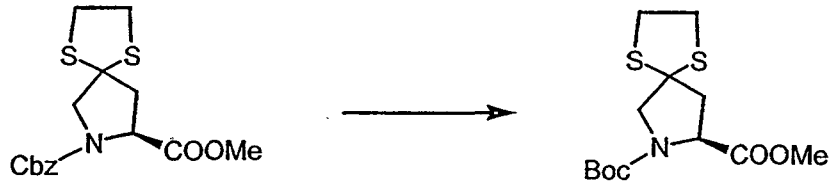
Step A Compound (3.6)



(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.

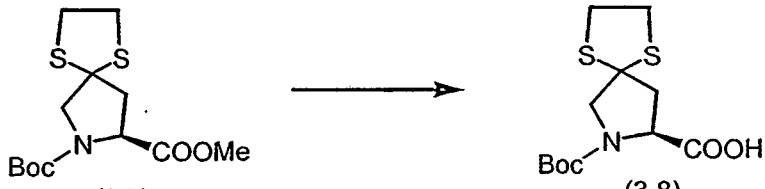
Step B Compound (3.7).



(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.

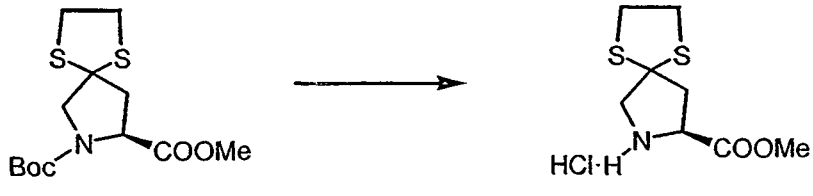
Step C Compound (3.8)



(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)

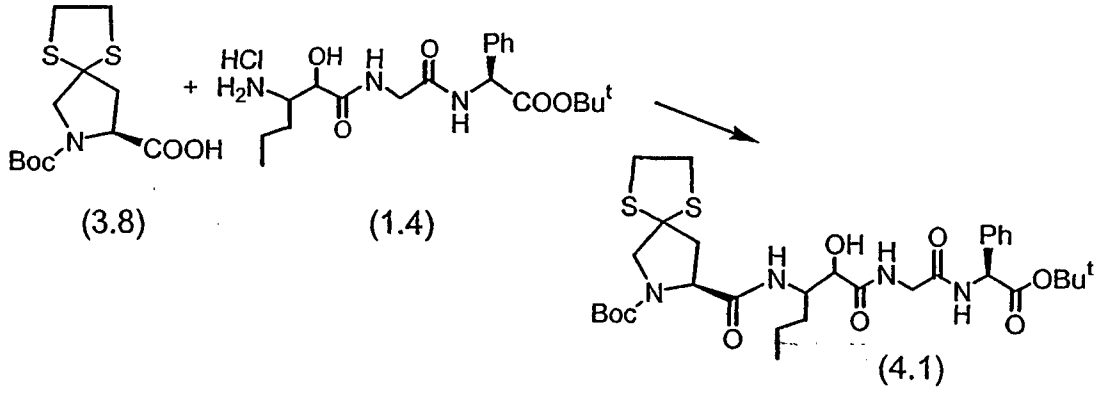


(3.7) (3.9)

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

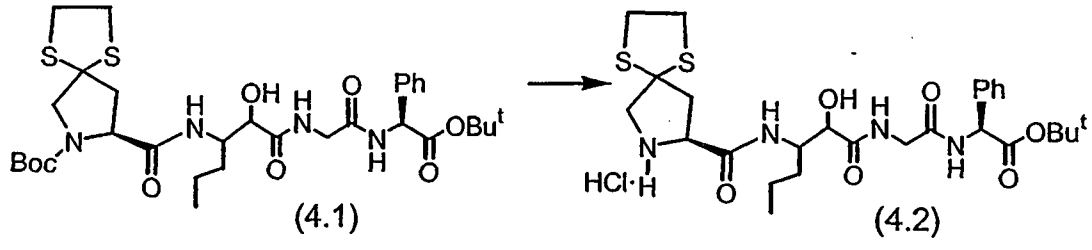
Step A Compound (4.1)



(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).

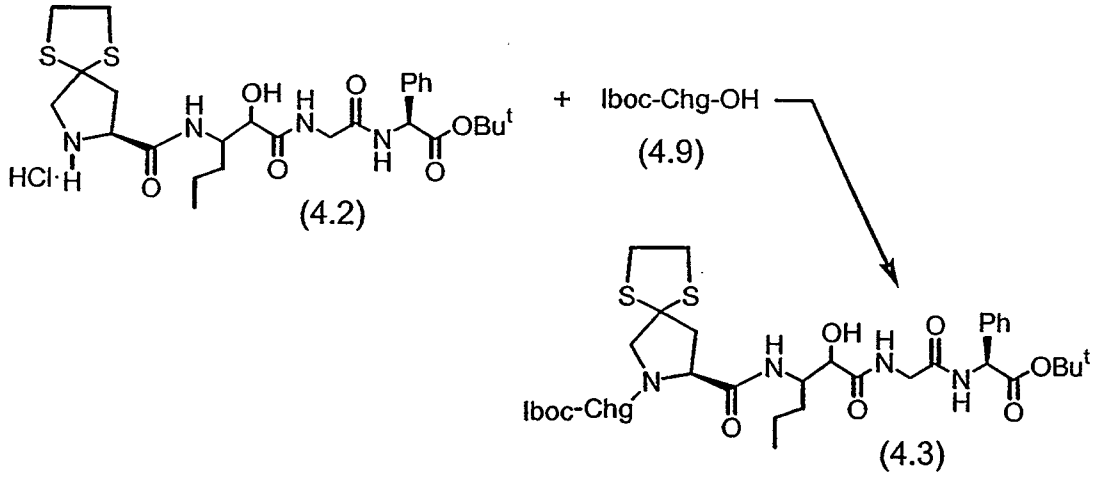
Step B Compound (4.2)



(4.1) (4.2)

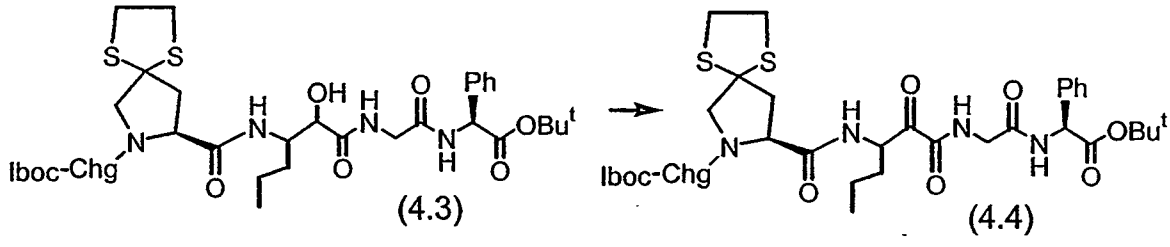
In essentially the same manner as Preparative Example 2, Step B, Compound (4.2) was prepared mass spec. (FAB) M+1 = 609.3.

Step C Compound (4.3)



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.

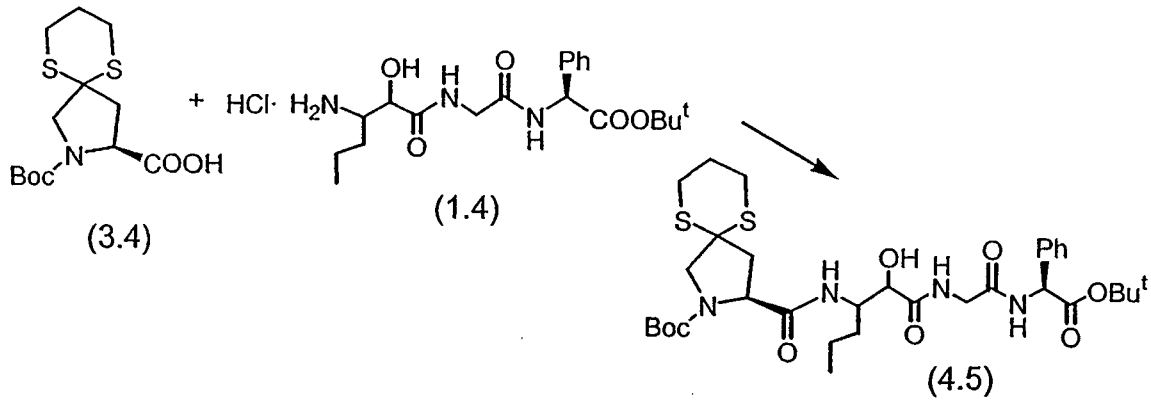
Step D Compound (4.4)



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

Preparative Example 11

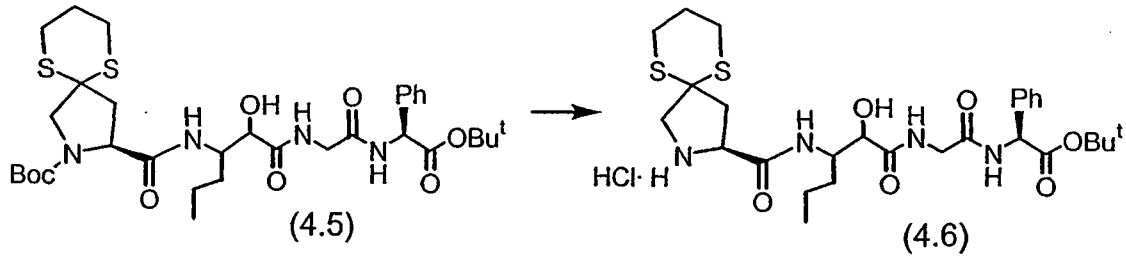
Step A Compound (4.5)



(3.4) (1.4) (4.5)

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

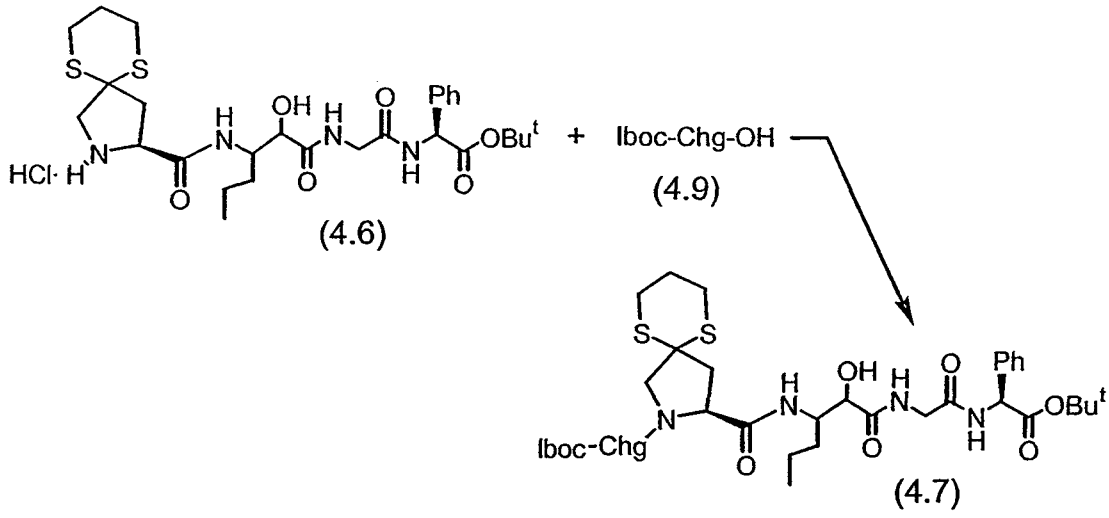
Step B, Compound (4.6)



(4.5) (4.6)

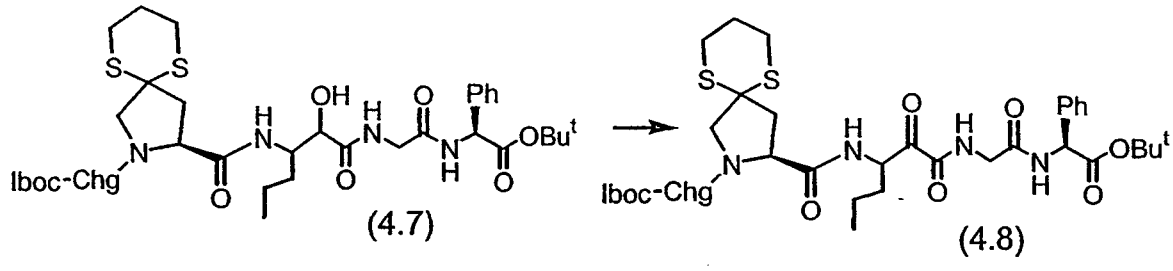
In essentially the same manner as Preparative Example 2, Step B, Compound (4.6) was prepared.

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).

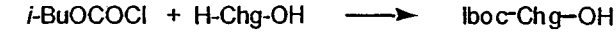
Step D, Compound (4.8)



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

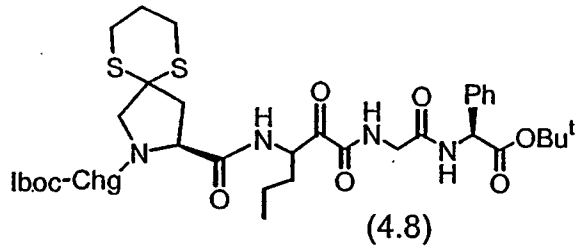
Compound (13.1)

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

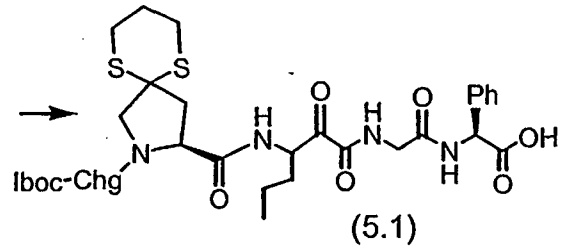
(4.01) (13.02) (13.1)

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



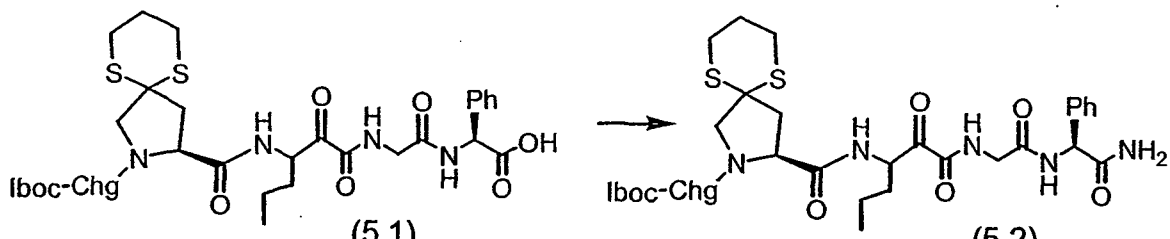
(4.8)



(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.

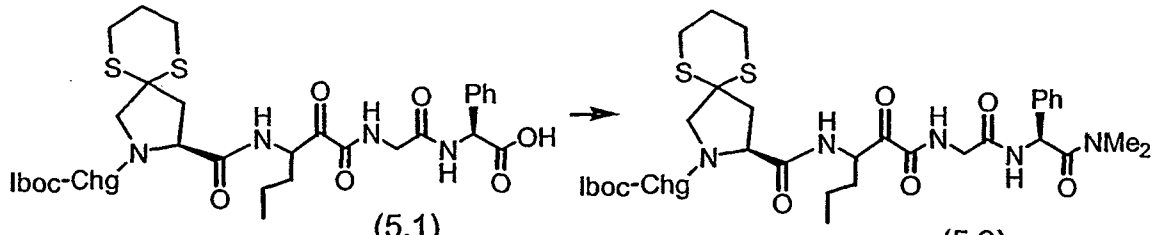
Step B Compound (5.2)



(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

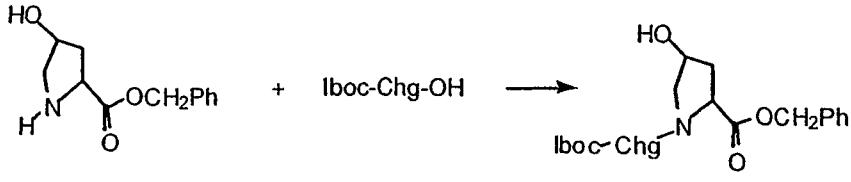


(5.1) (5.3)

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

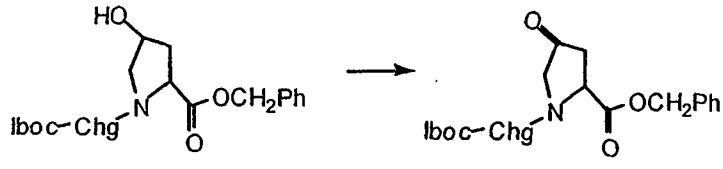
Step A Compound (6.2)



(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.

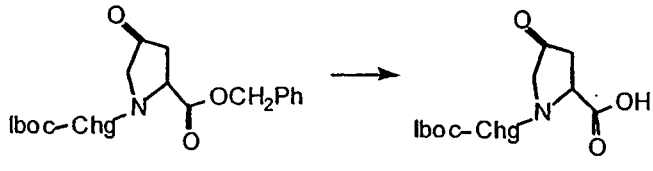
Step B Compound (6.3)



(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)



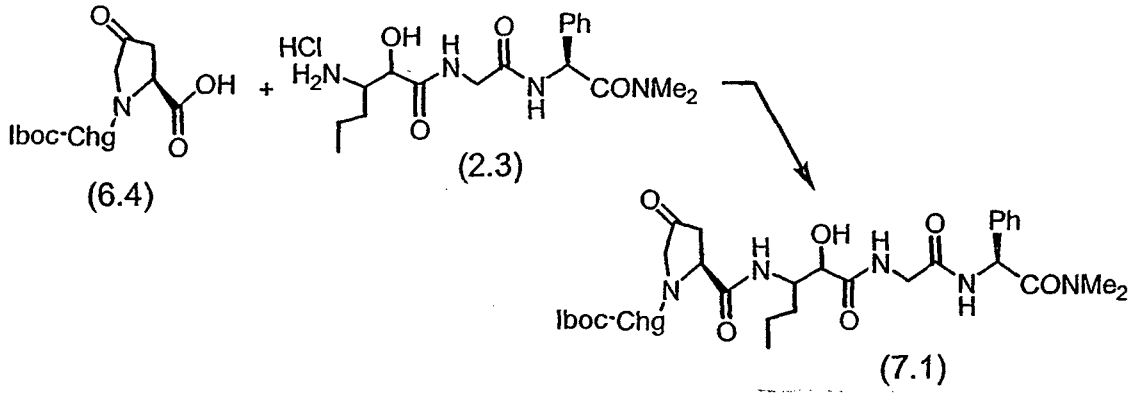
(6.3) (6.4)

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.

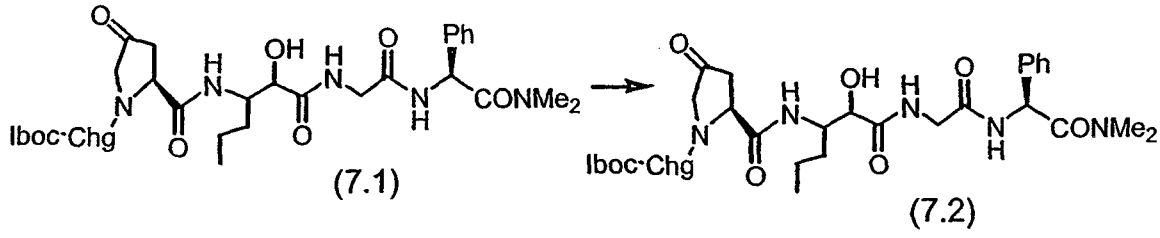
Preparative Example 17

Step A Compound (7.1)



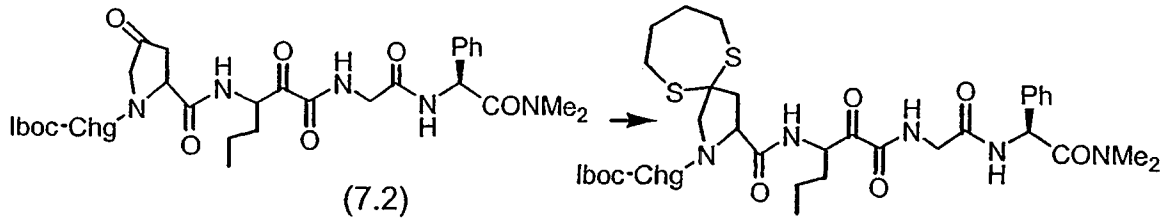
Compound (6.4) from Preparative Example 16, Step C, was reacted with Compound (2.3) from Preparative Example 6, Step B, in essentially the same manner as Preparative Example 2, Step A, to afford Compound (7.1), $C_{36}H_{54}N_6O_9$ (714.85), mass spec. (FAB) M+1 = 715.9.

Step B Compound (7.2)



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 procedures, the compounds in the attached **Table 2** were prepared. As a general note to all the Tables 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.

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

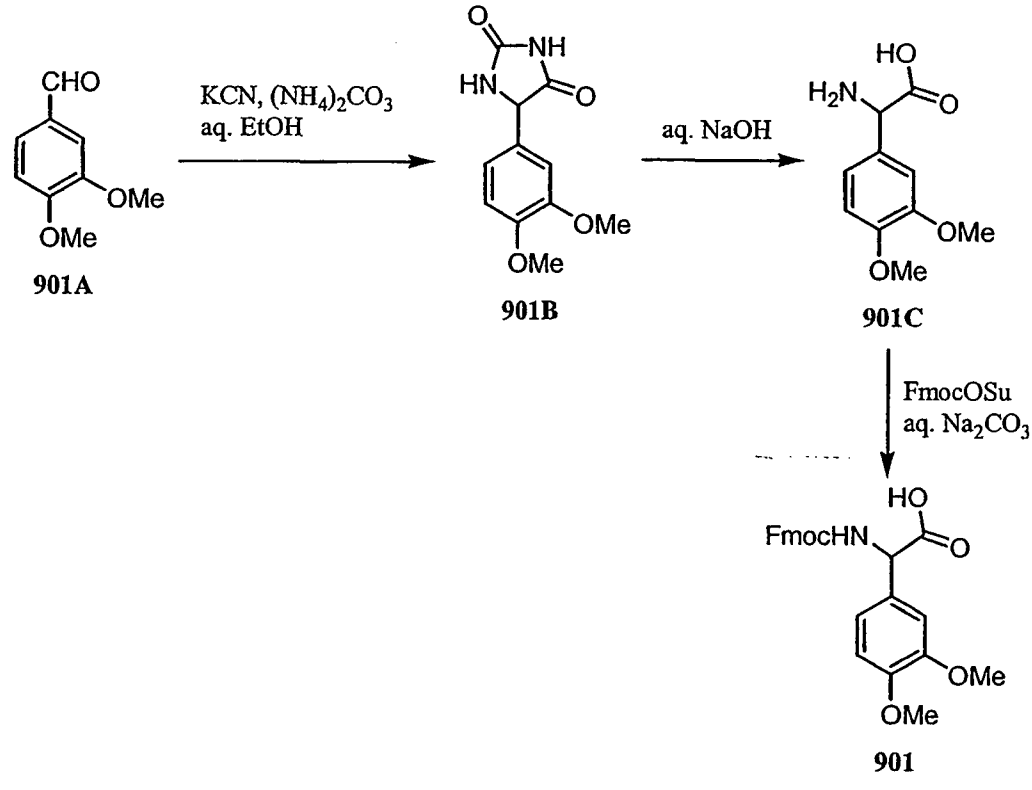
times). The coupling cycle was repeated with the next Fmoc-amino acid or capping group.

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)

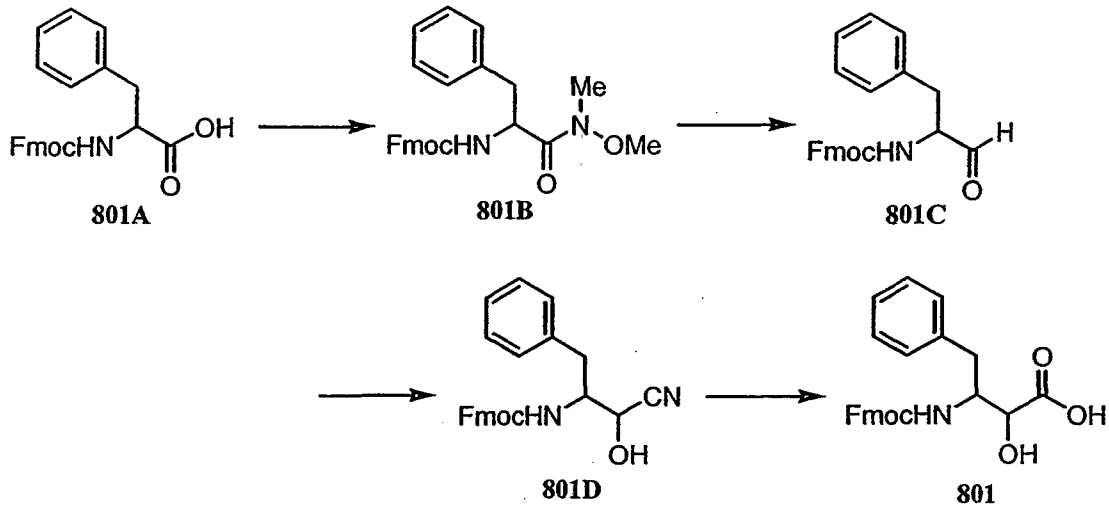


To a solution of potassium cyanide (1.465 g, 22.5 mmol) and ammonium carbonate (5.045 g, 52.5 mmol) in water (15 mL) was added a solution of 2,3-dimethoxybenzaldehye **901A** (2.5 g, 15 mmol) in ethanol (15 mL). The reaction mixture was heated at 40 °C for 24 h. The volume of the solution was reduced 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

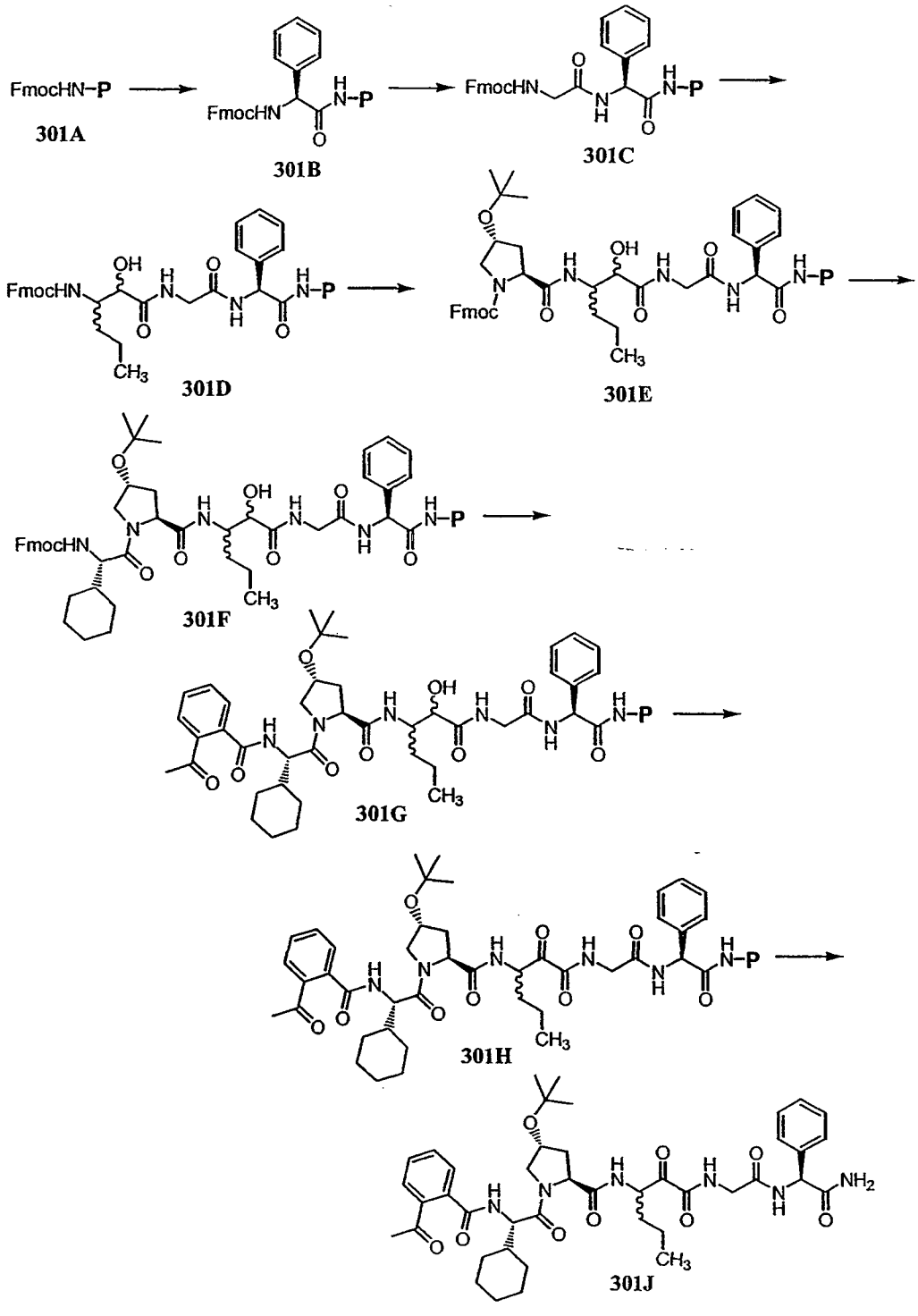
room temperature overnight. Toluene was added and the organic layer was washed with dilute hydrochloric acid, aqueous sodium bicarbonate solution and brine. The organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to afforded compound **801B** (4 g,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

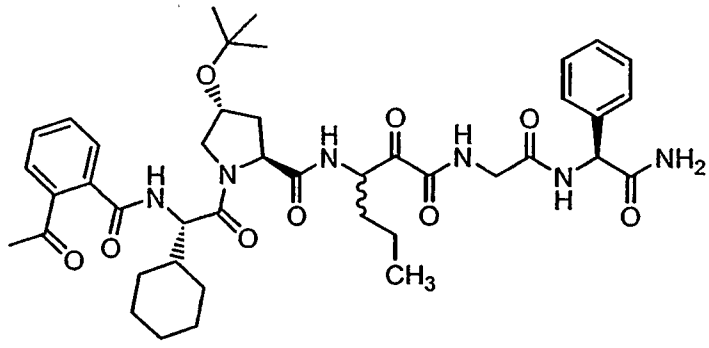
To a solution of compound **801D** (2.4 g, 6.03 mmol) in 1,4-dioxane (11 mL) was added concentrated hydrochloric acid (11 mL). The reaction mixture was heated at 80 °C for 3 h. Ethyl acetate (25 mL) and water (25 mL) was added. The organic layer was washed with brine and dried over anhydrous sodium sulfate. 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)

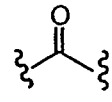


(301J)

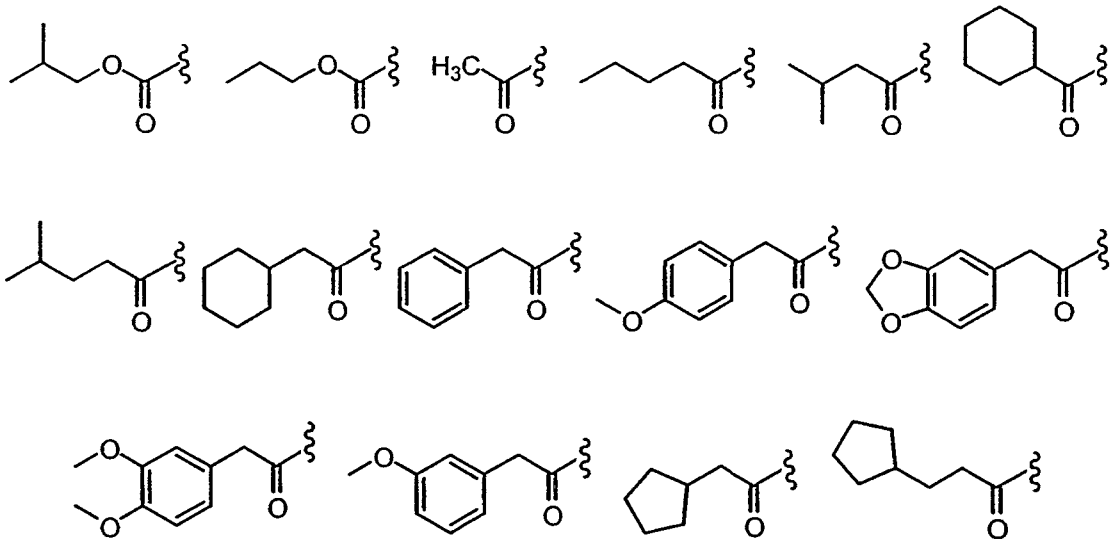
Resin-bound compound **301B**, **301C**, **301D**, **301E**, **301F** and **301G** were prepared according to the general procedure for solid-phase coupling reactions started with 100 mg of Fmoc-Sieber resin (0.03 mmol). Resin-bound compound **301G** was oxidized to resin-bound compound **301H** according 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^+.

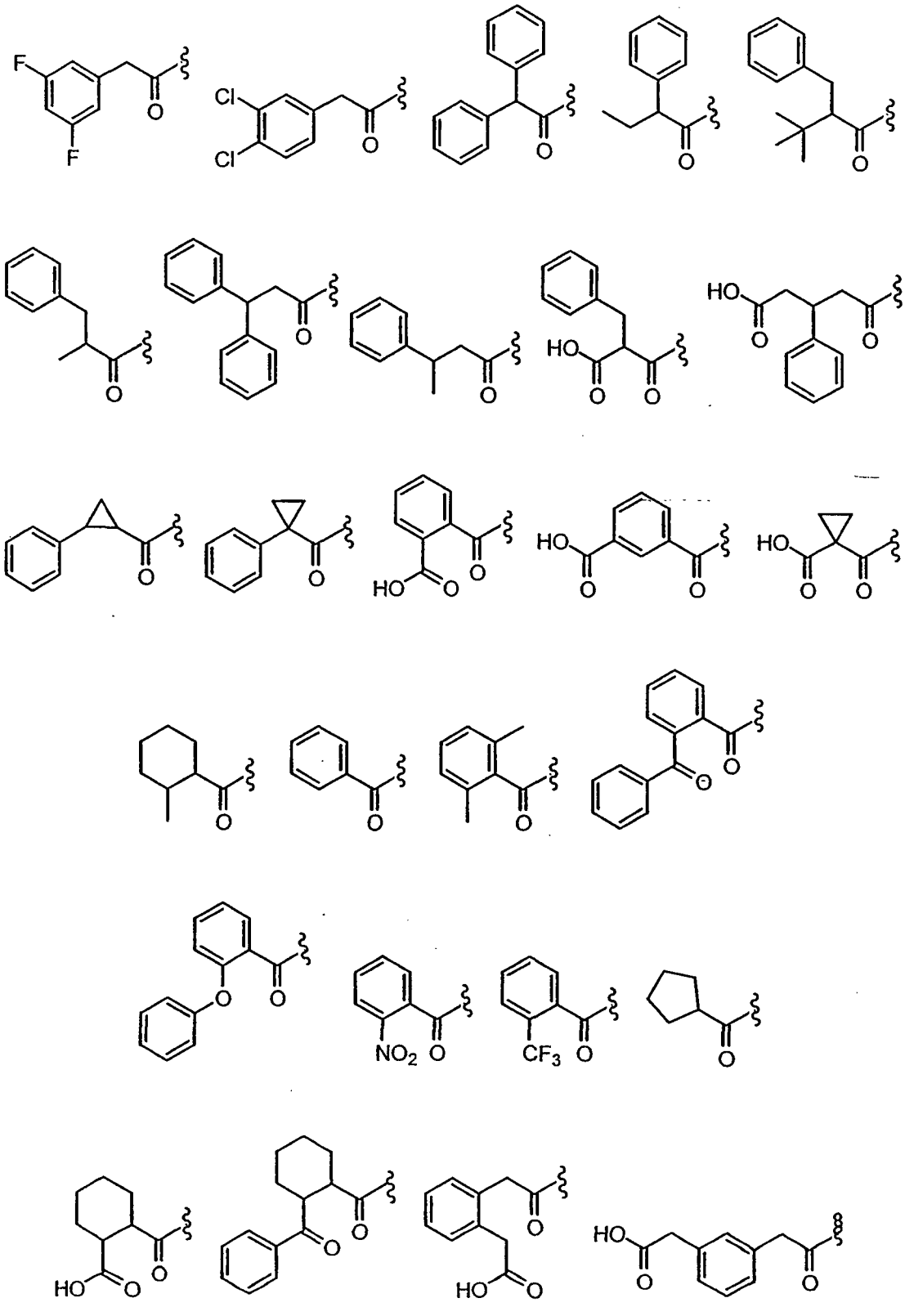
Using the solid phase synthesis techniques detailed above, and the following moieties for the various functionalities in the compound of Formula 1, the compounds in **Table 3** were prepared:

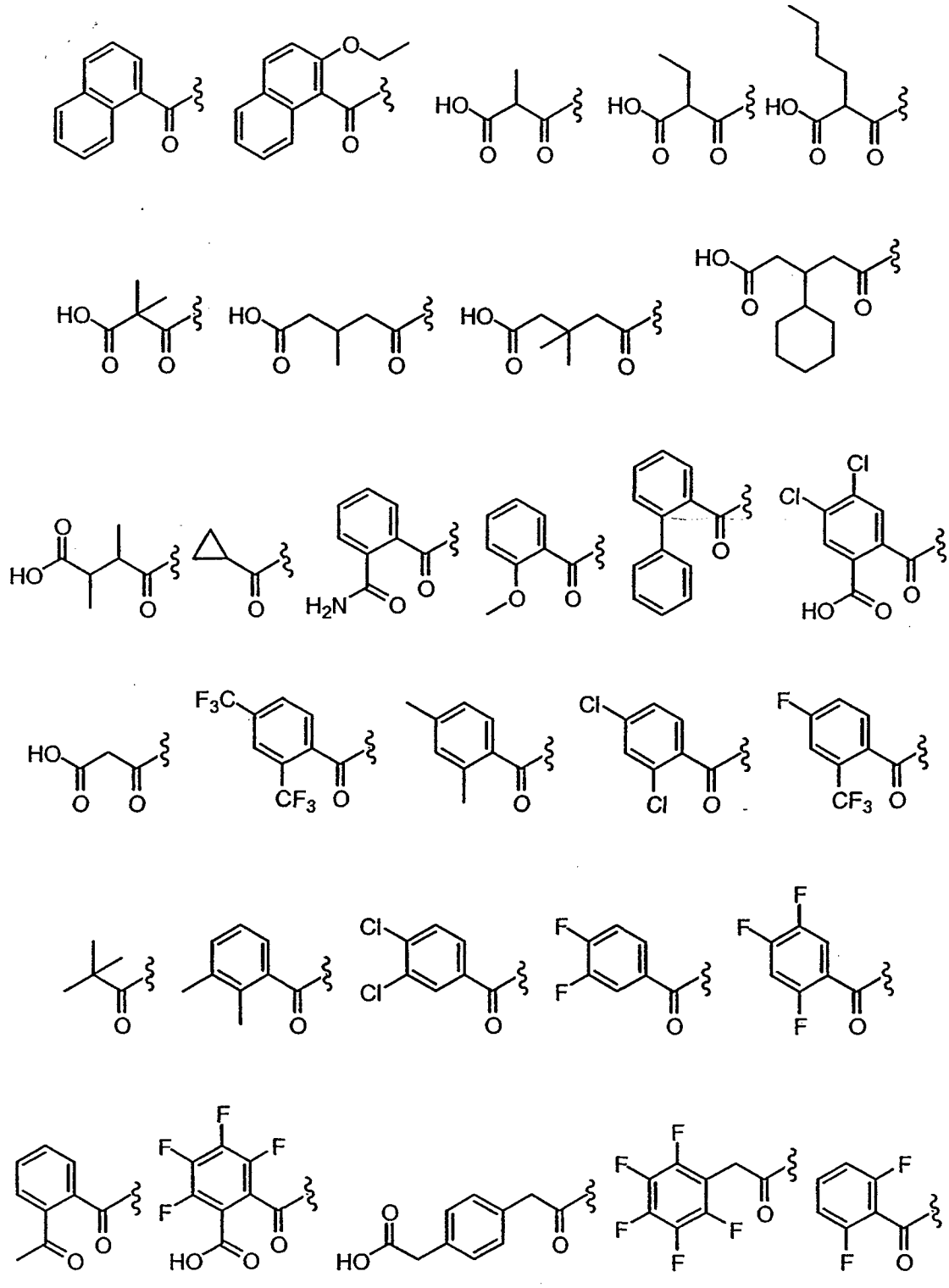
-W-:

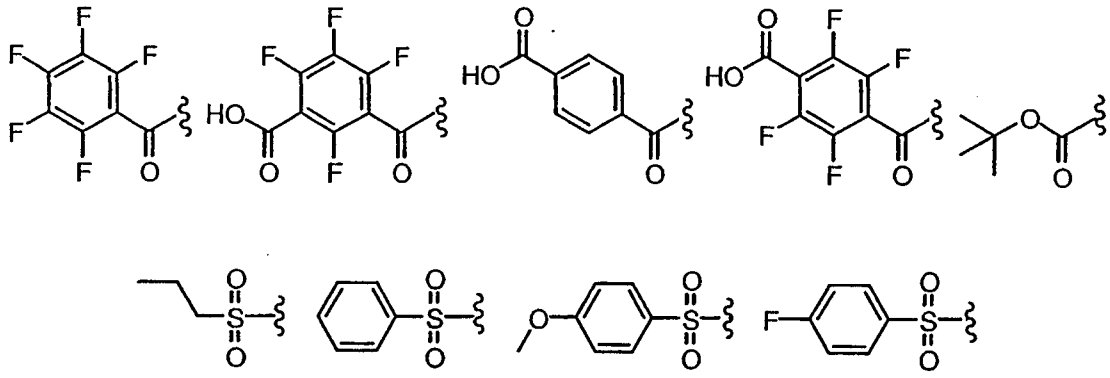


Y-W-:





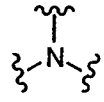




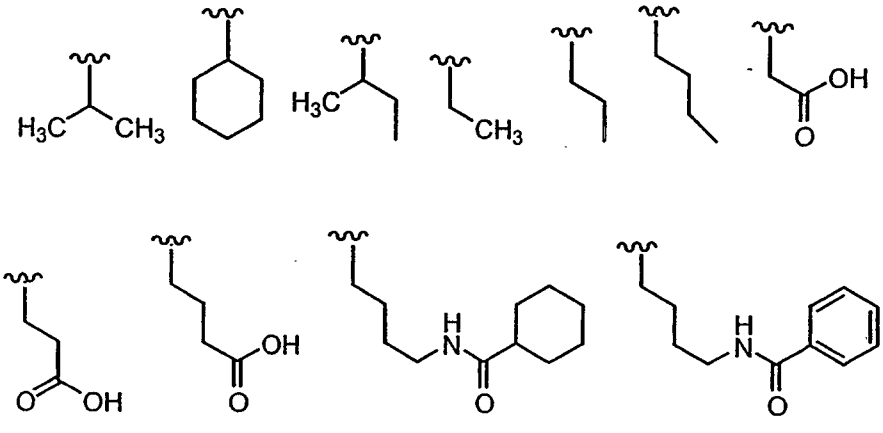
-R^4:

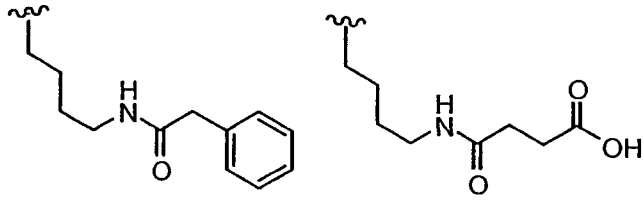


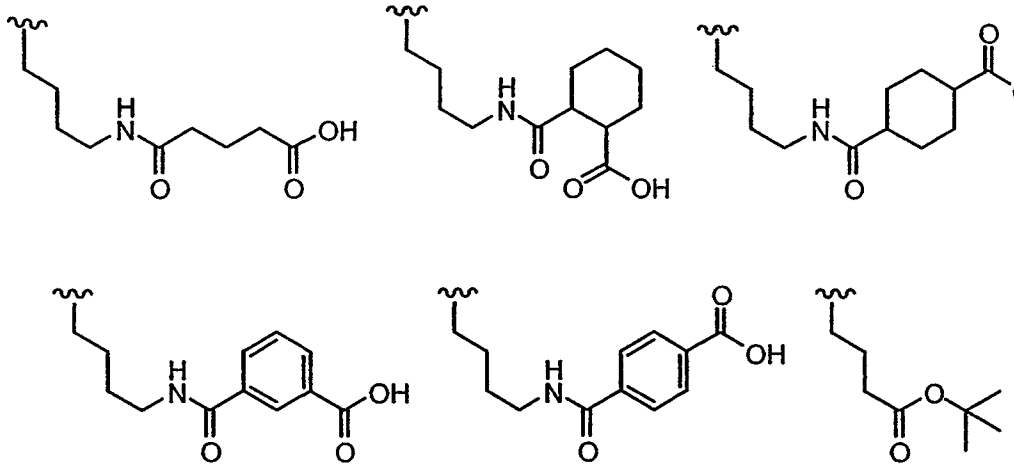
-Z-:

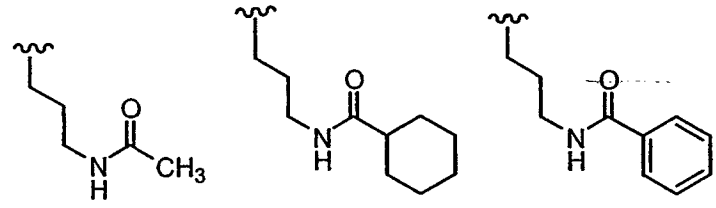


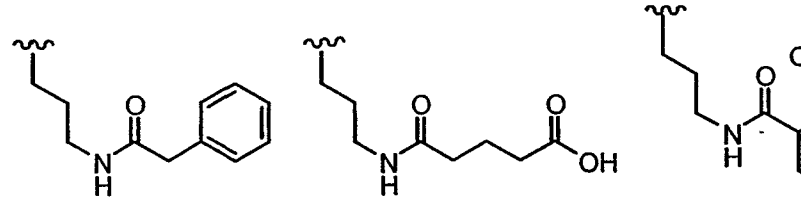
-R^3:

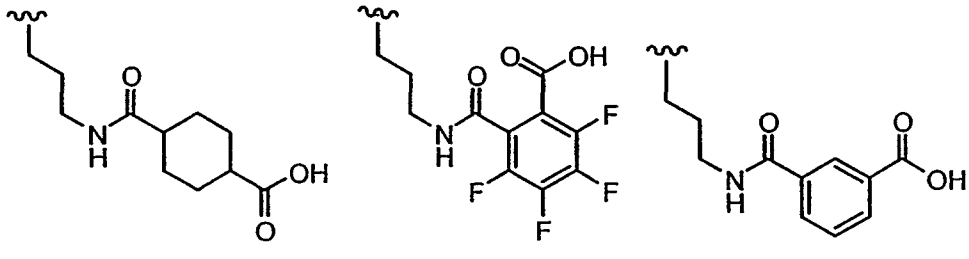


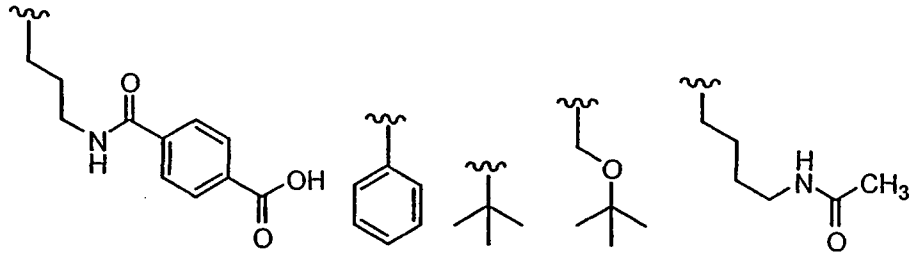




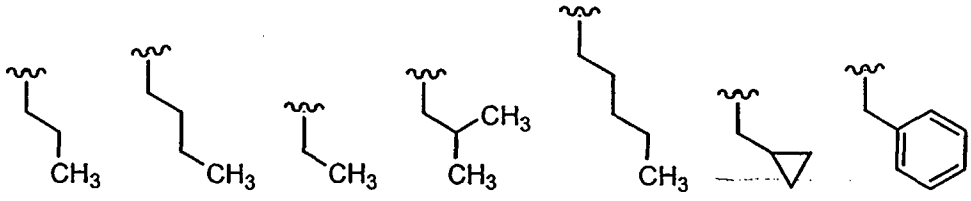




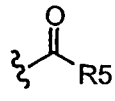




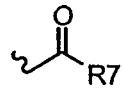
-R^2:



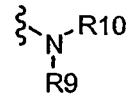
-R^1:



-R^5:



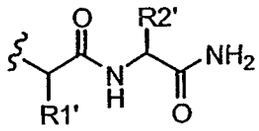
-R^7:



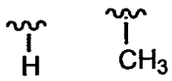
-R^9:



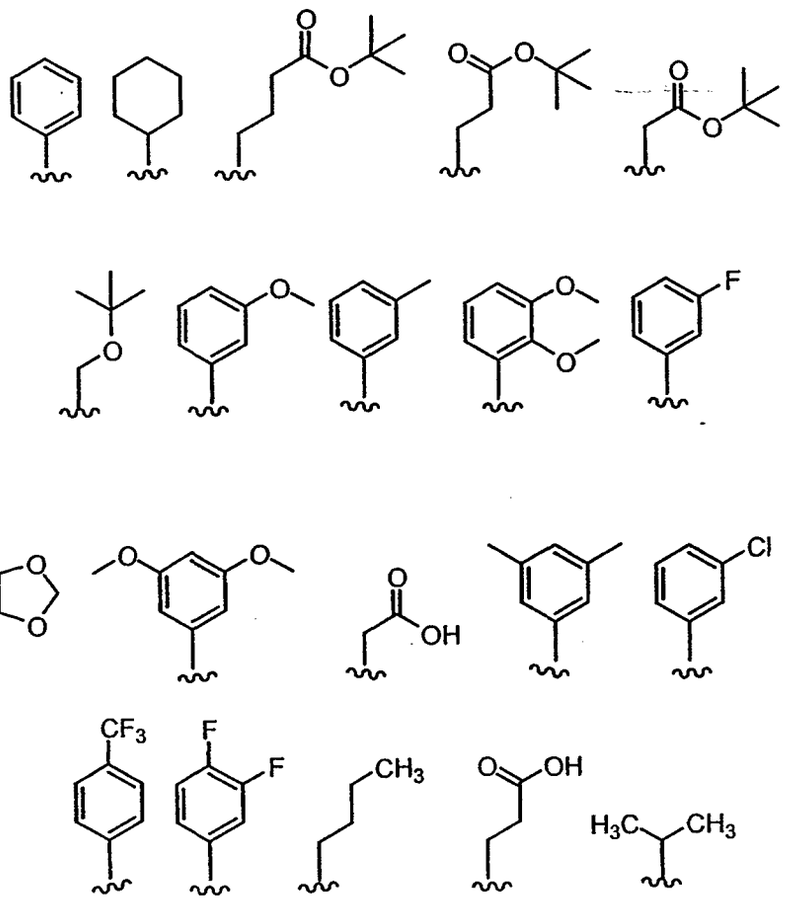
-R^{10}:



-$R^{1'}$:



-$R^{2'}$:



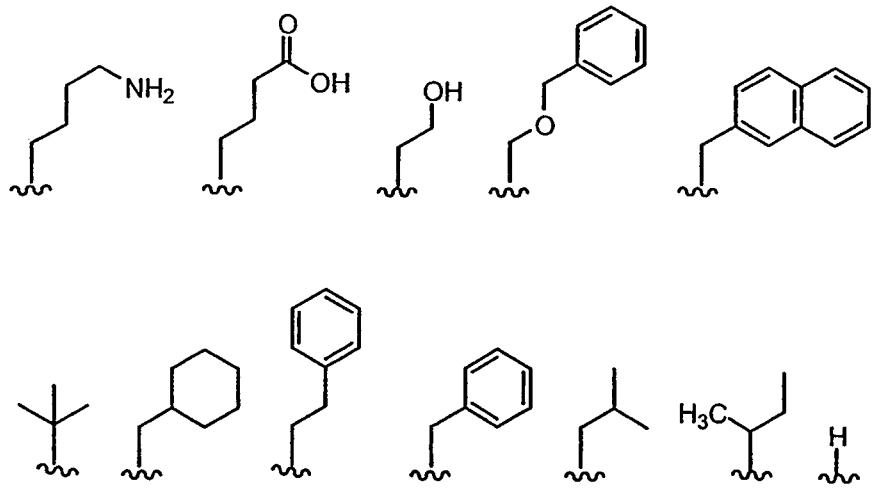
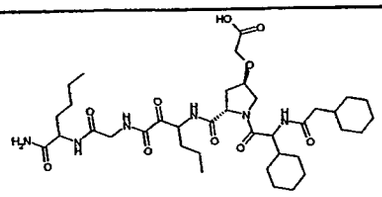
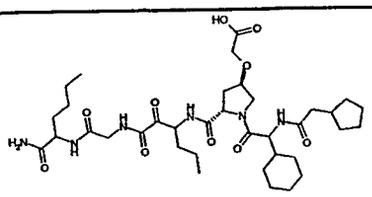
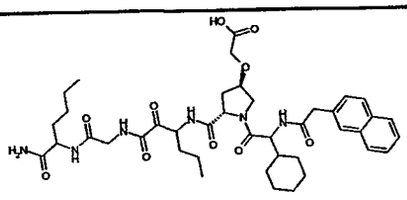
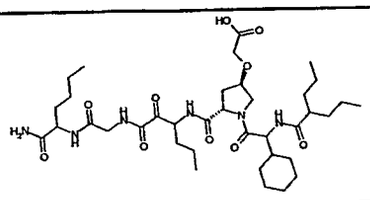
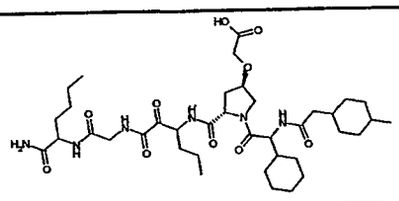
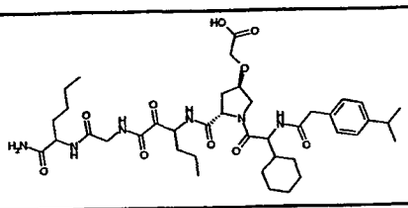
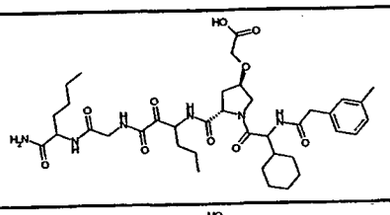
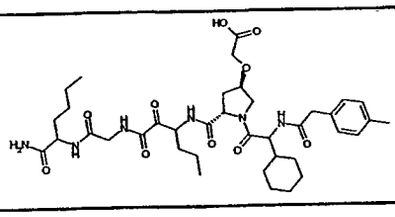
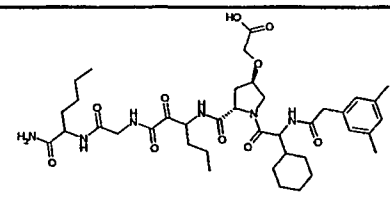
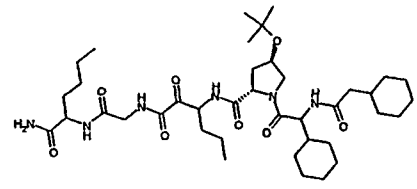
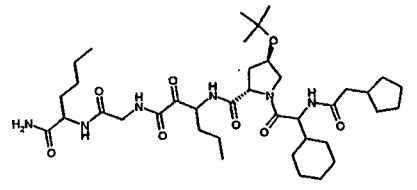
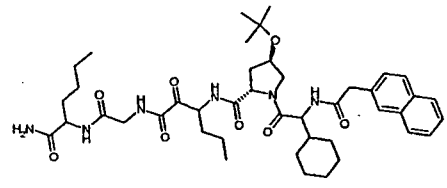
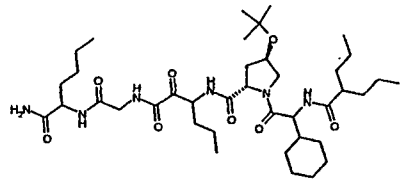
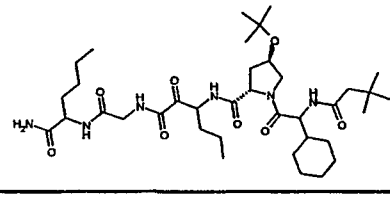
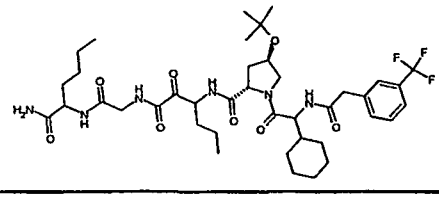
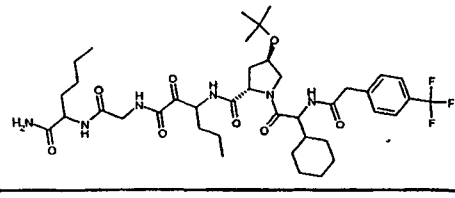
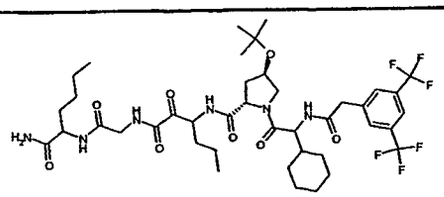
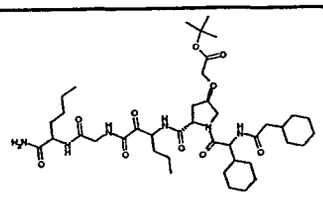
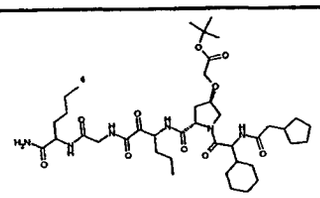
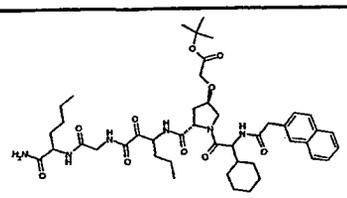
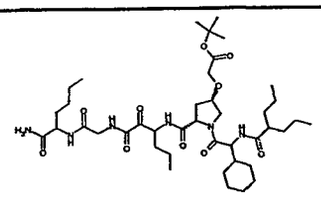
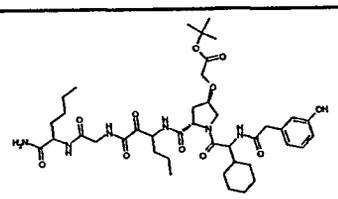
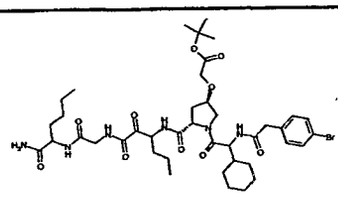
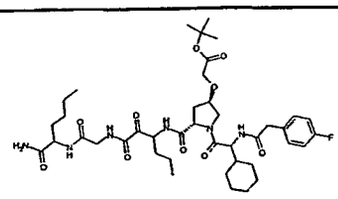
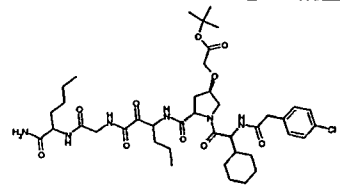
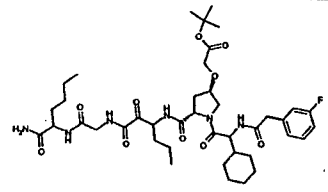
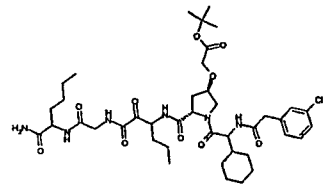
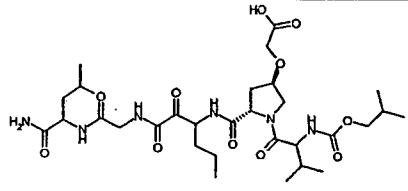
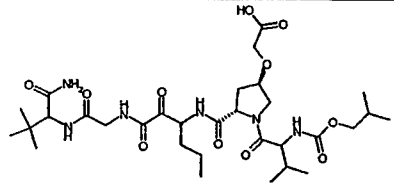
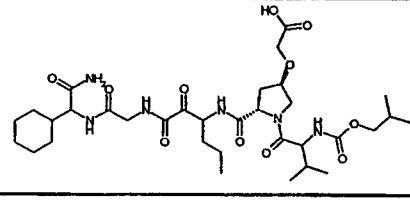
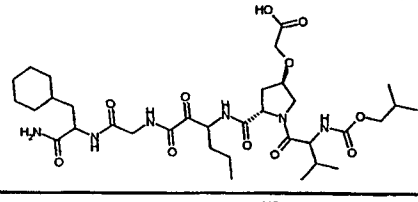
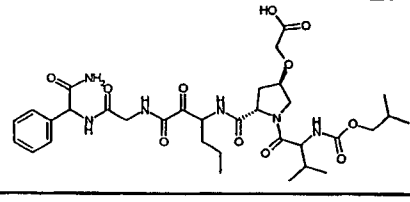


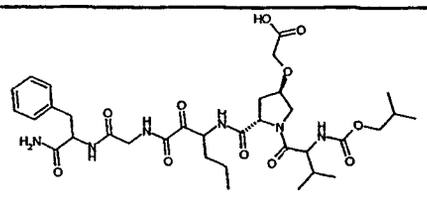
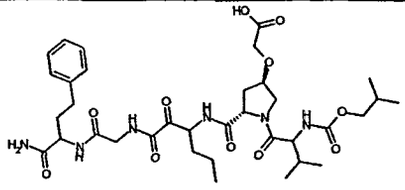
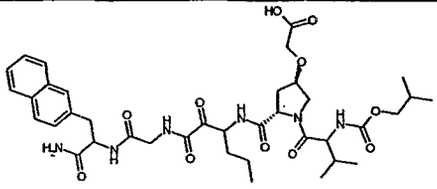
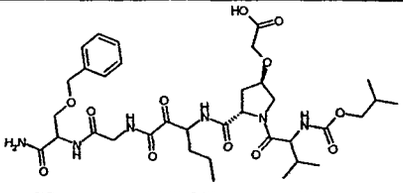
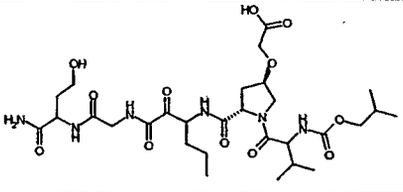
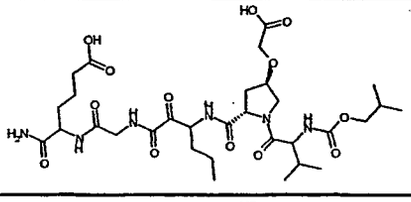
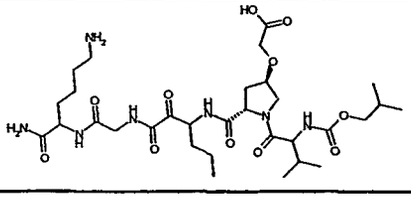
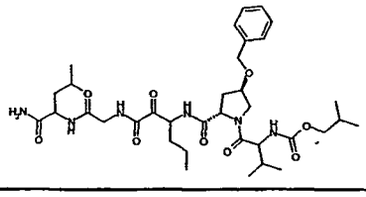
Table 3. Compounds prepared by Solid Phase Synthesis

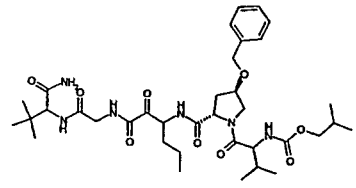
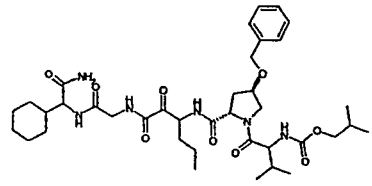
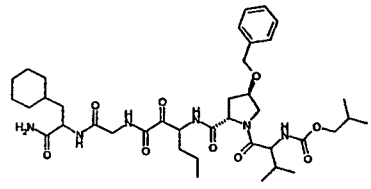
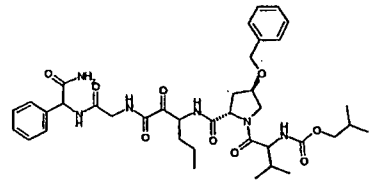
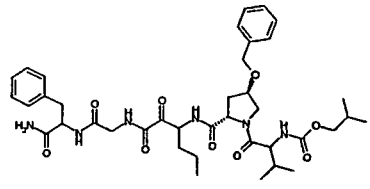
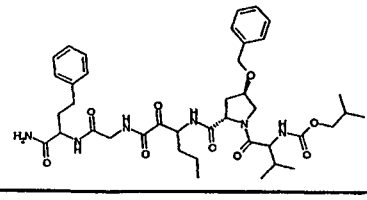
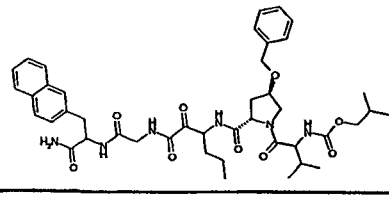
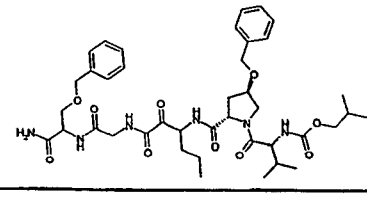
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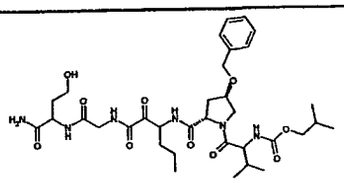
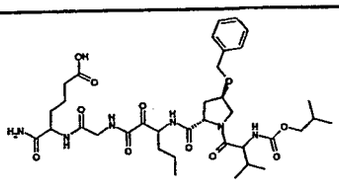
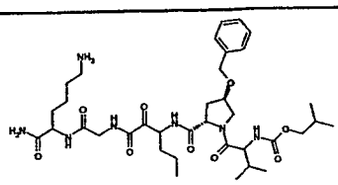
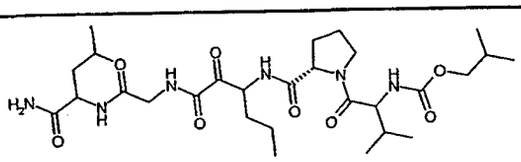
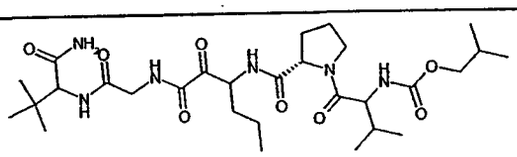
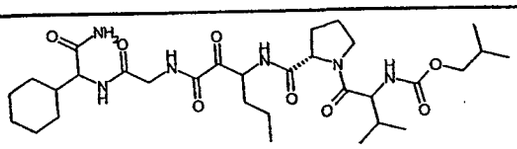
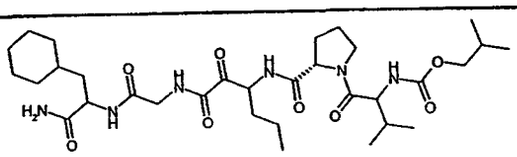
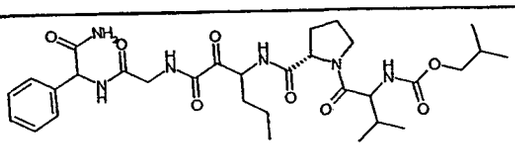
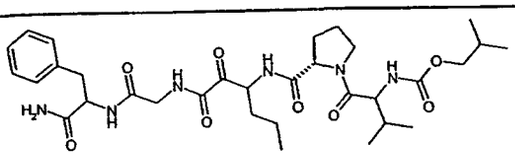
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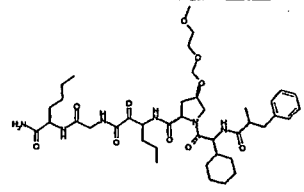
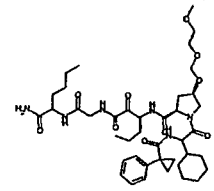
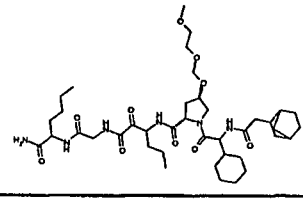
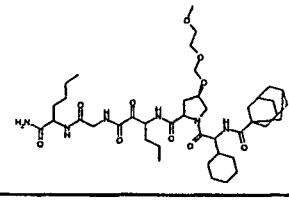
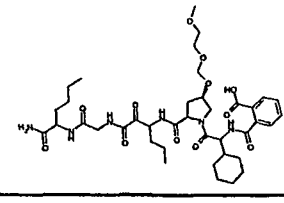
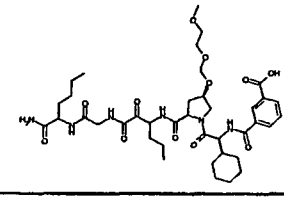
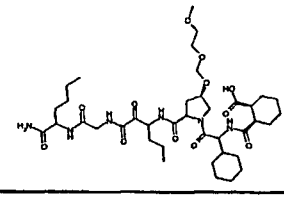
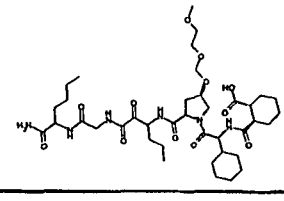
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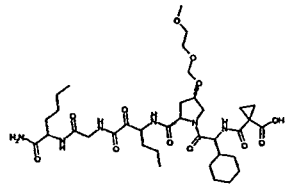
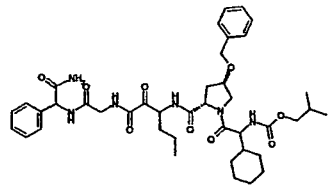
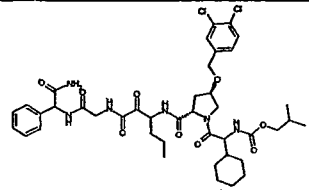
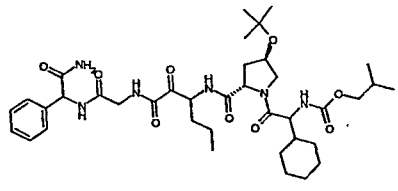
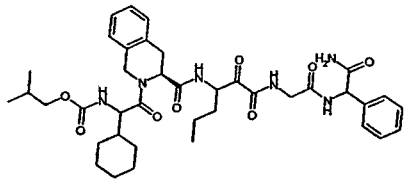
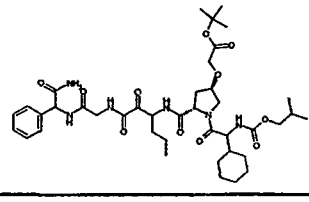
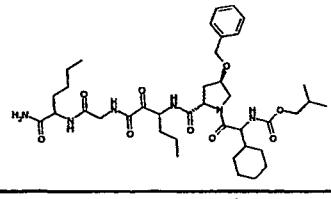
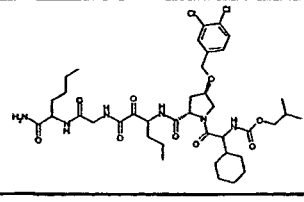
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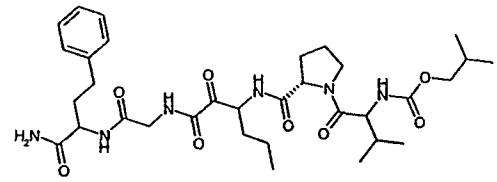
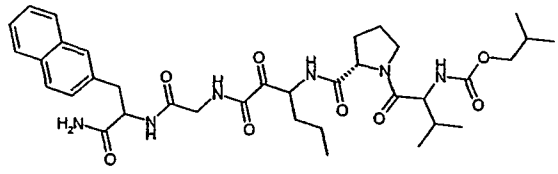
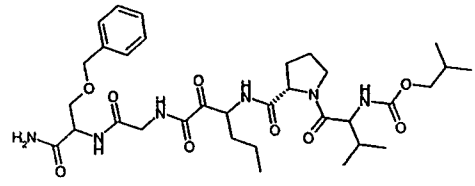
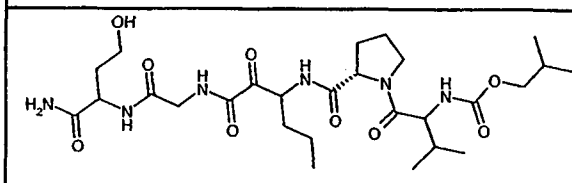
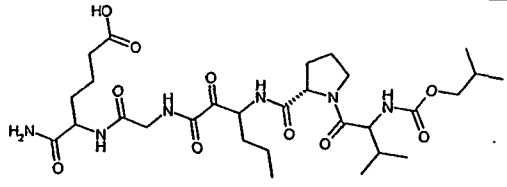
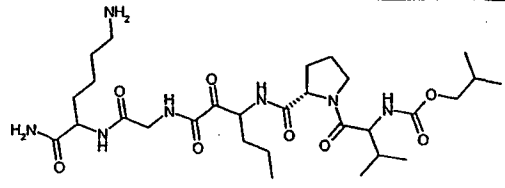
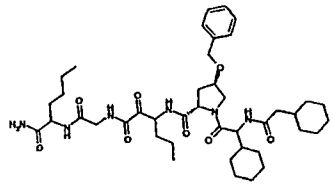
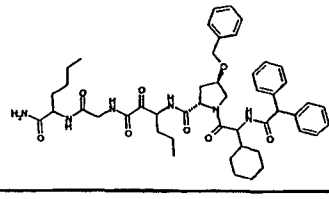
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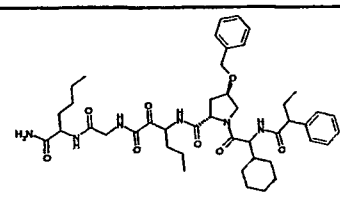
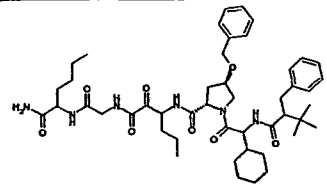
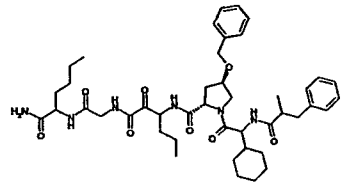
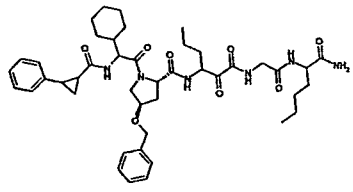
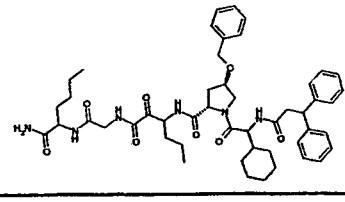
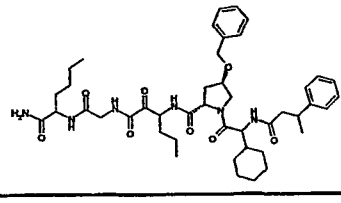
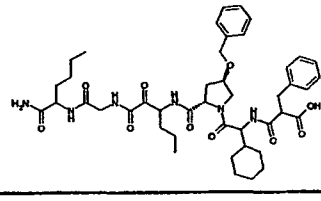
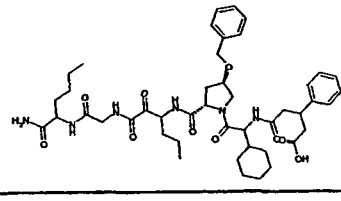
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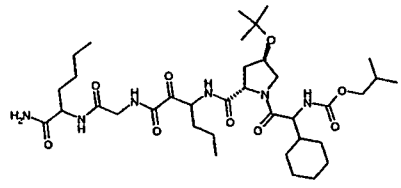
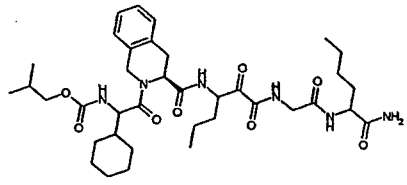
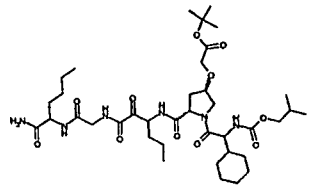
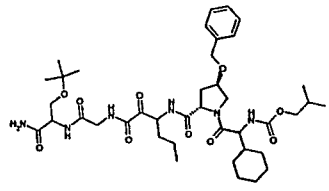
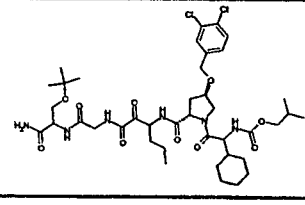
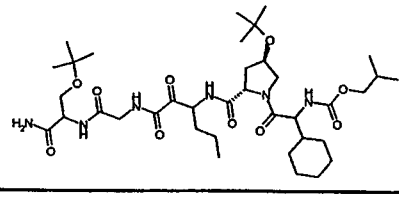
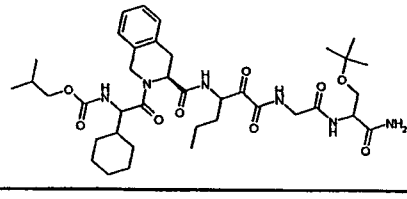
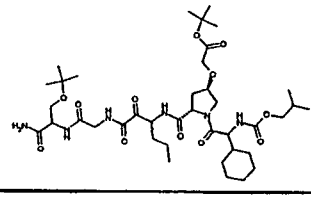
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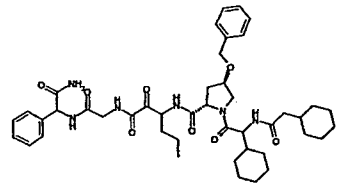
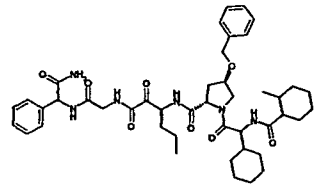
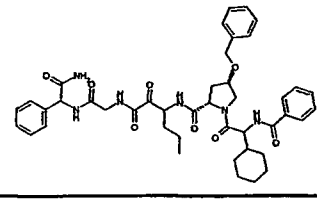
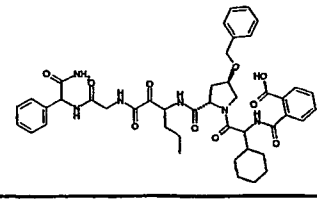
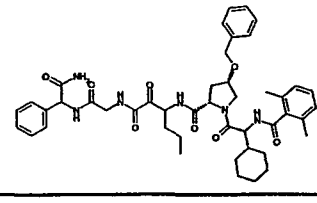
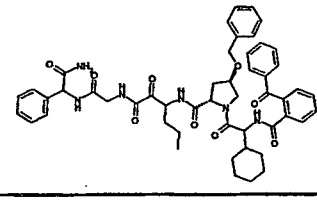
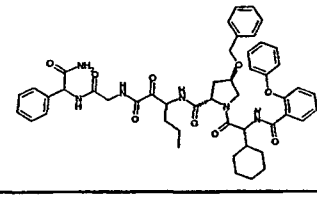
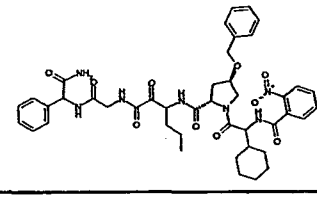
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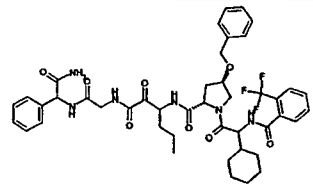
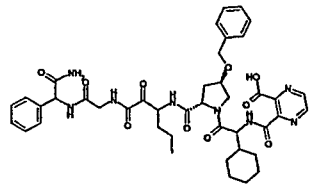
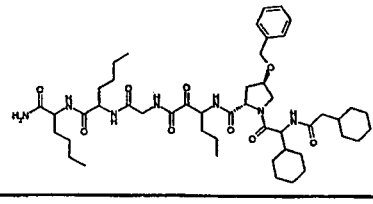
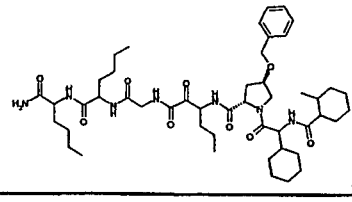
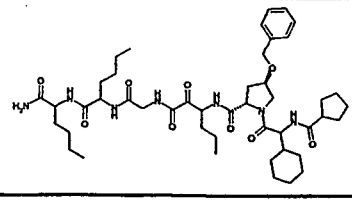
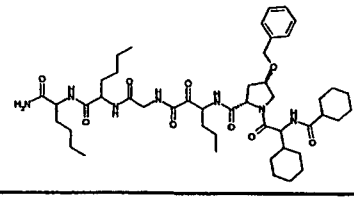
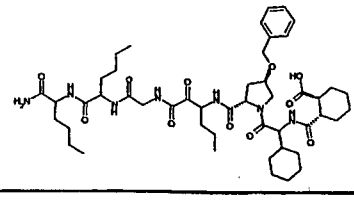
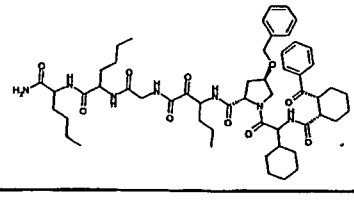
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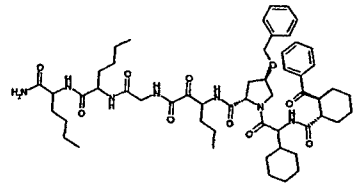
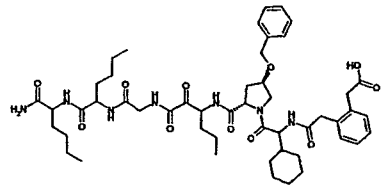
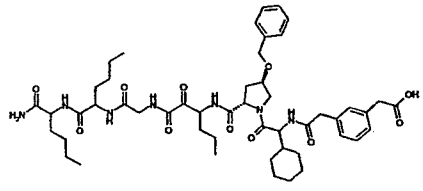
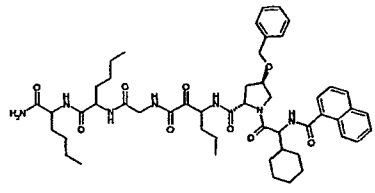
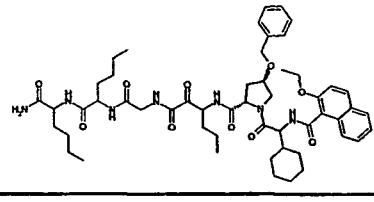
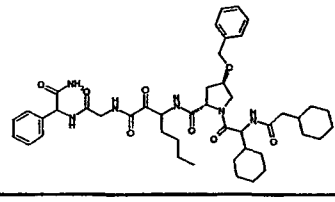
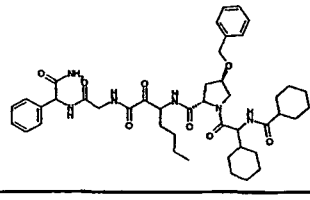
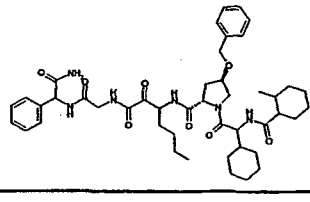
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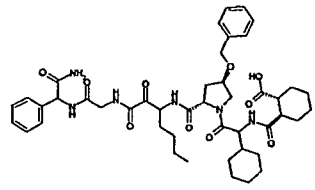
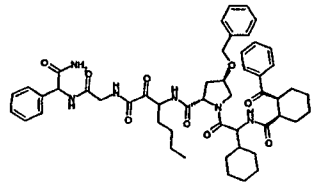
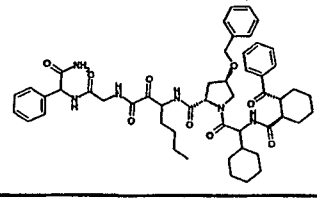
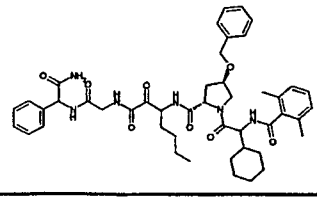
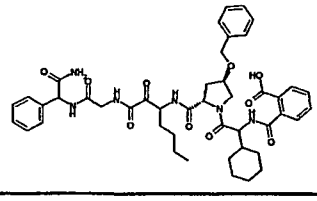
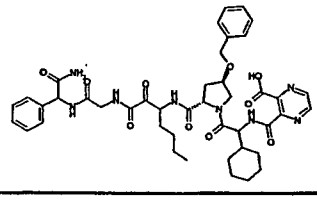
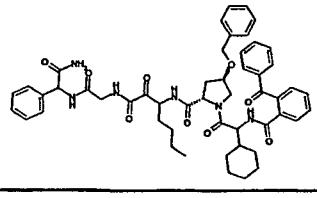
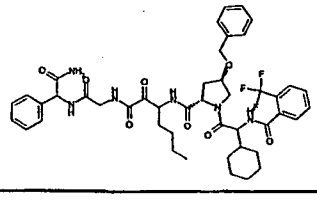
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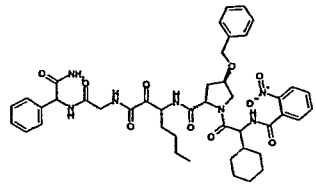
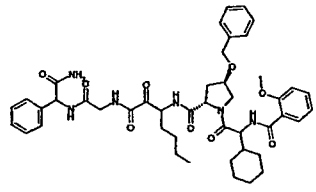
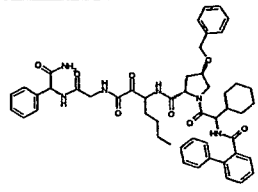
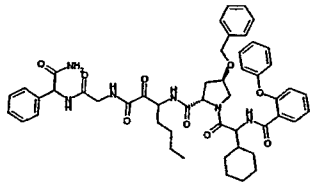
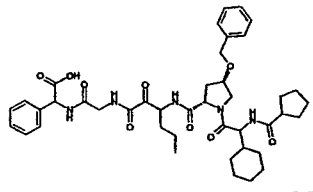
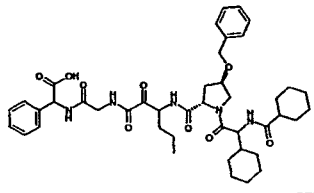
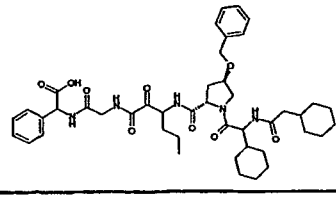
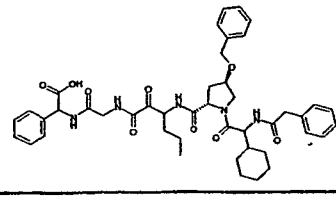
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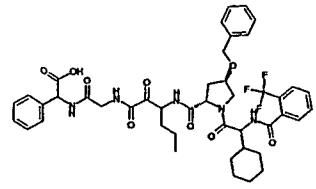
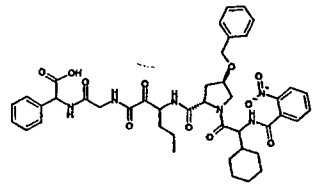
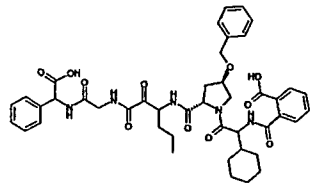
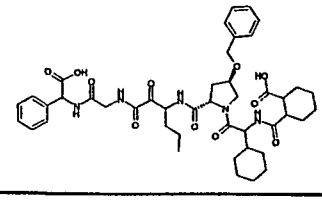
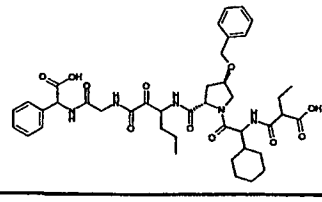
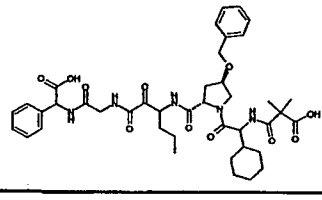
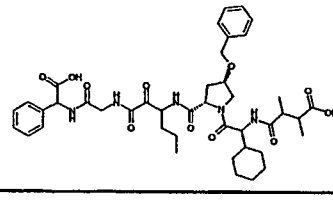
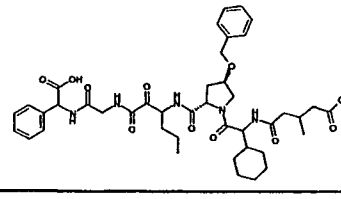
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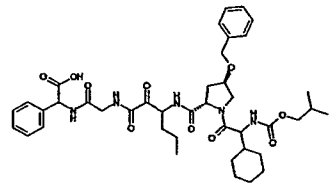
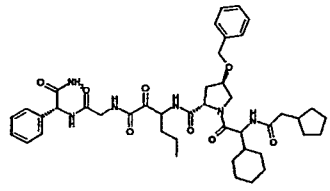
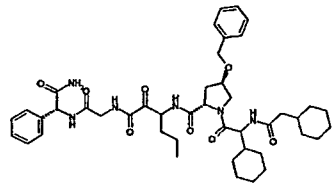
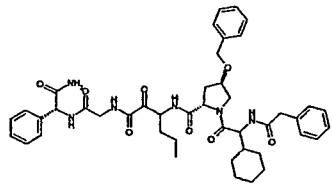
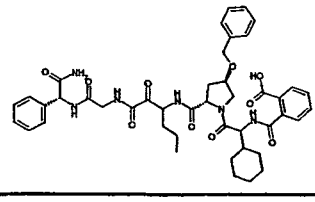
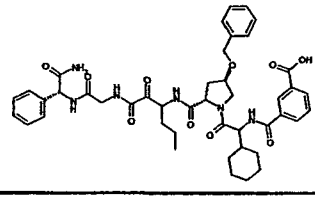
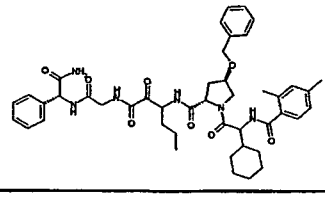
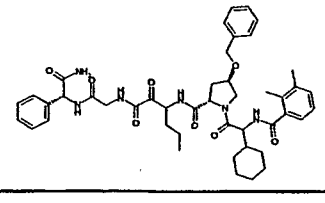
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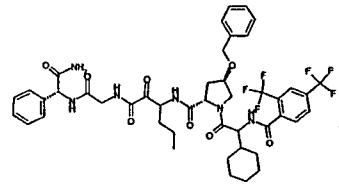
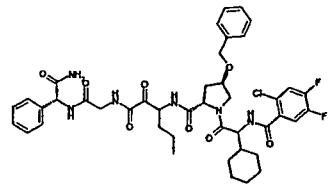
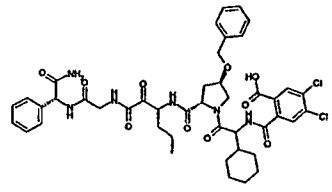
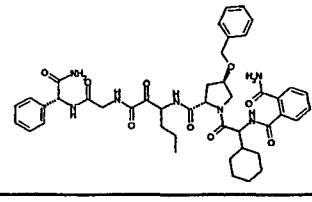
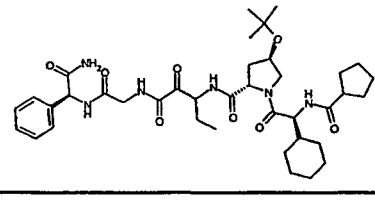
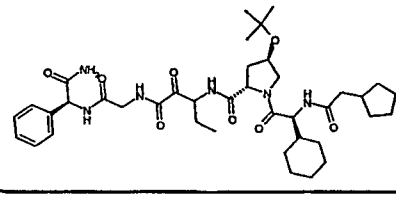
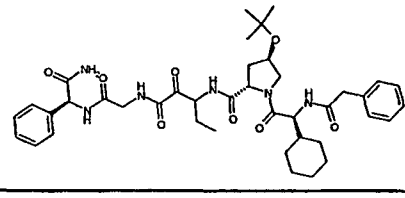
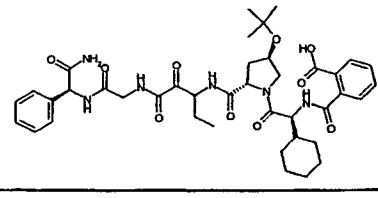
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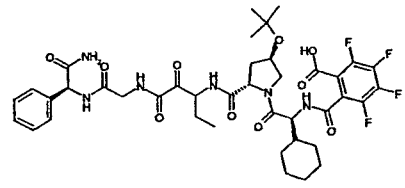
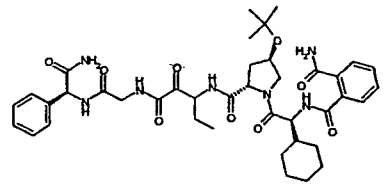
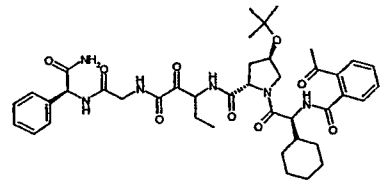
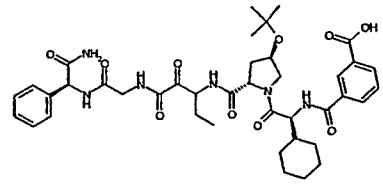
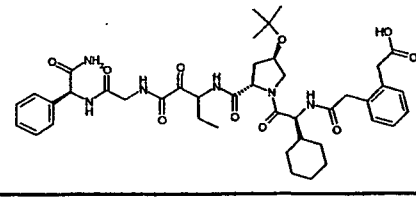
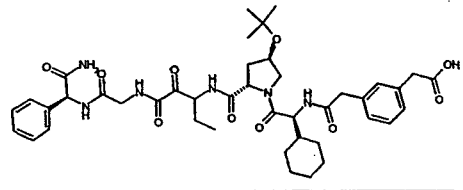
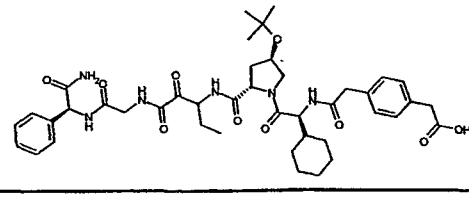
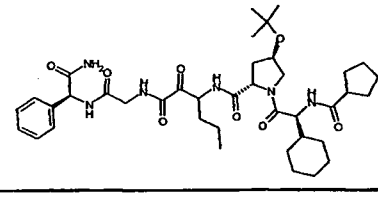
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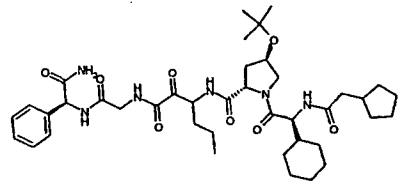
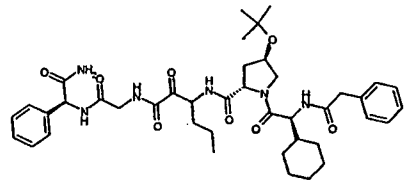
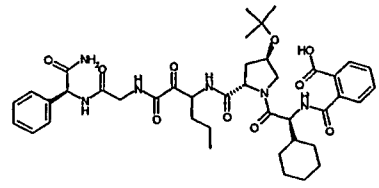
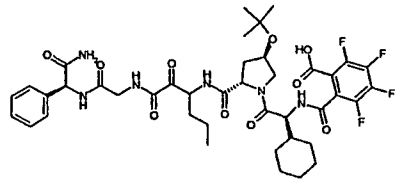
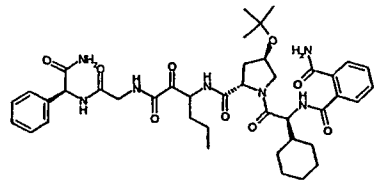
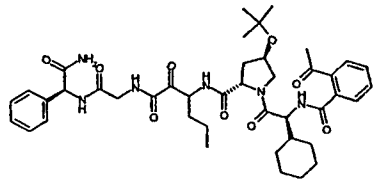
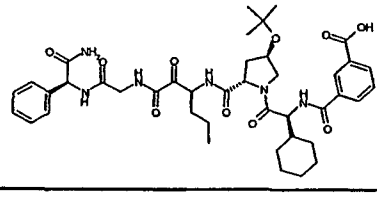
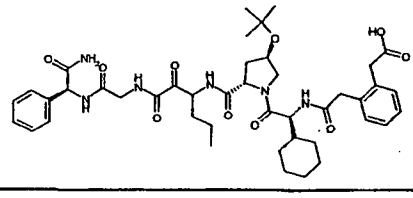
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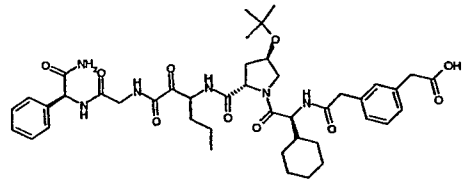
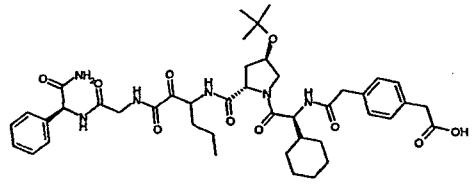
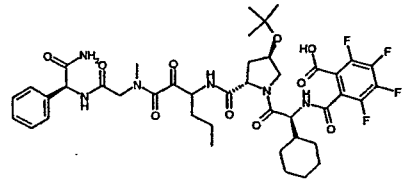
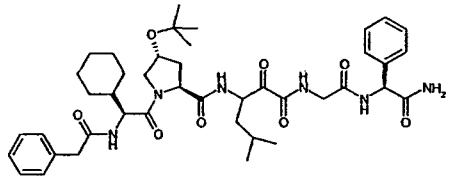
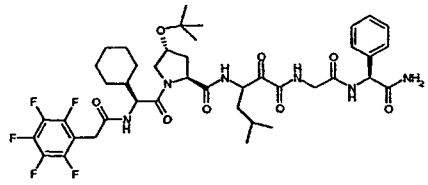
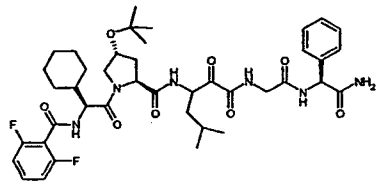
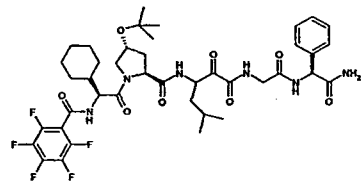
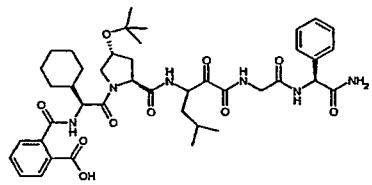
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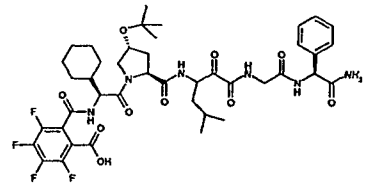
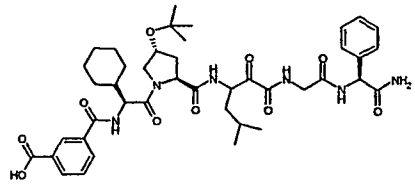
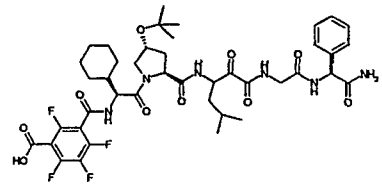
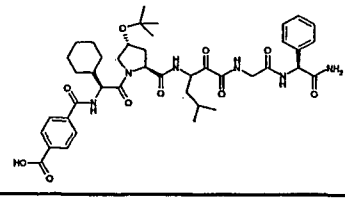
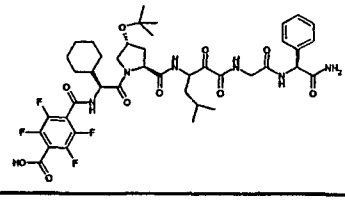
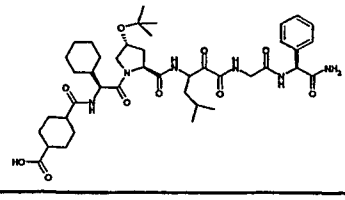
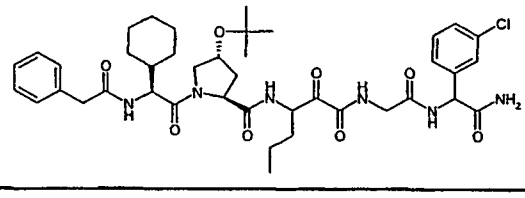
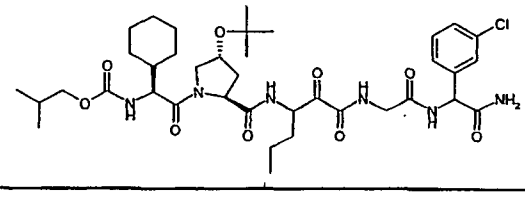
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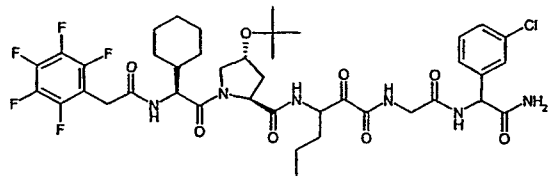
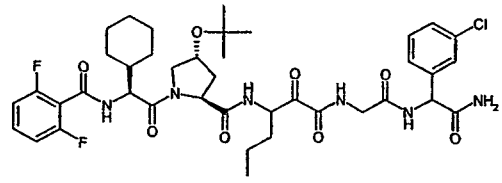
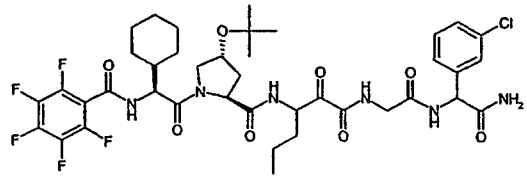
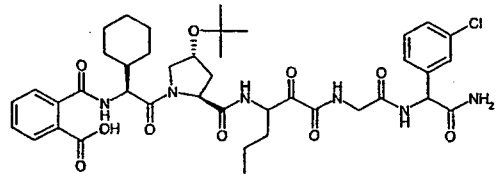
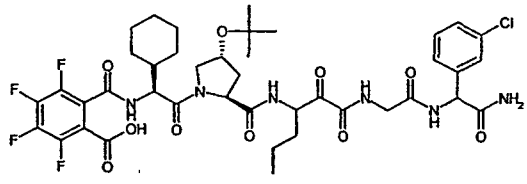
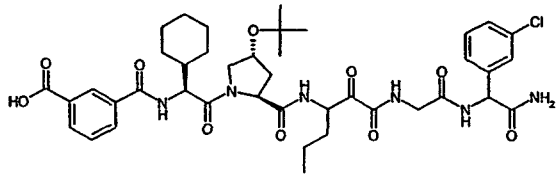
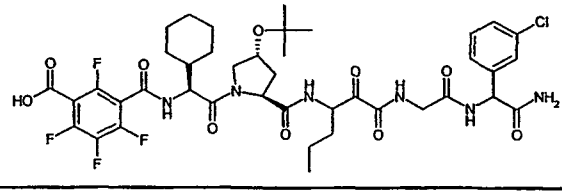
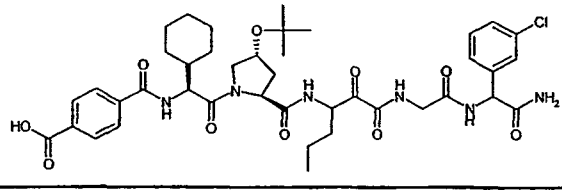
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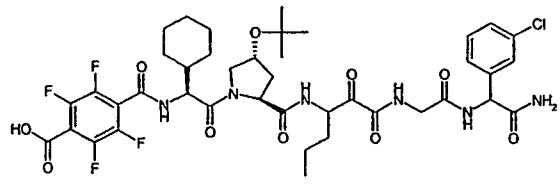
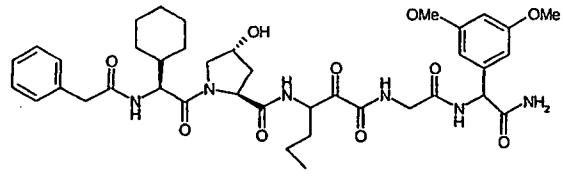
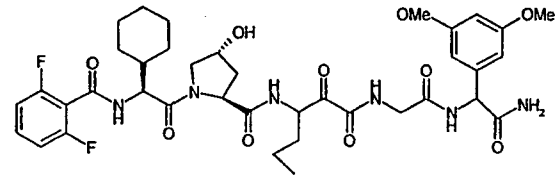
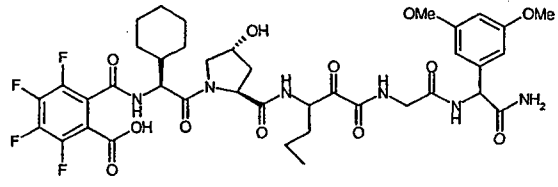
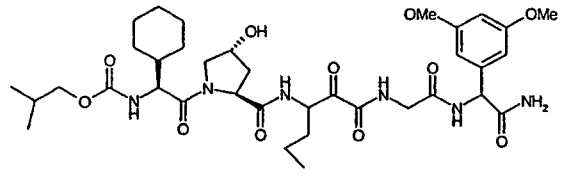
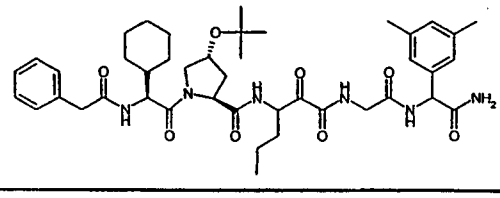
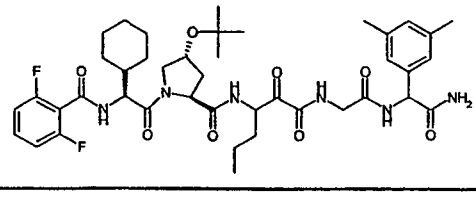
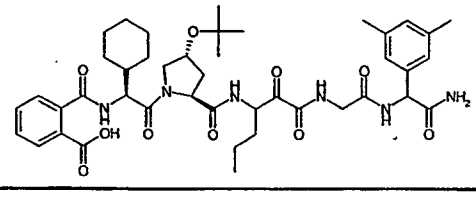
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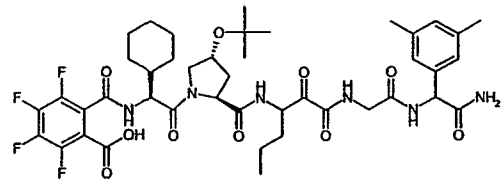
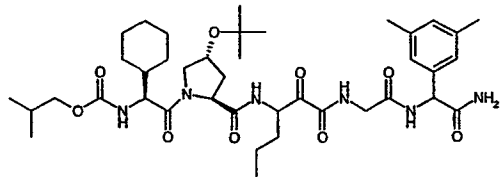
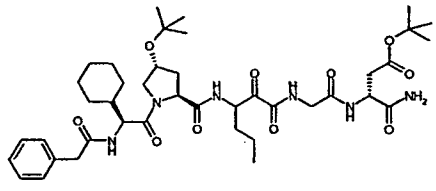
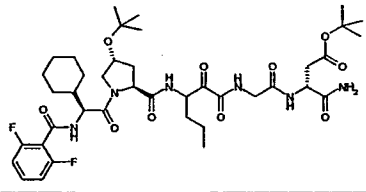
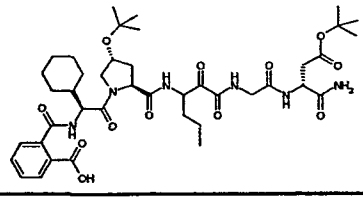
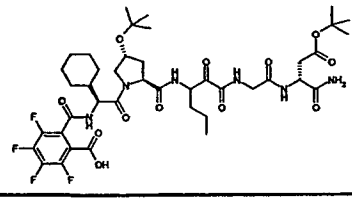
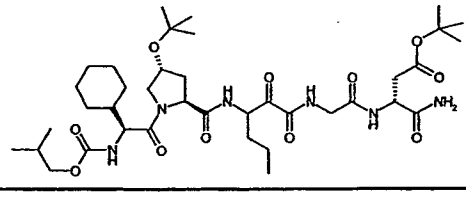
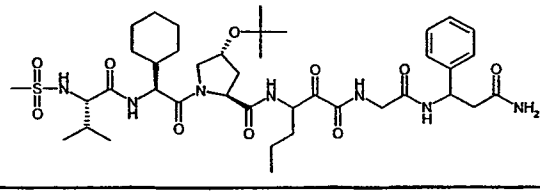
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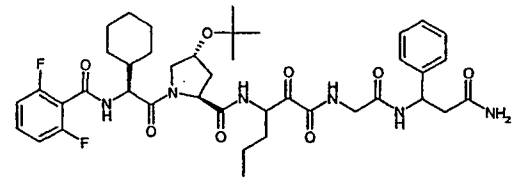
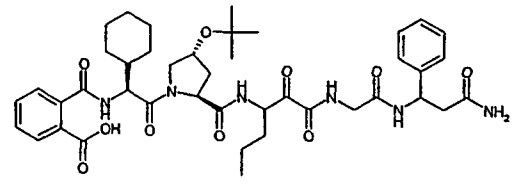
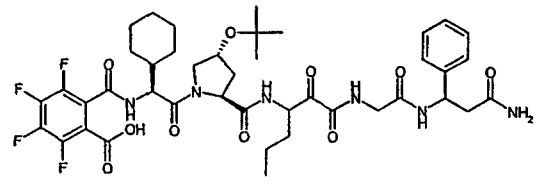
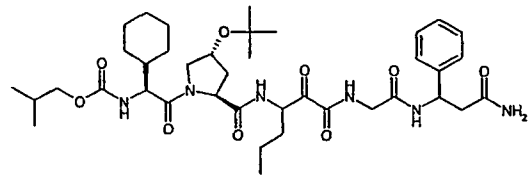
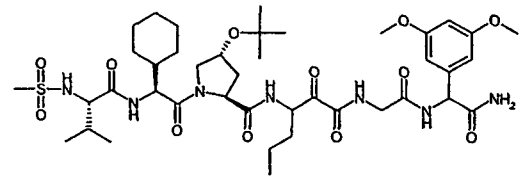
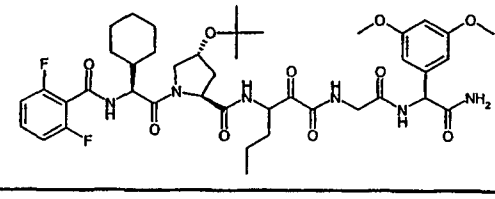
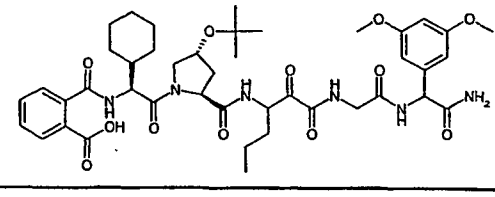
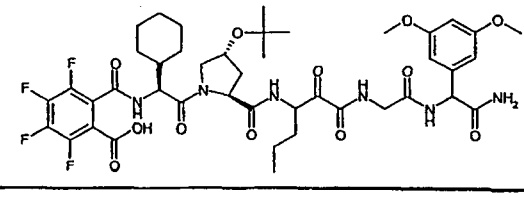
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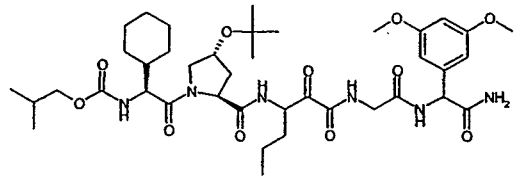
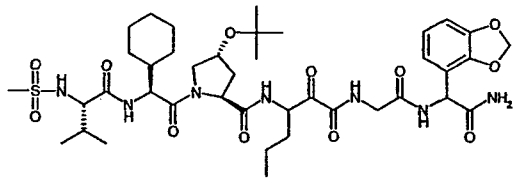
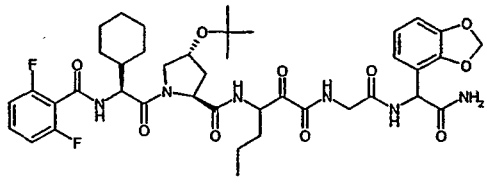
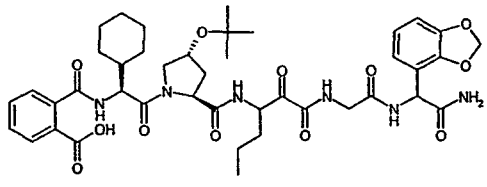
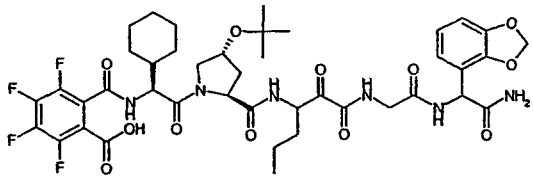
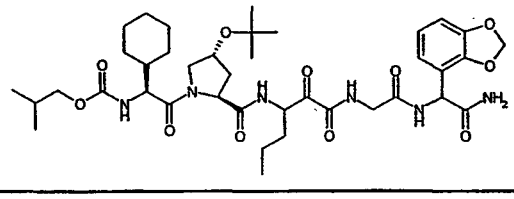
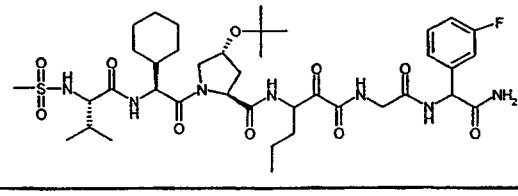
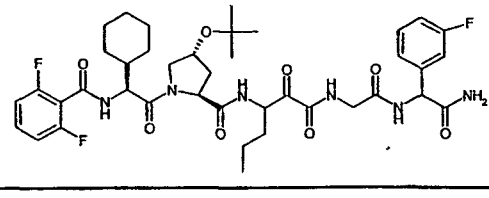
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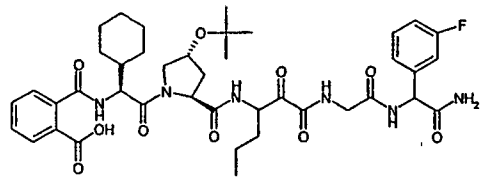
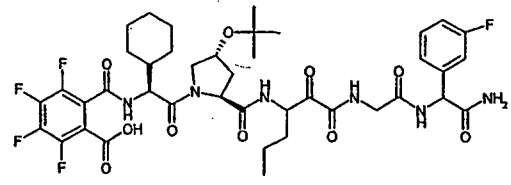
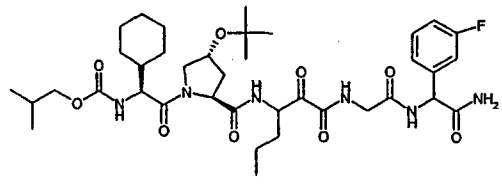
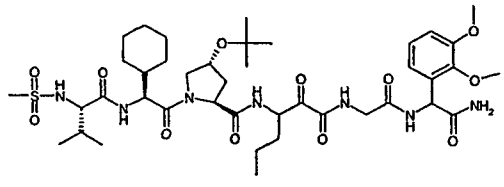
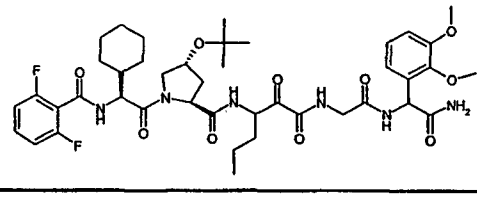
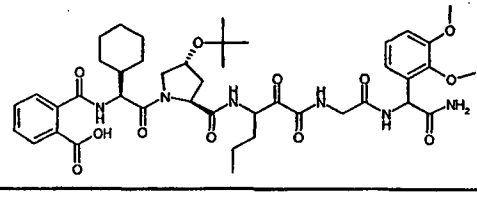
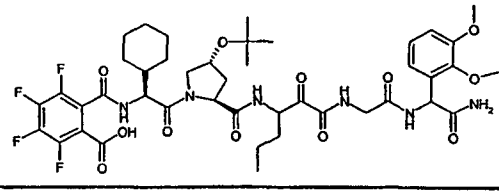
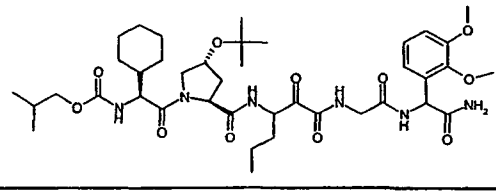
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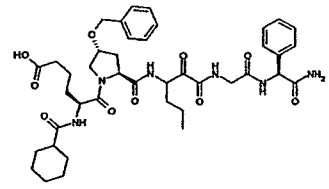
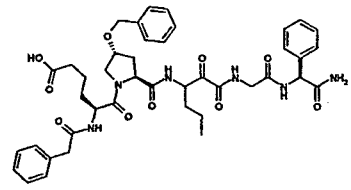
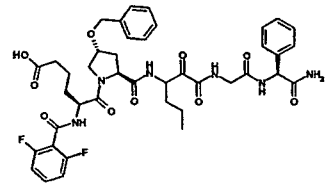
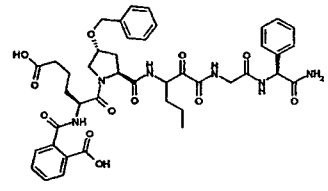
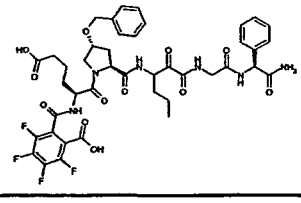
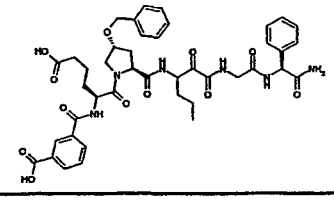
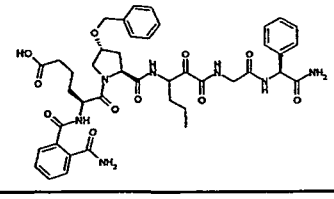
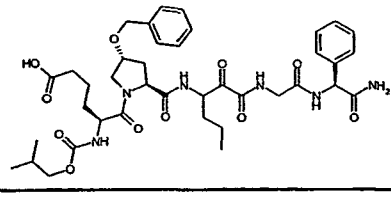
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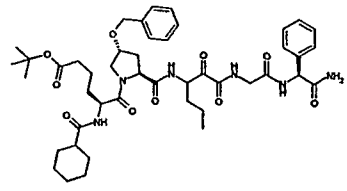
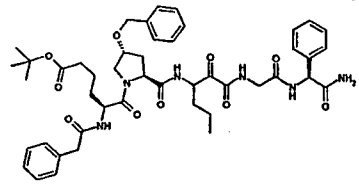
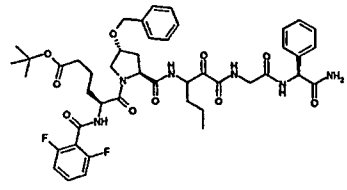
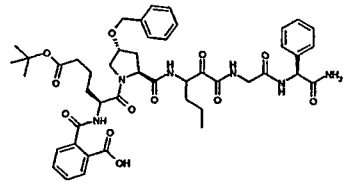
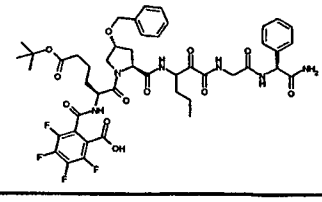
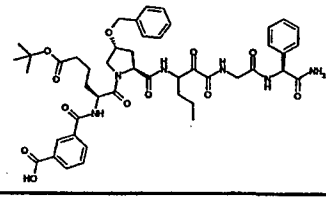
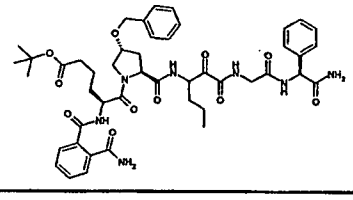
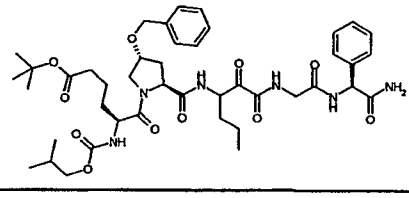
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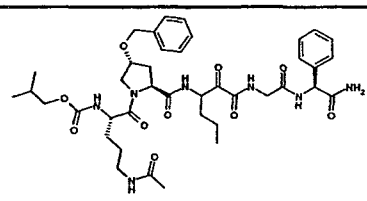
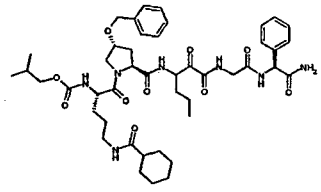
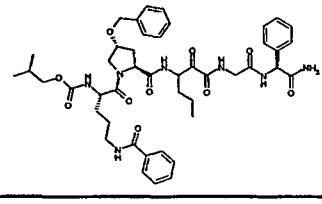
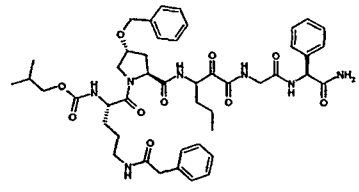
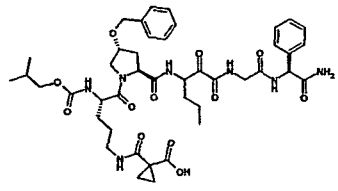
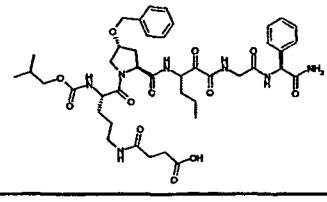
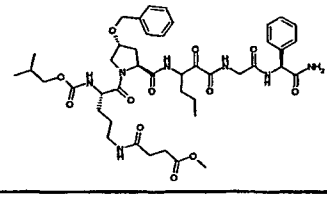
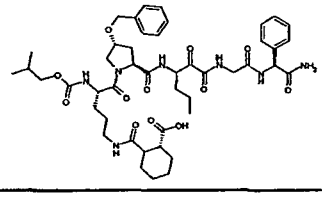
STRUCTURE	Ki* CLASS
	C
	C
	B
	C
	B
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	B
	B

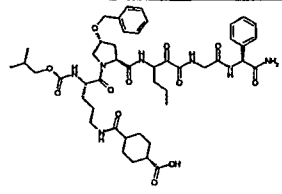
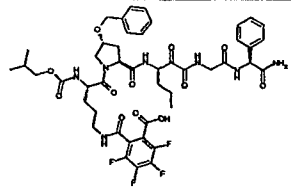
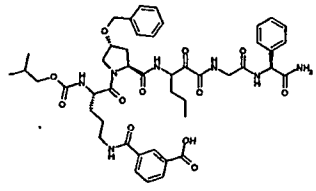
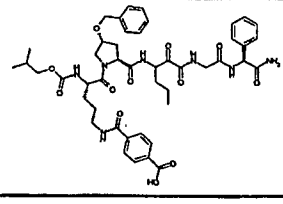
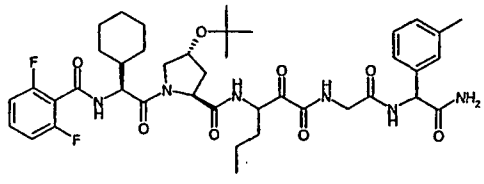
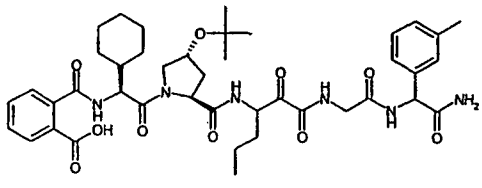
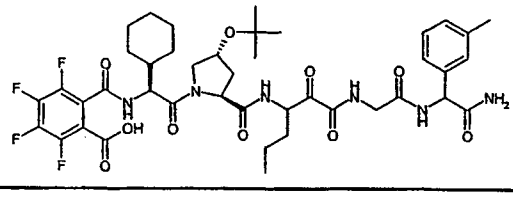
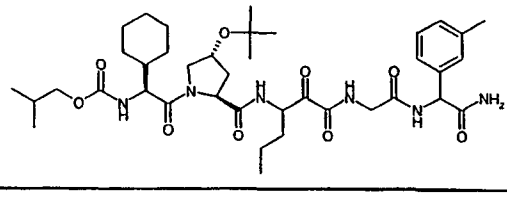
STRUCTURE	Ki* CLASS
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	B
	B
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	B
	B
	B

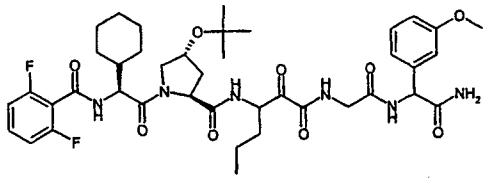
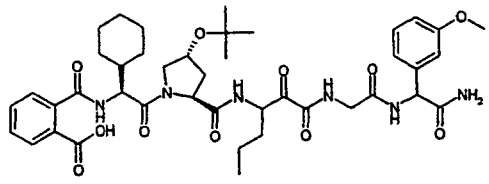
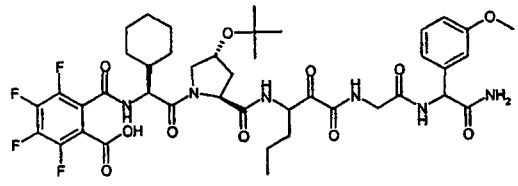
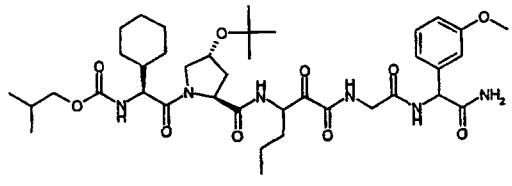
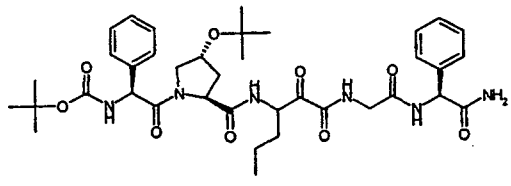
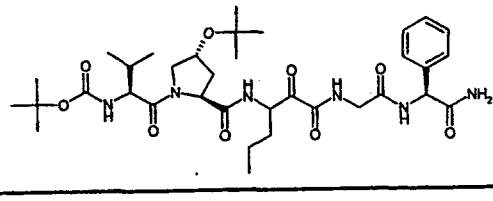
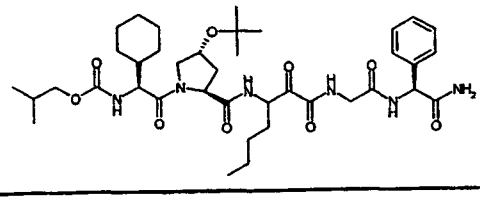
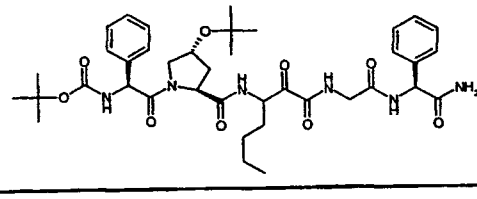
STRUCTURE	Ki* CLASS
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	B
	B
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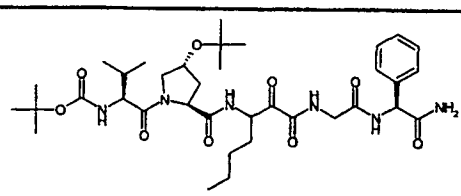
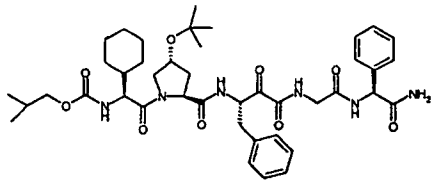
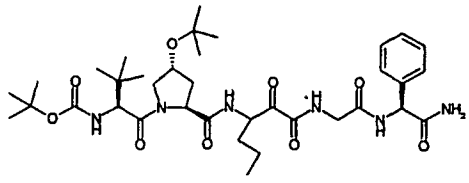
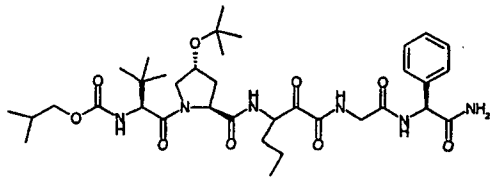
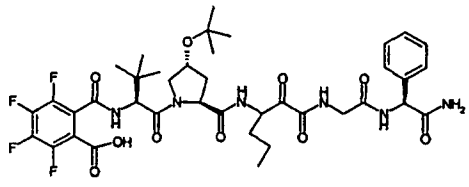
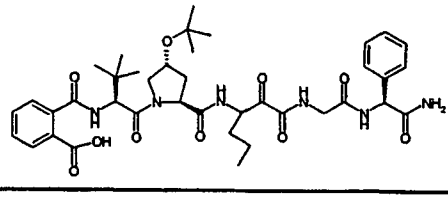
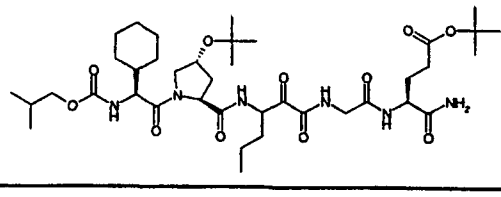
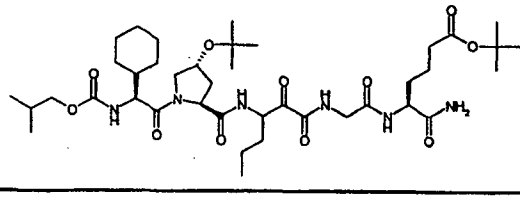
STRUCTURE	Ki* CLASS
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	B
	B
	B
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	C
	B
	B

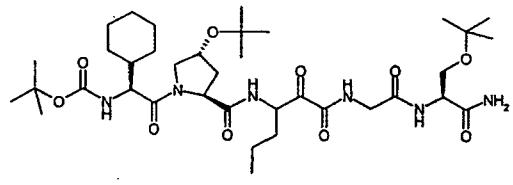
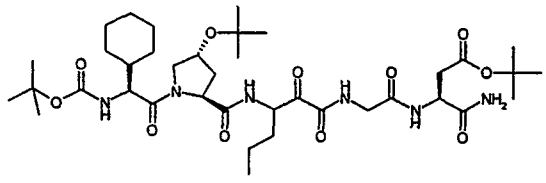
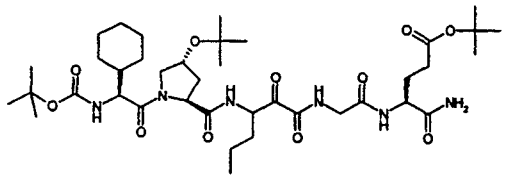
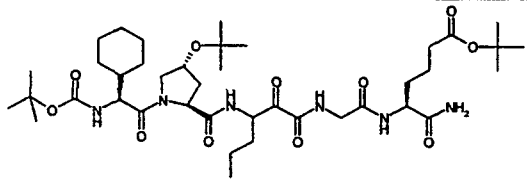
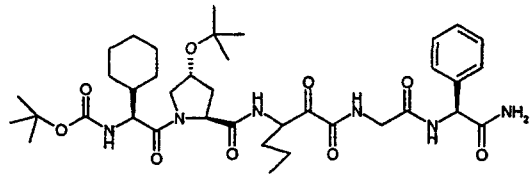
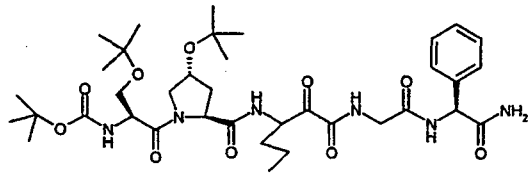
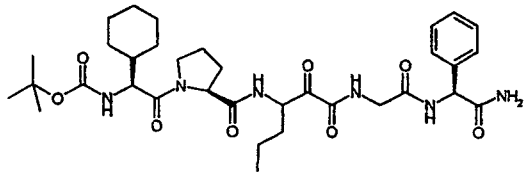
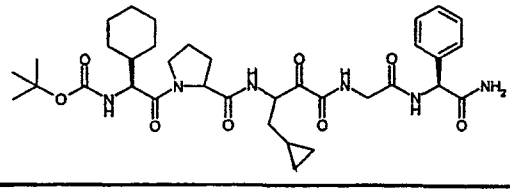
STRUCTURE	Ki* CLASS
	C
	C
	C
	C
	B
	C
	C
	C

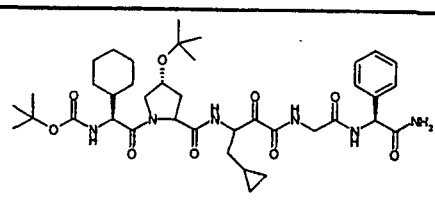
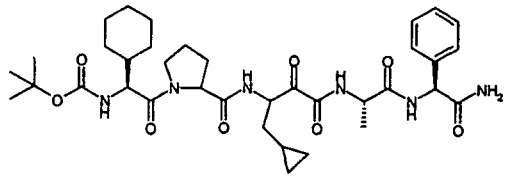
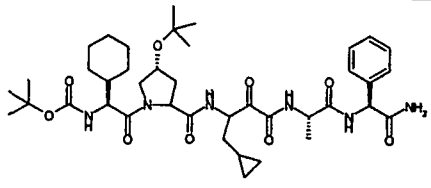
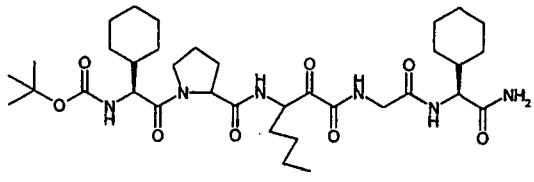
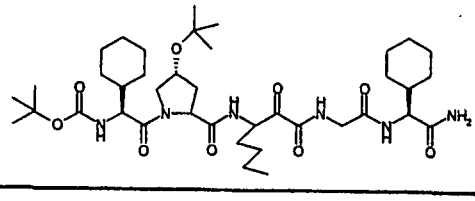
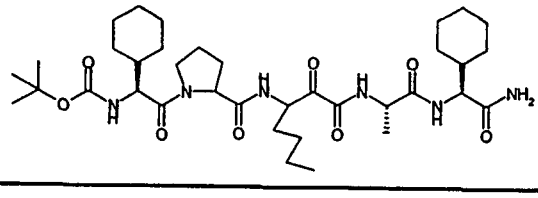
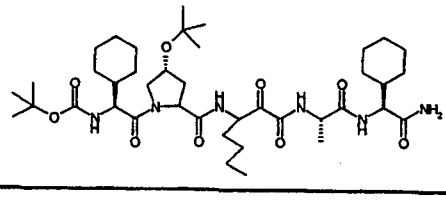
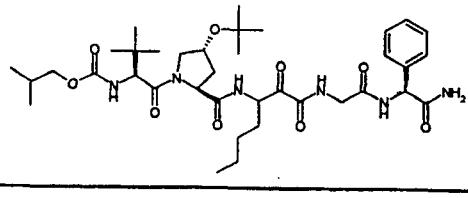
STRUCTURE	Ki* CLASS
	C
	C
	C
	C
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	C
	C

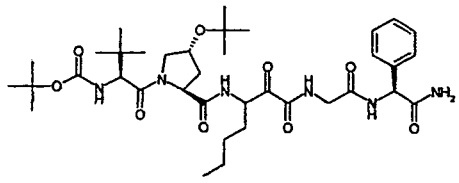
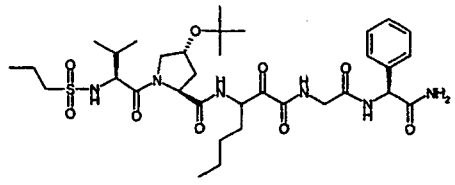
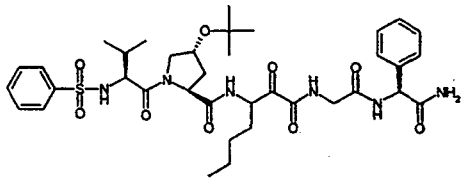
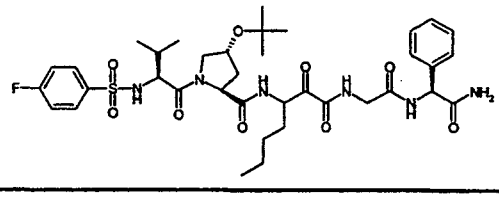
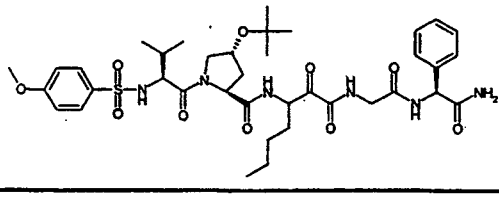
STRUCTURE	Ki* CLASS
	C
	C
	B
	B
	B
	B
	B
	B

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
	C
	C
	C
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	C
	C

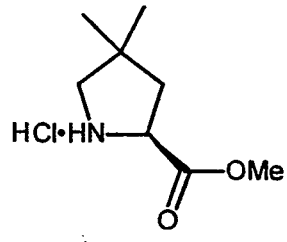
STRUCTURE	Ki* CLASS
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	C
	B
	C
	C
	C
	C
	B

STRUCTURE	Ki* CLASS
	B
	C
	C
	C
	C

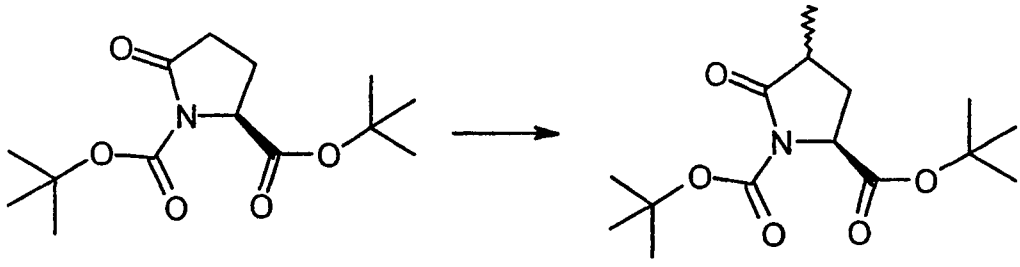
Additional compounds that were prepared and their activity (Ki*) ranges are given in the attached **Tables 4** and **5**. The procedure used to prepare the compounds in **Tables 4** and **5** is outlined below.

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

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

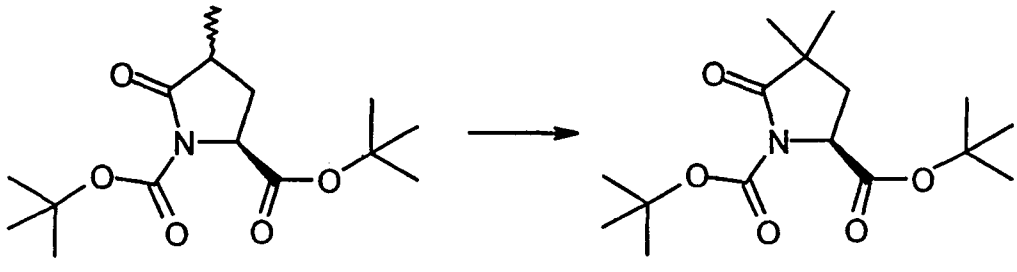


Step 1. Synthesis of tert-Butyl N-tert-butoxycarbonyl-4-methyl-L-pyroglutamate (Boc-PyroGlu(4-methyl)-OtBu):



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).

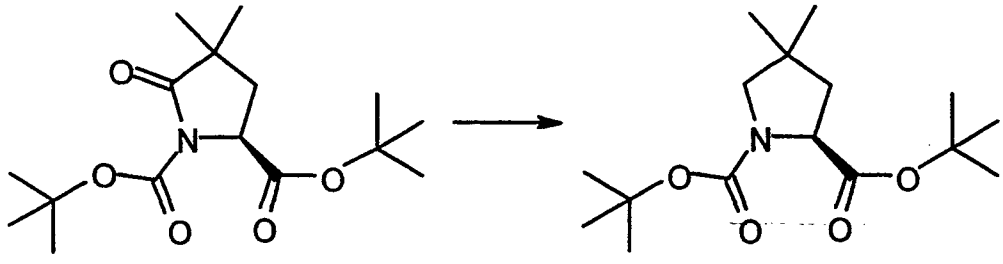
Step 2. Synthesis of tert-Butyl N-tert-butoxycarbonyl-4,4-dimethyl-L-pyroglutamate (Boc-PyroGlu(4,4-dimethyl)-OtBu):



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)

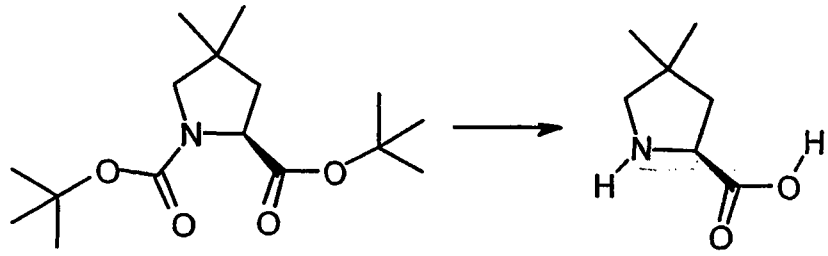


Modification of known procedure: Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron Letters* **1994**, 35(13), 2053-2056).

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

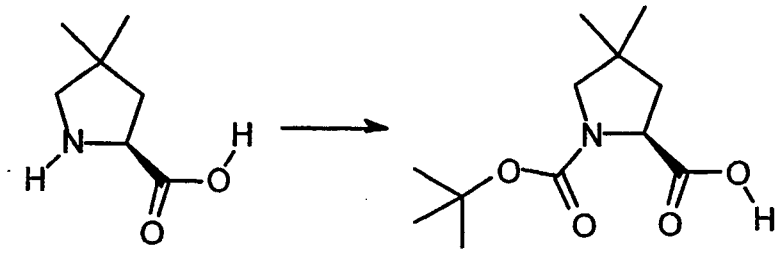
triethylsilane (310 μL, 2.0 mmol) and boron trifluoride diethyletherate (270 μL, 2.13 mmol) were added. After stirring at -78 °C for an additional two hours, the cooling bath was removed and saturated aqueous sodium bicarbonate (4 mL) was added. After 5 minutes the mixture was extracted with dichloromethane (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.

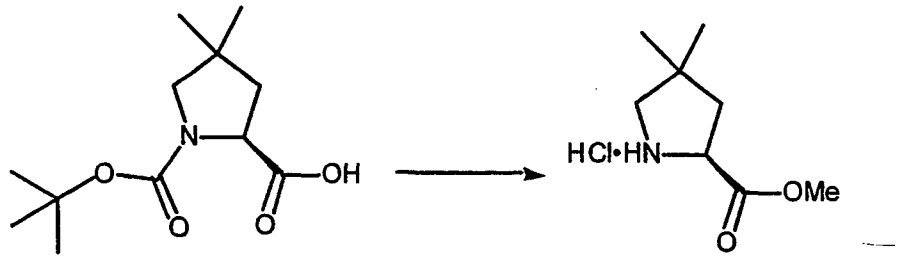
Step 5. Synthesis of N-tert-butoxycarbonyl 4,4-dimethylproline (Boc-Pro(4,4-dimethyl)-OH):



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

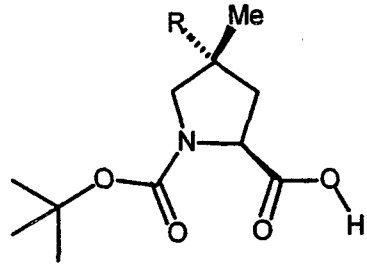
(50 mL) and washed with diethyl ether (3 x 40 mL). The aqueous layer was acidified to pH=3 with citric acid, then extracted with dichloromethane (3 x 40 mL). The combined organic layers were dried over sodium sulfate filtered and concentrated.

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



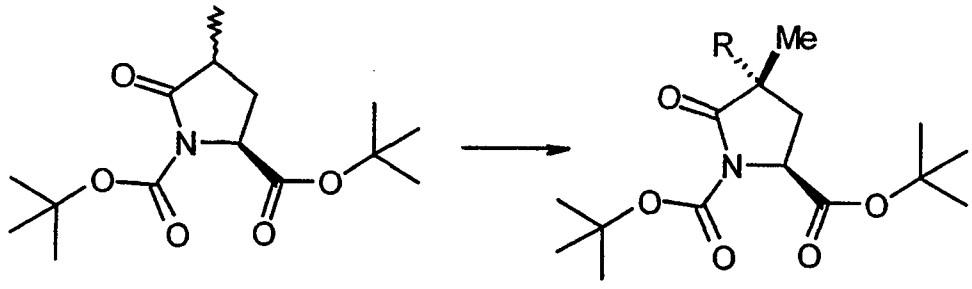
To a solution of Boc-Pro(4,4-diMe)-OH (0.5 g, 2.06 mmol) in anhydrous methanol (8 ml) was added dropwise thionylchloride (448 l, 6.18 mmol) and the reaction was stirred for six hours at room temperature. The reaction mixture was concentrated to an amorphous solid (377 mg, 95%).

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



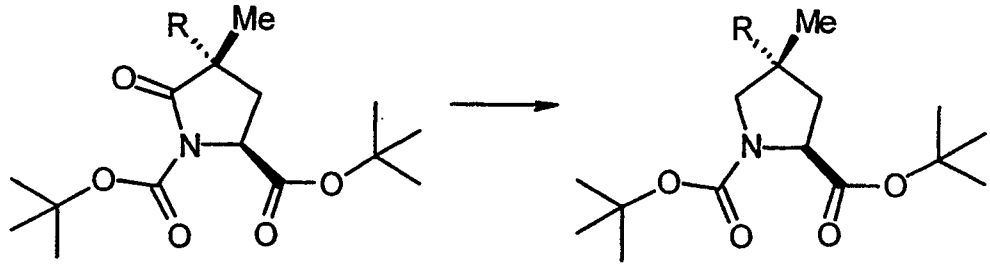
Compounds where R group is allyl and benzyl were synthesized following steps 1-4 below:

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.

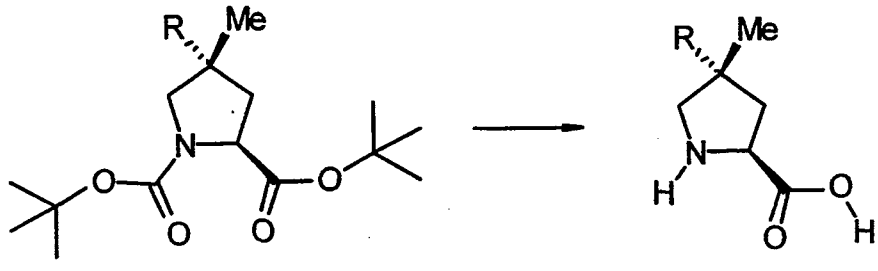
Step 2. Synthesis of tert-butyl N-tert-butoxycarbonyl-4-alkyl-4-methylproline:



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

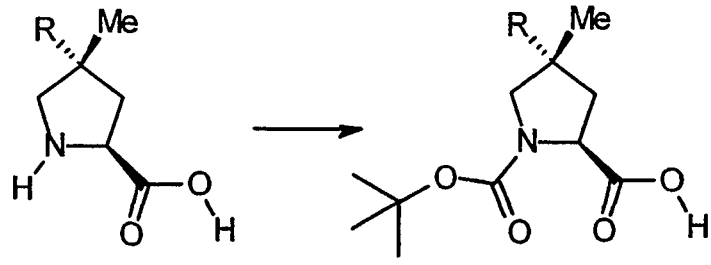
To a solution of tert-butyl N-tert-butoxycarbonyl-4-alkyl-4-methylpyroglutamate (16.6 mmol) in tetrahydrofuran (40 mL) stirring at -78 °C, was added a 1M solution of lithium triethylborohydride in tetrahydrofuran (20 mL, 20 mmol) dropwise over 10 minutes. After 120 minutes, the cooling bath was allowed 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:



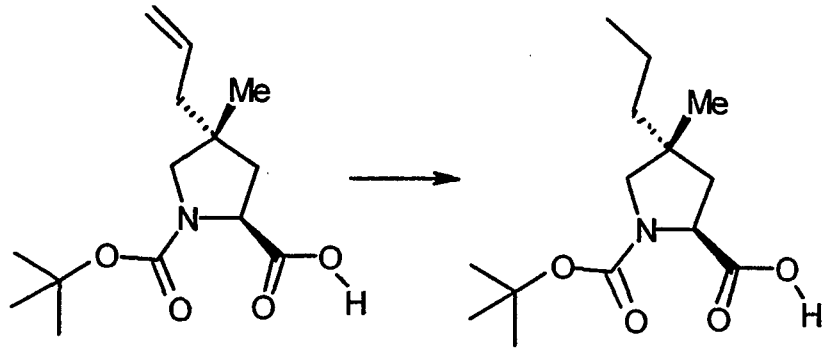
A solution of tert-butyl N-tert-butoxycarbonyl-4-alkyl-4-methylproline in dichloromethane (5 mL) and trifluoroacetic (5 mL) was stirred at room temperature for 5 hours. Toluene was added and the solution was concentrated and then dried under high vacuum.

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



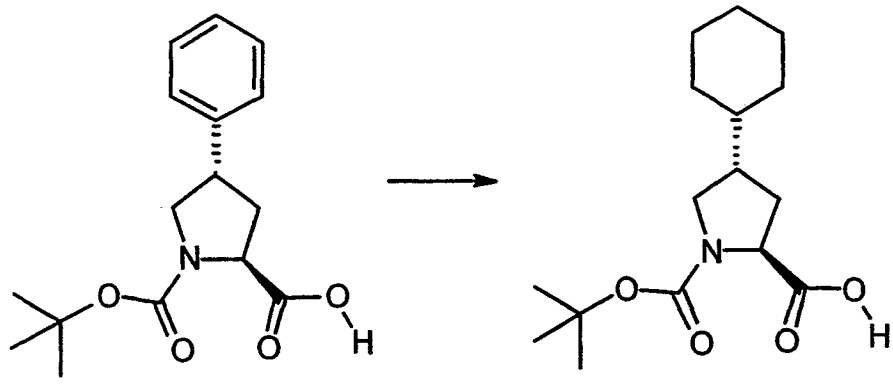
To a solution of 4-alkyl-4-methylproline trifluoroacetic salt (1.5 mmol) in dioxane (7 mL), acetonitrile (12 mL) and diisopropylethylamine (700 μL, 4 mmol) was added a solution of di-tert-butyl-dicarbonate (475 mg, 2.18 mmol) in acetonitrile(5 mL). After stirring for 12 hours at room temperature the 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:



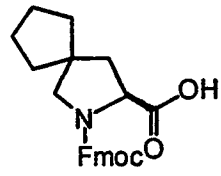
A solution of N-tertbutoxycarbonyl-4-allyl-4-methylproline (400 mg, 1.48 mmol) (see Example II Step 4) and 10% Pd on carbon (400 mg) in methanol (20 mL) was hydrogenated at 50 psi for 4 hours. The mixture was filtered and concentrated.

Example IV. Synthesis of Boc-4-cyclohexylproline:

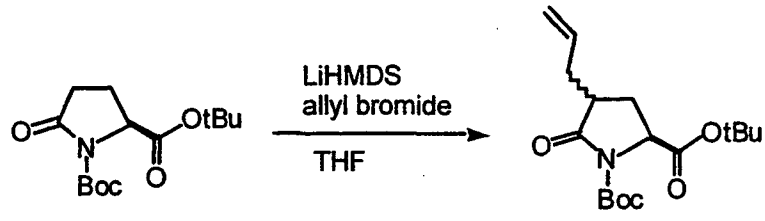


A solution of the commercially available Boc-4-phenylproline (750 mg) and 5% Rh on carbon (750 mg) in methanol (15 mL) was hydrogenated at 50 psi for 24 hours. The mixture was filtered and concentrated to give 730 mg of product.

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



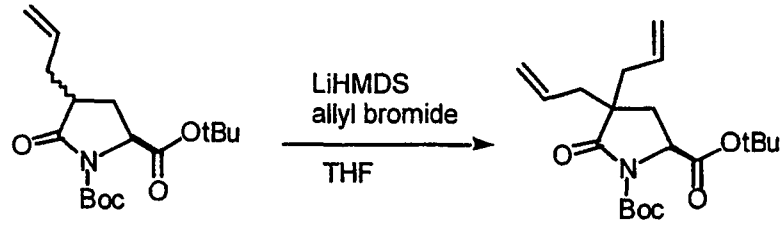
Step 1. Synthesis of Boc-pyroglutamic(4-allyl)-tert-butylester :



To a cooled (-78 °C) solution of the commercially available N-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.

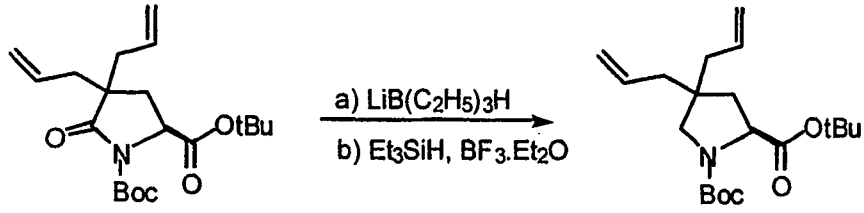
Flash column chromatography carried out in 2:8 ethylacetate: hexanes afforded the product (6 g, 53%). NMR δ ppm (CDCl3): 5.7 (m, 1H), 5.1 (dd, 2H), 4.4 (m, 1H), 2.6 (m, 2H), 2.4 (m, 1H), 1.8-2.2 (m, 1H), 1.45 (s, 9H), 1.4 (s, 9H).

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:

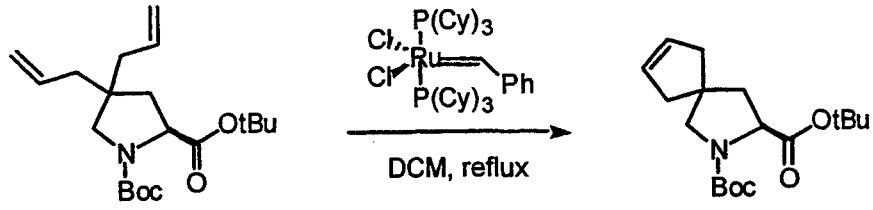


Part a: To a cooled (-78 °C) solution of Boc-PyroGlu(4,4-diallyl)-tert-butylester (2.13 g, 5.83 mmol) in tetrahydrofuran (14 ml) was added lithium triethylborohydride (1M in tetrahydrofuran, 7.29 ml, 7.29 mmol) over five minutes. After two hours at -78 °C, the reaction was warmed-up to 0 °C and quenched 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

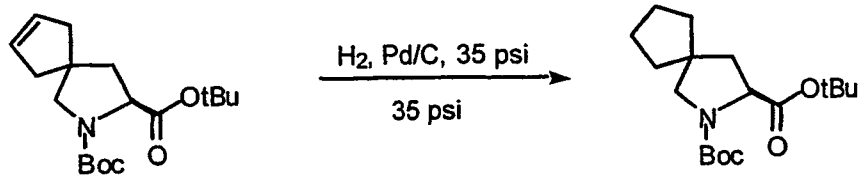
etherate (776 µl, 6.12 mmol). After thirty minutes more triethylsilane (931 µl, 5.83 mmol) and boron trifluoride diethyl etherate etherate (776 µl, 6.12 mmol) were added and the reaction was stirred at -78 °C for three hours at which time the reaction was quenched by the slow addition of saturated sodium 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).

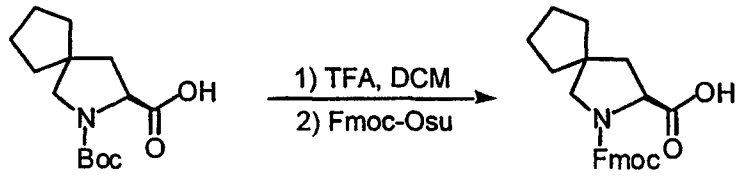
Step 5. Synthesis of Boc-Pro(4-spirocyclopentane)-tert-butylester:



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

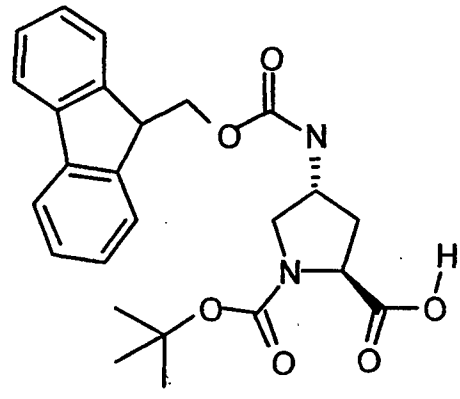
shaker and was hydrogenated for three hours at 35 psi in the presence of 10% palladium on carbon (300 mg). The catalyst was filtered off and the filtrate was concentrated to a colorless oil (1.26 g). NMR δ ppm (CDCl3): 4.1 and 4.2 (t, 1H, rotamers, 3.4 (d, 1H), 3.2 (d, 1H), 2.1 (m, 1H), 1.9 (m, 1H),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

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

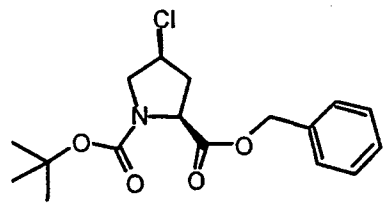


The Boc-Pro(4-spirocyclopentane)-tert-butylester (1.26, 3.9 mmol) was treated with dichloromethane (10 ml) and trifluoroacetic acid (15 ml) for three hours. The reaction mixture was concentrated and the yellow oil obtained was dissolved in water (6 ml). Fluorenylmethyl succinyl carbonate (1.45 g, 4.3 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:

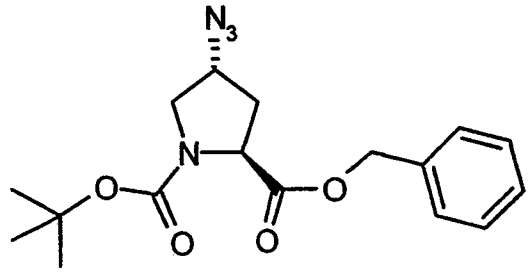


Step 1. Synthesis of N^{α}-tert-butoxycarbonyl-cis-4-chloro-L-proline benzyl ester:



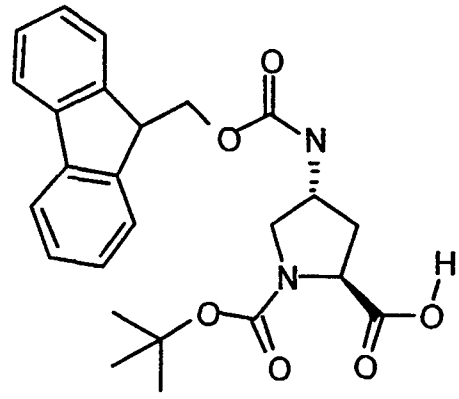
A mixture of the commercially available N-tert-butoxycarbonyl-trans-4-hydroxy-proline (8.79 g, 38 mmol), potassium carbonate (13.0 g, 94 mmol), benzyl bromide (4.5 ml, 38 mmol) and dimethylformamide (150 mL) was stirred for 18 h. Addition of ethyl acetate (100 mL) was followed by filtration. The white 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:



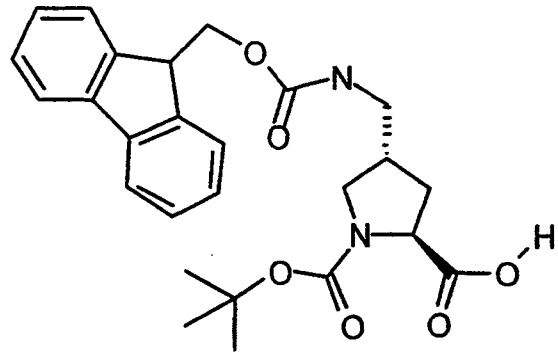
A solution of N^{α}-tert-butoxycarbonyl-cis-4-chloro-L-proline benzyl ester (9.0 g, 26.5 mmol) and sodium azide (7.36 g, 113 mmol) in dimethylformamide (270 mL) was heated at 75°C for 2 days. Water (100 mL) was added and the reaction mixture was extracted with ethyl acetate (3 x 100 mL). The combined 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:

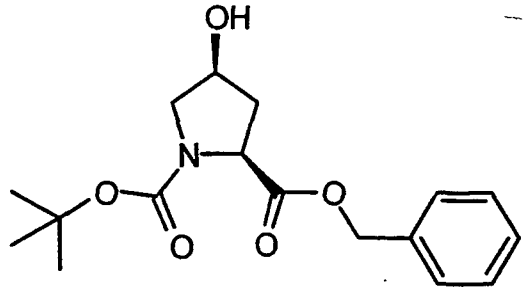


A mixture of N-α-t-butoxycarbonyl-trans-4-azido-L-proline benzyl ester (8.59 g, 24.8 mmol) and 10% palladium on carbon (900 mg) in ethanol (500 mL) was hydrogenated at 50 psi for 14 h using a Parr hydrogenation apparatus. The mixture was filtered, concentrated, dissolved in methanol (60 mL), refiltered 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):



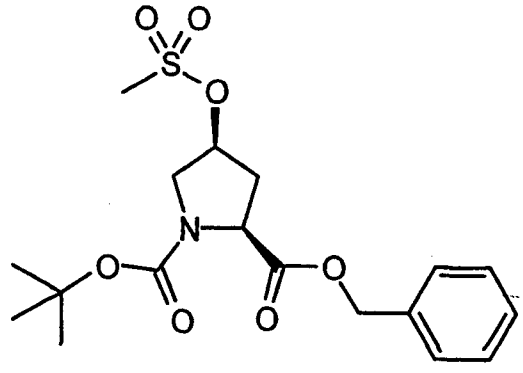
Step 1. Synthesis tert-butoxycarbonyl cis-4-hydroxy-L-proline benzyl ester (Boc-Pro(4-cis-OH)-OBn):



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),

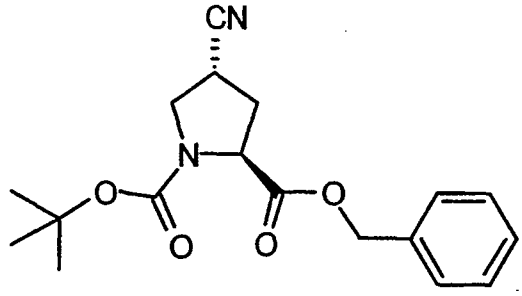
dried (sodium sulfate), filtered and concentrated. The crude product was purified by flash chromatography using 40-60% ethyl acetate in hexanes to give the title compound (10.04 g, 31.24 mmol, 82%).

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



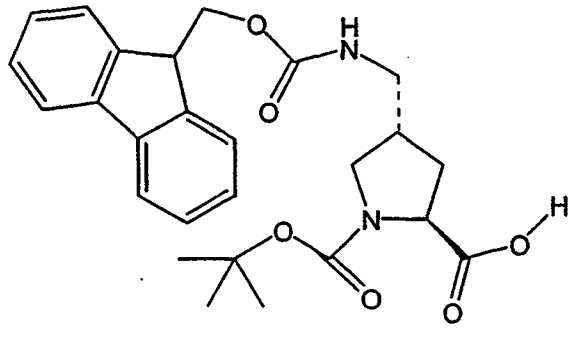
To a solution of Boc-Pro(4-cis-OH)-OBn (8.45 g, 26.3 mmol) in pyridine (65 mL) at 0°C, was added methanesulfonyl chloride (3.4 mL, 44 mmol) dropwise over 7 min. The reaction mixture was allowed to warm to room temperature over 2 h, then stirred overnight. A solution of 10% water in pyridine (20 mL) was 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%).

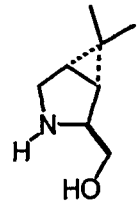
Step 4. N-t-butoxycarbonyl-4-trans-(N-fluorenylmethyloxycarbonyl aminomethyl)-L-proline (Boc-Pro(4t-MeNHFmoc)-OH) :



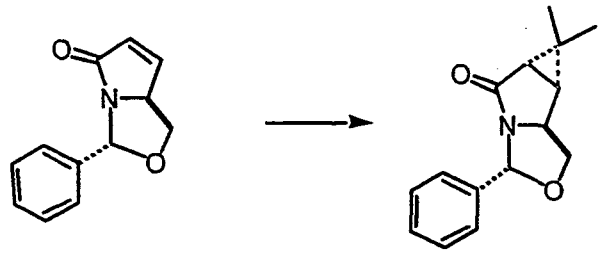
A mixture of the compound of Step 3 above (2.31 g, 7 mmol), water (10 mL), methanol (85 mL) and 10% palladium on carbon (700 mg) was hydrogenated at 50 psi for 11 h using a Parr hydrogenation apparatus. The mixture was filtered and concentrated. Water (15 mL) and sodium carbonate (1.5 g, 14.2 mmol) was 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:

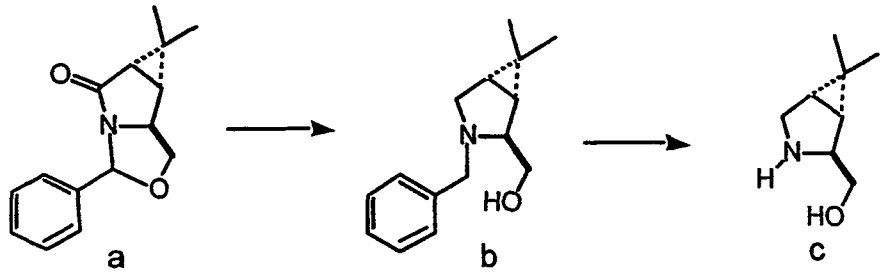


Step I. Cyclopropanation reaction (*Tetrahedron Lett.* 1993, 34(16), 2691 and 2695):



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):

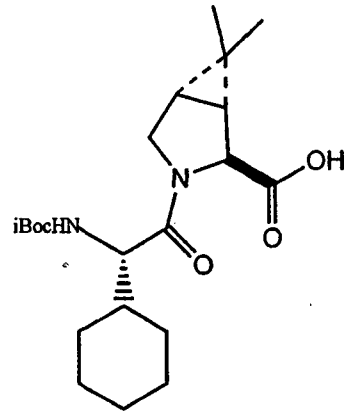


a b c

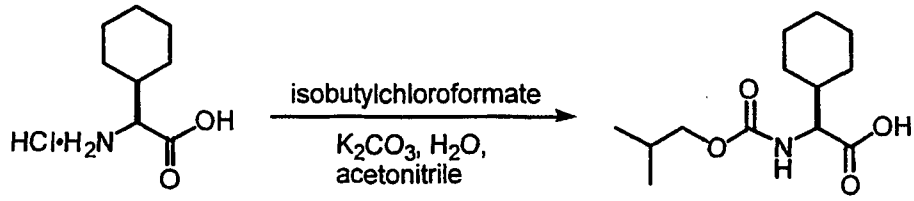
A mixture of the product obtained in step 1 above (1.23 grams, 5.06 mmol) and lithium aluminum hydride (1.0 M in THF, 15 mL, 15 mmol) was heated at reflux for 5 hours. After cooling to 0 °C, the remaining aluminum hydride was carefully quenched by the dropwise addition of saturated aqueous sodium sulfate

(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 :



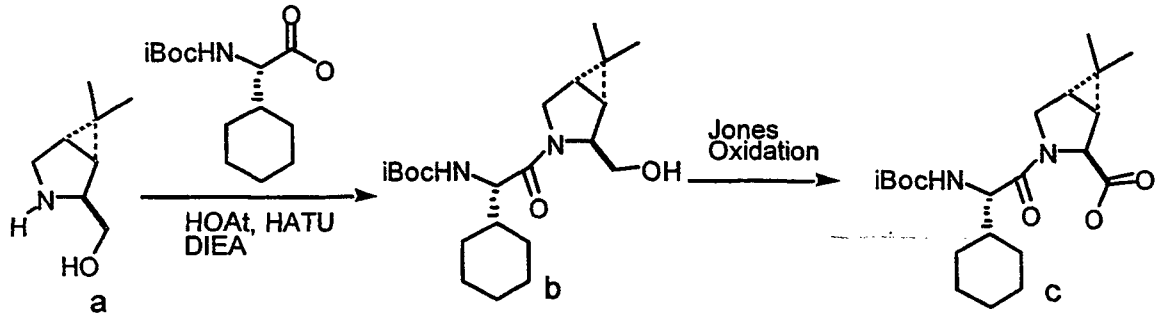
Step 1. Synthesis of isobutyloxycarbonyl- cyclohexylglycine (iBoc-G(Chx)-OH):



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 × 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

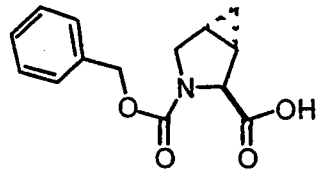
To a solution of iBoc-G(Chx)-OH (890 mg, 3.45 mmol) in acetonitrile (20 mL) was added HATU (1.33 g, 3.5 mmol), HOAt (476 mg, 3.5 grams) and then diisopropylethylamine (2.5 mL, 14 mmol). After a 2 minutes, 3,4-isopropylideneprolinol (485 mg, 3.43 mmol) was added and the reaction mixture was stirred overnight. 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

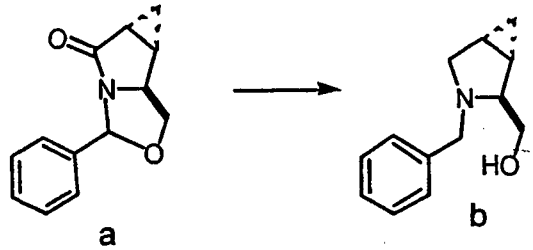
To a solution of dipeptide alcohol iBoc-G(Chx)-3,4-isopropylideneprolinol (100 mg, 0.26 mmol) in acetone (2 mL) stirring at 0 °C was added Jones reagent (300 μL) dropwise over 5 min. [Jones Reagent: Prepared from chromium trioxide (13.4 g) and concentrated sulfuric acid (11.5 mL) diluted with water to 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:



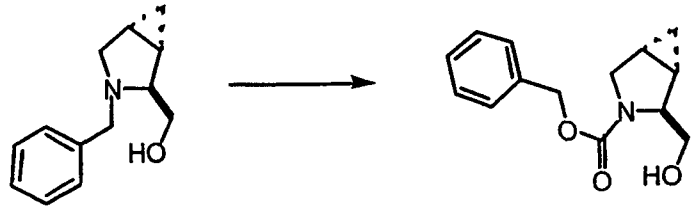
Step 1. Synthesis of N-benzyl-3,4-methanoprolinol:



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.

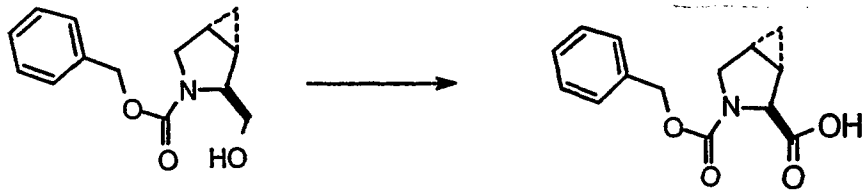
Step 2. Synthesis of N-benzyloxycarbonyl-3,4-methanoprolinol (CBz-P(3,4-CH2)-ol):



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

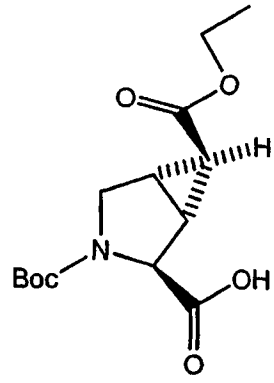
hydrogenated at 50 psi for 16 hours. The reaction mixture was filtered to remove the carbon-based catalyst and the filtrate was concentrated. The residue was dissolved in water/dioxane (100 mL) and diisopropylethylamine (3.2 mL) was added. Benzyl chloroformate (2.76 mL, 16.2 mmol) was added and the reaction 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):



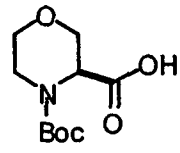
To a solution of N-Cbz-3,4-methanoprolinol (2.2 g, 8.90 mmol) in acetone (68 mL) stirring at 0 °C, was added Jones reagent (6.6 mL) dropwise over 5 min. [Jones Reagent: Prepared from chromium trioxide (13.4 g) and concentrated sulfuric acid (11.5 mL) diluted with water to a total volume of 50 mL.] After 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:



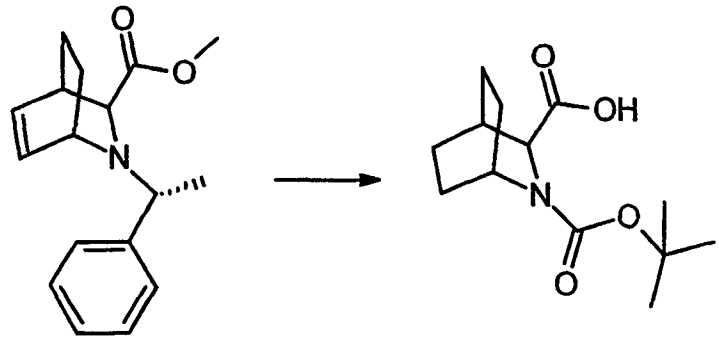
The synthesis of the title compound was carried out according to the published procedure: Marinozzi, M.; Nataini, B.; Ni, M.H.; Costantino, G.; Pellicciari R. *IL Farmaco* (1995) 50 (5), 327-331.

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.

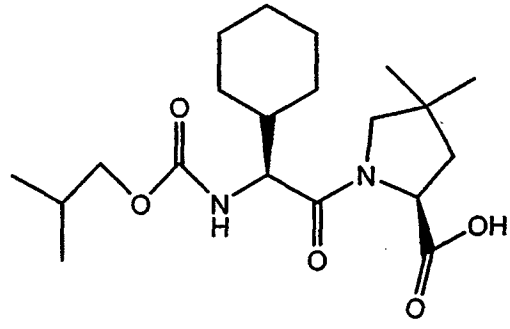
Example XIII. Synthesis of N-tert-butoxycarbonyl 2-aza-3S-hydroxycarbonyl-[2,2,2]-bicyclooctane:



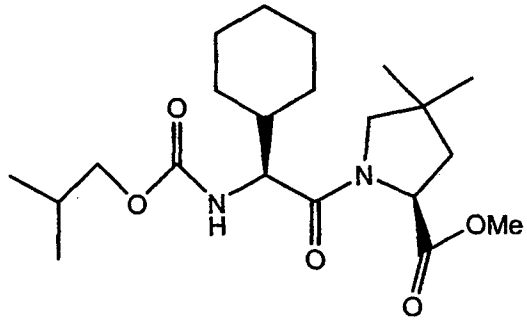
A solution of crude 2-aza-2-(1-phenylethyl)-3S-methoxycarbonyl-[2,2,2]-bicyclooct-5-ene (10 mmol) (Tetrahedron (1992) 48(44) 9707-9718) and 10% Pd on carbon (1 g) in methanol (30 mL) was acidified with 12N HCl then hydrogenated at 50 psi for 16 hours using a Parr hydrogenation apparatus. The

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):



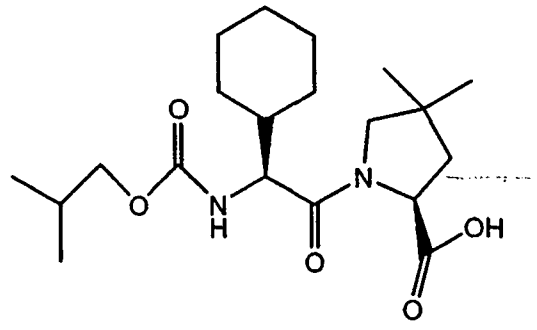
Step I. Synthesis of iBoc-G(Chx)-P(4,4-dimethyl)-OMe:



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,

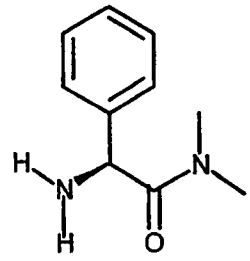
1.75 mmol), TBTU (845 mg, 2.63 mmol) and diisopropylethylamine (1.35 mL, 7.8 mmol). The reaction mixture was stirred at room temperature for 18 hours. The reaction mixture was concentrated and the remaining residue was dissolved in ethylacetate. The organic layer was washed twice with 10 ml portions 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:

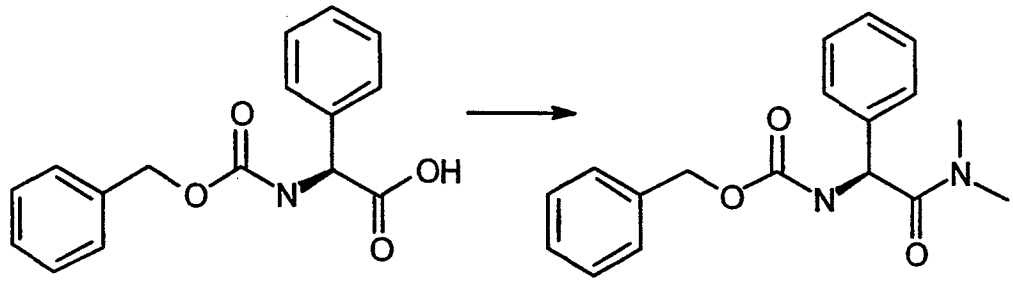


The methyl ester obtained in Step 1 above (612 mg, 1.54 mmol) in methanol (6 ml) was saponified in the presence of 2M lithium hydroxide (1.16 ml) for three hours. The methanol was removed under reduced pressure and the remaining residue was diluted with ethylacetate and acidified to pH=2 with 1N hydrochloric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

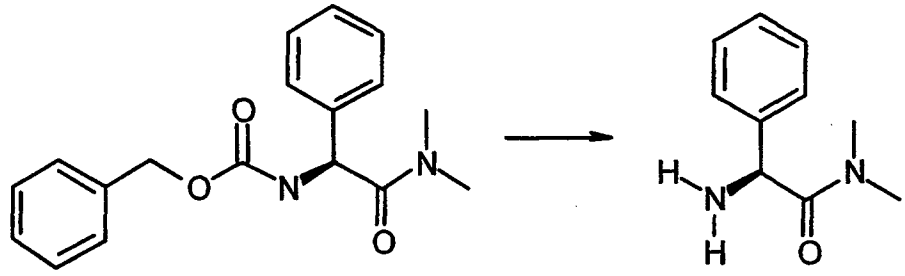
Example XV. Synthesis of L-phenylglycine dimethylamide



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



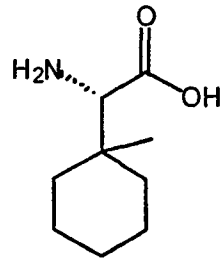
N-benzyloxycarbonyl-L-phenylglycine (25g, 88 mmols) was dissolved in THF (800mL) and cooled to -10 ^{o}C. N-methylmorpholine (9.7 mL, 88 mmols) and isobutylchloroformate (11.4 mL, 88.0 mmols) were added and the mixture allowed to stir for 1 minute. Dimethylamine (100 mL, 2M in THF) was added and the 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:

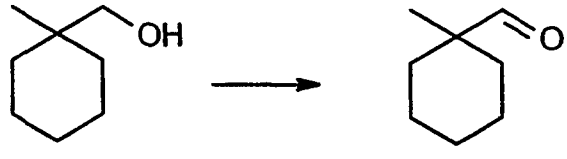


Step 1. 1-methyl-1-hydroxymethylcyclohexane



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%).

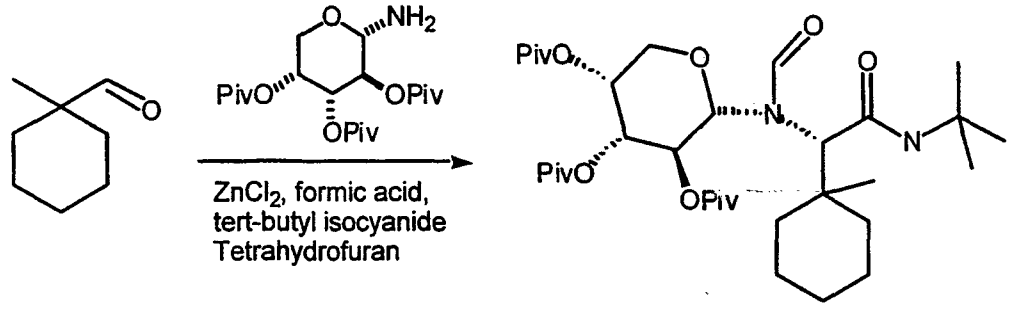
Step 2. 1-methylcyclohexylcarboxaldehyde:



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%).

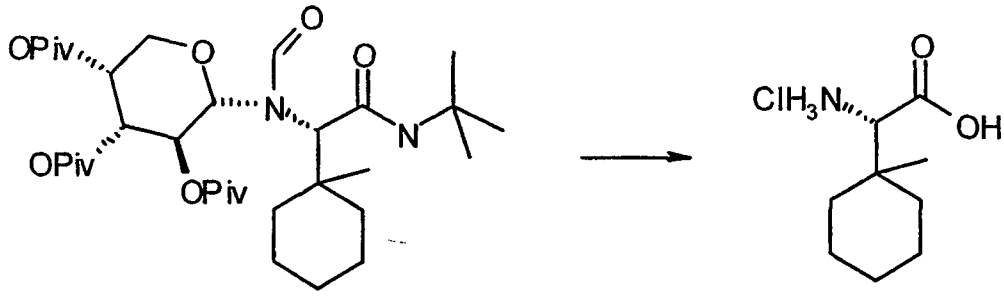
Step 3. Synthesis of N-formyl-N-glycosyl- 1-methylcyclohexyl- tert-butylamide :



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).

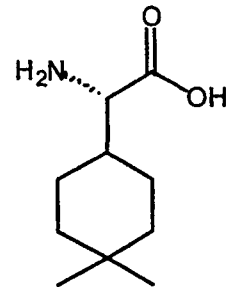
To a solution of 1-methylcyclohexylcarboxaldehyde (1.17 g, 8.34 mmol), 2,3,4-tri-O-pivaloyl- -D-arabinosylamine (8.3 g, 20.7 mmol), formic acid (850 µL, 22.2 mmol) and tert-butylisocyanide (2.4 mL, 21.2 mmol) in tetrahydrofuran (170 mL) at –30 °C was added 0.5M zinc chloride in tetrahydrofuran (41 mL, 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:

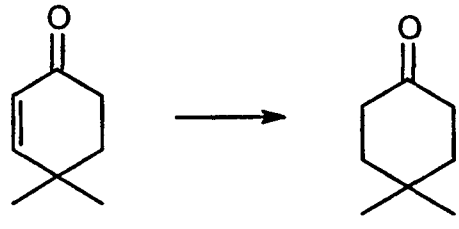


A solution of the product obtained in step 3 above (4.3 g, 6.6 mmol) in dichloromethane (30 mL) and saturated anhydrous methanolic HCl (30 mL) was stirred overnight. The solution was concentrated and the residue was dissolved in water (100 mL) and washed with pentane (2 x 100 mL). The aqueous layer was 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:



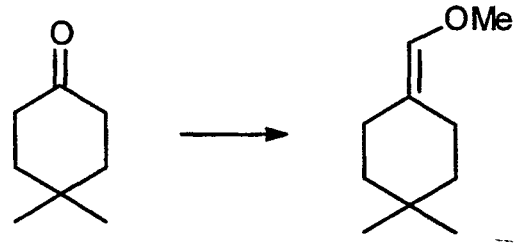
Step 1. Synthesis of 4,4-dimethylcyclohexanone:



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

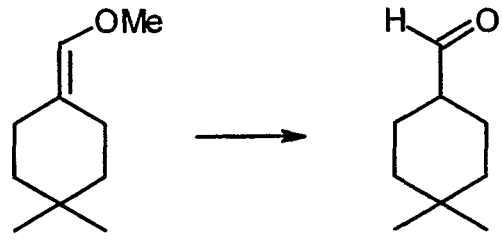
cooled to 0 °C. Jones reagent (40 mL) was added over 30 min and the cooling bath was removed. After 2 days the excess acetone was evaporated and the resulting residue was dissolved in water and diethylether. The ether layer was washed with water until colorless, dried, filtered and concentrated to give 4,4-dimethylcyclohexanone (7.4 g, 58.6 mmol, 64%).

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



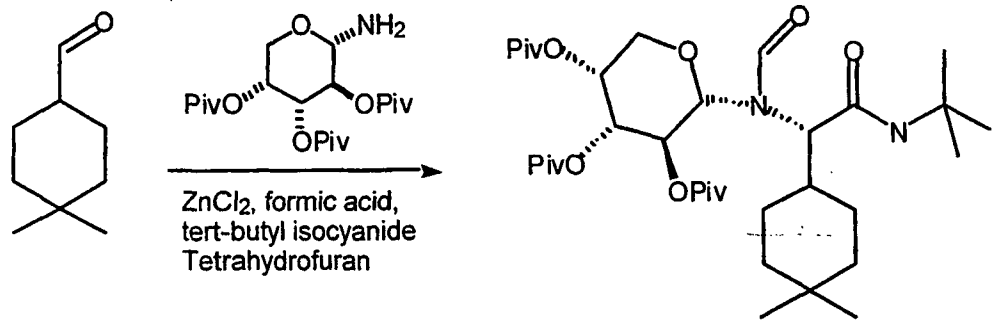
To a solution of methoxymethyl triphenylphosphonium chloride (8.6 g) in tetrahydrofuran (125 mL) at 0 °C was added n-butyllithium (1.6M in hexanes, 14.3 mL) over 10 min. After 30 min the reaction mixture was cooled to –78 °C and a solution of 4,4-dimethylcyclohexanone (2.45 g, 19.1 mmol) in tetrahydrofuran (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:



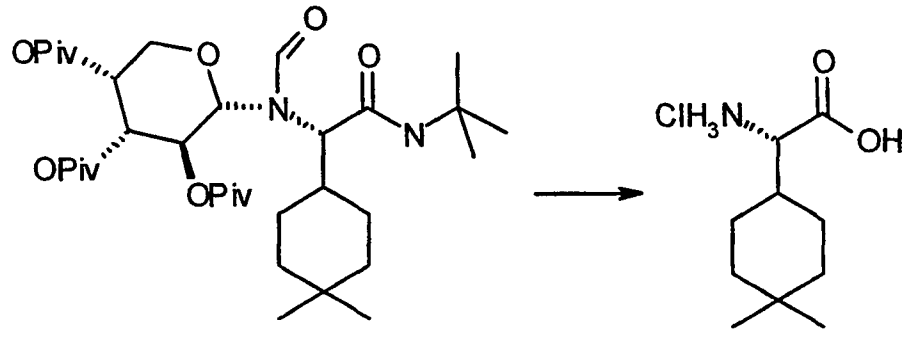
A solution of the methyl enol ether of 4,4-dimethylcyclohexylcarboxaldehyde (1.925 g, 12.5 mmol) (Step II above), tetrahydrofuran (100 mL) and 6M HCl (20 mL) was stirred at room temperature for 4 hours. The reaction mixture was diluted with hexanes, diethylether, brine and water. The organic layer was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



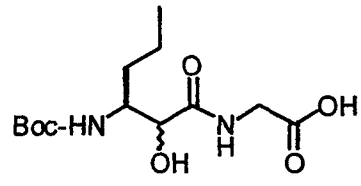
To a solution of 4,4-dimethylcyclohexylcarboxaldehyde (1.17 g, 8.34 mmol), 2,3,4-tri-O-pivaloyl-α-D-arabinosylamine (3.43 g, 8.55 mmol), formic acid (350 μL, 9.17 mmol) and tert-butylisocyanide (990 μL, 8.76 mmol) in THF (70 mL) at –30 °C was added 0.5M zinc chloride in tetrahydrofuran (17 mL, 8.5 mmol). 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:

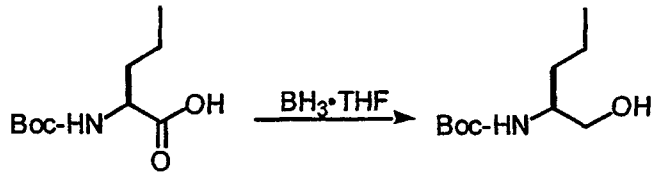


A solution of the Ugi product obtained in step 4 above (2.1 g, 3.3 mmol) in dichloromethane (20 mL) and saturated anhydrous methanolic HCl (20 mL) was stirred overnight. The solution was concentrated and the residue was dissolved in water (100 mL) and washed with pentane (2 x 100 mL). The aqueous layer 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:

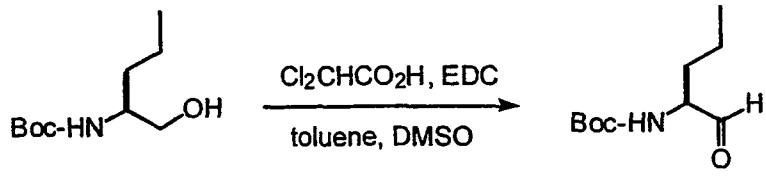


Step 1. Preparation of Boc-norvalinol:



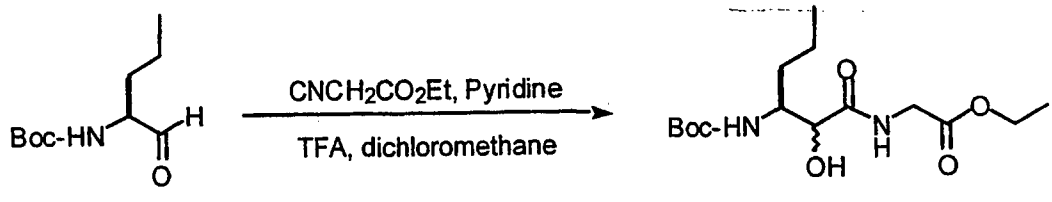
To a solution of Boc-norvaline (25.0 g, 0.115 mol) in tetrahydrofuran (461 mL), cooled to 0°C, was added borane/tetrahydrofuran complex (461 mL of a 1.0M solution in tetrahydrofuran) dropwise. After 1h at 0°C, the solution was warmed to room temperature over a period of 1.5h. TLC indicated that the reaction 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:



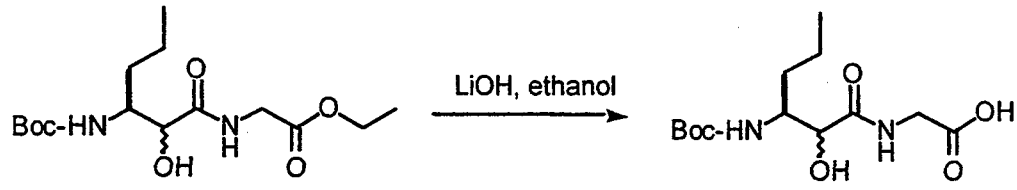
To Boc-norvalinol (7.77 g, 38 mmol), in anhydrous dimethylsulfoxide (153 mL) and toluene (153 mL) was added EDC (73.32g, 382 mmol). After the solution was cooled to 0°C, dichloroacetic acid (15.8 mL, 191 mmol) was added dropwise. After addition was complete, the reaction was stirred for 15 min. The solution 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:



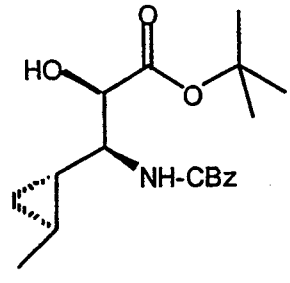
To a solution of the crude Boc-norvalinal (4.18 g, 20.77 mmol) in dichloromethane (83 mL) was added ethylisocyanoacetate (2.72 ml, 24.93 mmol) and pyridine (6.72 ml, 83.09 mmol). After the solution was cooled to 0°C, trifluoroacetic acid (4.15 ml, 41.54 mmol) was added dropwise. After stirring for 1h, 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:

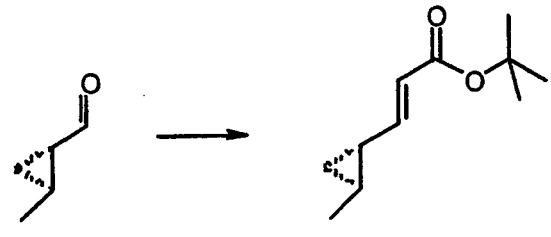


The product obtained (Boc-nVal-(CHOH)-Gly-OEt) (1.52 g, 4.70 mmol) dissolved in ethanol (23 ml) was saponified with 1N lithium hydroxide (18.81 ml) for two hours at room temperature. The reaction mixture was acidified to pH ≅ 2 with Dowex® 50 WX8 ion exchange resin, stirred for 20 minutes and then filtered. 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:



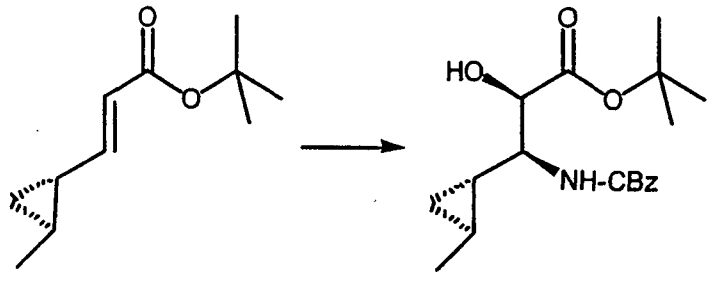
Step 1:



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

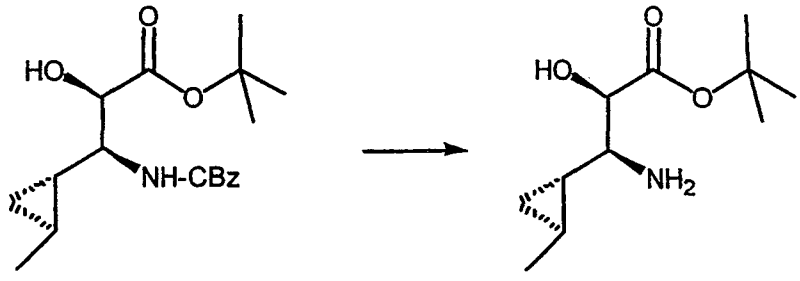
was quenched with saturated ammonium chloride (20 mL) and the organic layer was separated, washed with 50 mL brine and dried over sodium sulfate, filtered and concentrated to afford 3.5 g of a clear oil. Flash chromatography (20% ethylacetate in hexanes) afforded pure unsaturated tert-butylester (1.4 g).

Step 2:



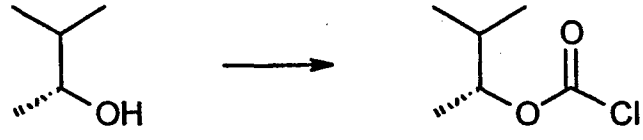
To a solution of benzyl carbamate (3.55g, 23.5 mmols) in n-propanol (24 mL) was added a solution of sodium hydroxide (900 mg ,22.7 mmol)in water (48 mL), followed by tert-butylhypochlorite (2.57 mL, 22.7 mmol). After 15 minutes the reaction was cooled to 0 ^{o}C and $(DHQ)_2PHAL$ (350 mg, 0.45 mmol) 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).

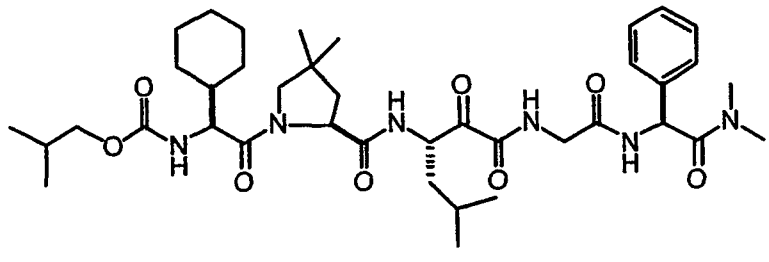
Example XX. Synthesis of 1R,2-dimethylPropyl chloroformate:



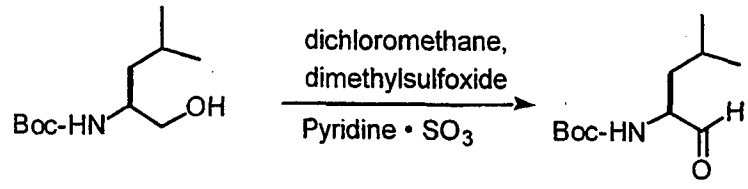
To the commercially available 2R-hydroxy-3-methylbutane (410 mg, 4.65 mmol) was added a solution of 20% phosgene in toluene (1 mL, 2 mmol). The solution was stirred for 6 hours to generate the chloroformate (2 mmol) which was reacted directly and immediately with the desired amine. The S-isomer was synthesized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

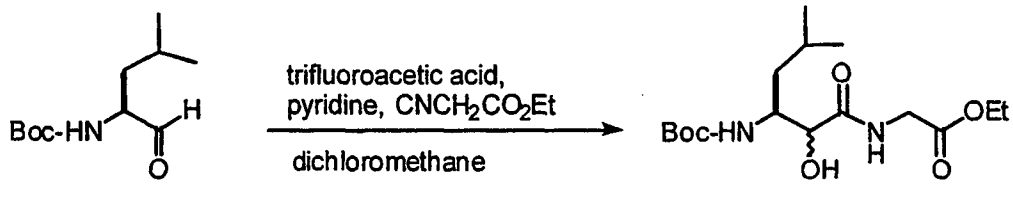


Step 1. Synthesis of tert-butyloxycarbonyl-leucinal (Boc-Leu-CHO):



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.

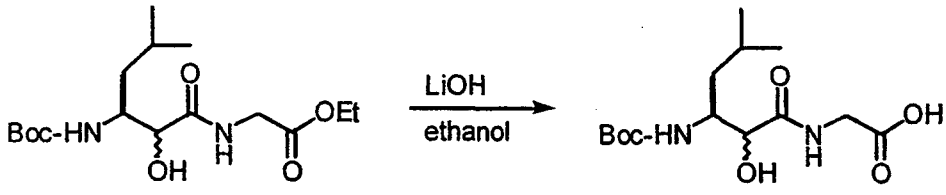
Step 2. Synthesis of Boc-2-hydroxy-3-amino-5-methyl hexanoyl-glycine ethyl ester (Boc-Leu-(CHOH)-Gly-OEt):



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

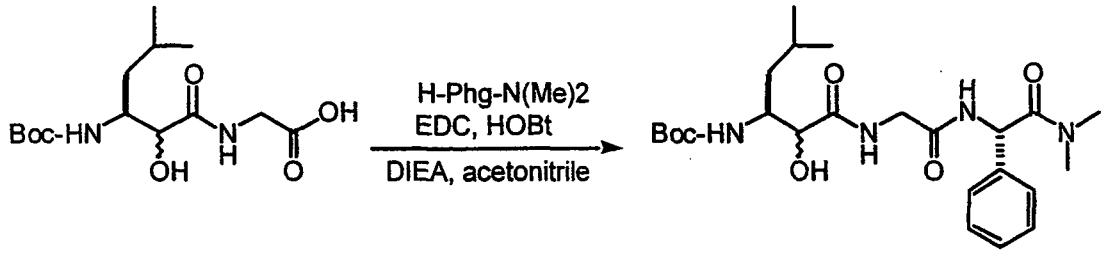
2" x 6" silica gel column using 10% ethylacetate in hexanes (800 ml) followed by 1:1 ethylacetate in hexanes (800 ml). The fractions corresponding to the product were pooled and concentrated to yield 980 mg (79%) product.

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.

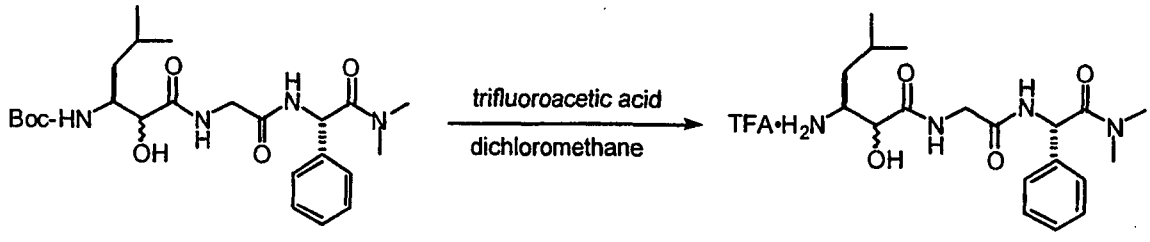
Step 4. Synthesis of Boc-Leu-(CHOH)-Gly-Phg-dimethylamide:



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

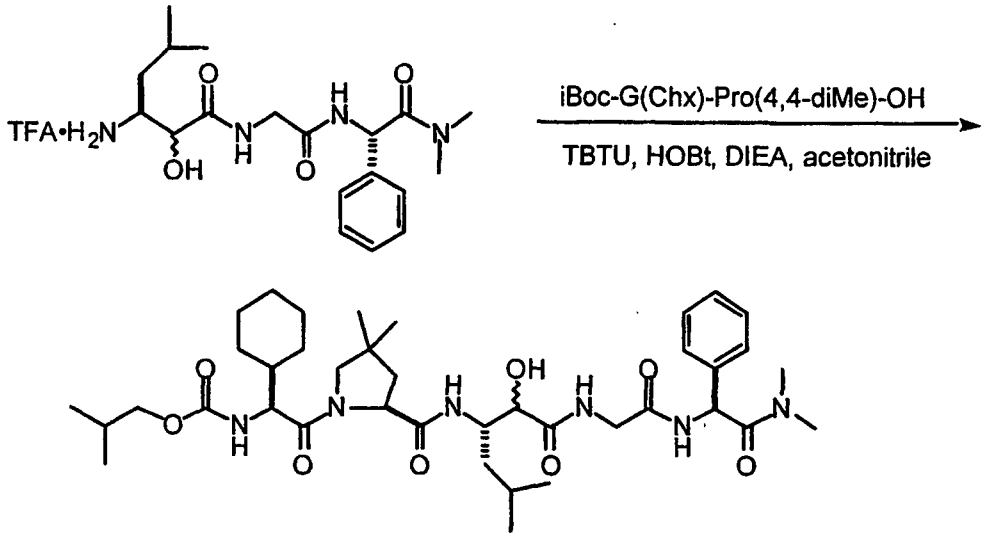
flash chromatography in a 2" × 6" silica gel column using 4:1 ethylacetate: hexanes (700 ml) followed by ethylacetate (1000 ml) and 10% methanol in dichloromethane (600 ml). The fractions corresponding to the product were pooled and concentrated to yield 445 mg (80%) white solid.

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.

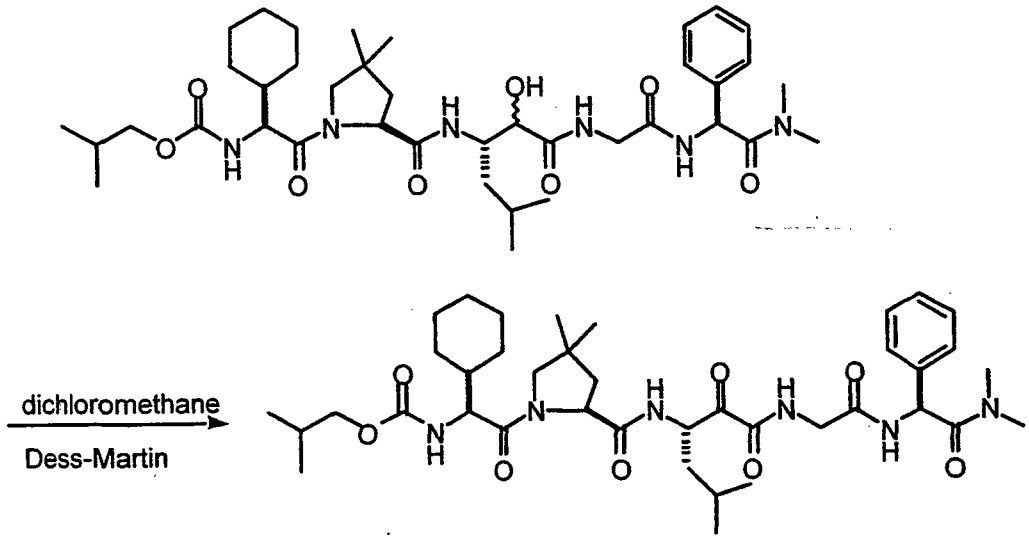
Step 6. Synthesis of iBoc-G(Chx)-Pro(4,4-dimethyl)-Leu-(CHOH)-Gly-Phg-dimethylamide:



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 × 5 ml), saturated sodium bicarbonate solution (2 × 5 ml), and brine (2 × 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 × 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 × 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).

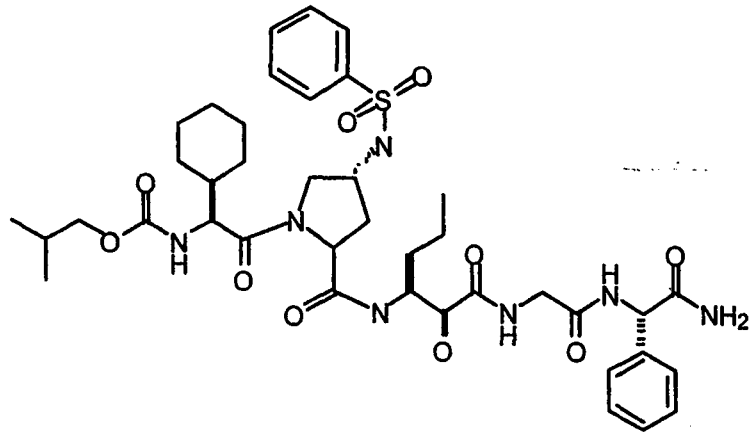
Procedure C: *Boc deprotection*: The Boc-protected resin was treated with a 1:1 mixture of dichloromethane and trifluoroacetic acid for 20-60 minutes (10 mL solvent/ gram resin). The reagents were drained and the resin was washed successively with dichloromethane, dimethylformamide, 5% diisopropylethylamine 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 (2×) 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%).

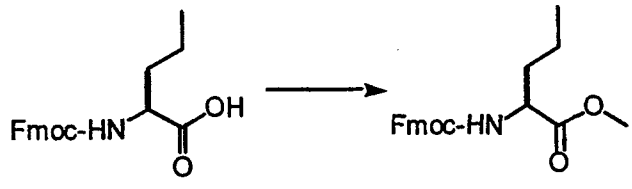
b) Synthesis of allyl isocyanoacetate:



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).

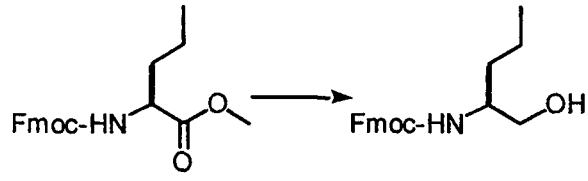
B) Synthesis of 9-fluorenylmethoxycarbonyl-norvalinal (steps a-c below):

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



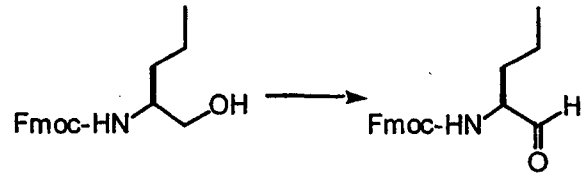
To a chilled solution of the commercially available Fmoc-norvaline (25 g, 73.75 mmol) in anhydrous methanol (469 ml) was added thionyl chloride (53.76 ml, 737.5 mmol) over one hour. TLC in ethylacetate taken an hour later confirmed the completion of the reaction (R_f = 0.85). The reaction mixture was 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 × 500 ml), saturated sodium bicarbonate (3 × 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):

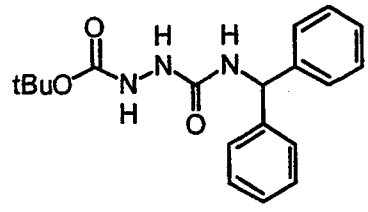


To a solution of Fmoc-norValinol (21.70 g, 66.77 mmol) in dichloromethane (668 ml) was added triethylamine (37.23 ml, 267 mmol) and the solution was cooled to 0°C. A suspension of pyridine sulfur trioxide complex (42.51 g, 267 mmol) in dimethylsulfoxide (96 ml) was added to the chilled solution. After 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 × 50 ml), 1N

saturated sodium bisulfate (2 × 50 ml), saturated sodium bicarbonate (2 × 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.

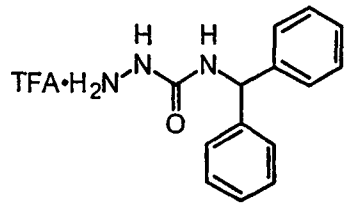
C) Synthesis of diphenylmethyl semicarbazide (dpsc) trifluoroacetate salt (steps a-b below):

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



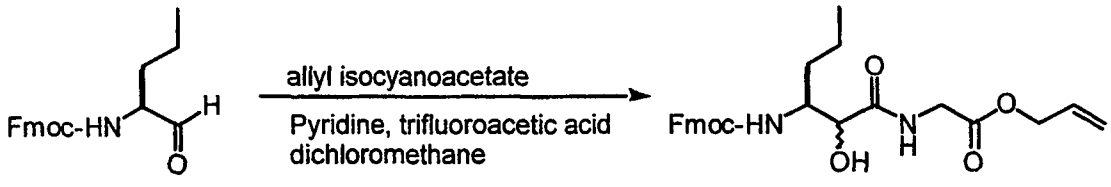
To a solution of carbonyldiimidazole (16.2 g, 0.10 mole) in dimethylformamide (225 ml) was added a solution of t-butyl carbazate (13.2 g, 0.100 mol) in dimethylformamide (225 ml) dropwise over 30 minutes. Diphenylmethylamine (18.3 g, 0.10 mol) was added next over 30 minutes. The reaction was allowed 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, $CF_3\underline{C}O_2H$).

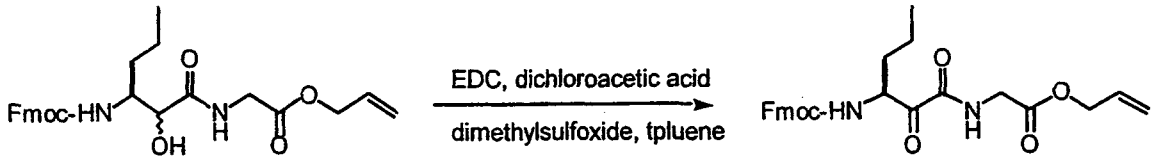
D) Synthesis of Fmoc-nVal-(CHOH)-Gly-Oallyl:



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),

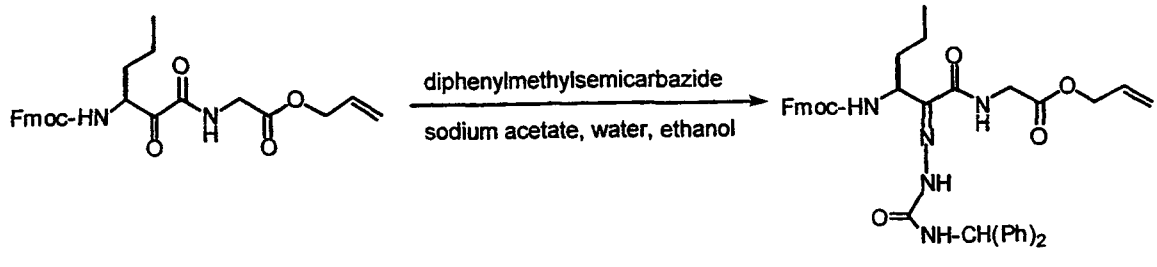
4.3-4.4 (m, 2H), 4.15-4.25 (m, 1H), 4.01 (s, 1H), 3.9-4.0 (m, 3H), 1.5-1.6 (m, 2H), 1.35-1.45 (m, 3H), 0.9 (m, 3H).

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).

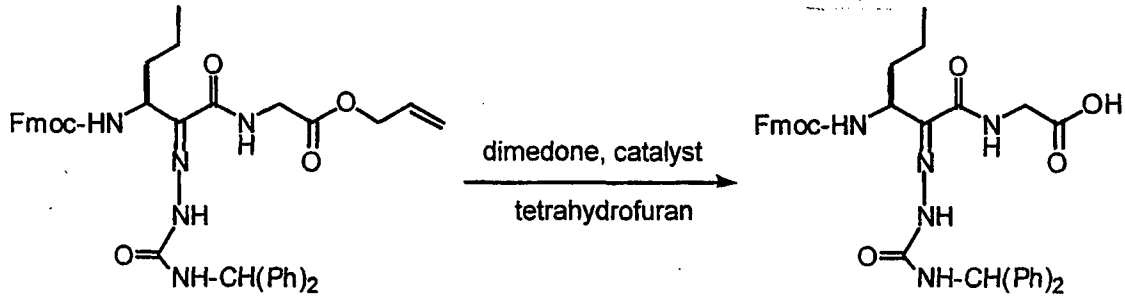
F) Synthesis of Fmoc-nVal-(dpsc)-Gly-Oallyl:



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 × 10 ml), saturated sodium bicarbonate (2 × 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.

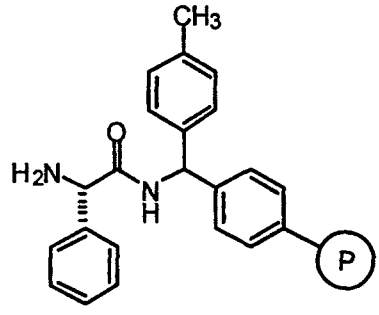
G) Synthesis of Fmoc-nVal-(dpsc)-Gly-OH:



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

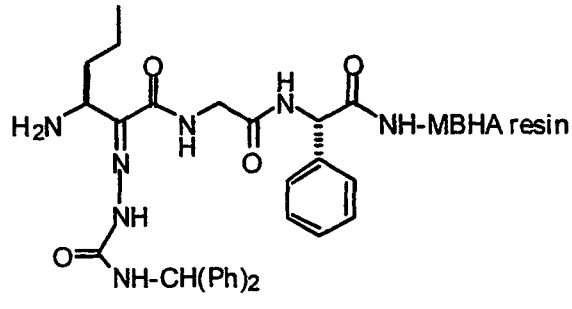
in 9:1 dichloromethane: methanol showed two spots (cis and trans isomers). NMR δ ppm (CD_3OD): 7.75 (m, 2H), 7.6 (m, 3H), 7.2-7.4 (m, 14H), 6.1-6.2 (m, 1H), 4.25-4.4 (m, 2H), 4.1-4.2 (m, 2H), 3.85 (s, 2H), 1.6-1.8 (m, 2H), 1.3-1.5 (m, 2H), 0.95 (t, 3H).

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.

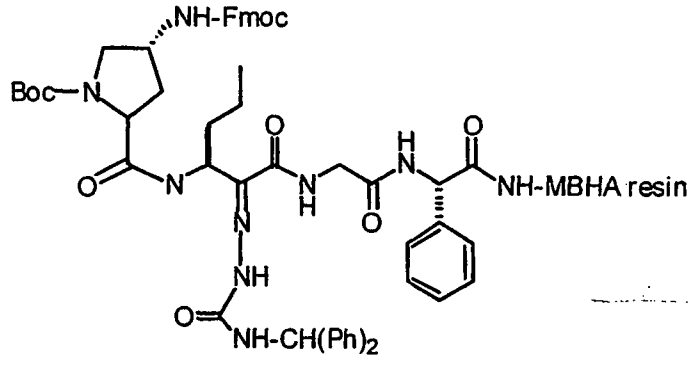
Step 3. Synthesis of H-nVal(dpsc)-Gly-Phg-MBHA resin:



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

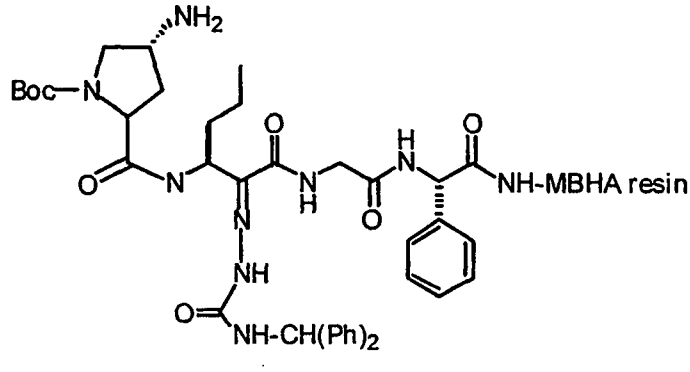
Procedure A. After 18 hours, quantitative ninhydrin analysis indicated 99.91% coupling efficiency. The resin was subjected to Fmoc deprotection according to procedure B. A qualitative ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction.

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



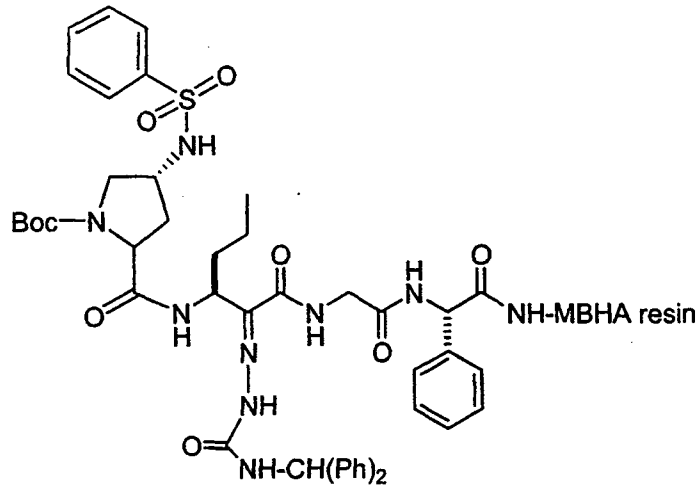
The compound H-nVal(dpsc)-Gly-Phg-MBHA resin (Step 3 above) (600 mg, 0.8 mmol/g, 0.67 mmol) was transferred to a fritted polypropylene tube and was coupled to Boc-Pro(4t-NHFmoc)-OH (Example VI, Step 3) (610 mg, 1.34 mmol) according to procedure A. After 18 hours, quantitative ninhydrin analysis indicated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

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



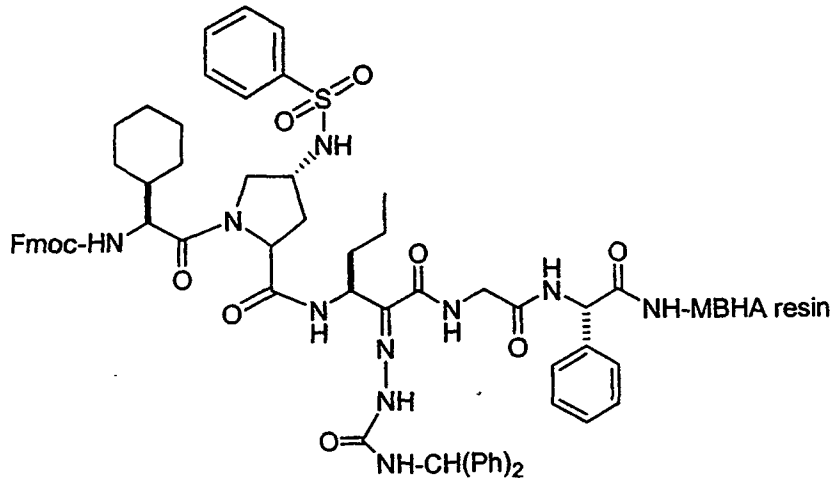
The resin from the previous step (Boc-Pro(4t-NHFmoc)-nVal(dpsc)-Gly-Phg-MBHA resin) was subjected to Fmoc deprotection according to procedure B. A qualitative ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction.

Step 6. Synthesis of Boc-Pro(4t-NHSO$_2$Bn)-nVal(dpsc)-Gly-Phg-MBHA resin:



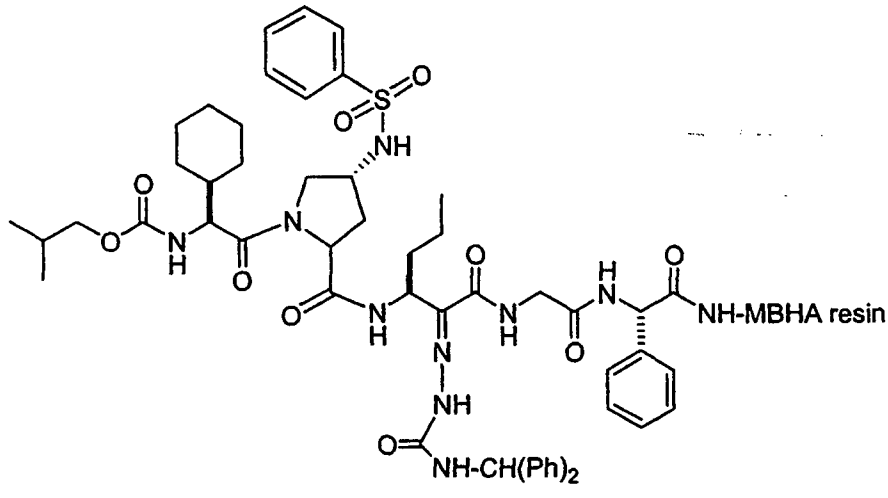
To the resin obtained from the previous step (Boc-Pro(4t-NH$_2$)-nVal(dpsc)-Gly-Phg-MBHA resin) (0.2 g, 0.22 mmol) suspended in NMP (2 ml) was added 2,4,6-collidine (0.24 ml, 1.79 mmol) and benzenesulfonyl chloride and the reaction was shaken for 18 hours. The solvent was drained and the resin was washed 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$_2$Bn)-nVal(dpsc)-Gly-Phg-MBHA resin:



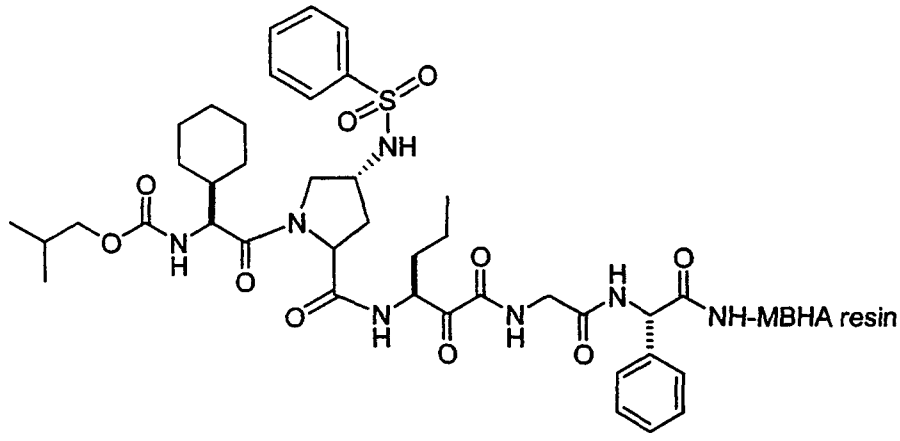
The resin obtained in the previous step (Boc-Pro(4t-NHSO$_2$Bn)-nVal(dpsc)-Gly-Phg-MBHA resin) was subjected to the Boc deprotection procedure according to Procedure C. Fmoc-G(Chx) (0.17 g, 0.45 mmol) was then coupled according to procedure A. After 18 hours qualitative ninhydrin analysis showed colorless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



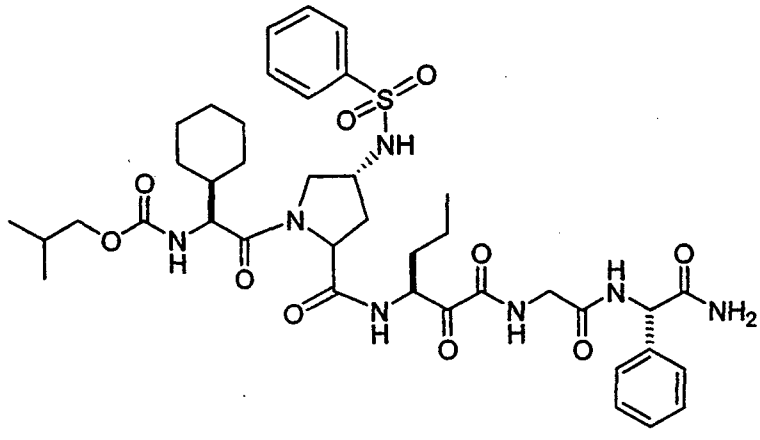
The resin obtained in the previous step (Fmoc-G(Chx)-Pro(4t-NHSO2Bn)-nVal(dpsc)-Gly-Phg-MBHA resin) was subjected to Fmoc deprotection according to procedure B. A ninhydrin assay on a small aliquot gave dark blue resin and solution, indicating a successful reaction. To the resin (0.2 g, 0.22 mmol) suspended 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:



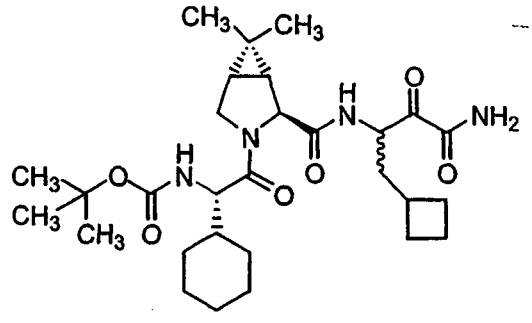
The resin of the previous step (iBoc-G(Chx)-Pro(4t-NHSO$_2$Bn)-nVal(CO)-Gly-Phg-MBHA resin) (100 mg) was subjected to HF cleavage condition (Procedure E) to yield the desired crude product. The material was purified by HPLC using a 2.2 x 25 cm reverse phase column, containing a C-18 resin comprised of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

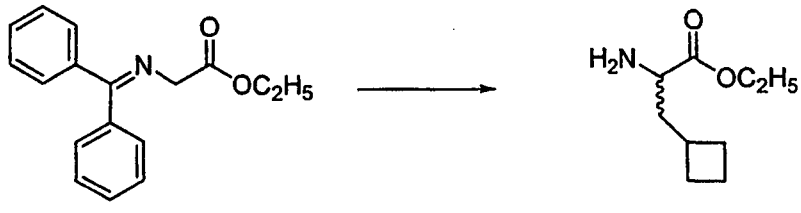
Representative procedures to prepare additional inventive compounds are shown below, and the compounds prepared by such procedures are listed in **Table 5.**

Example XXIII : Preparation of a Compound of Formula XXIII:



XXIII

Step 1.

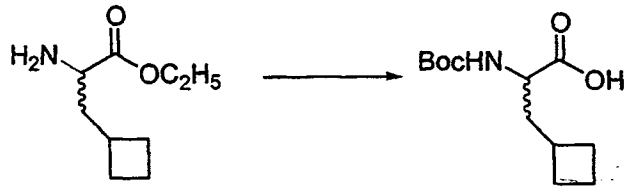


XXIIIa **XXXIIIb**

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.

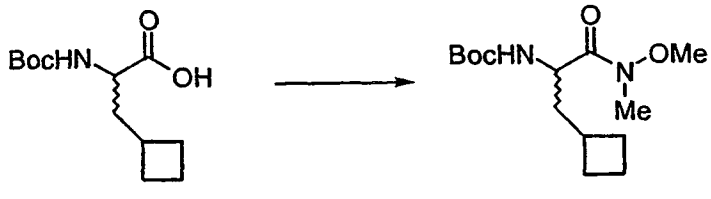
Step 2.



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•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.

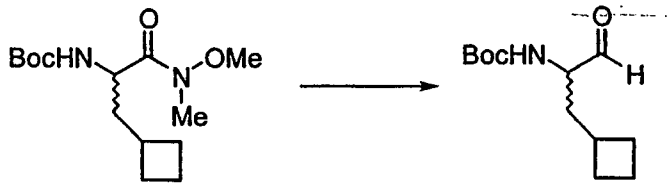
Step 3.



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.

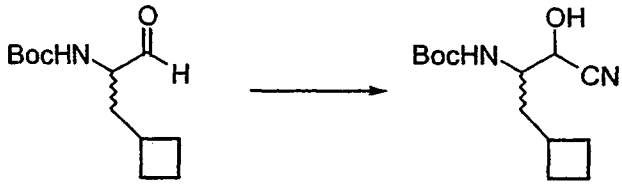
Step 4.



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).

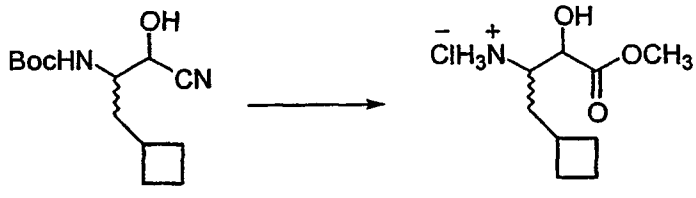
Step 5.



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.

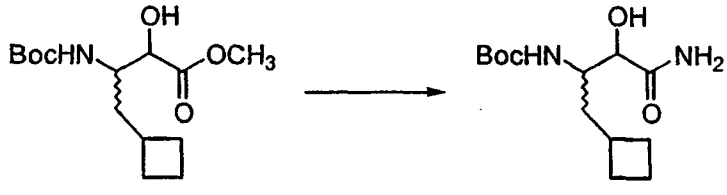
Step 7.



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.



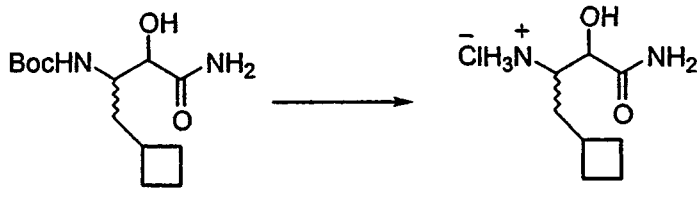
XXIIIh XXIIIi

A solution of methyl ester **XXIIIh** (3g, 10.5 mmol) in THF/H_2O (1:1) was treated with LiOH•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.)

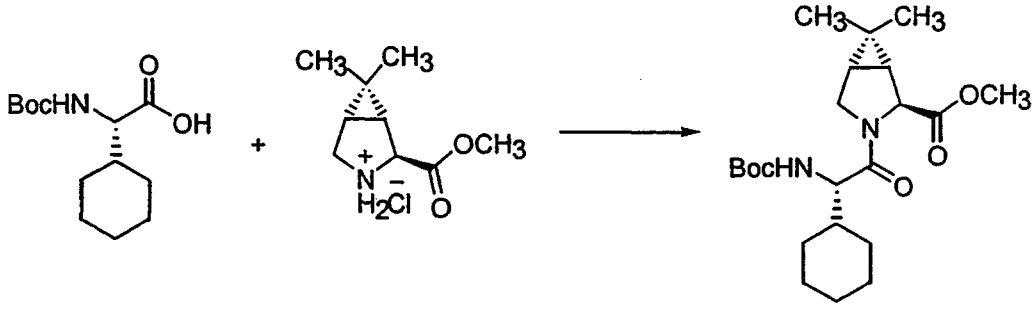
Step 9.



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.

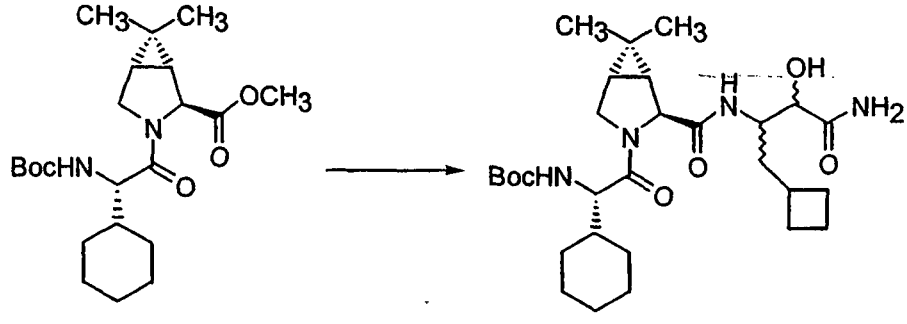


XXIIIk **XXIIIl** **XXIIIm**

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.

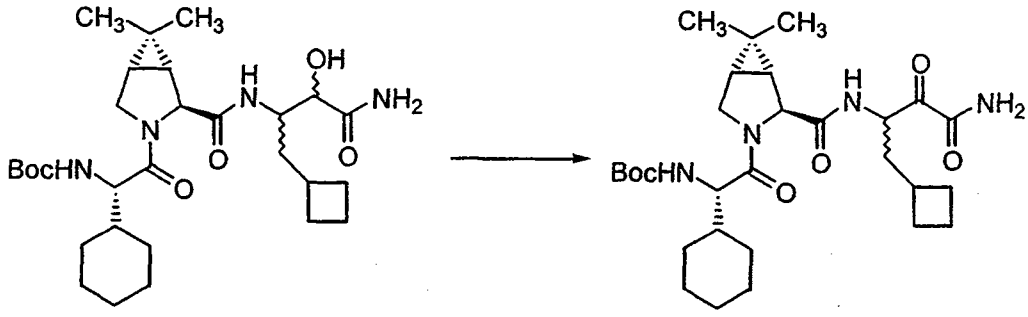


XXIIIm XXIIIn

A solution of methyl ester **XXIIIm** (4.0 g, 9.79 mmol) in THF/H_2O (1:1) was treated with LiOH•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.

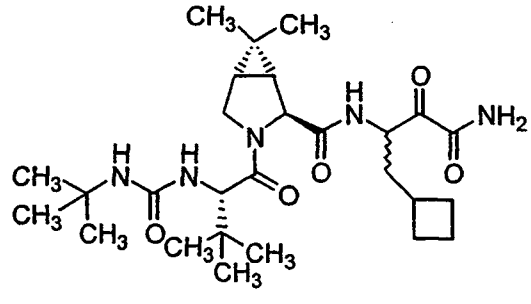
Step12.



XXIIIn XXIII

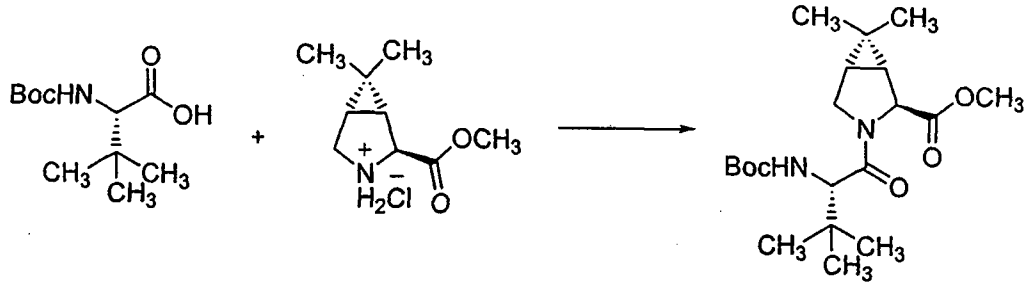
A solution of amide **XXIIIn** (2.08 g, 3.79 mmol) in toluene and DMSO (1:1 20 mL) at 0 °C was treated with EDCI (7.24 g, 37.9 mmol) and dichloroacetic acid (2.42 g, 19.9 mmol) and stirred at rt. for 4 h. The reaction mixture was diluted with CH_2Cl_2, washed with sat'd. $NaHCO_3$, and brine. The organic 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

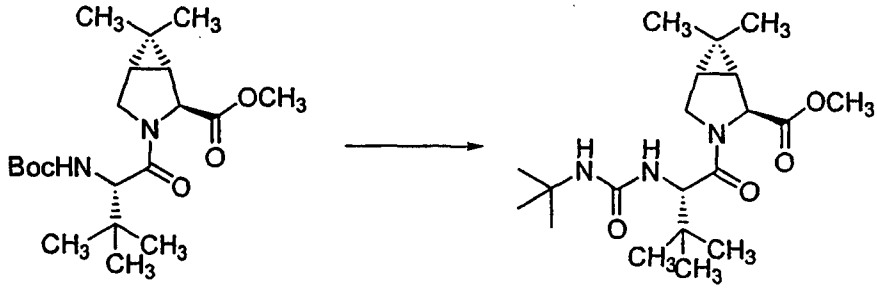
Step 1.



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.

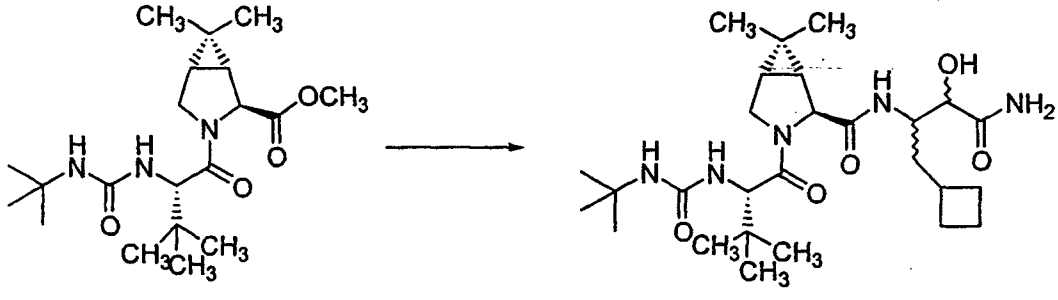


XXIVb XXIVc

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.

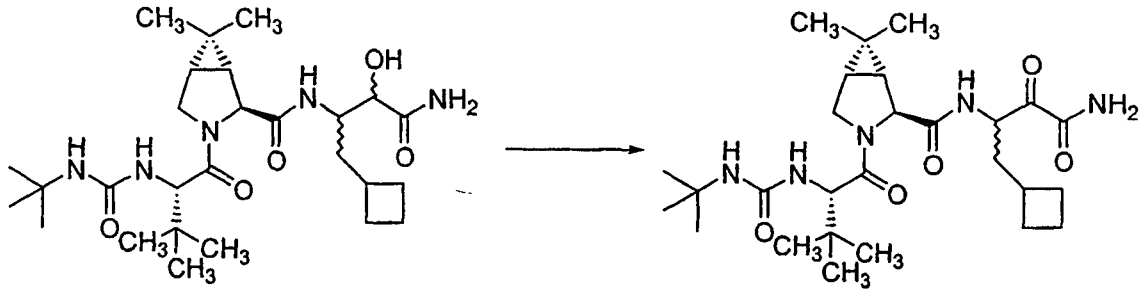


XXIVc **XXIVd**

A solution of methyl ester **XXIVc** (381 mg, 1.0 mmol) in THF/H_2O (1:1, 5 mL) was treated with $LiOH•H_2O$ (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.

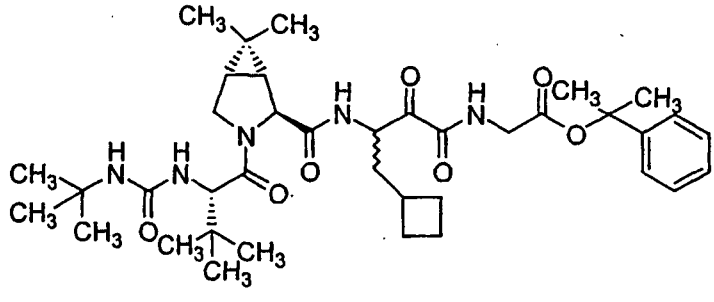
Step 4.



XXIVd XXIV

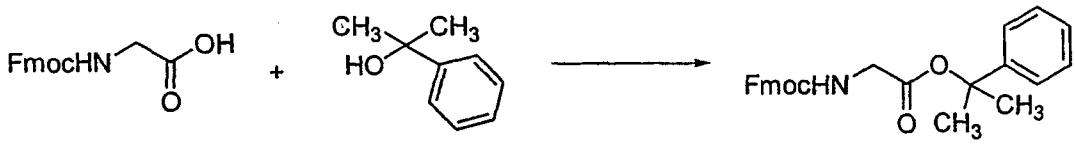
A solution of amide **XXIVd** (470 mg, 0.9 mmol) in toluene and DMSO (1:1 20 mL) at 0 °C was treated with EDCI (1.72 g, 9.0 mmol) and dichloroacetic acid (0.37 mL, 4.5 mmol) and stirred at 0 °C for 4h. The reaction mixture was diluted with CH_2Cl_2, and washed with satd. $NaHCO_3$, and brine. The organic 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 Prepration 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.

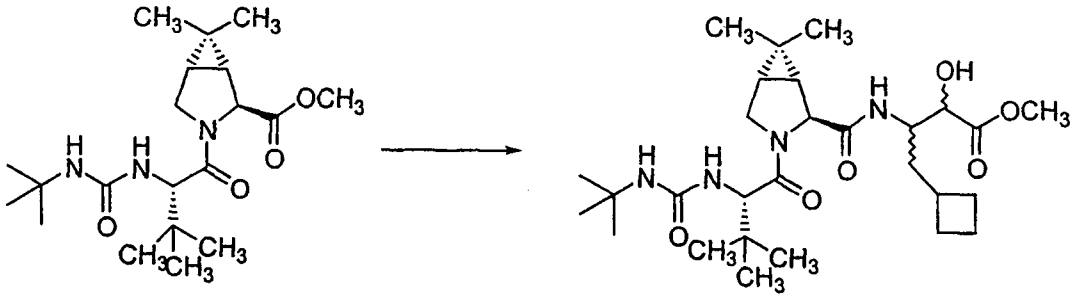
Step 2.



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.

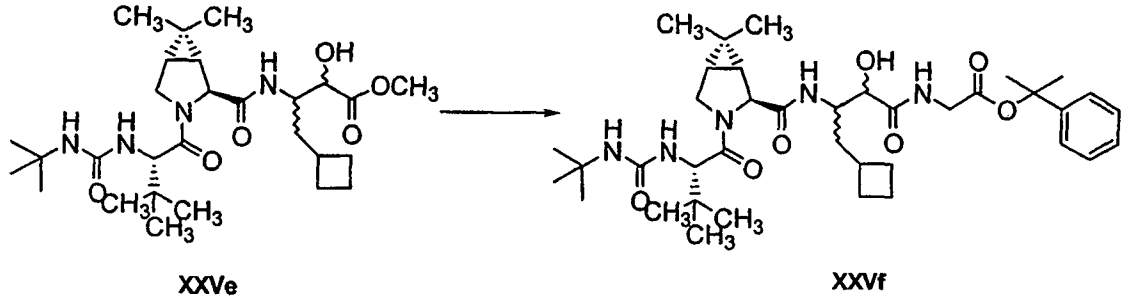


XXIVc XXVe

A solution of methyl ester **XXIVc** (381 mg, 1.0 mmol) in THF/H_2O (1:1, 5 mL) was treated with LiOH•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.

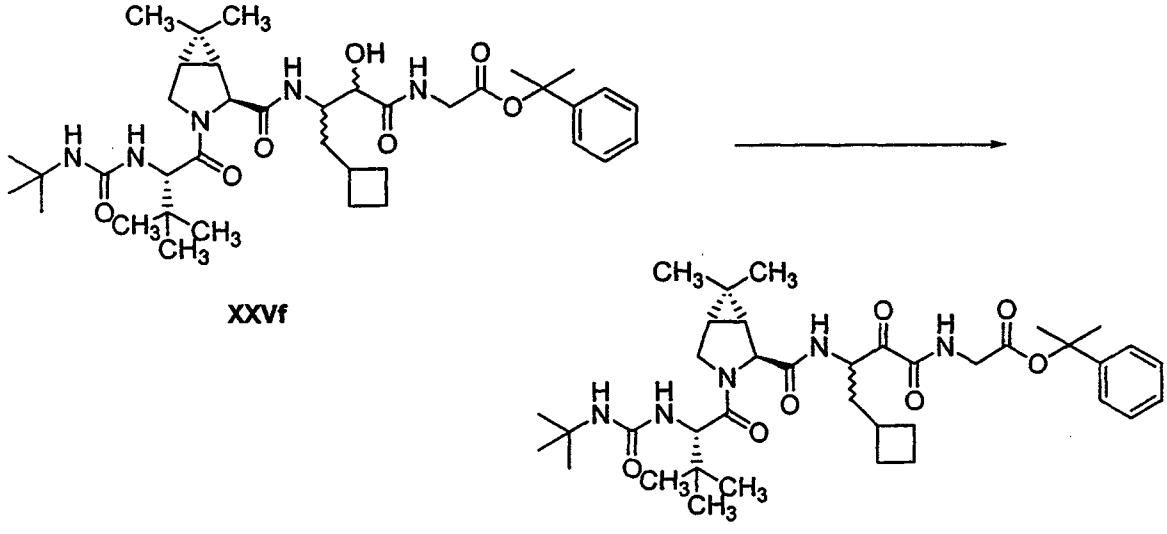


XXVe XXVf

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.

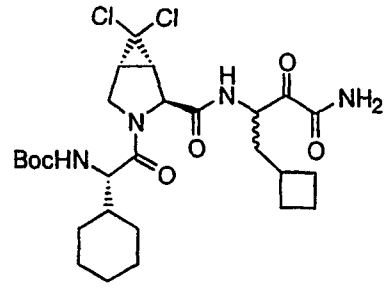


XXVf **XXV**

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

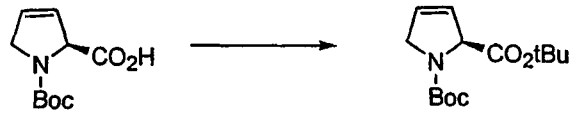
reaction mixture was stirred for 30 min and extractred with CH_2Cl_2 (3x30 mL). The combined organic layers were extracted with satd. NaHCO3, brine, dried ($MgSO_4$) filtered concentrated in *vacuo* and purified by chromatography (SiO_2, acetone/Hexanes 1:5) to yield XXV (122 mg) as a colorless solid.

Example XXVI Preparation of a compound of Formula XXVI:



XXVI

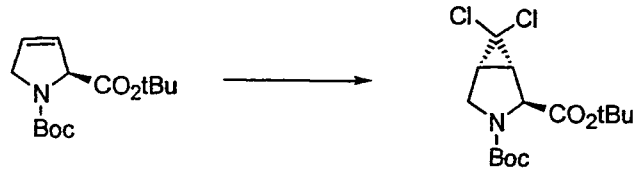
Step 1:



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%).

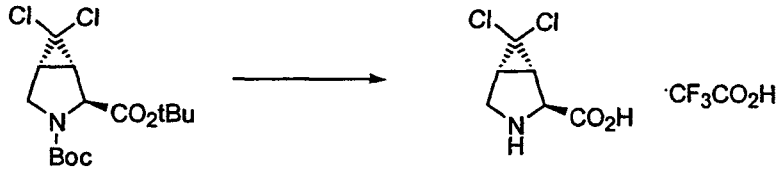
Step 2:



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.

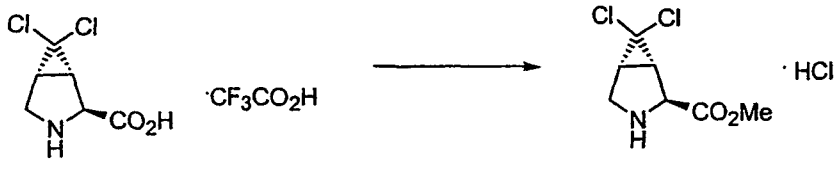
Step 3:



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.

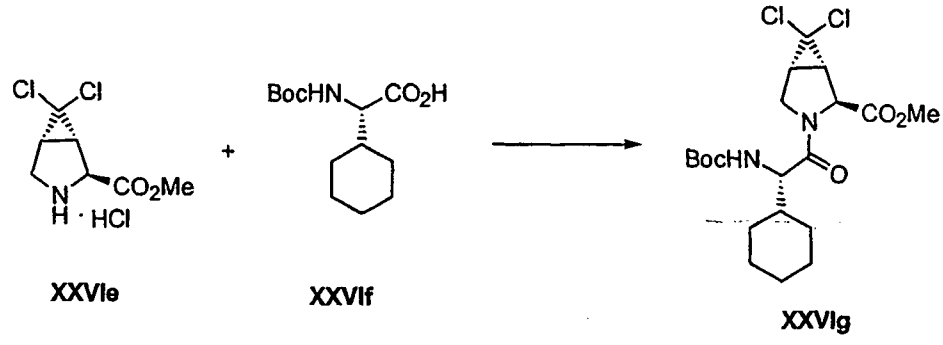
Step 4



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.

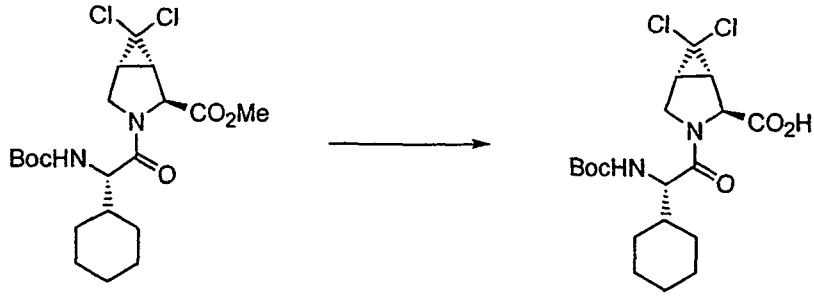
Step 5:



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.

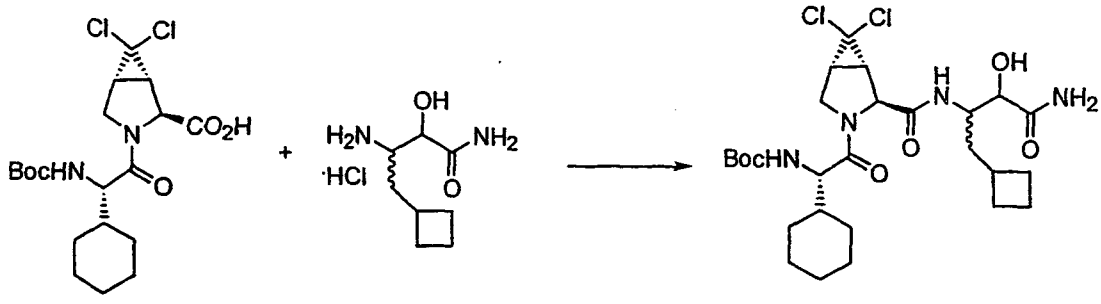
Step 6:



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).

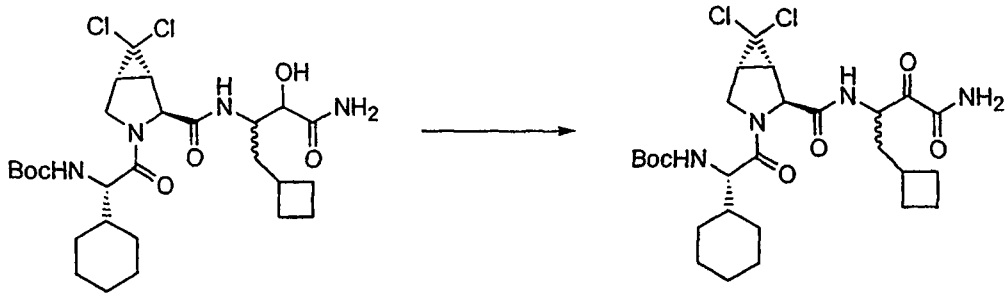
Step 7:



XXVIh XXIIIj XXVIi

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

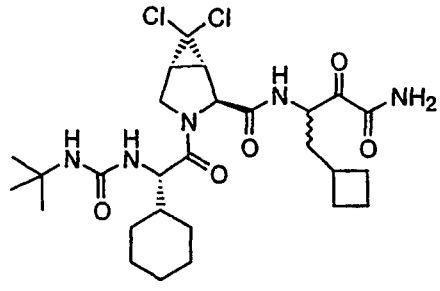
Step 8:



XXVIi XXVI

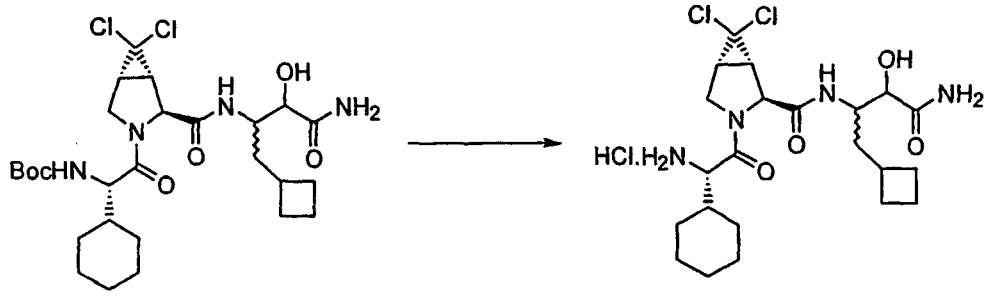
The desired product **XXVI** was prepared according to the procedure in Example XXIII, Step 12.

Example XXVII: Preparation of compound of formula XXVII:



XXVII

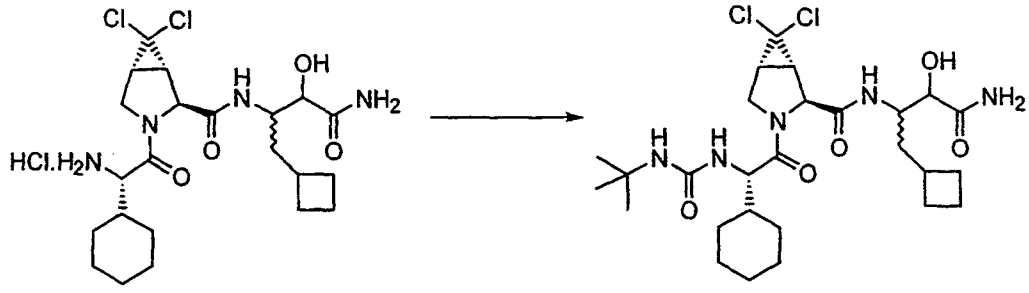
Step 1



XXVIi XXVIIa

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

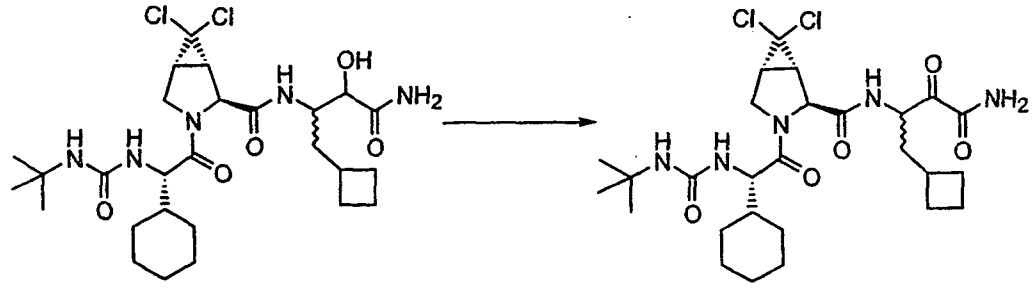
Step 2



XXVIIa **XXVIIb**

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

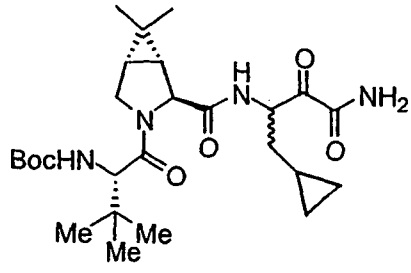
Step 3



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

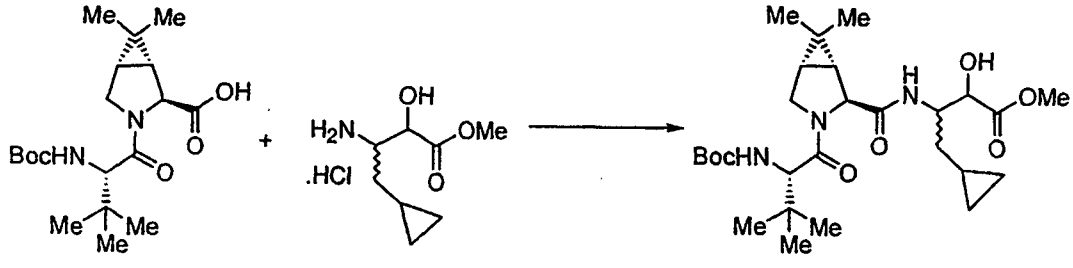
Step 1:



XXVIIIa **XXVIIIb**

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

Step 2:

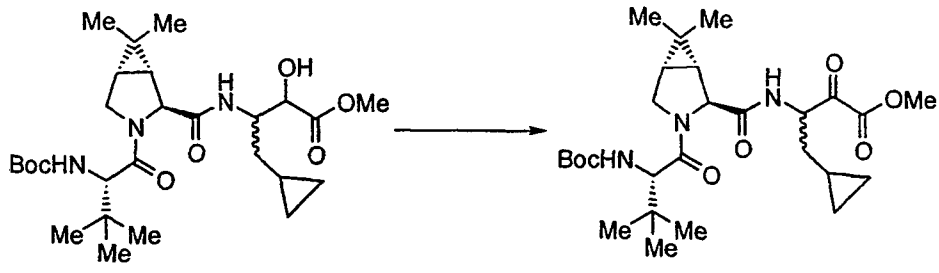


XXVIIIc **XXVIIIb** **XXVIIId**

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.**

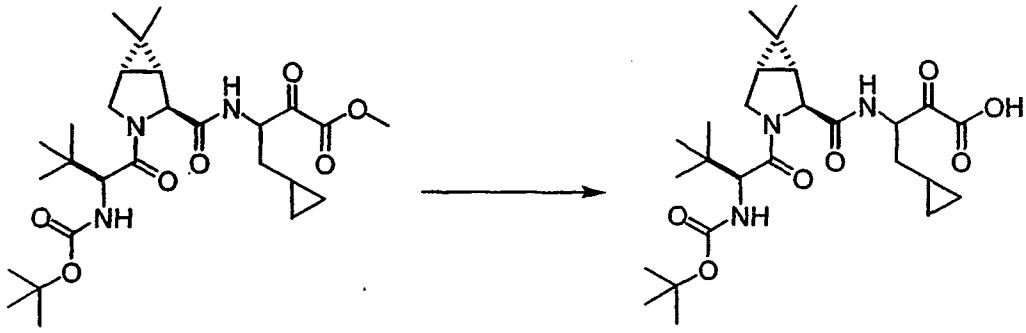
Step 3:



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:

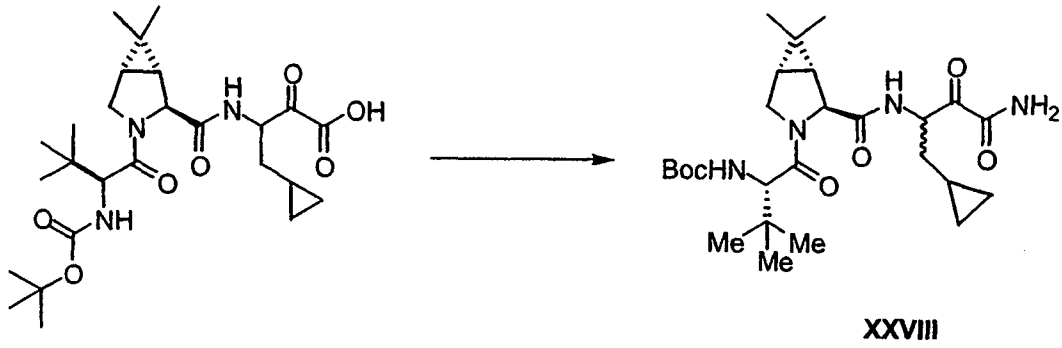


XXVIIIe **XXVIIIf**

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 ($M+H^+$).

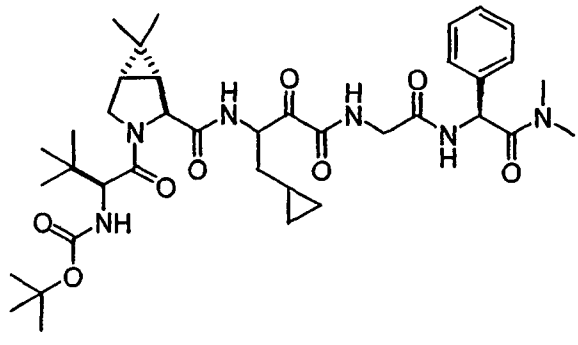
Step 5:



XXVIIIf **XXVIII**

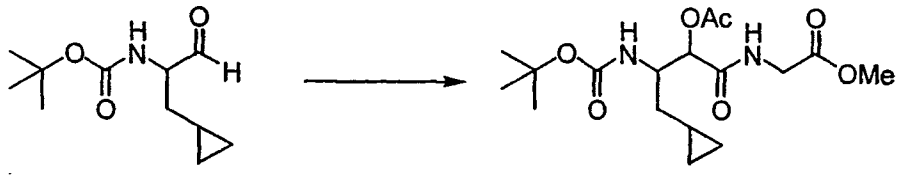
The product of Step 5 (0.15g) was dissolved in CH_2Cl_2 and reacted with HATU (0.137g), NH_4Cl (0.08g, 5equiv.) and DIPEA (0.53 mL). After 2 hours at room temperature, the reaction was diluted with EtOAc, washed with a 10% citric acid solution, then a saturated $NaHCO_3$ solution. The EtOAc layer was 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).

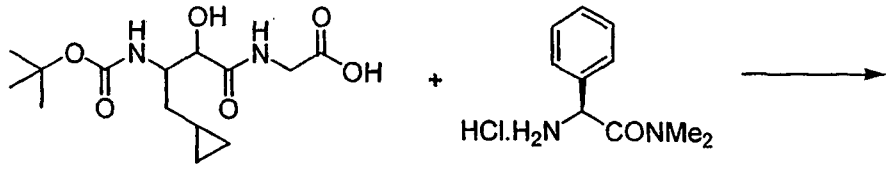
Step2:



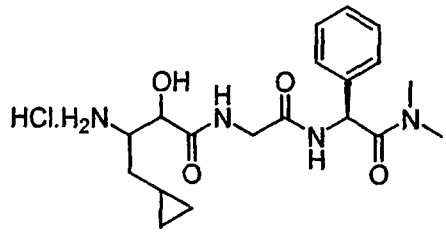
XXIXa **XXIXb**

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:



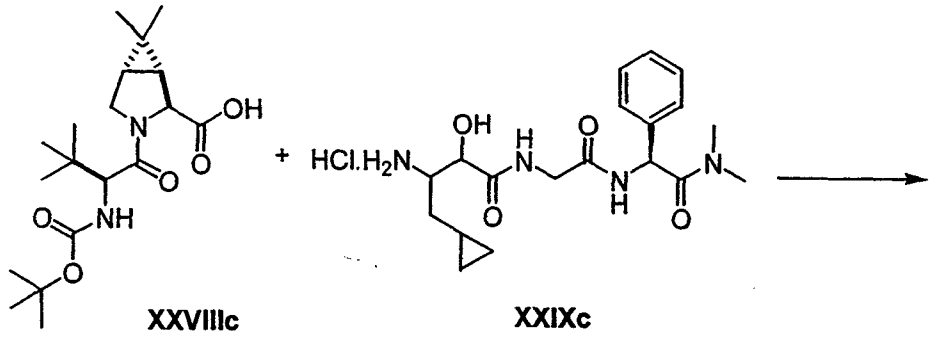
XXIXb XV



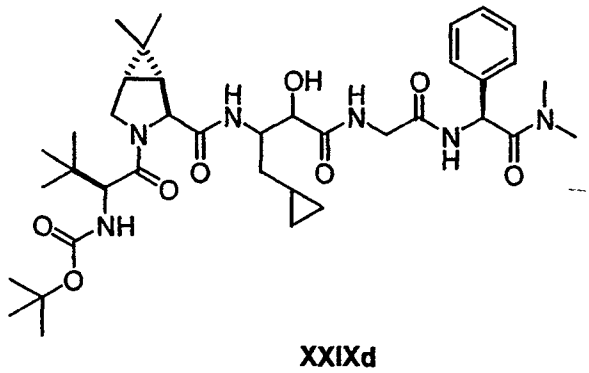
XXIXc

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:



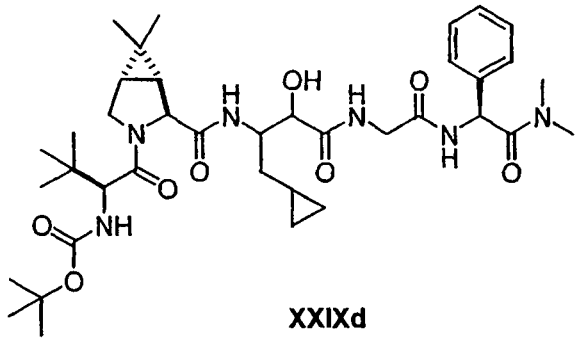
XXVIIIc XXIXc



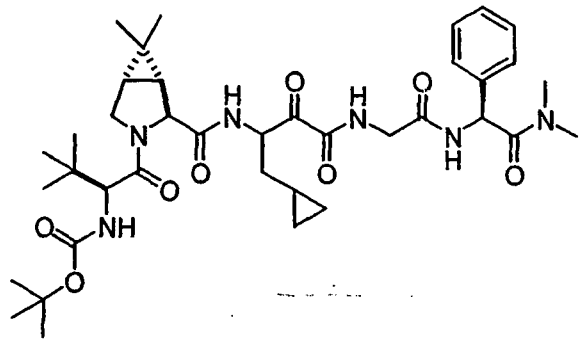
XXIXd

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:



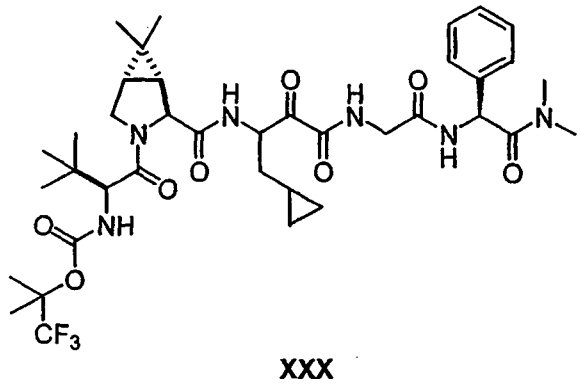
XXIXd



XXIX

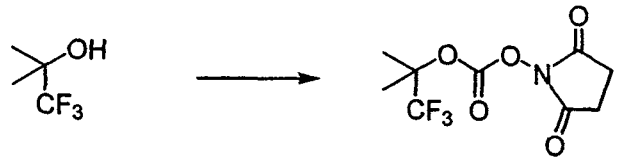
The product of Step 4 (4.2g) was reacted with Dess-Martin reagent (6.4g) in the manner previously described in preparative Example XX, Step 7. Purification by flash column chromatography (100% EtOAc, silica) furnished 3 g of the final product **XXIX**. Mass spectrum (LCMS) 725 ($M+H^+$).

Example XXX: Preparation of a compound of formula XXX:



XXX

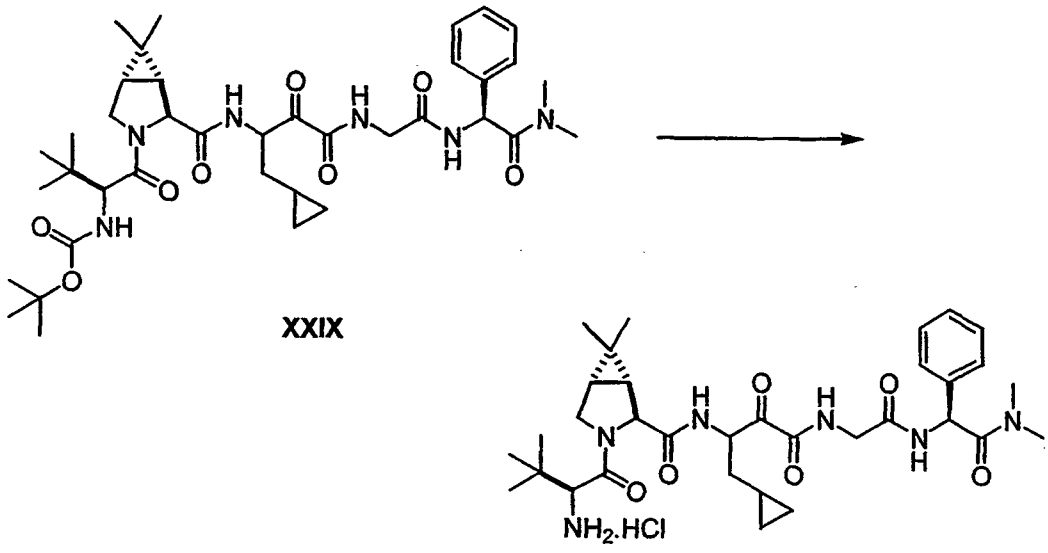
Step 1:



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:



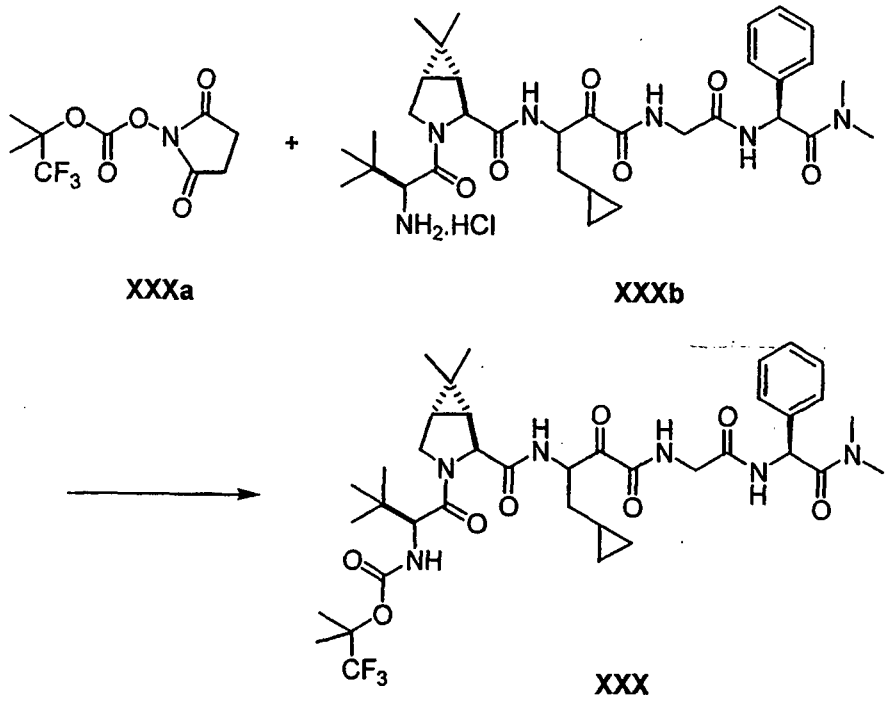
XXIX

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:

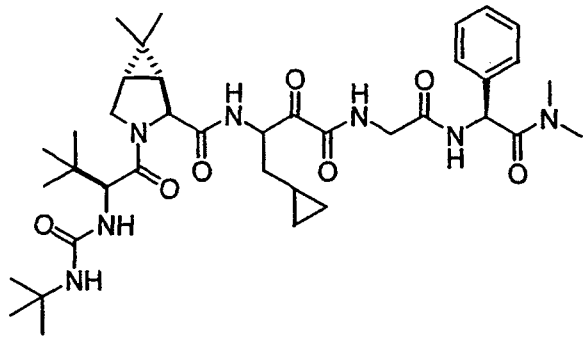


XXXa **XXXb**

XXX

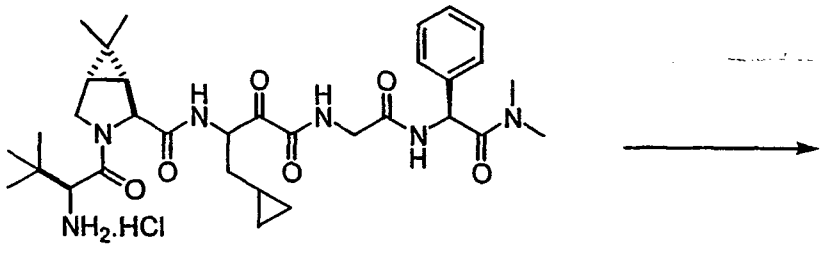
To a room temperature solution of **XXXb** (0.05g) in CH_2Cl_2 (5 mL) was added DIPEA (0.040 mL) **XXXa** (1.5 equiv., 0.030g), followed by 1 crystal of DMAP. After 30 minutes, reaction was diluted with EtOAc (20 mL) and washed with HCl 1.5 N then $NaHCO_3$ then brine. EtOAc layer was dried over $MgSO_4$, 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:

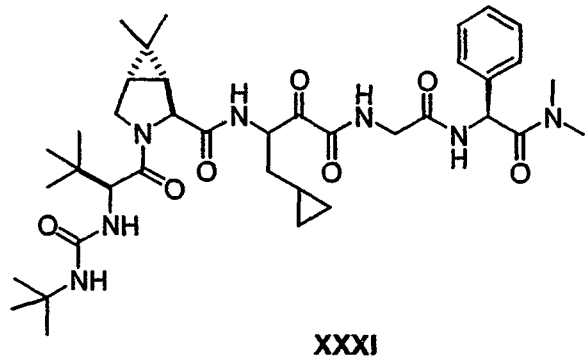


XXXI

Step 1:



XXXb

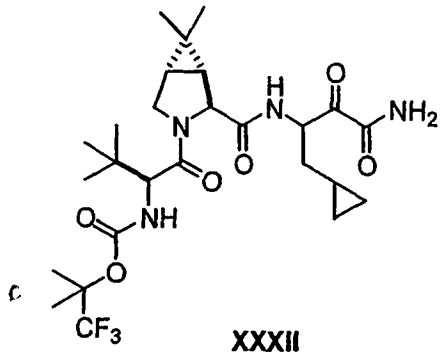


XXXI

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

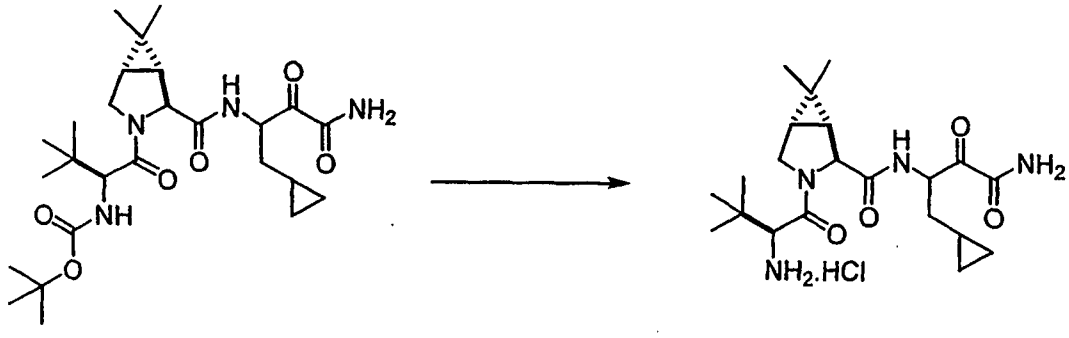
(100% EtOAc, silica) furnished the final product **XXXI** (0.021g). Mass spectrum (LCMS) 724 ($M+H^+$).

Example XXXII: Preparation of a compound of formula XXXII:



XXXII

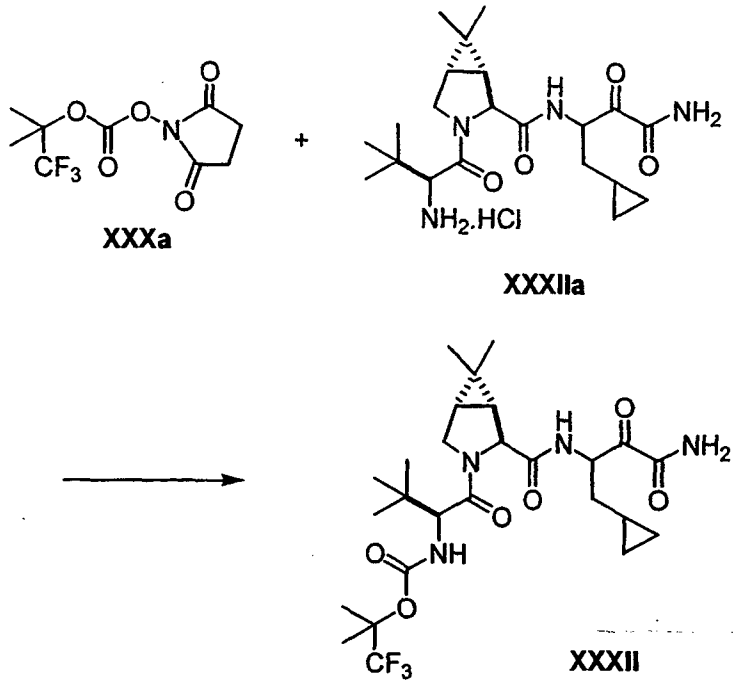
Step 1:



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:



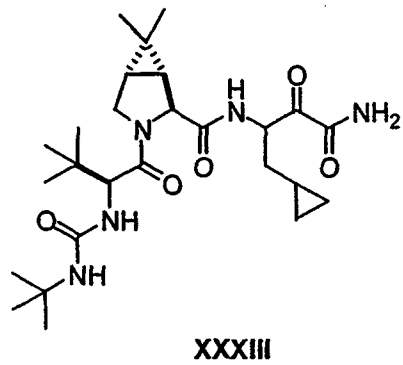
XXXa

XXXIIa

XXXII

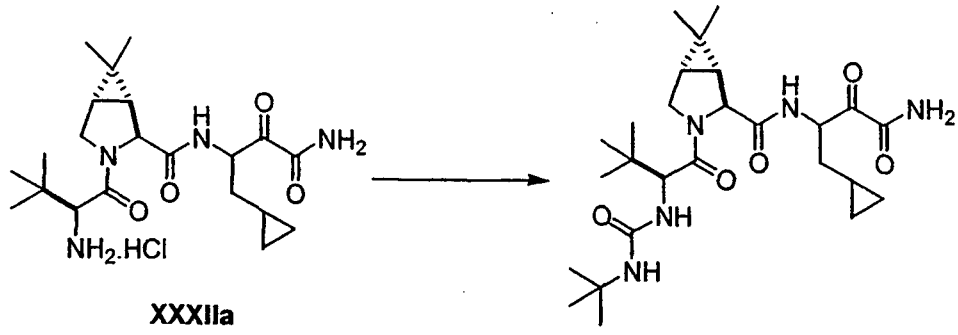
The amine **XXXIIa** was reacted with **XXXa** in the manner previously described in preparative Example XXX, Step 3 to afford the desired product **XXXII**. Mass spectrum (LCMS) 508 ($M+H^+$).

Example XXXIII: Preparation of a compound of formula XXXIII:



XXXIII

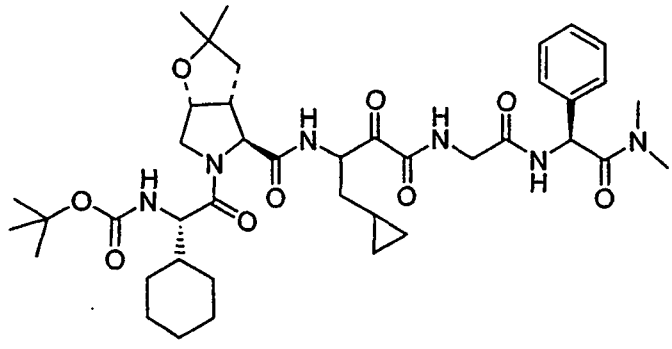
Step 1:



XXXIIa XXXIII

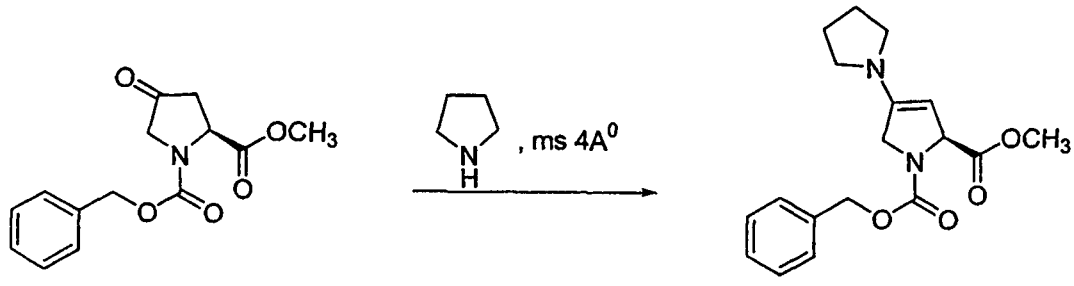
The amine **XXXIIa** was reacted with *tert*-butylisocyanate in the manner previously described in Example XXXI, Step 1, to afford the product **XXXIII**. Mass spectrum (LCMS) 561 ($M+H^+$).

Example XXXIV: Preparation of a compound of formula XXXIV:



XXXIV

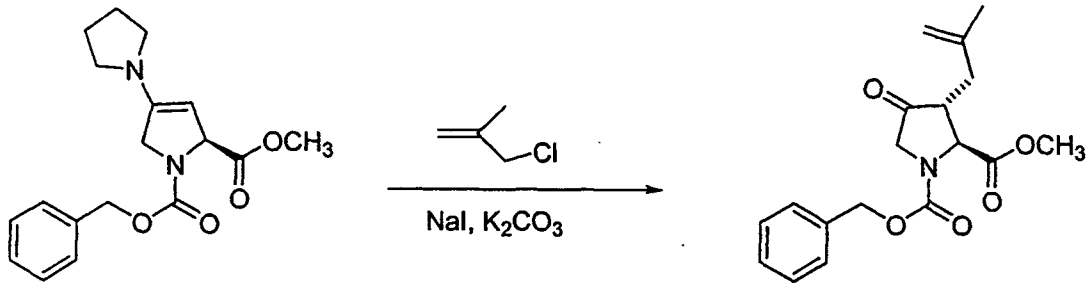
Step 1:



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

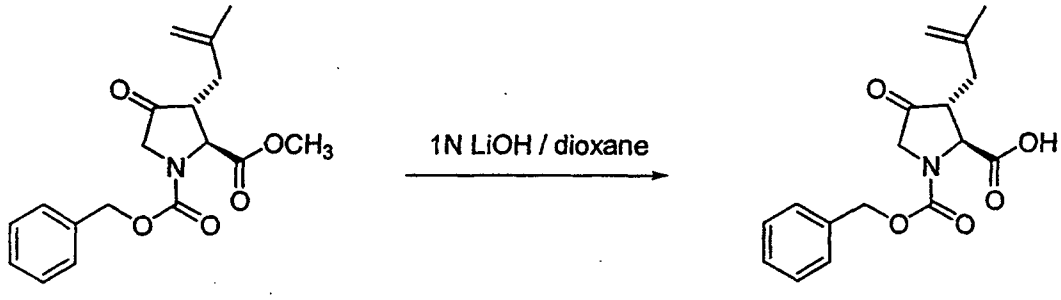
resulting brown slurry was stirred at room temperature under N_2 for 24 h, filtered and washed with anhydrous CH_3CN. The combined filtrate was concentrated to yield the desired product.

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.

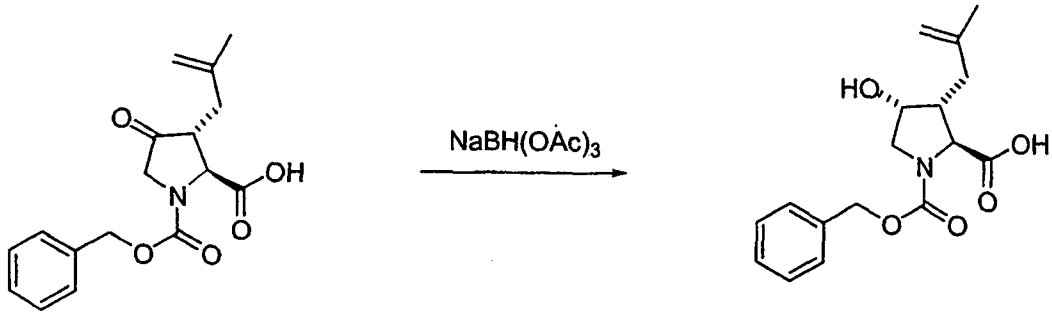
Step 3:



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

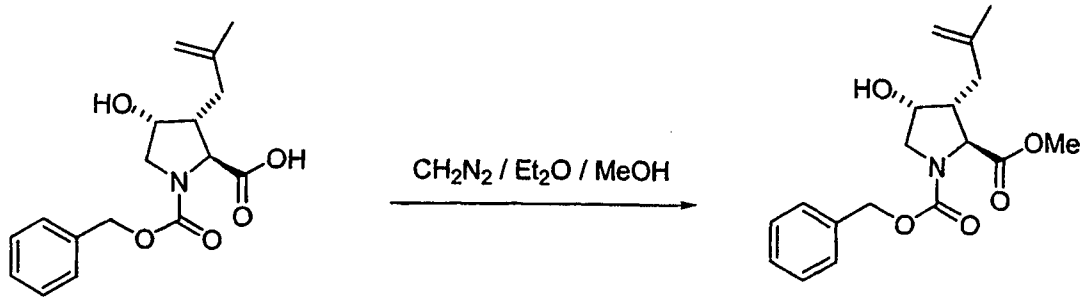
extracted with EtOAc (2 x 100 mL). Combined organic layer was washed with brine, dried over $MgSO_4$, concentrated to give the desired acid (3.40 g).

Step 4:



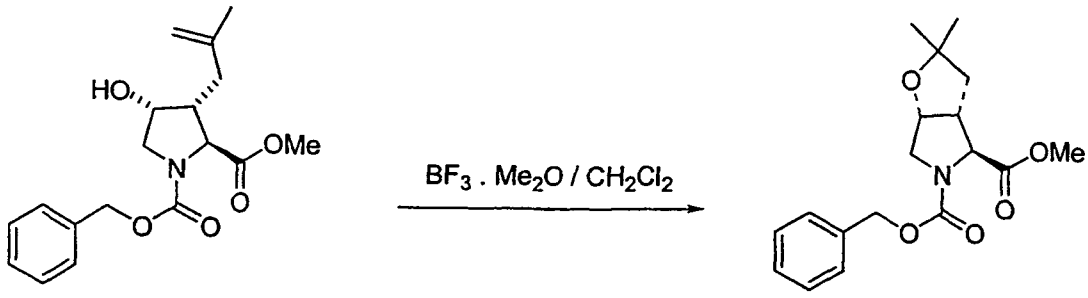
To a suspension of $NaBH(OAc)_3$ (3.93g, 18.5 mmoL) in CH_2Cl_2 (55 mL) was added a solution of product from preceding step in anhydrous CH_2Cl_2 (20 mL) and acetic acid (2 mL). The slurry was stirred at ambient temperature for 20 h . Ice cold water (100 mL) was added to the slurry and stirred for 1/2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

Step 5:



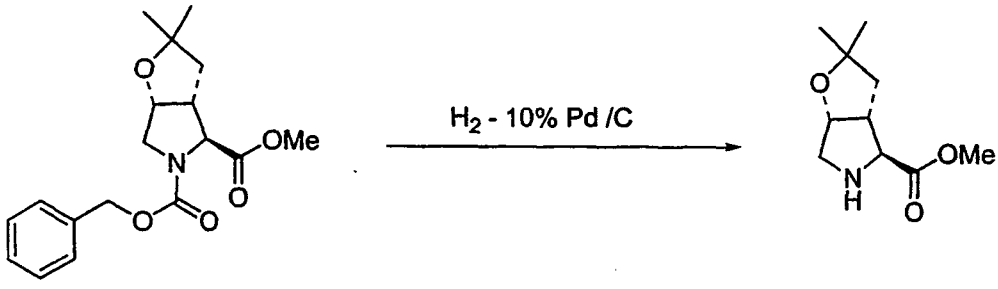
To a solution of the product from preceding step (1.9g) in MeOH (40 mL) was treated with excess of CH_2N_2 / Et_2O solution and stirred for overnight. The reaction mixture was concentrated to dryness to yield a crude residue. The residue was chromatographed on silica gel, eluting with a gradient of EtOAc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

Step 6:



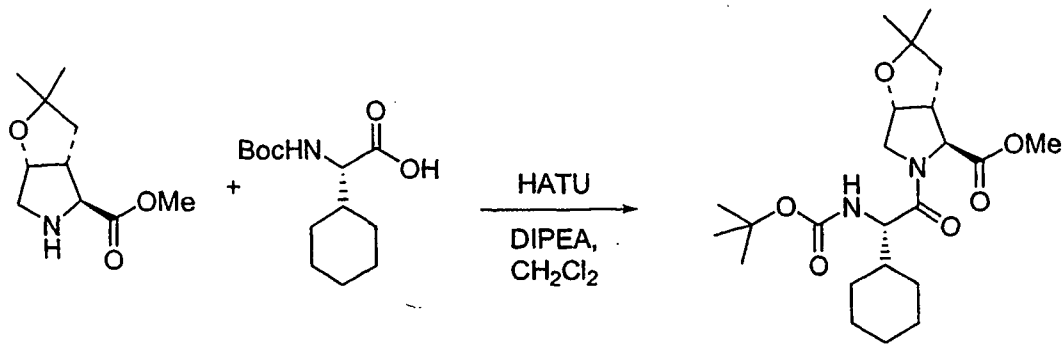
To a solution of product from preceding step (1.36 g) in anhydrous CH_2Cl_2 (40 mL) was treated with BF_3. Me_2O (0.7 mL). The reaction mixture was stirred at ambient temperature for 20 h and quenched with sat. $NaHCO_3$ (30 mL) ad stirred for 1/2 hr. Organic layer was separated and combined organic 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:



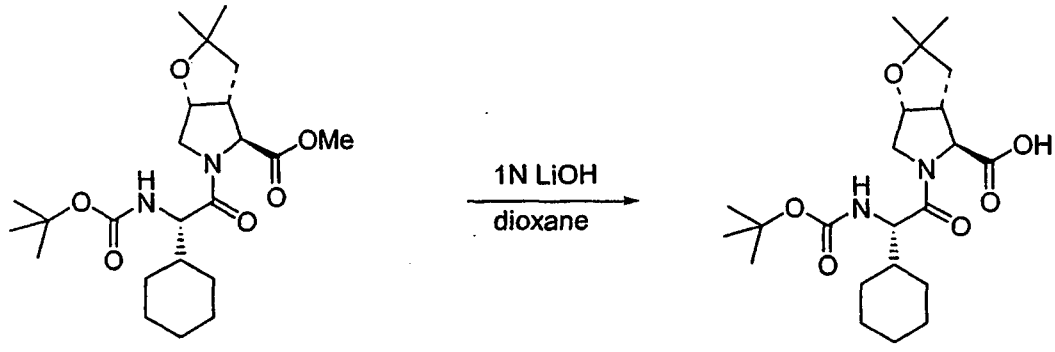
To a solution of the product (0.92 g) from preceding step in MeOH (30 mL) was added 10 % Pd/C (0.16 g) at room temperature and hydrogenated at ambient temperature under 1 atm. Pressure. The reaction mixture was stirred for 4 h and concentrated to dryness to yeild the desired compound.

Step 8:



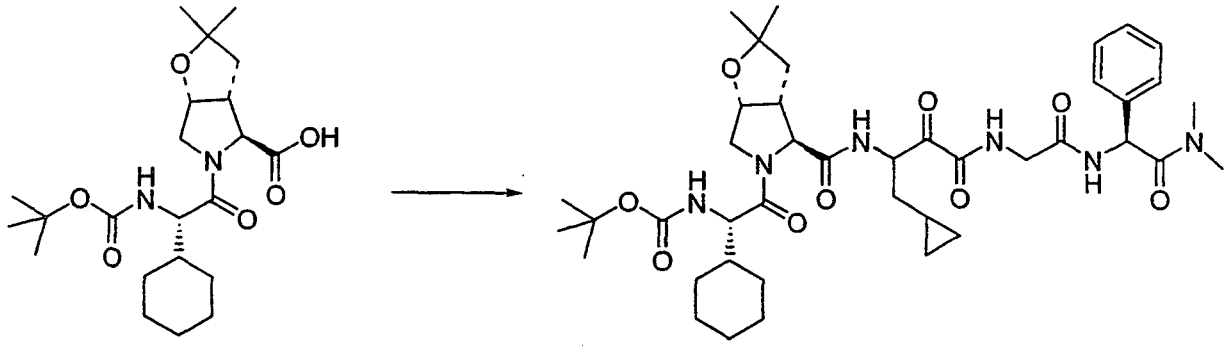
The desired product was prepared according to the procedure in Example XXIII, Step 10.

Step 9:



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

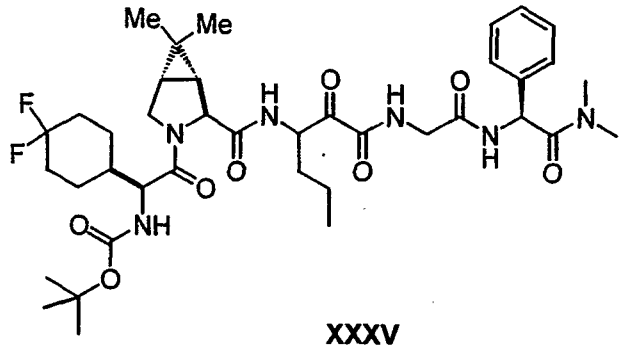
Step 10:



XXXIV

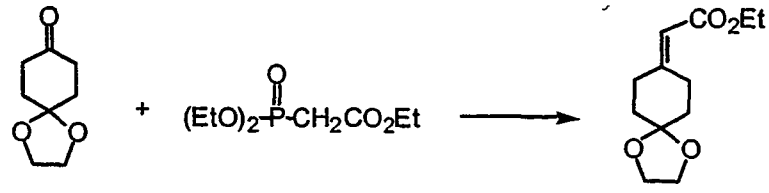
The desired product **XXXIV** was prepared according to the procedure in Example XXIX, Steps 4-5.

Example XXXV: Preparation of a compound of formula XXXV:



XXXV

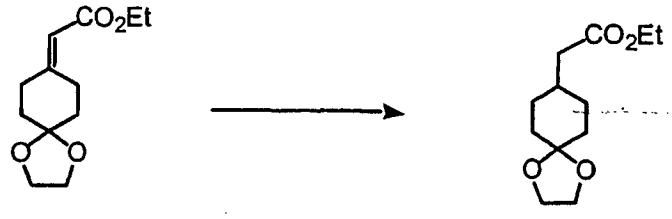
Step 1:



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

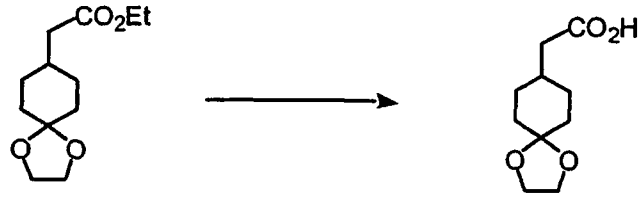
added dropwise, and the resulting solution was stirred at RT for 18 hours. The reaction mixture was then cooled to 0°C, treated with cold aqueous citric acid, and the mixture was extracted with EtOAc. The extract was washed with saturated aqueous $NaHCO_3$, then brine; then dried over anhydrous Na_2SO_4, 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 ($M+H^+$).

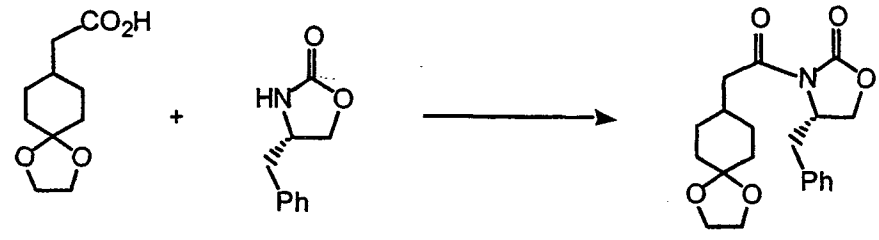
Step 3:



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 ($M+H^+$).

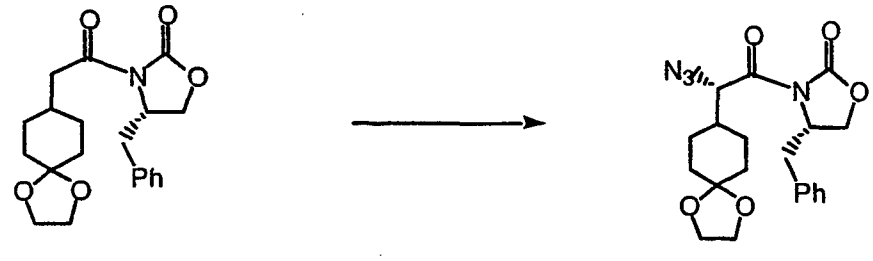
Step 4:



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.

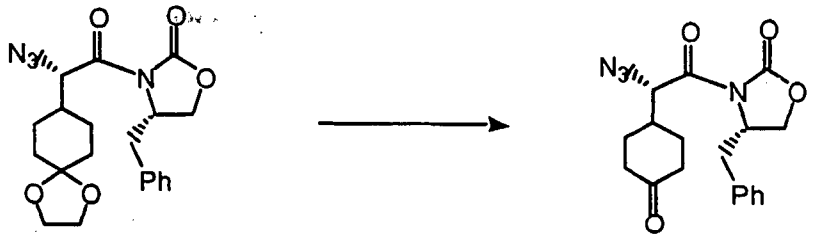
2. A solution of (S)-4-benzyl-2-oxazolidinone (2.66 g) in THF (22 mL) was cooled to -78°C, and a 1.6 M solution (9.38 mL) of n-butyllithium in hexane was added dropwise. After an additional 0.33 hour stirring at this temperature, the solution was transferred via canula to the cold solution of part 1. 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.

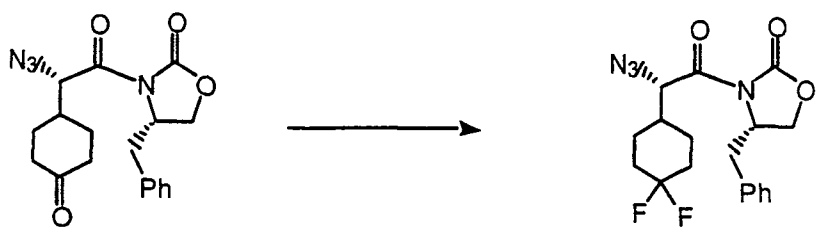
Step 6:



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).

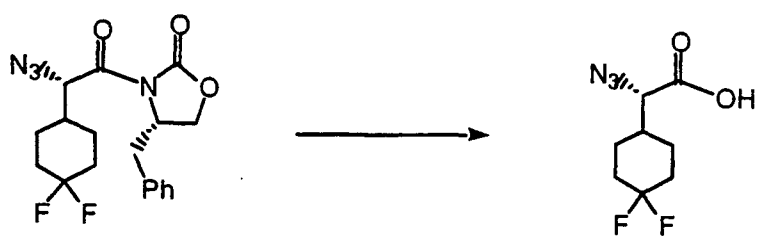
Step 7:

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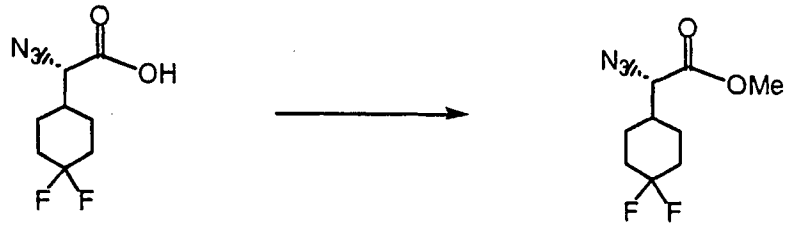
The product of the preceding step (8.2 g) was dissolved in CH_2Cl_2 (16 mL) and treated with diethylaminosulfur trifluoride (DAST, 7.00 mL) at RT for 3 hours. The reaction was poured over ice/water (200 cc), and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$, then brine; 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:



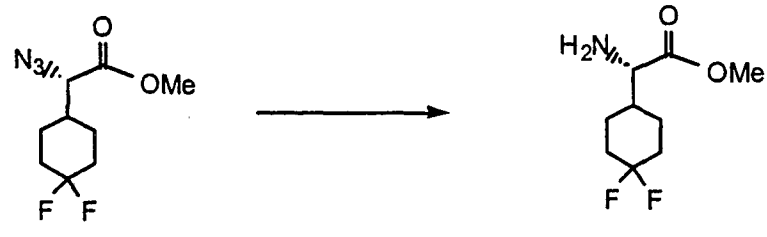
The product of the preceding step (3.7 g) was dissolved in a mixture of THF (150 mL) and water (48 mL), cooled to 0°C, treated with 30% H_2O_2 (3.95 mL), and then with $LiOH \cdot H_20$ (0.86 g). The mixture was stirred for 1 hour at 0°C, then quenched with a solution of Na_2SO_3 (5.6 g) in water (30 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:



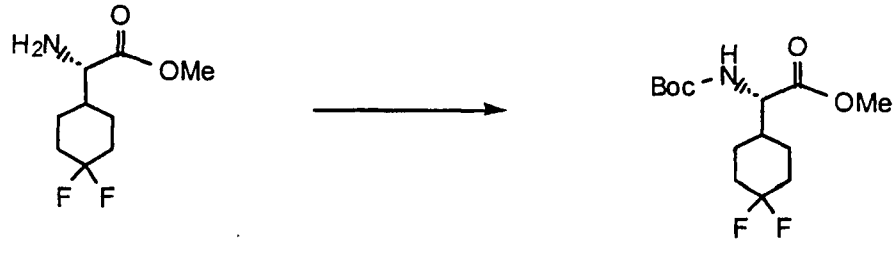
The product of the preceding example (2.6 g) was dissolved in Et_2O (50 mL) and treated dropwise with a solution of $CH2N_2$ in Et_2O until the solution remained yellow. The solution was stirred for 18 hours, then evaporated under vacuum to afford the title compound (2.8), which was used directly in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

Step 10:



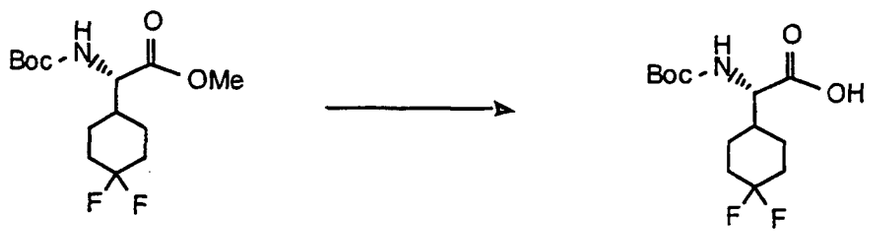
The product of the preceding step (1.95 g) was dissolved in MeOH (150 mL), treated with formic acid (1.7 mL), then treated with 10% Pd/C (3.3 g, Degussa type E101) under 1 atm of hydrogen for 1.5 hours. The mixture was filtered and the filtrate evaporated to afford the title compound (2.1 g) as the formic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

Step 11:



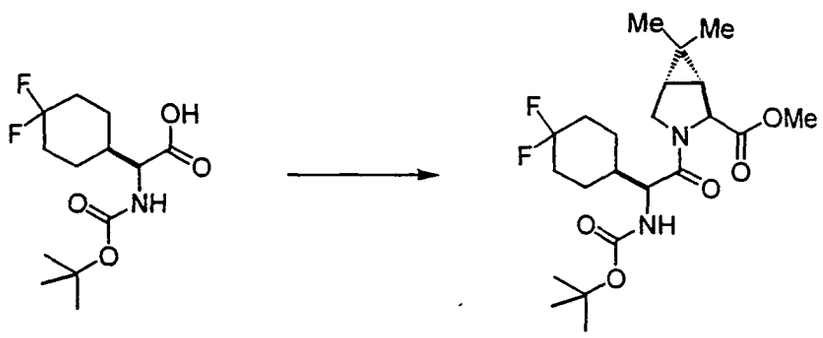
The product of the preceding step (2.1 g) was dissolved in 1,4-dioxane (100 mL) and di-*tert*-butyl dicarbonate (1.9 g) was added, followed by diisopropylethylamine (2.9 mL). The solution was stirred for 18 hours, and concentrated under vacuum. The residue was treated with aqueous 5% KH_2PO_4 and the 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:



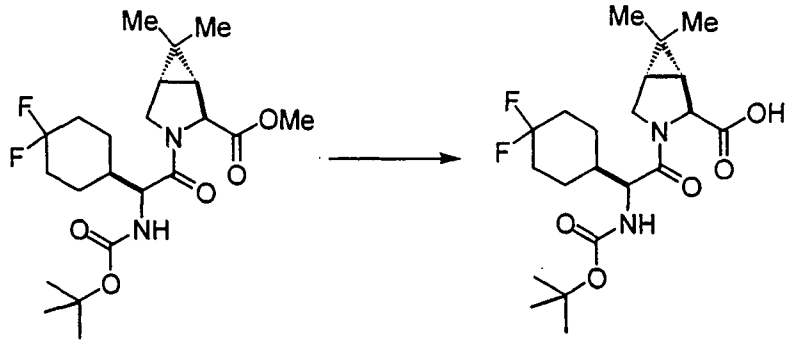
The product of the preceding step (2.5 g) was dissolved in 1,4-dioxane (35 mL), treated with aqueous 1M LiOH (17 mL), and stirred for 2 hours. The mixture was quenched with ice/water (125 cc), the mixture was acidified to pH 3-4 with 3N HCl, and extracted with EtOAc. The extract was dried over anhydrous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

Step 13:



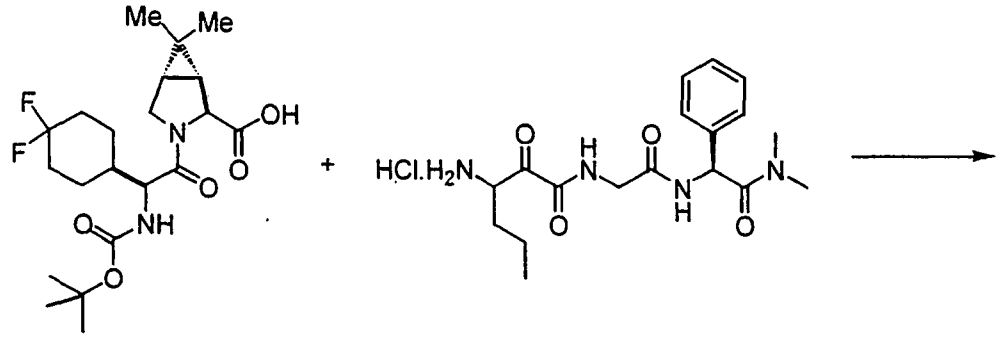
The desired product was prepared according to the procedure in Example XXIII, Step 10.

Step 14:



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

Step 15:

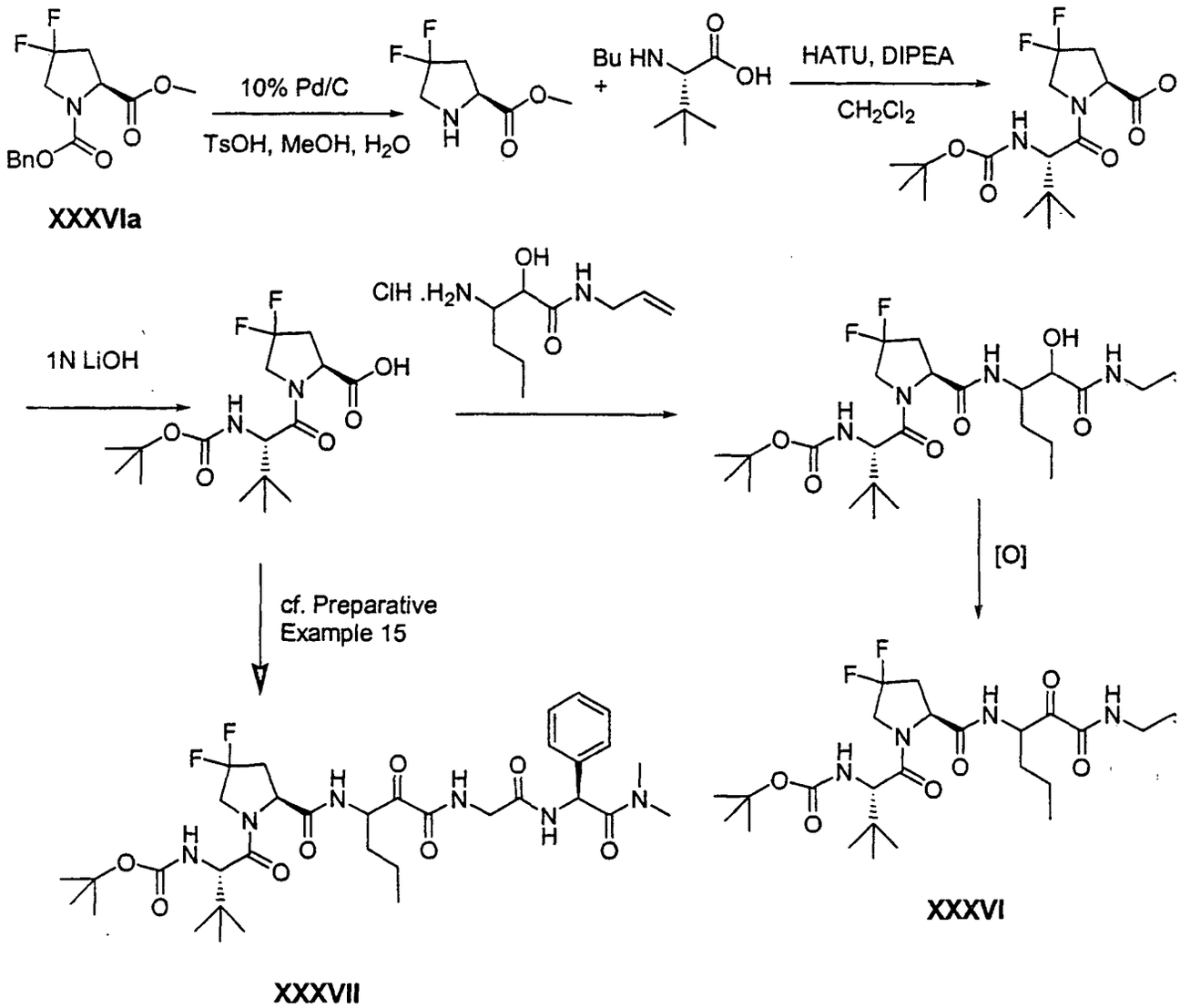


XXXV

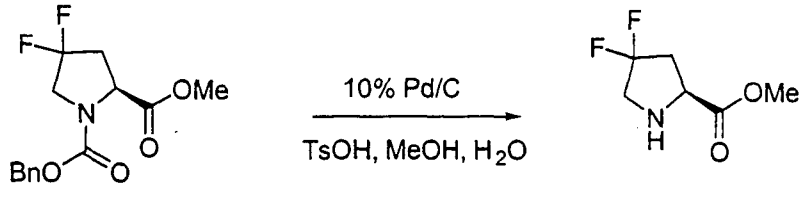
The desired acid product was prepared according to the procedure in Example XXIX, Step 4.

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:

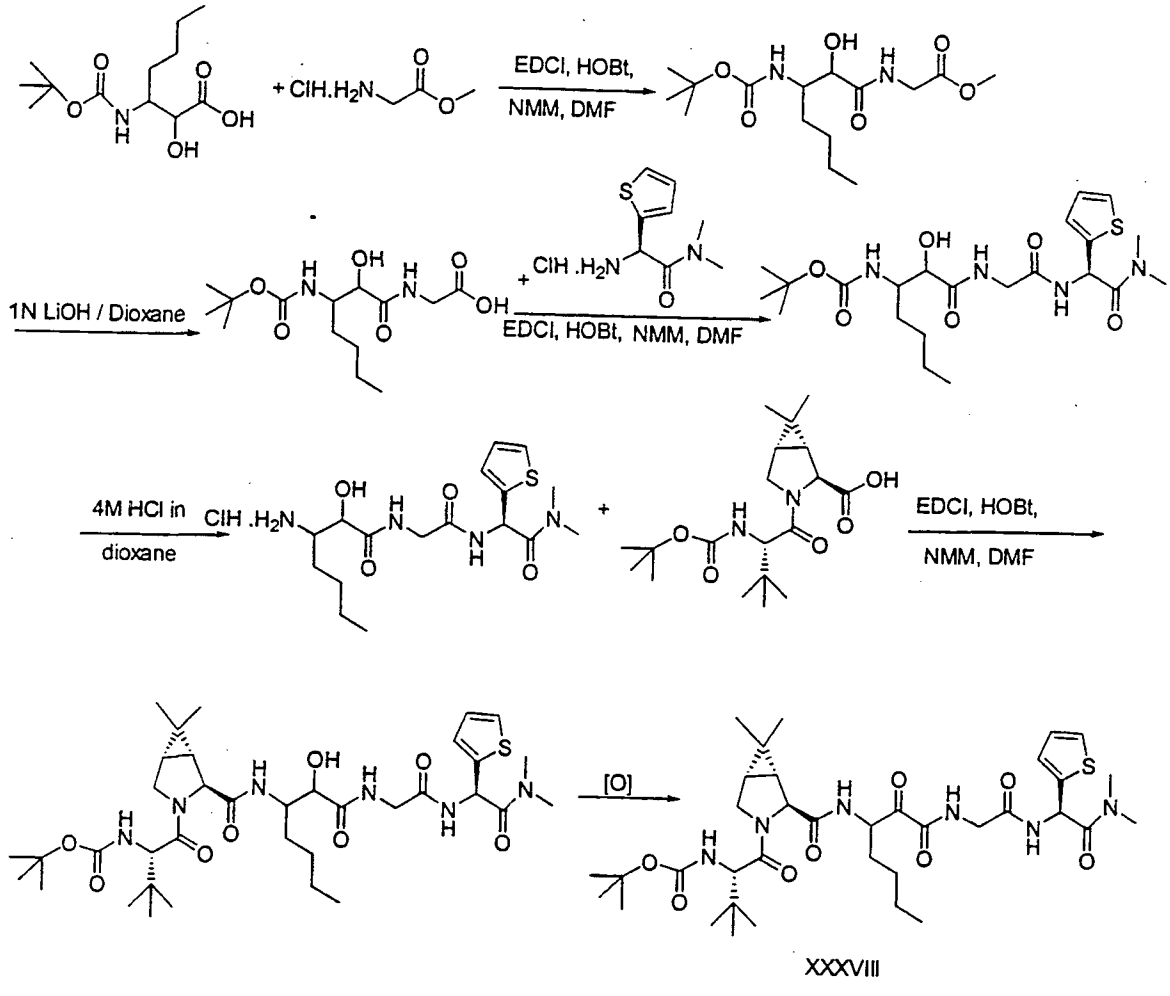


XXXVIa **XXXVIb**

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.

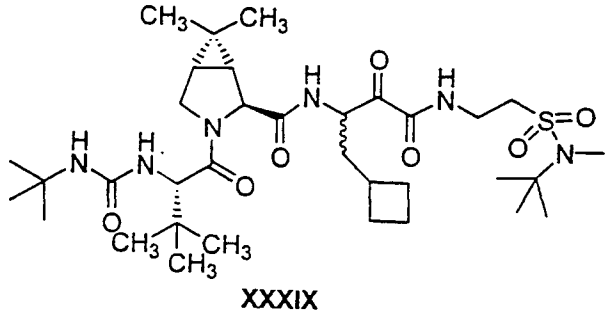
Example XXXVIII. Preparation of a compound of formula XXXVIII:

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



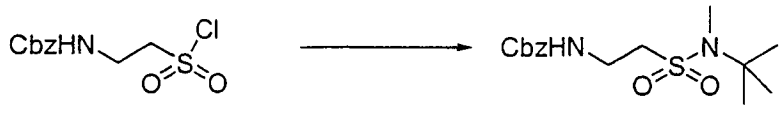
XXXVIII

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.

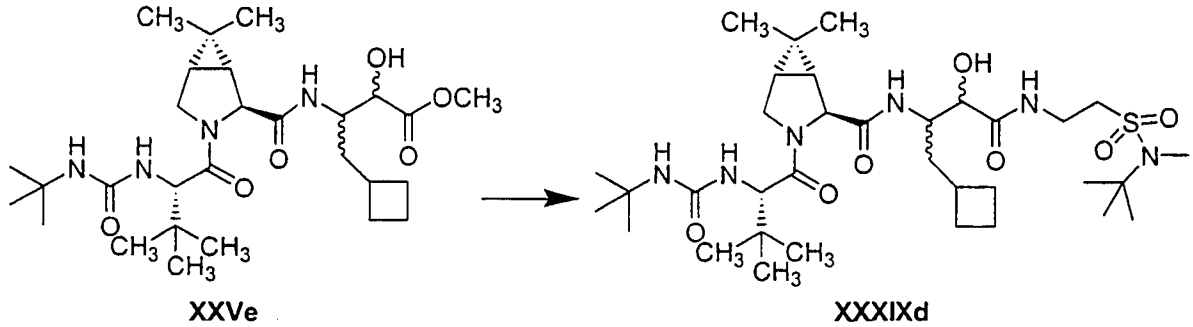
Step 2:



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.

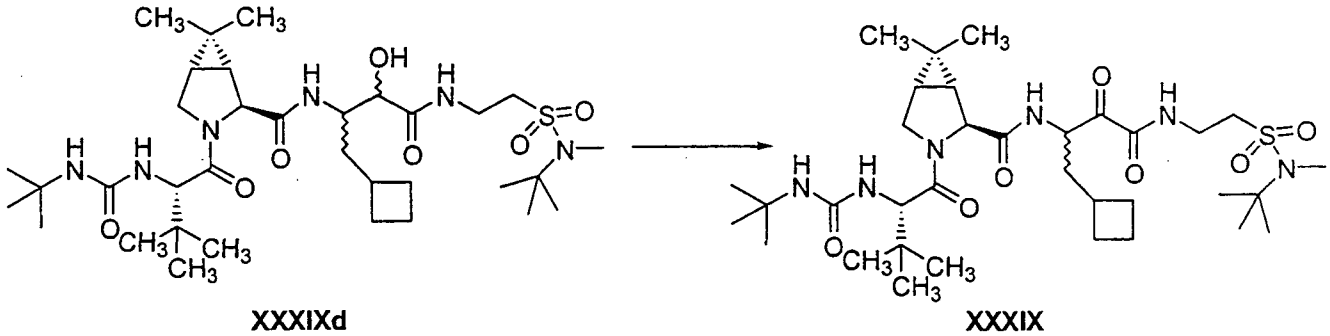
Step 3:



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.

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.

000158

Table 2

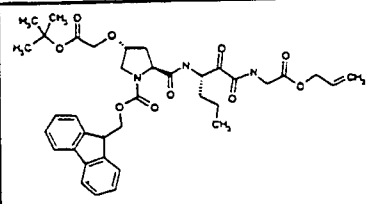
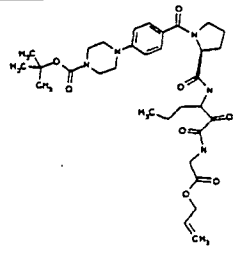
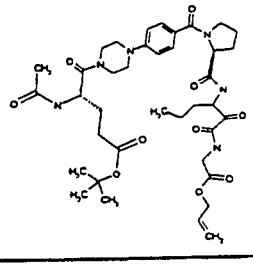
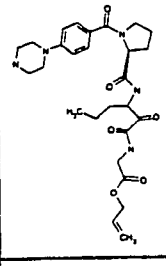
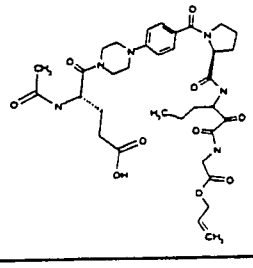
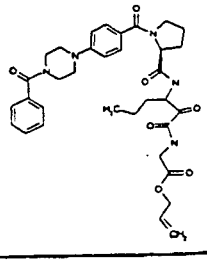
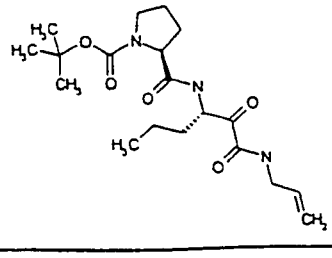
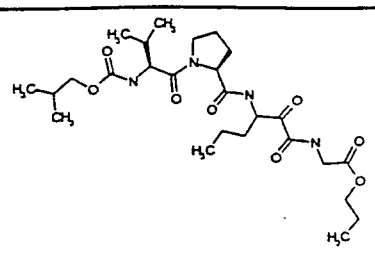
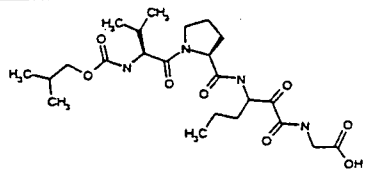
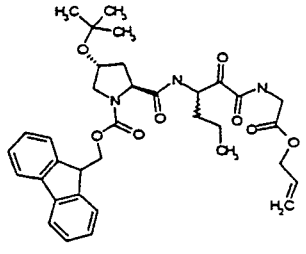
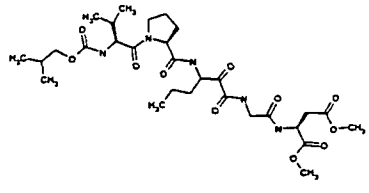
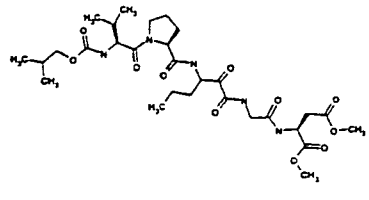
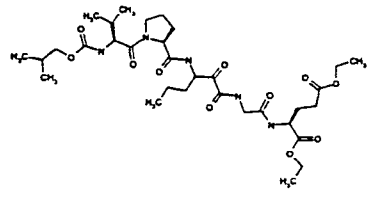
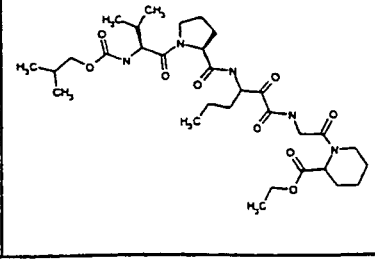
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4		527.6259
5		698.7799
6		631.7352
7		381.476

Table 2

8		540.6626
9		498.5813
10		633.7482
11		641.7249
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13		683.8061
14		637.7802

000159

Table 2

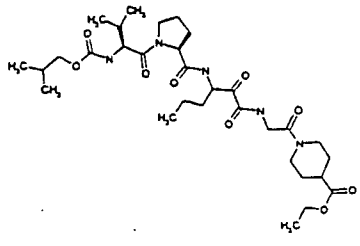
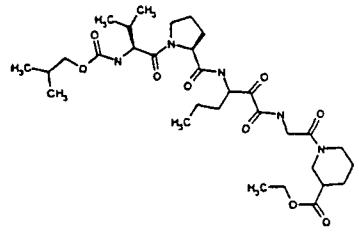
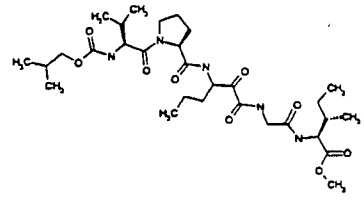
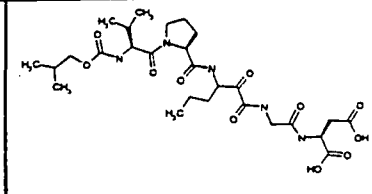
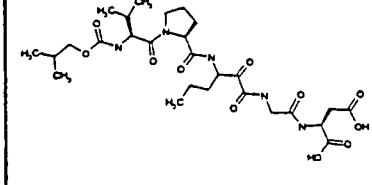
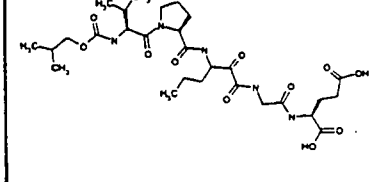
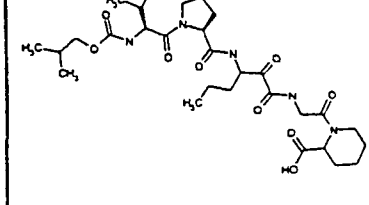
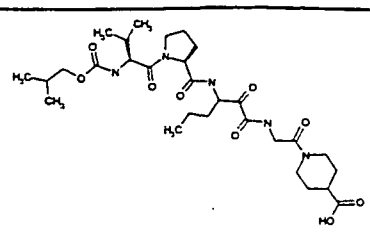
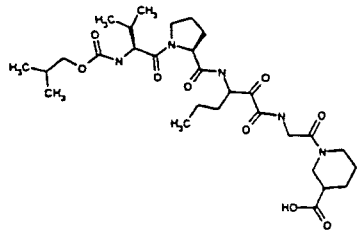
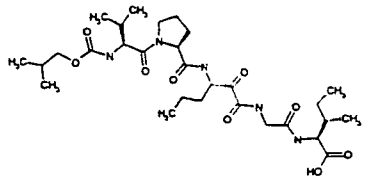
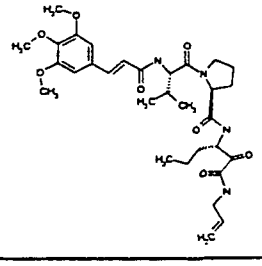
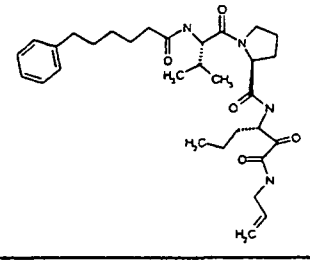
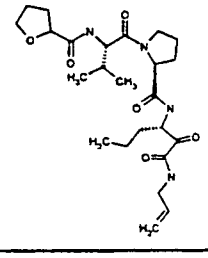
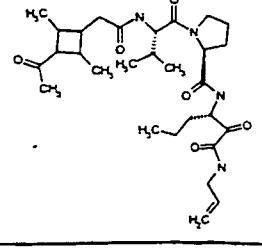
15		637.7802
16		637.7802
17		625.769
18		613.6707
19		613.6707
20		627.6978
21		609.726

Table 2

22		609.726
23		609.726
24		611.742
25		600.7183
26		554.7361
27		478.5937
28		546.7132

000160

Table 2

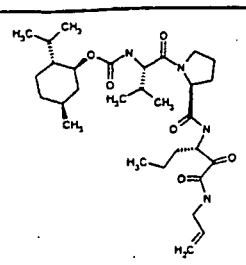
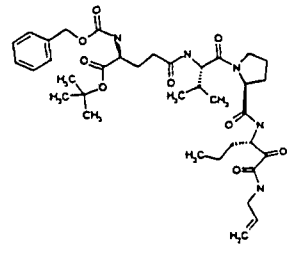
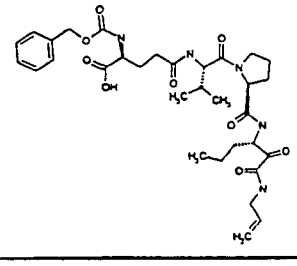
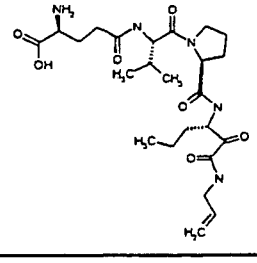
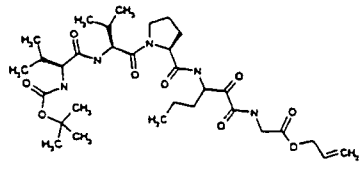
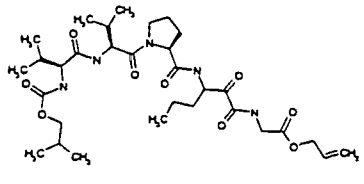
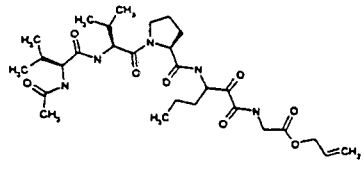
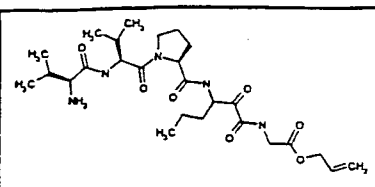
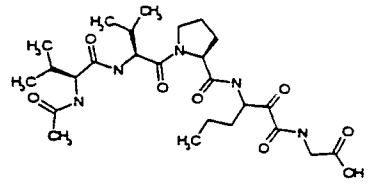
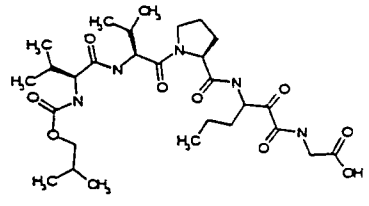
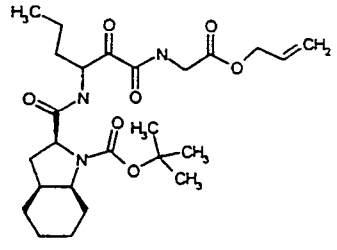
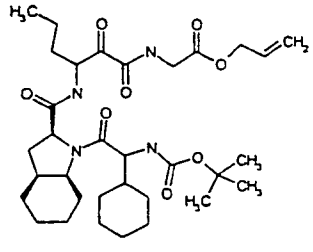
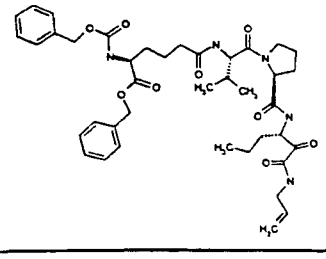
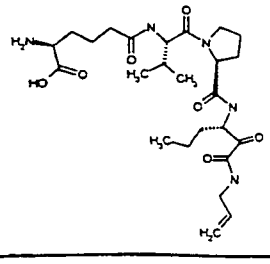
29		562.7562
30		699.8519
31		643.7435
32		509.6077
33		637.7802
34		637.7802
35		579.6995

Table 2

36		537.6619
37		539.6342
38		597.7149
39		493.6055
40		632.8044
41		747.8965
42		523.6348

000161

Table 2

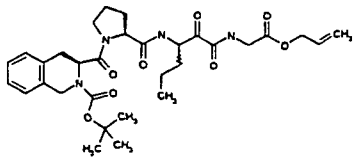
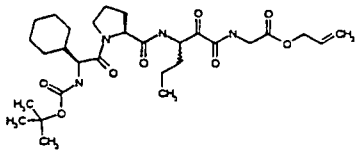
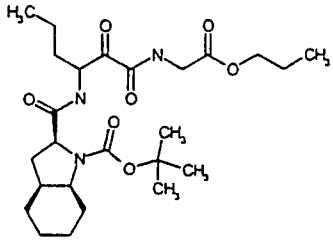
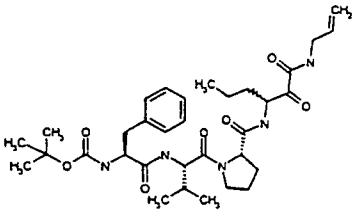
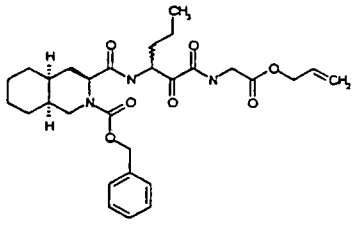
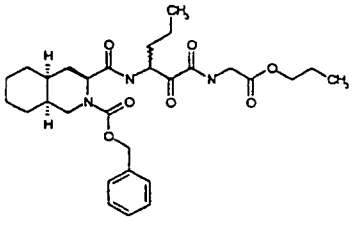
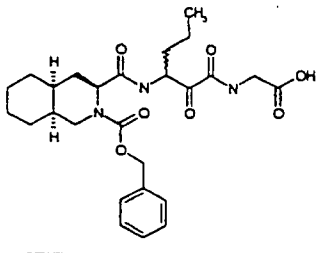
43		598.7024
44		578.712
45		495.6214
46		627.7878
47		541.6501
48		543.666
49		501.5847

Table 2

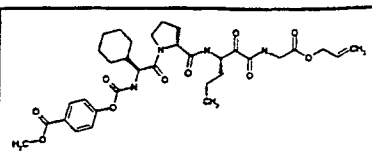
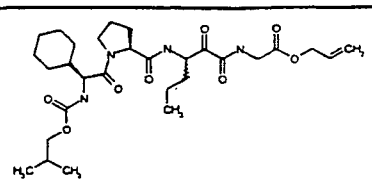
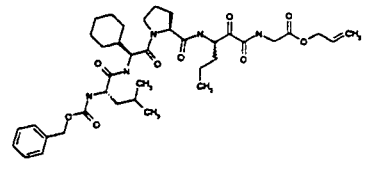
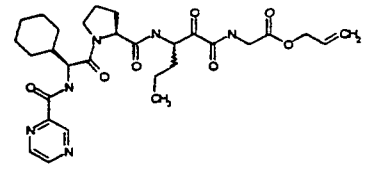
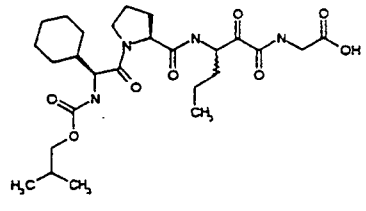
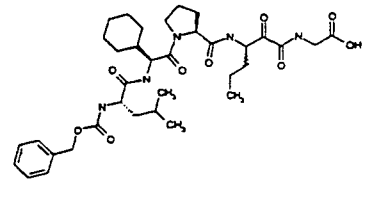
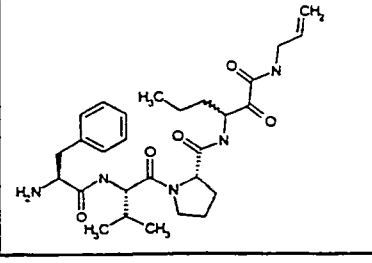
50		656.7394
51		578.712
52		725.8901
53		584.6782
54		538.6467
55		685.8248
56		527.6695

Table 2

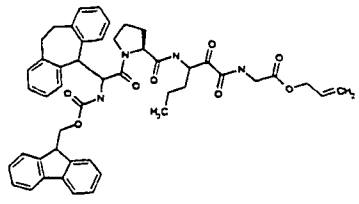
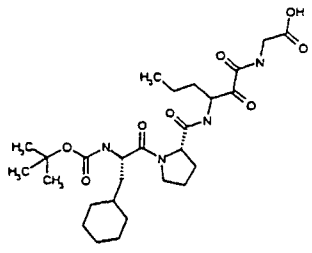
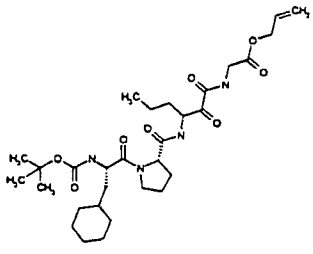
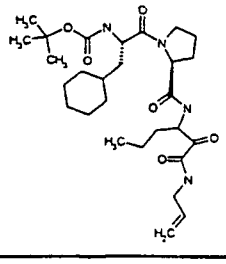
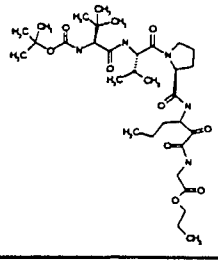
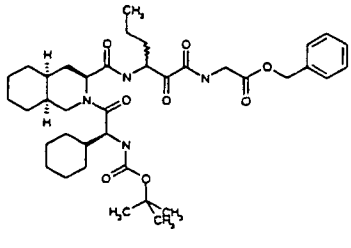
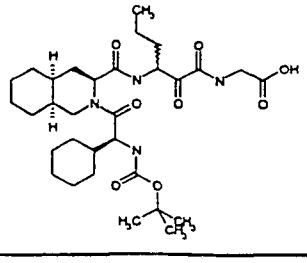
57		810.9557
58		552.6737
59		592.7391
60		534.702
61		653.8232
62		696.892
63		606.7662

Table 2

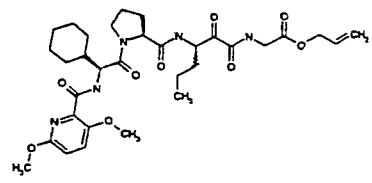
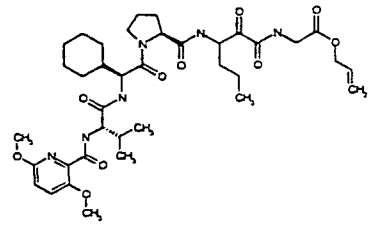
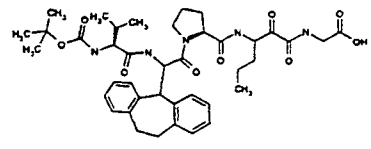
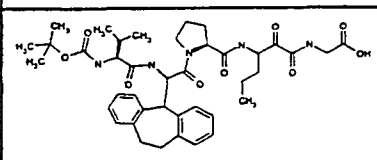
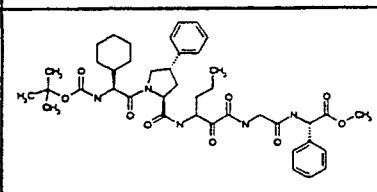
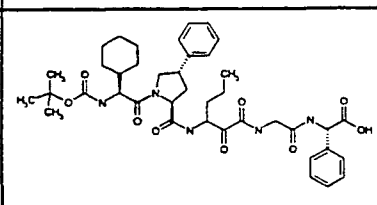
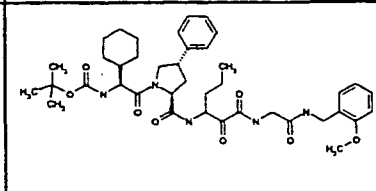
64		643.7435
65		742.8771
66		747.8965
67		747.8965
68		761.9236
69		747.8965
70		733.913

Table 2

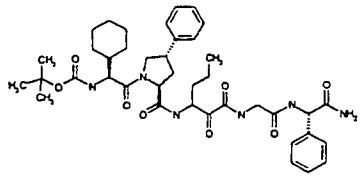
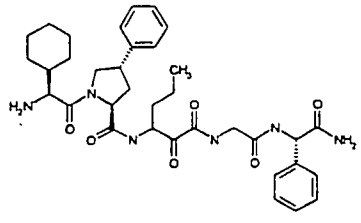
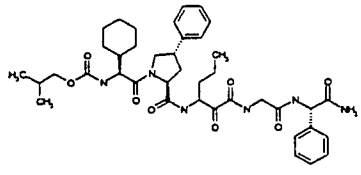
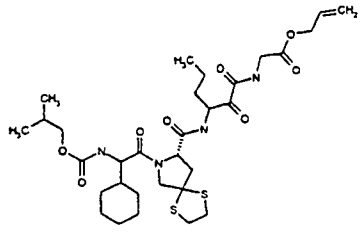
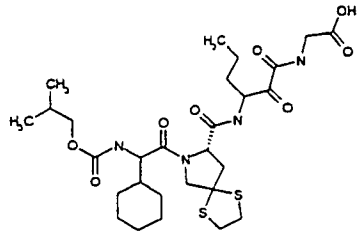
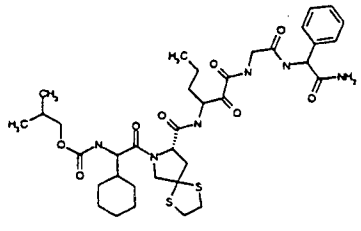
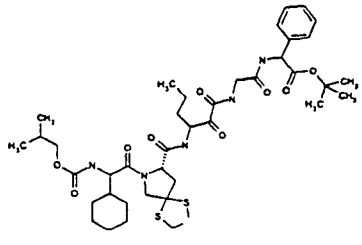
71		746.9118
72		646.7935
73		746.9118
74		668.8782
75		628.8129
76		760.9792
77		818.0723

Table 2

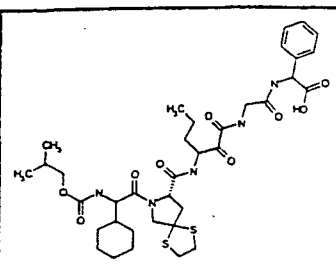
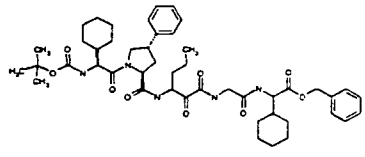
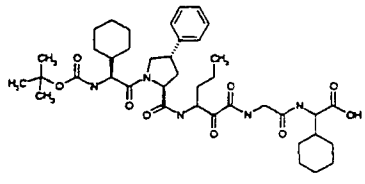
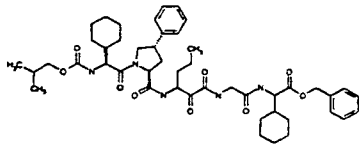
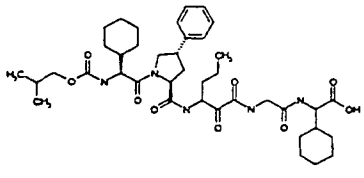
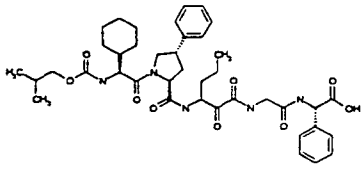
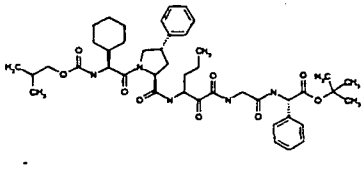
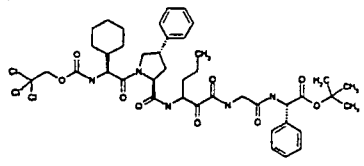
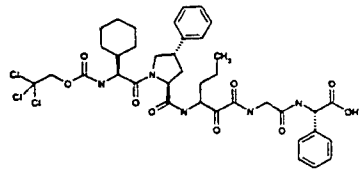
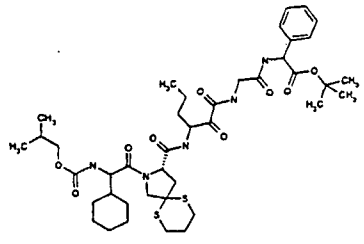
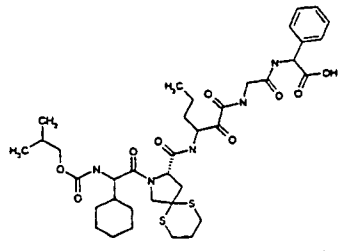
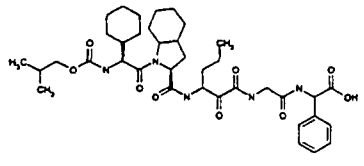
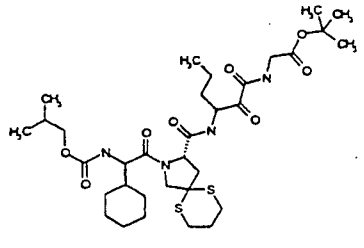
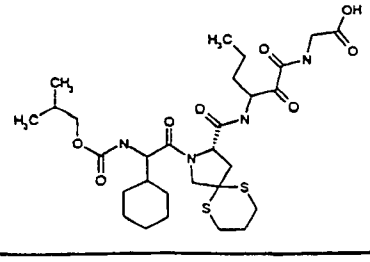
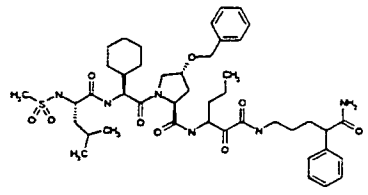
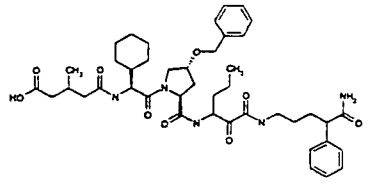
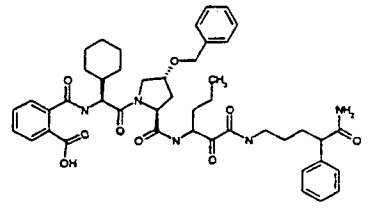
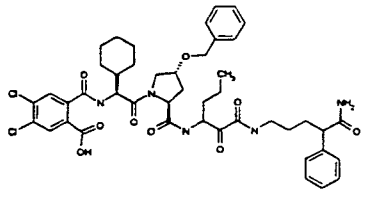
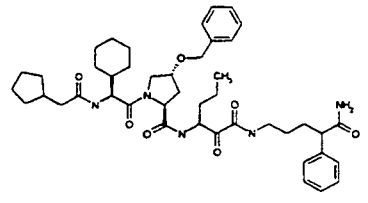
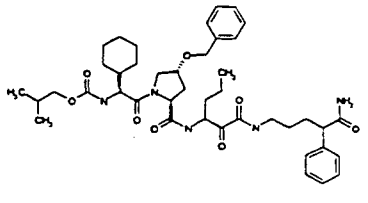
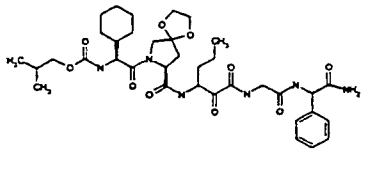
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79		844.0702
80		753.9443
81		844.0702
82		753.9443
83		747.8965
84		804.0049

Table 2

85		879.2858
86		823.1774
87		832.0994
88		775.9911
89		725.8901
90		698.9483
91		642.84

000164

Table 2

92		853.0995
93		789.9778
94		809.9682
95		878.8583
96		772.006
97		761.9672
98		728.85

000165

Table 2

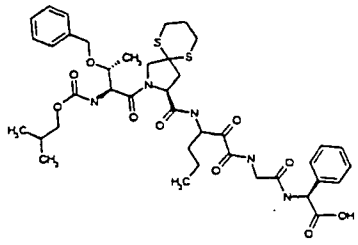
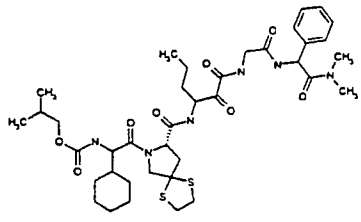
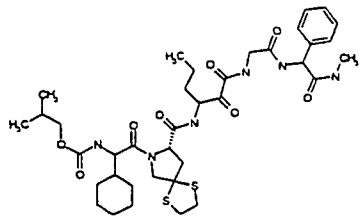
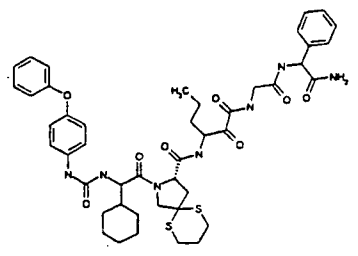
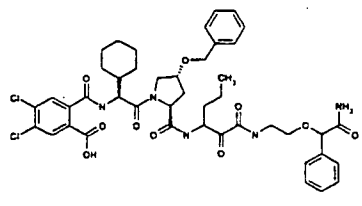
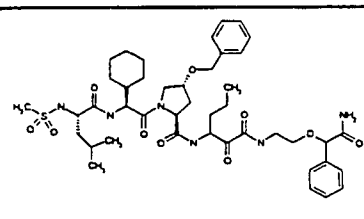
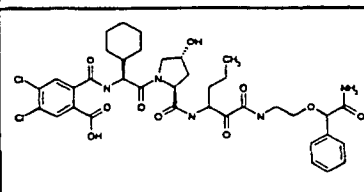
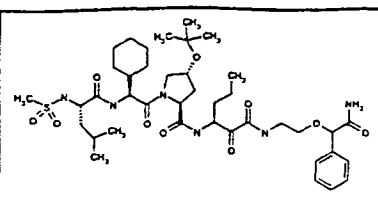
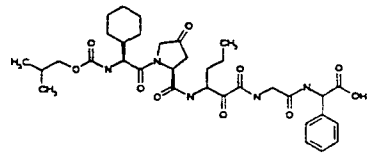
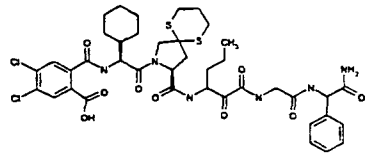
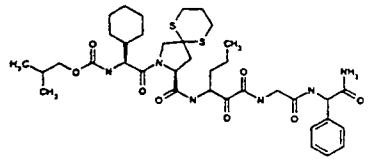
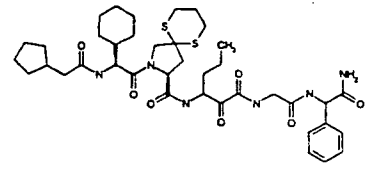
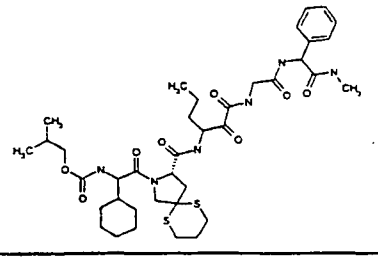
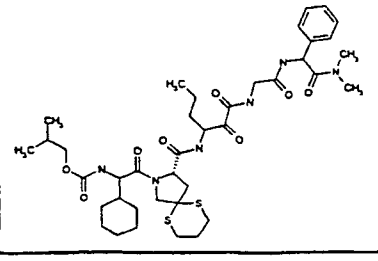
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100		789.0334
101		775.0063
102		886.1102
103		880.8306
104		855.0718
105		790.7047

Table 2

106		821.0543
107		685.7812
108		891.8973
109		775.0063
110		785.0452
111		789.0334
112		803.0605

000166

Table 2

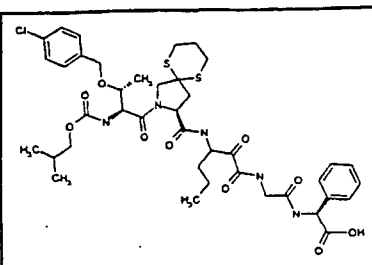
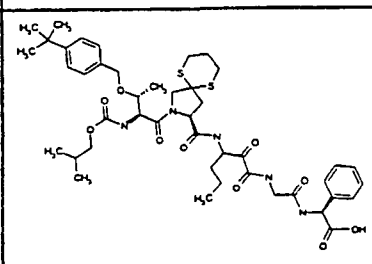
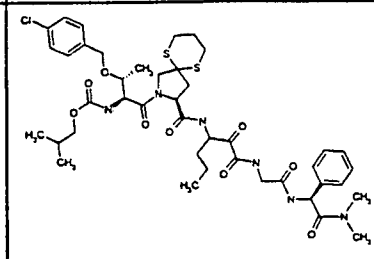
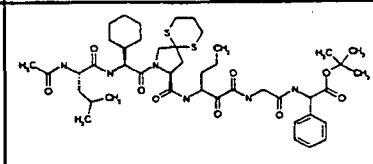
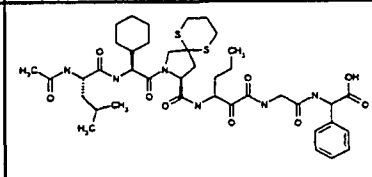
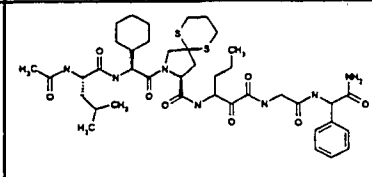
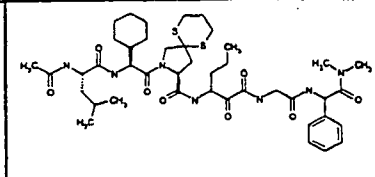
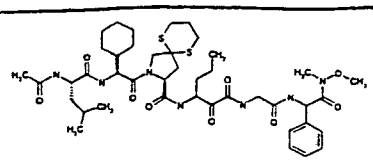
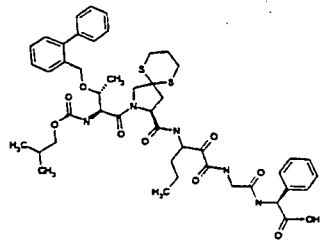
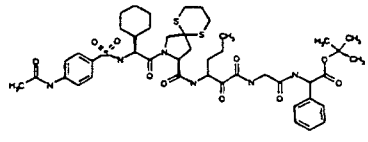
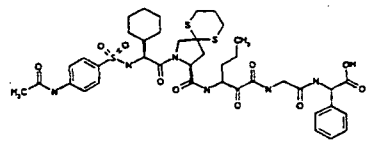
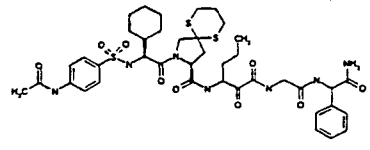
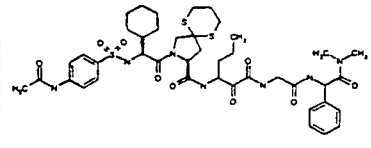
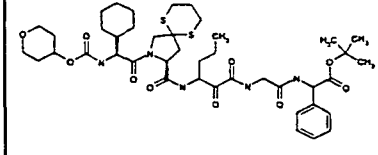
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114		884.1323
115		889.5384
116		887.1794
117		831.071
118		830.0863
119		858.1405

Table 2

120		874.1399
121		904.1227
122		929.195
123		873.0867
124		872.1019
125		900.1561
126		860.11

030167

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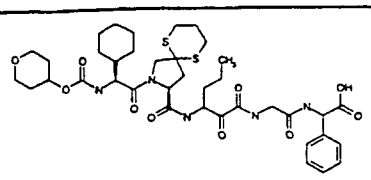
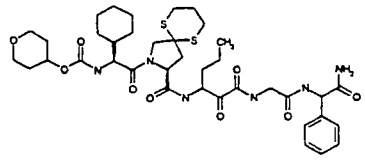
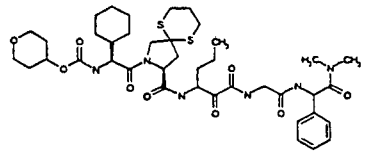
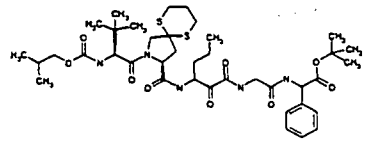
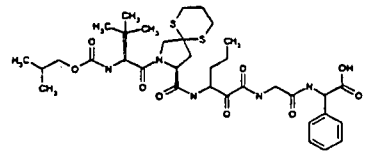
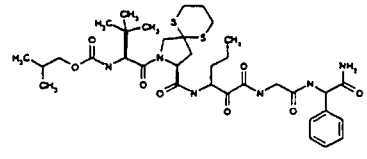
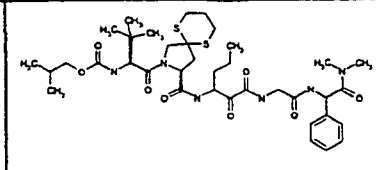
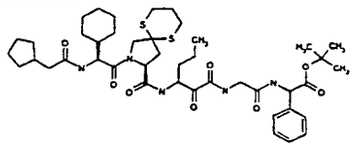
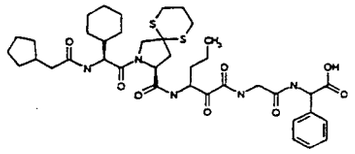
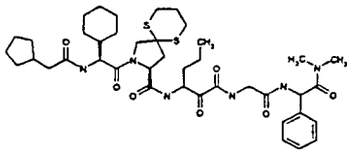
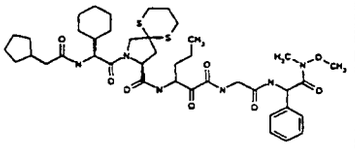
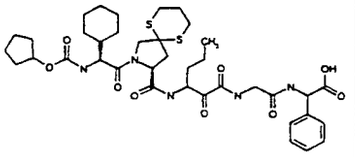
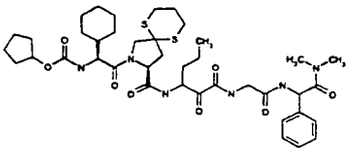
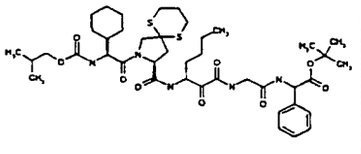
127		804.0016
128		803.0169
129		831.071
130		806.0612
131		749.9528
132		748.9681
133		777.0223

Table 2

134		842.1382
135		786.0299
136		813.0994
137		829.0988
138		788.0022
139		815.0717
140		846.1265

000168

Table 2

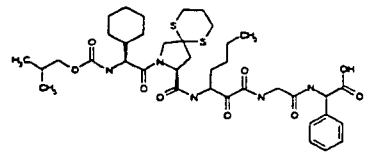
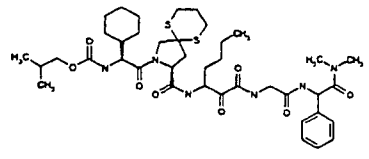
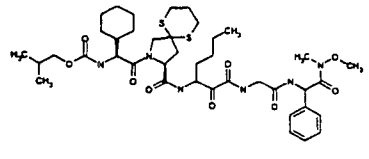
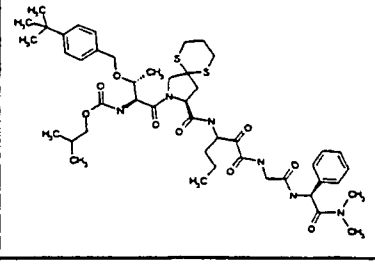
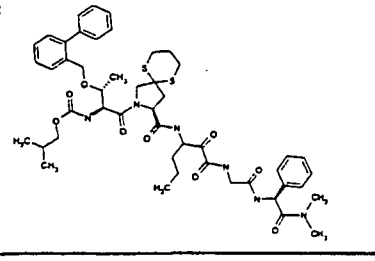
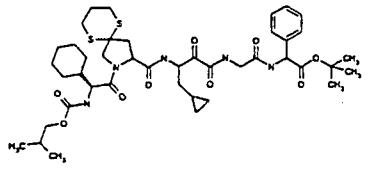
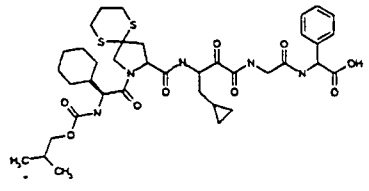
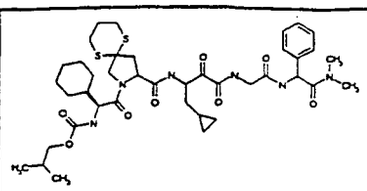
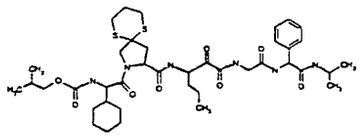
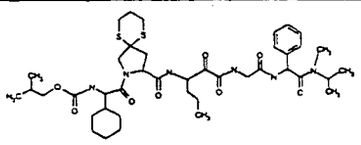
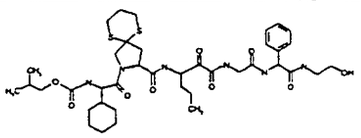
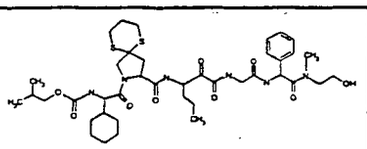
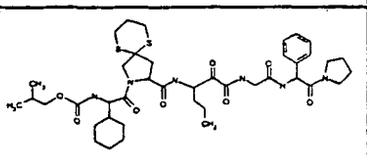
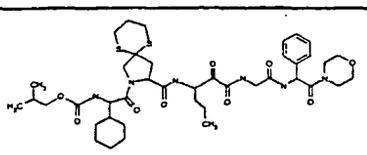
141		790.0181
142		817.0876
143		833.087
144		911.2017
145		931.1921
146		844.1106
147		788.0022

Table 2

148		815.0717
149		817.0876
150		831.1147
151		819.0599
152		833.087
153		829.0988
154		845.0981

080159

Table 2

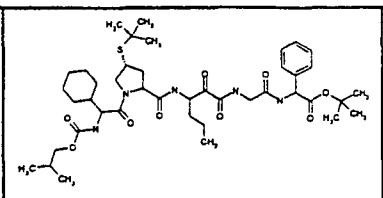
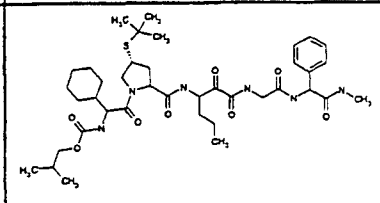
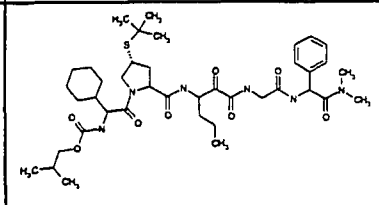
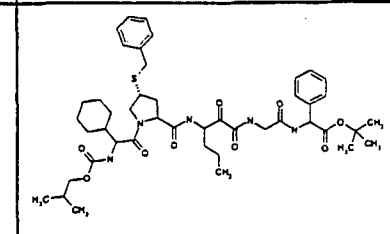
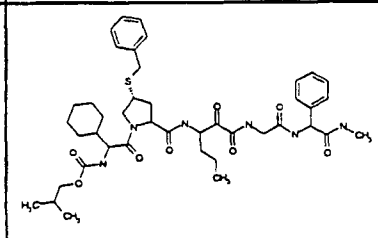
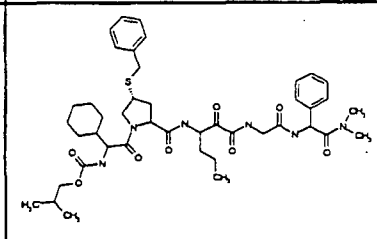
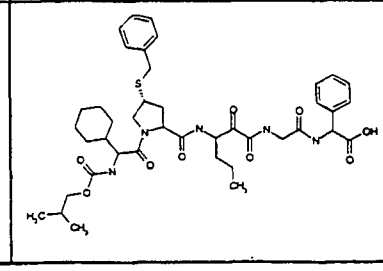
155		816.0784
156		773.0125
157		787.0396
158		850.0959
159		807.03
160		821.0571
161		793.9876

Table 2

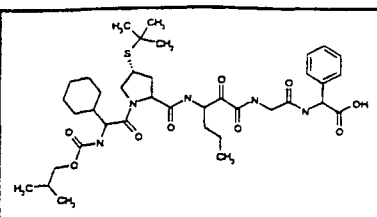
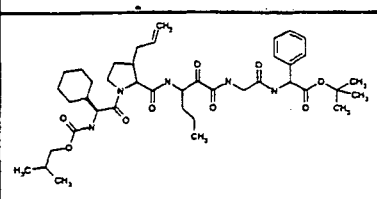
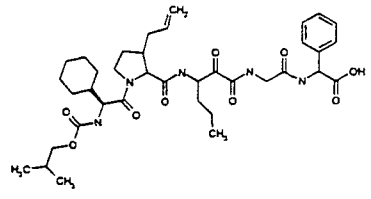
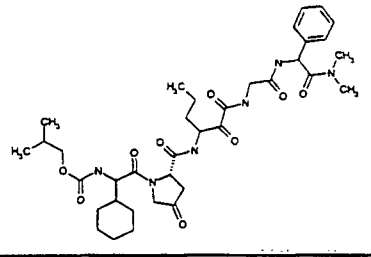
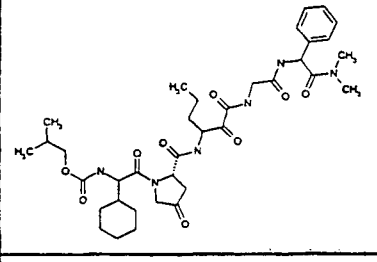
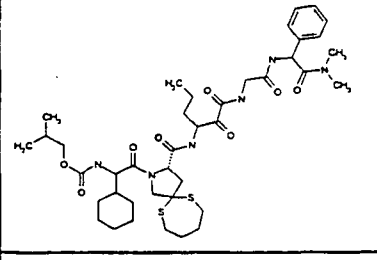
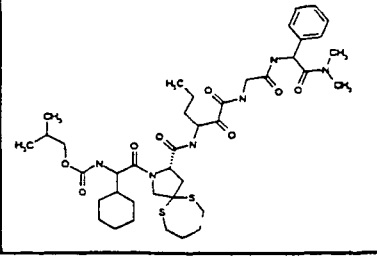
162		759.9701
163		767.9714
164		711.863
165		712.8506
166		712.8506
167		817.0876
168		817.0876

Table 2

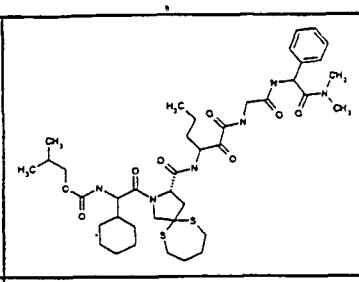
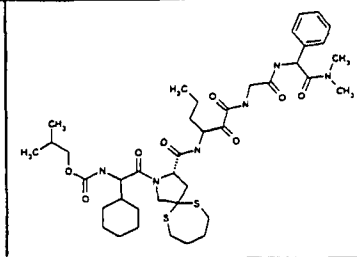
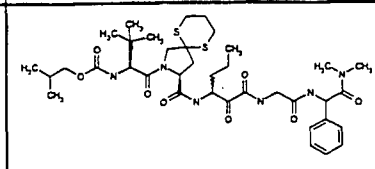
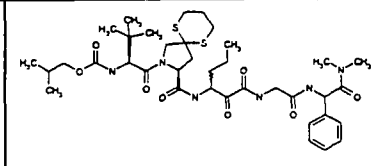
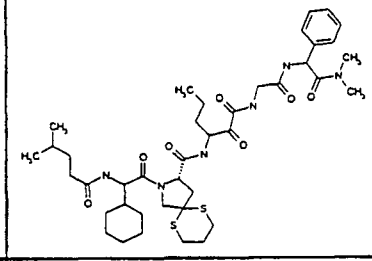
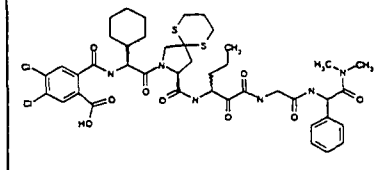
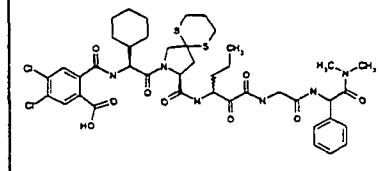
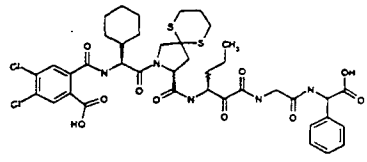
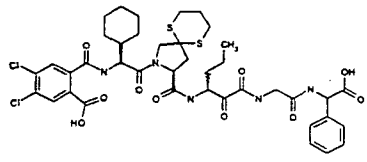
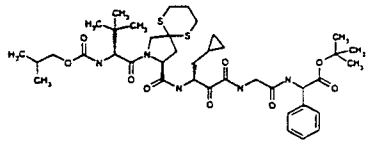
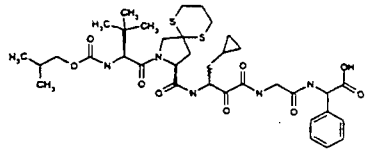
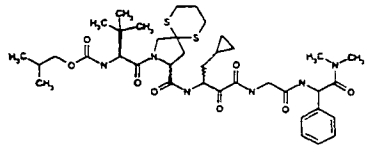
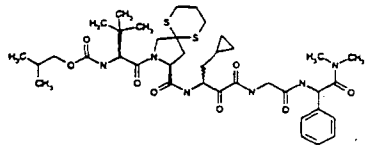
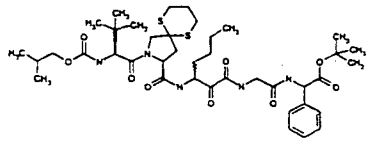
169		817.0876
170		817.0876
171		777.0223
172		777.0223
173		801.0882
174		919.9515
175		919.9515

Table 2

176		892.8821
177		892.8821
178		818.0723
179		761.964
180		789.0334
181		789.0334
182		820.0883

000171

Table 2

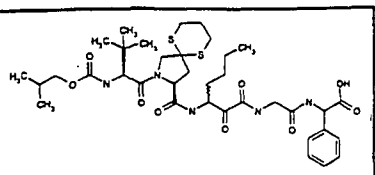
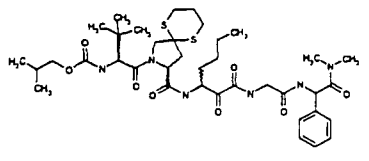
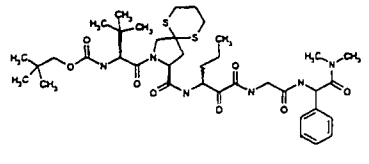
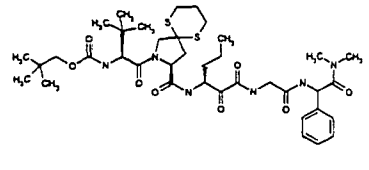
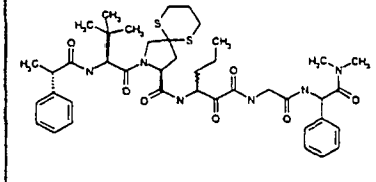
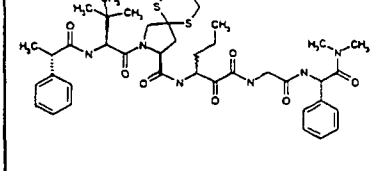
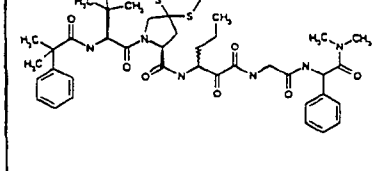
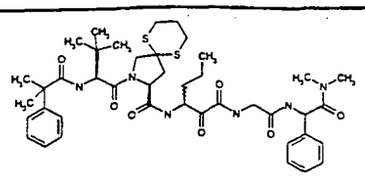
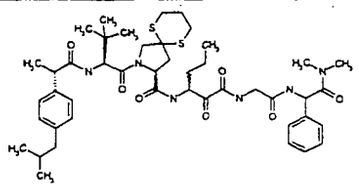
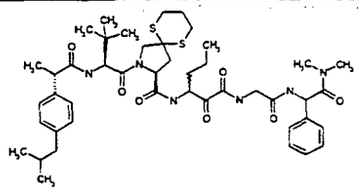
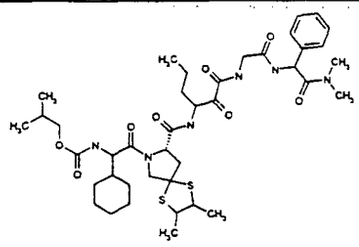
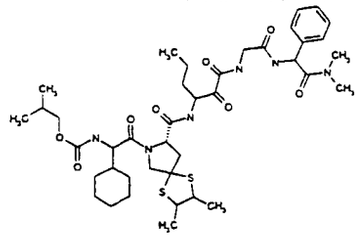
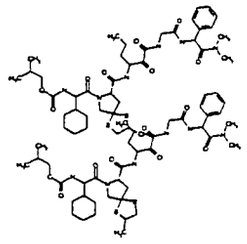
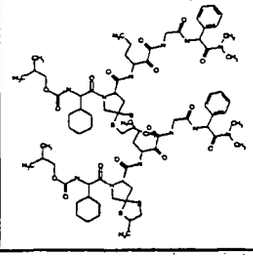
183		763.9799
184		791.0494
185		791.0494
186		791.0494
187		809.0674
188		809.0674
189		823.0945

Table 2

190		823.0945
191		865.1758
192		865.1758
193		817.0876
194		817.0876
195		1606.121
196		1606.121

000172

Table 2

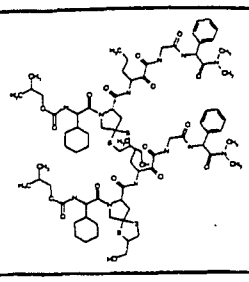
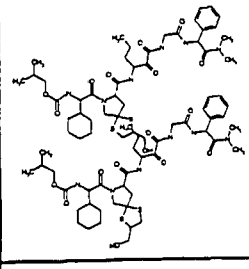
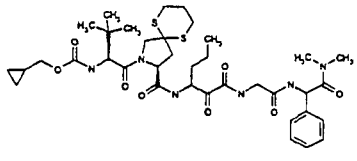
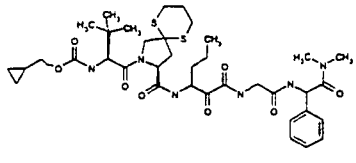
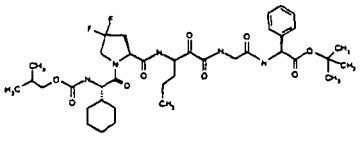
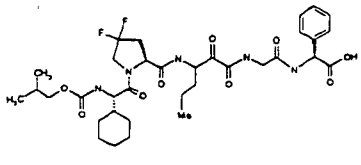
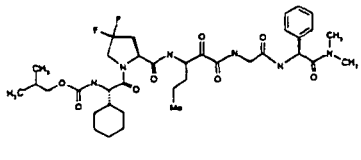
197		1638.12
198		1638.12
199		775.0063
200		775.0063
201		763.887
202		707.7786
203		734.848

Table 2

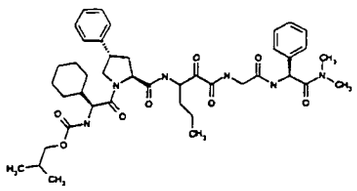
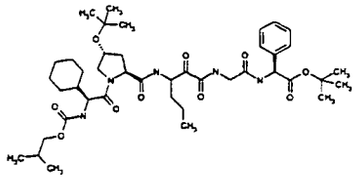
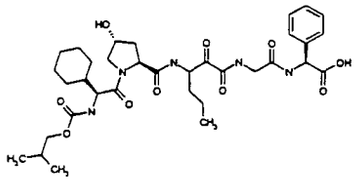
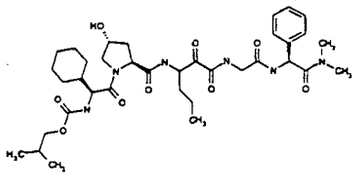
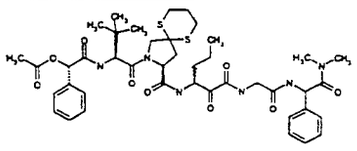
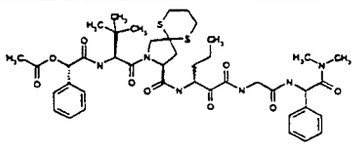
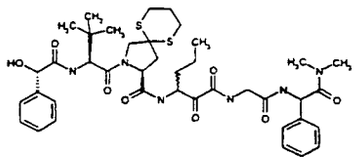
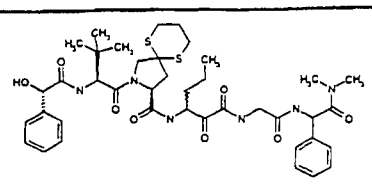
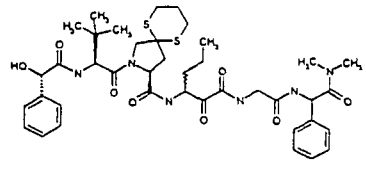
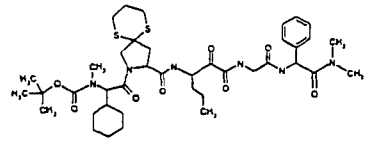
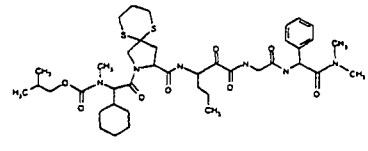
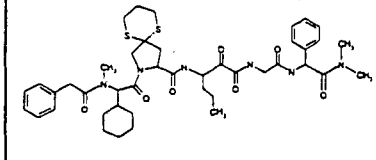
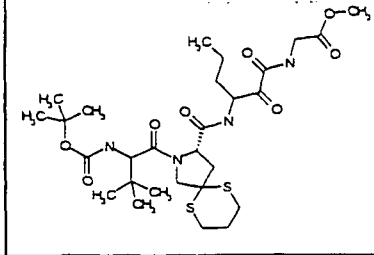
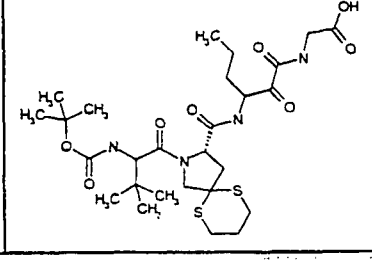
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205		800.0139
206		687.7971
207		714.8666
208		853.0774
209		853.0774
210		811.0398

Table 2

211		811.0398
212		811.0398
213		817.0876
214		817.0876
215		835.1057
216		630.8288
217		616.8018

000173

Table 2

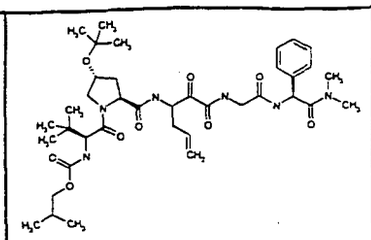
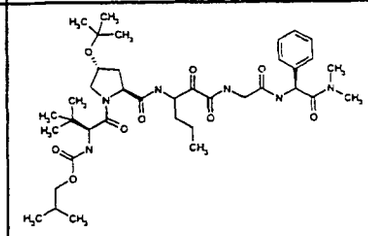
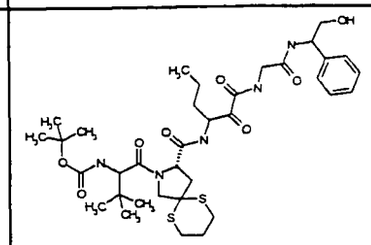
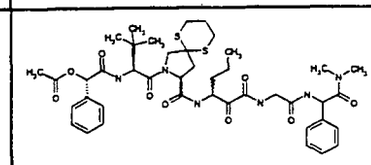
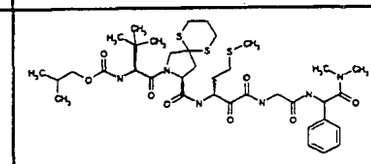
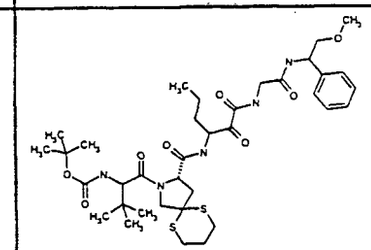
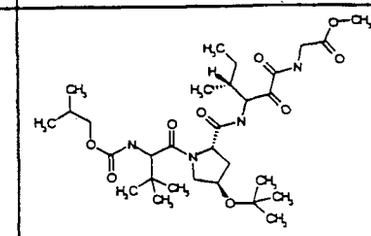
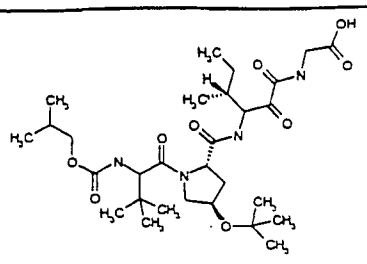
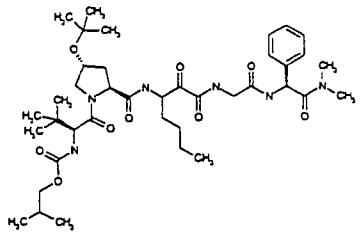
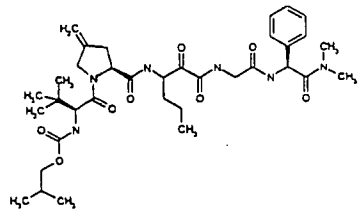
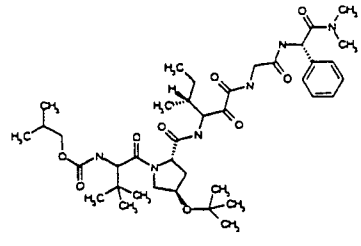
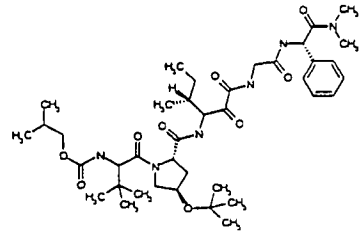
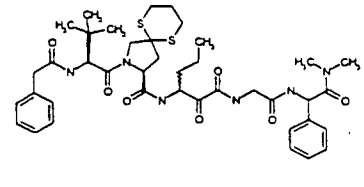
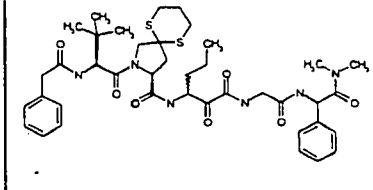
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219		744.9367
220		735.9694
221		853.0774
222		809.0862
223		749.9965
224		612.7703

Table 2

225		598.7432
226		758.9638
227		684.8401
228		758.9638
229		758.9638
230		795.0404
231		795.0404

000174

Table 2

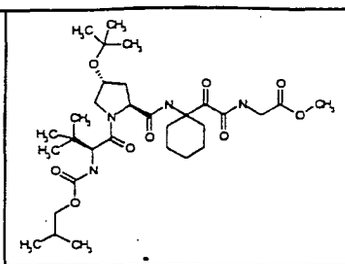
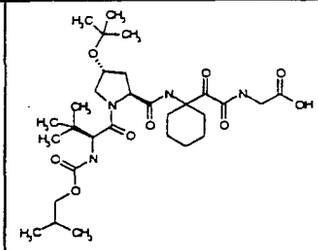
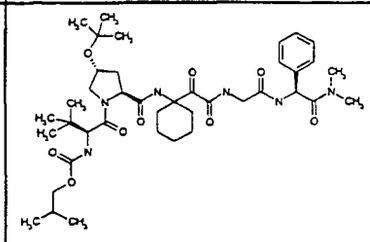
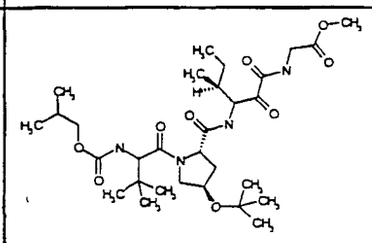
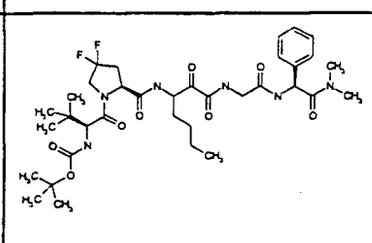
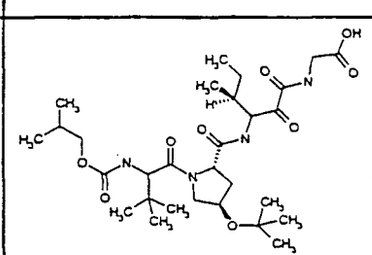
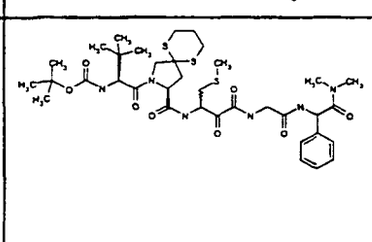
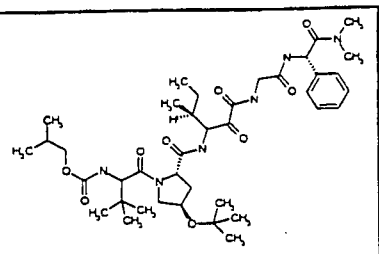
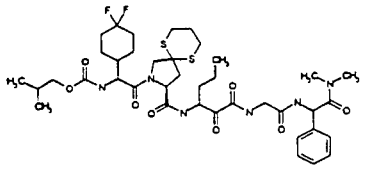
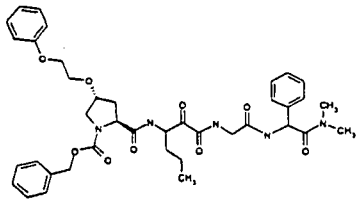
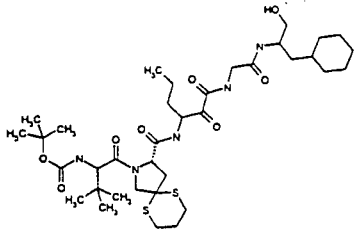
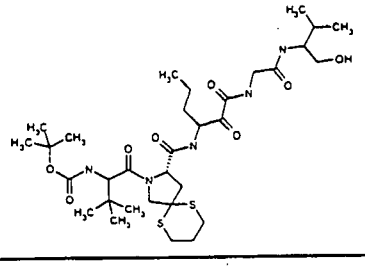
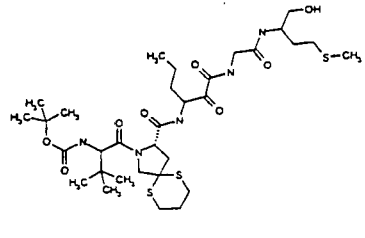
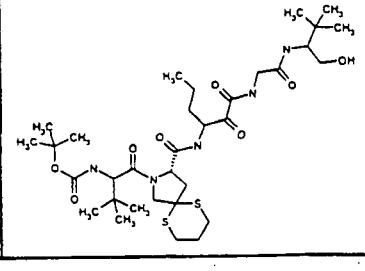
232		624.7815
233		610.7544
234		770.9749
235		612.7703
236		722.8369
237		598.7432
238		795.0592

Table 2

239		758.9638
240		839.0414
241		729.8375
242		756.0443
243		701.9518
244		734.0159
245		715.9789

000175

Table 2

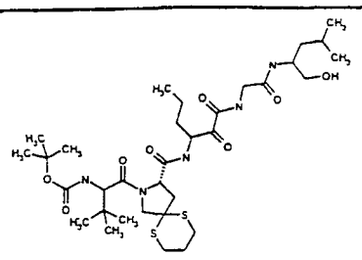
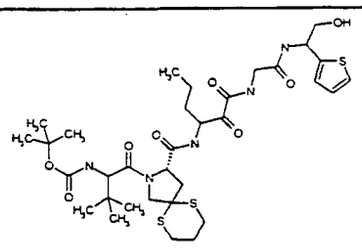
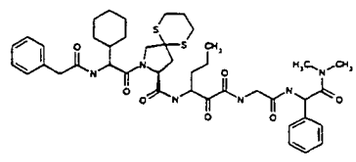
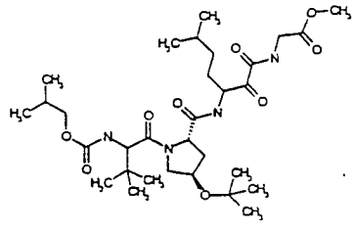
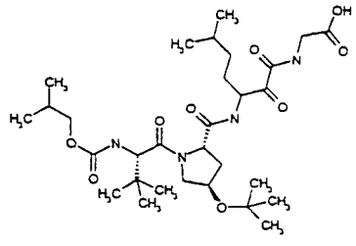
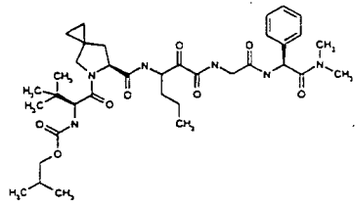
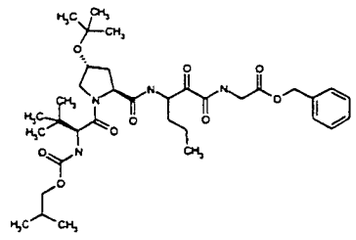
246		715.9789
247		741.9951
248		821.0786
249		626.7974
250		612.7703
251		698.8672
252		674.842

Table 2

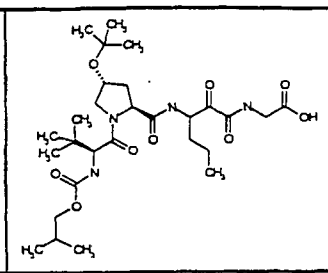
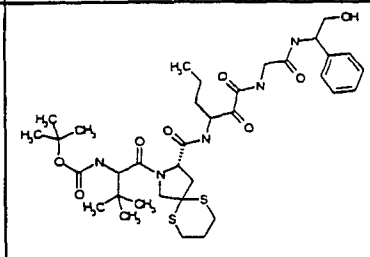
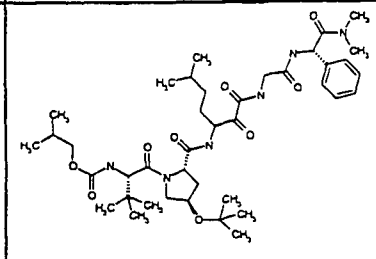
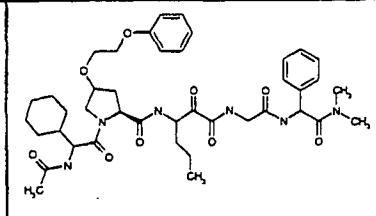
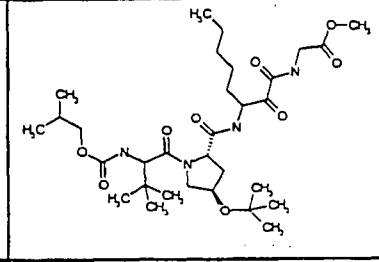
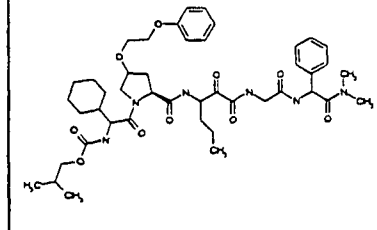
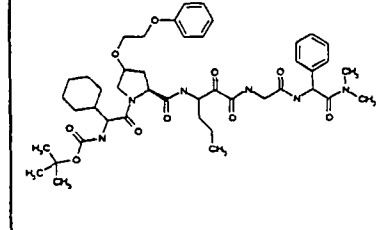
253		584.7162
254		735.9694
255		772.9909
256		776.9383
257		626.7974
258		835.0189
259		835.0189

Table 2

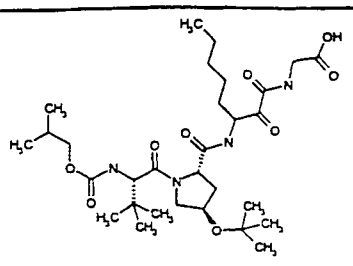
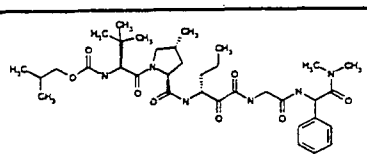
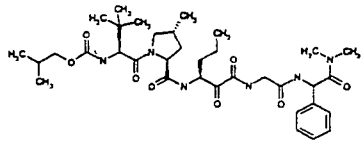
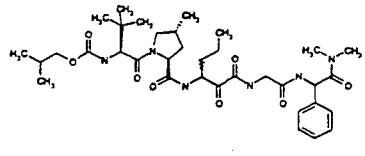
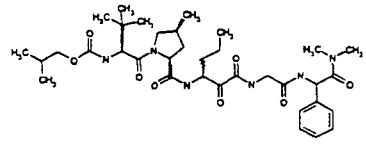
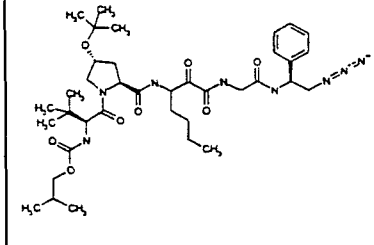
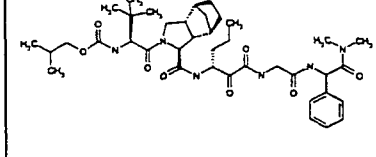
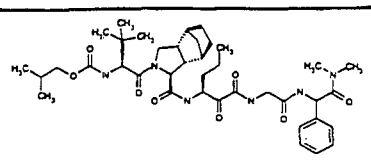
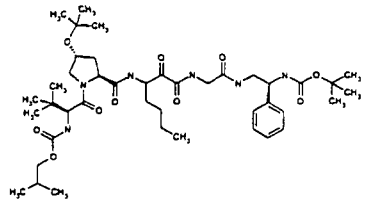
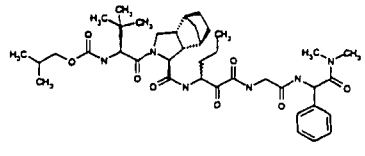
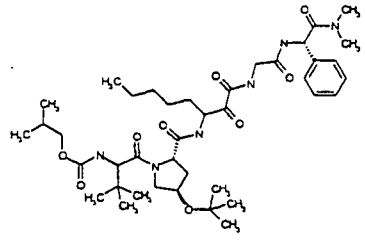
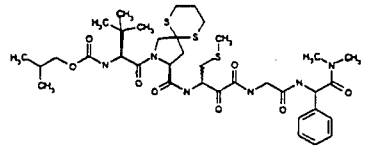
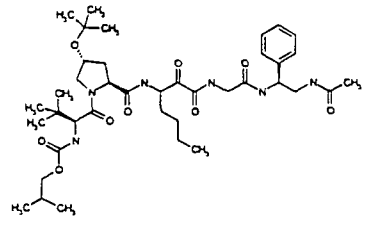
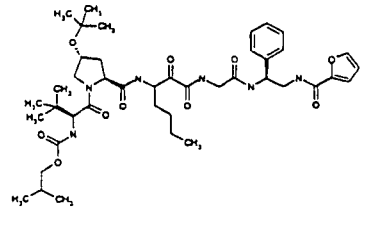
260		612.7703
261		686.856
262		686.856
263		686.856
264		686.856
265		742.9236
266		738.9325

Table 2

267		738.9325
268		817.0444
269		738.9325
270		772.9909
271		795.0592
272		758.9638
273		810.9966

000177

Table 2

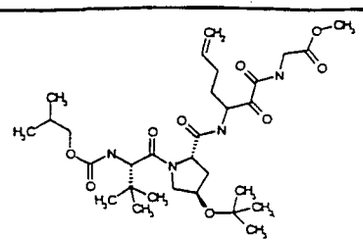
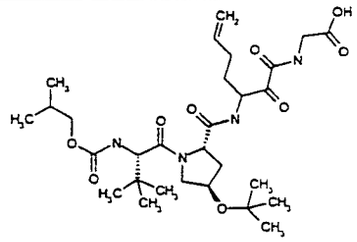
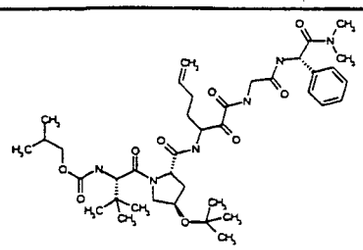
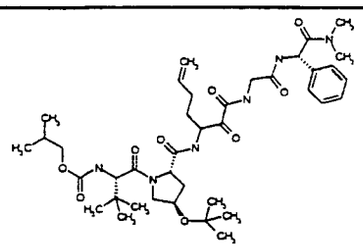
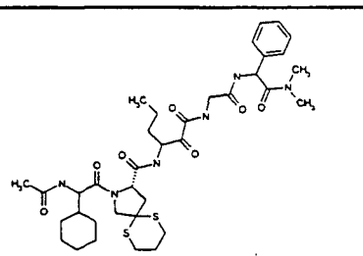
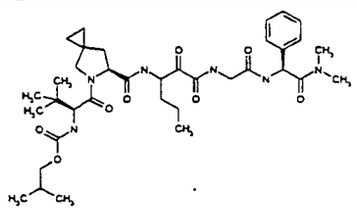
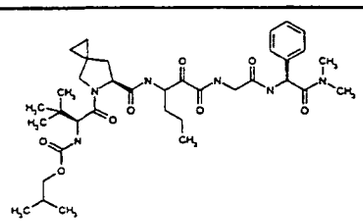
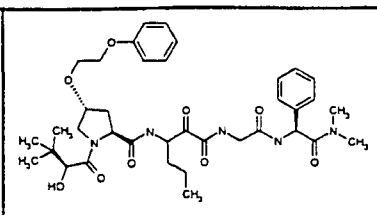
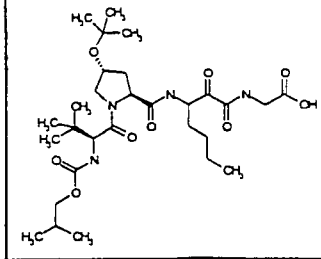
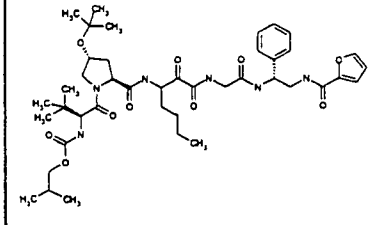
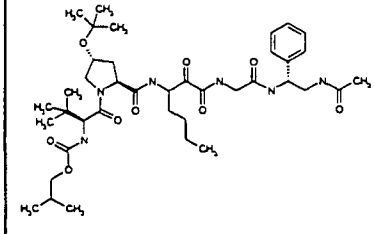
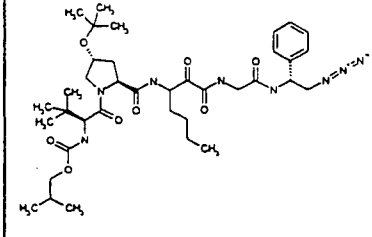
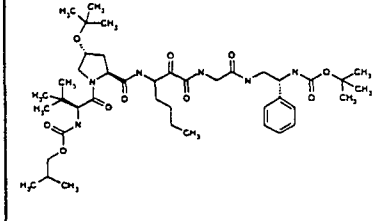
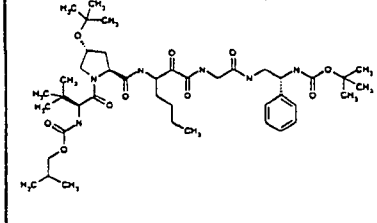
274		610.7544
275		596.7273
276		756.9479
277		756.9479
278		744.9799
279		698.8672
280		698.8672

Table 2

281		709.8471
282		598.7432
283		810.9966
284		758.9638
285		742.9236
286		817.0444
287		817.0444

000178

Table 2

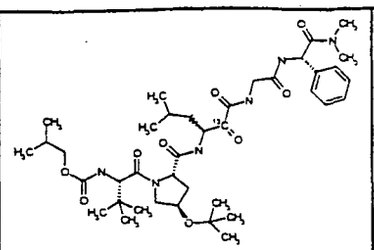
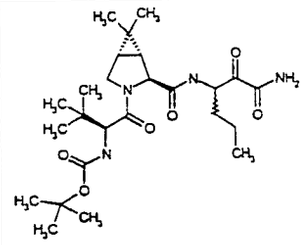
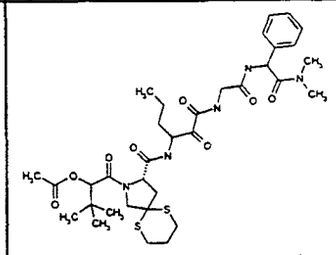
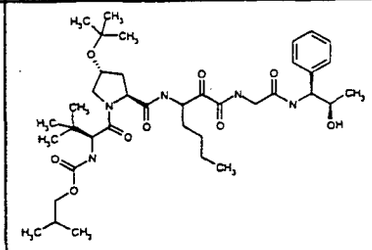
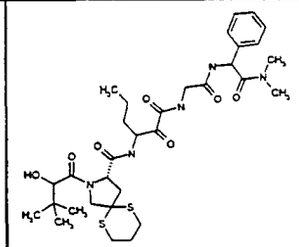
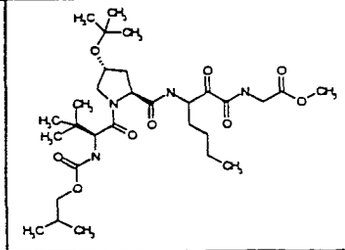
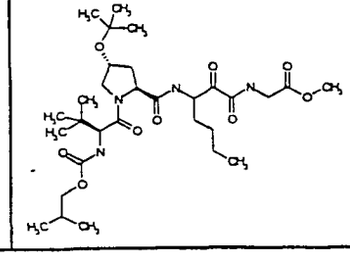
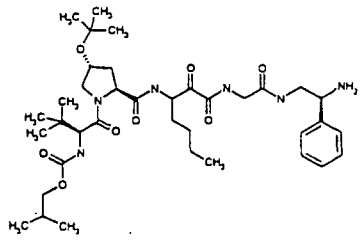
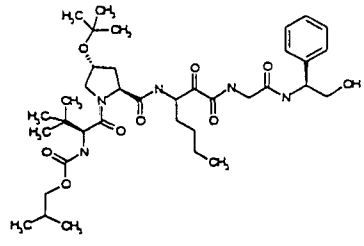
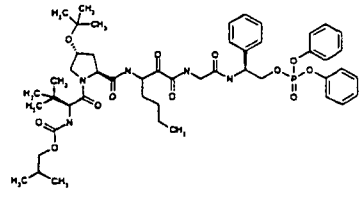
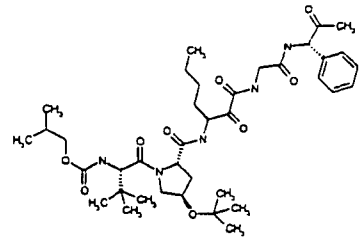
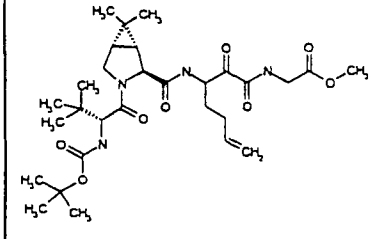
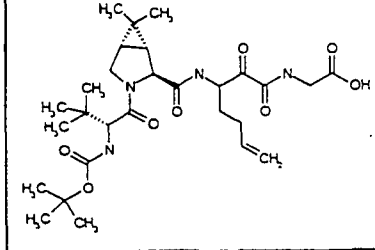
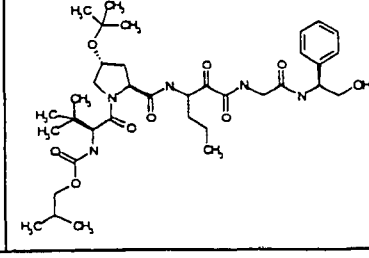
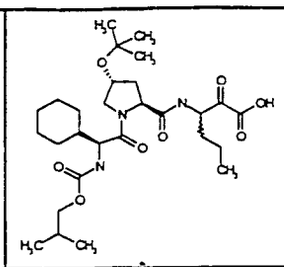
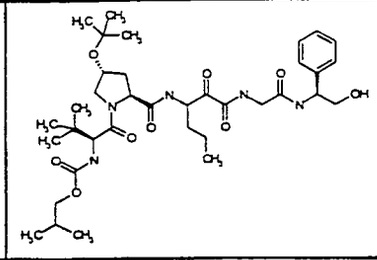
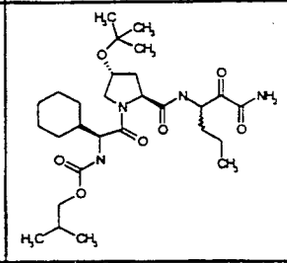
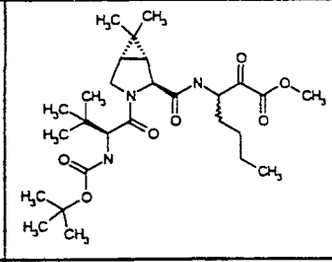
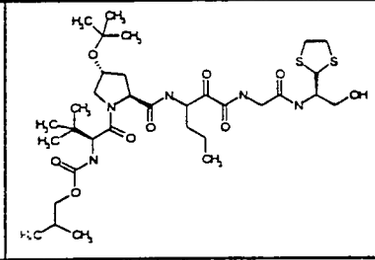
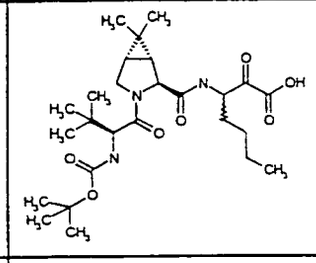
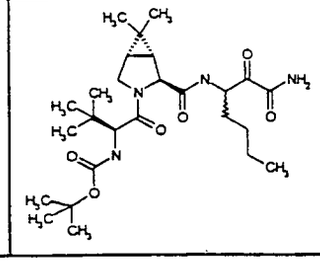
288		759.9526
289		494.6367
290		719.9263
291		731.938
292		677.8887
293		612.7703
294		612.7703

Table 2

295		716.9261
296		717.9109
297		950.0884
298		729.9221
299		578.712
300		564.6849
301		703.8838

030179

Table 2

302		553.7021
303		703.8838
304		552.7173
305		523.6756
306		731.9783
307		509.6485
308		508.6638

000180

Table 2

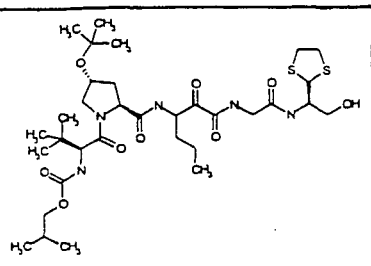
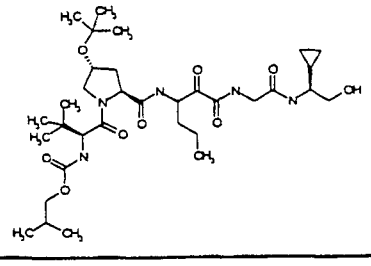
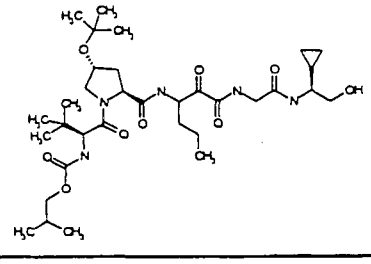
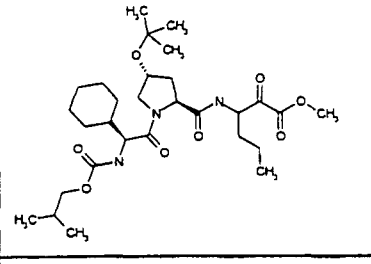
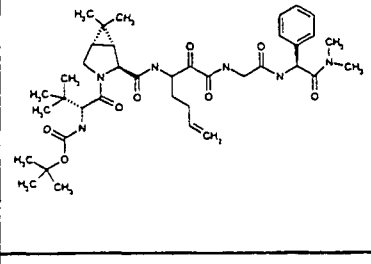
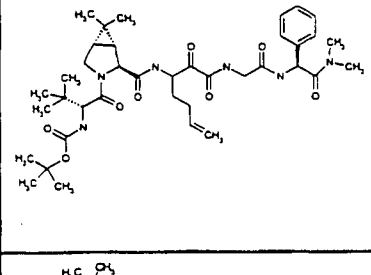
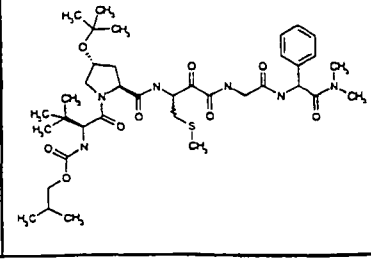
309		731.9783
310		667.8503
311		667.8503
312		567.7292
313		724.9054
314		724.9054
315		762.9736

Table 2

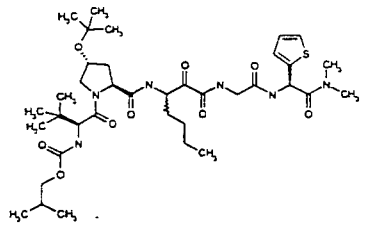
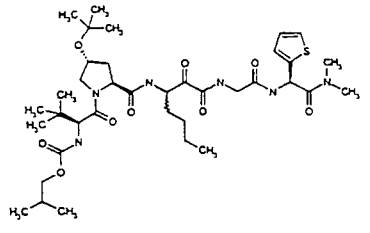
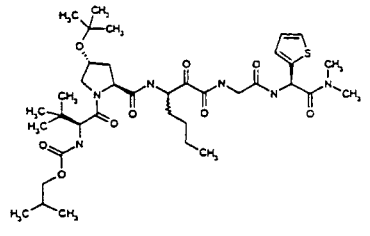
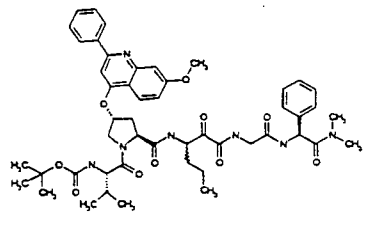
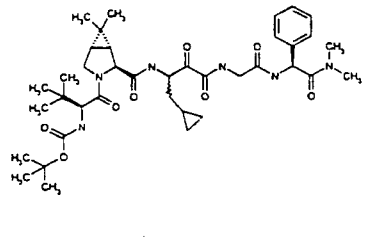
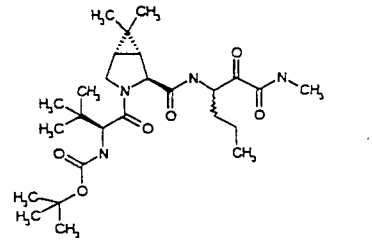
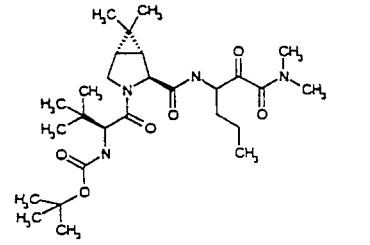
316		764.9896
317		764.9896
318		764.9896
319		908.0734
320		724.9054
321		508.6638
322		522.6909

Table 2

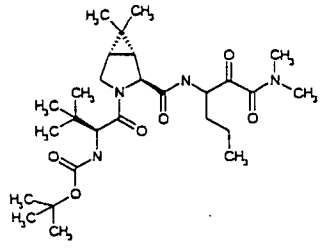
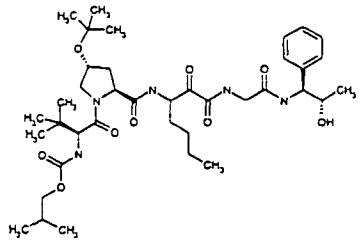
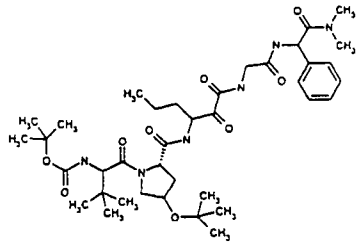
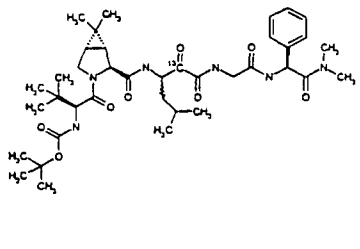
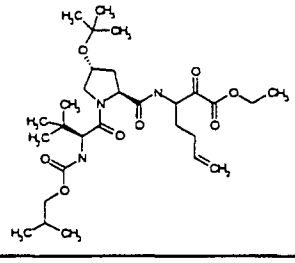
323		522.6909
324		731.938
325		744.9367
326		727.9102
327		567.7292

Table 2

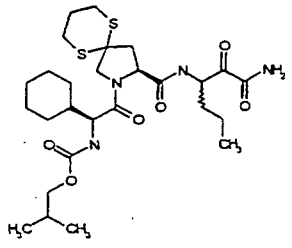
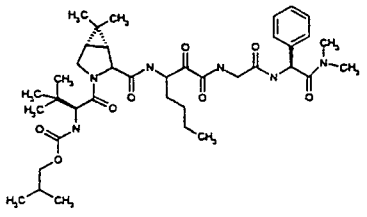
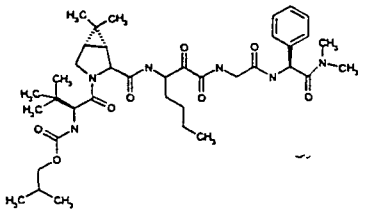
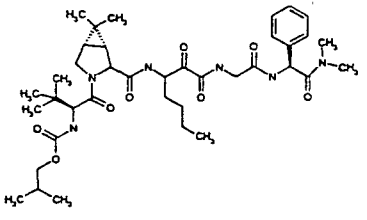
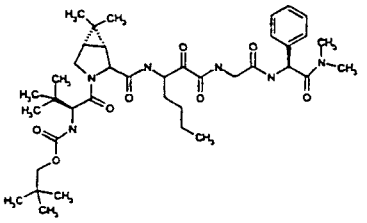
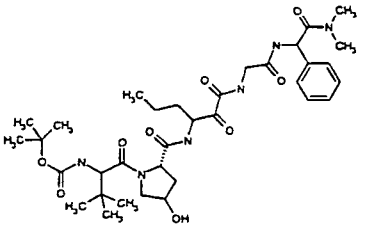
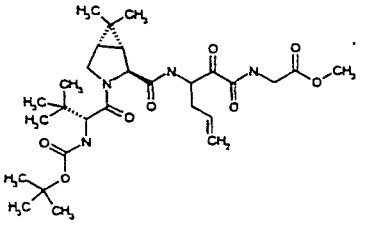
328		584.8029
329		726.9214
330		726.9214
331		726.9214
332		740.9484
333		688.8284
334		564.6849

Table 2

000182

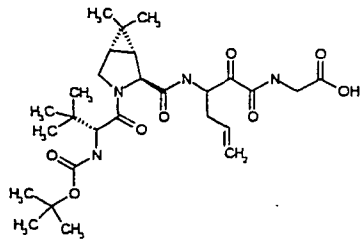
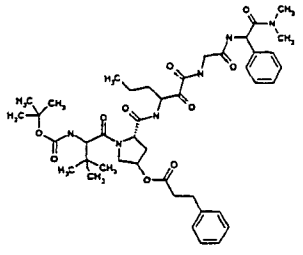
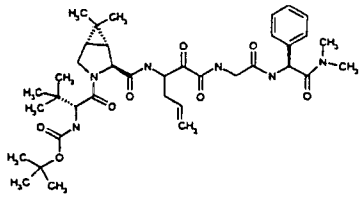
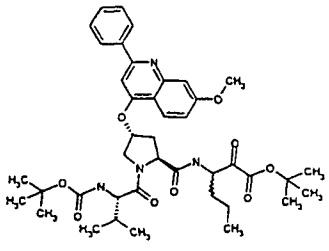
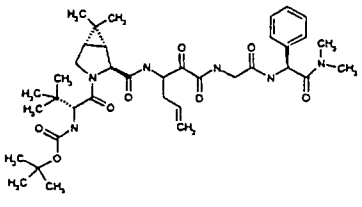
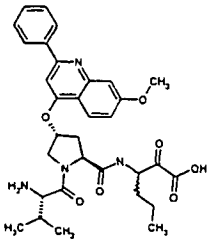
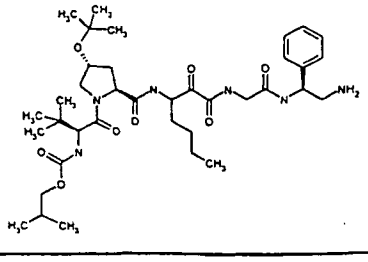
335		550.6578
336		820.9918
337		710.8784
338		746.9089
339		710.8784
340		590.6823
341		716.9261

Table 2

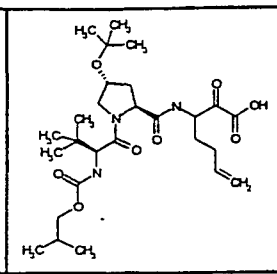
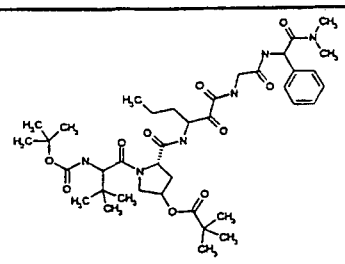
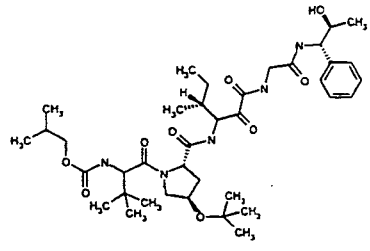
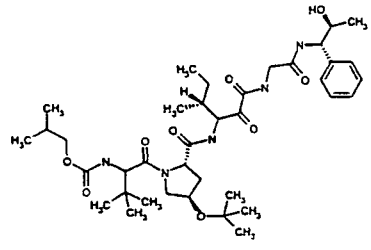
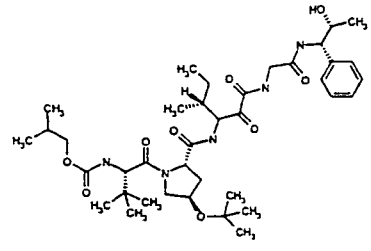
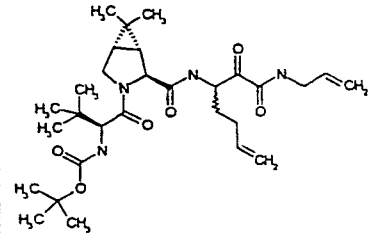
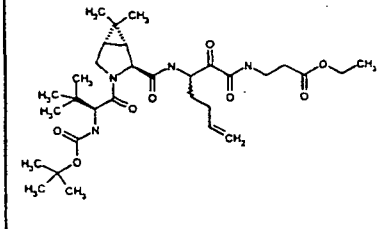
342		539.675
343		772.9473
344		731.938
345		731.938
346		731.938
347		546.7132
348		606.7662

Table 2

030183

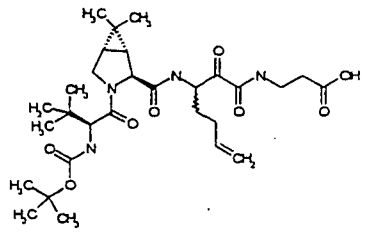
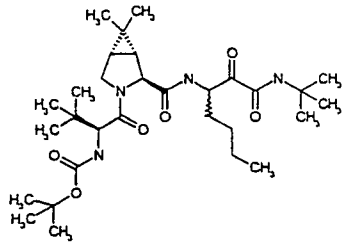
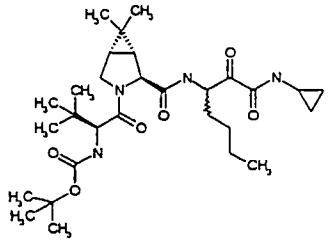
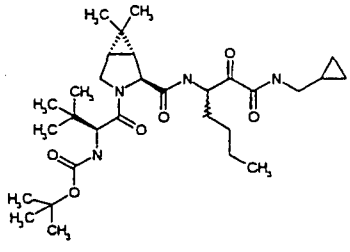
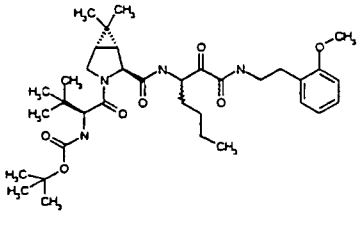
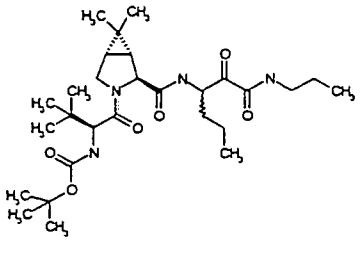
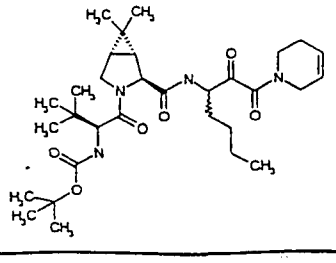
349		578.712
350		564.7722
351		548.7291
352		562.7562
353		642.8432
354		536.718
355		574.7673

Table 2

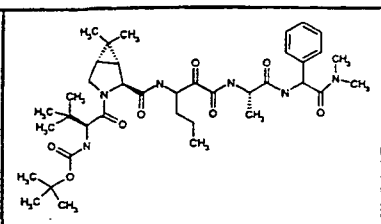
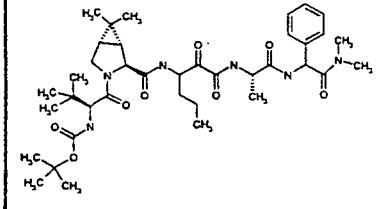
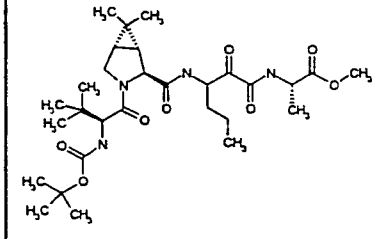
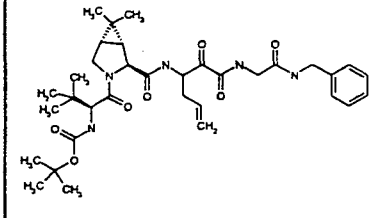
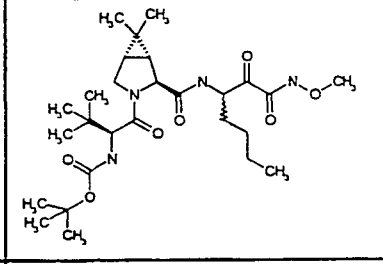
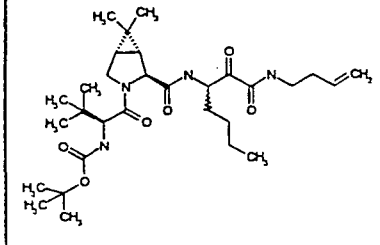
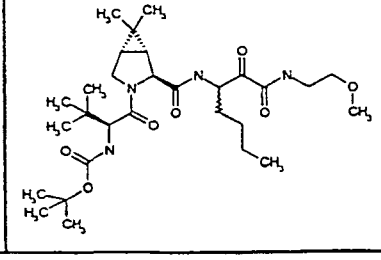
356		726.9214
357		726.9214
358		580.7279
359		639.799
360		538.6902
361		562.7562
362		566.7444

Table 4

000184

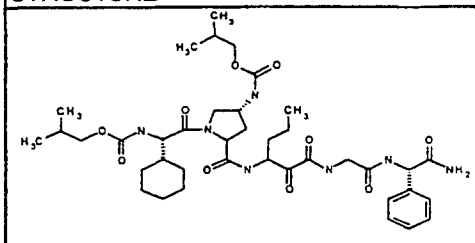
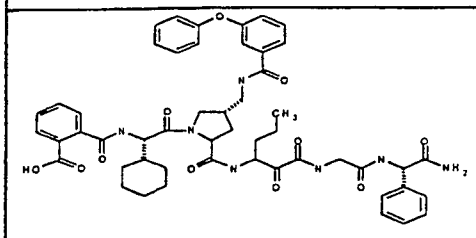
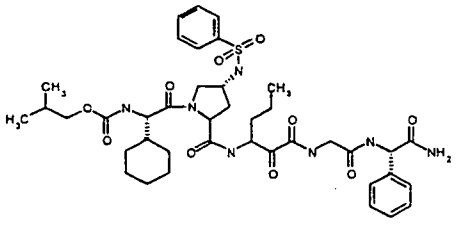
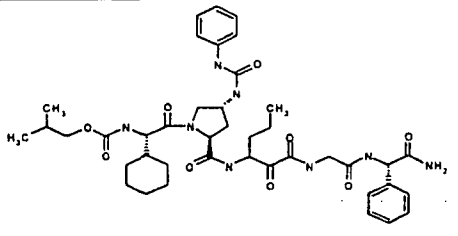
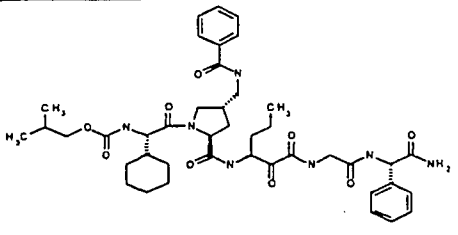
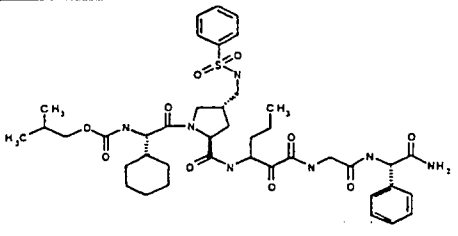
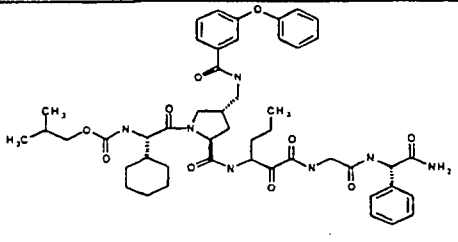
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4t-NHiBoc)-nV-(CO)-G-G(Ph)-Am	A
	(2-CO2)PhCO-G(Chx)-P(4t-MeNHCOPh(3-OPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-NHSO2Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-UreaPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHCOPh)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHSO2Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-MeNHCOPh(3-OPh))-nV-(CO)-G-G(Ph)-Am	B

Table 4

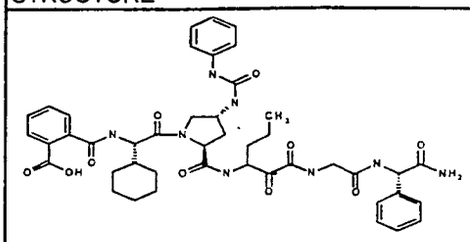
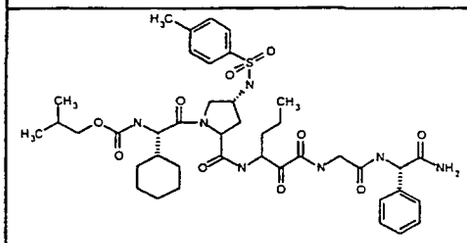
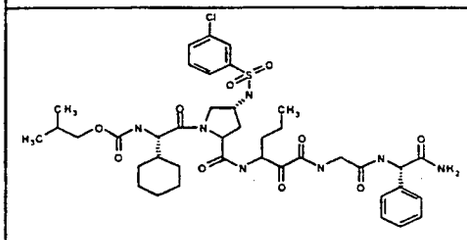
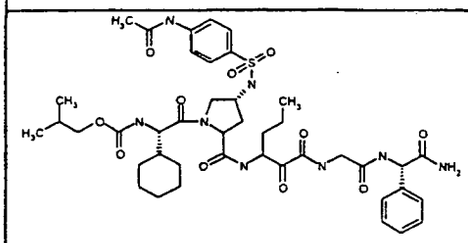
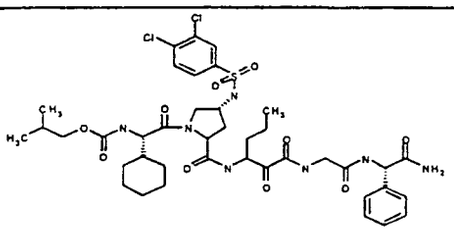
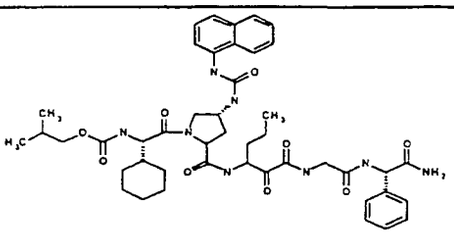
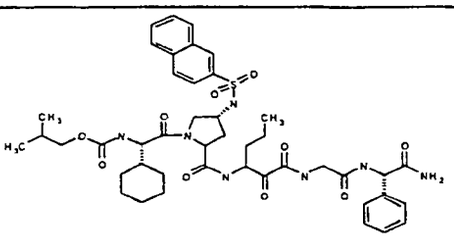
STRUCTURE	NAME	Ki* Range
	(2-CO2)PhCO-G(chx)-P(4t-UreaPh)-nV-(CO)-G-G(ph)-Am	C
	iBoc-G(Chx)-P(4t-NHSO2-(4Me)Ph)-nV(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-(3Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-(4-NHAc)Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-NHSO2-(3,4-diCl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	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

030185

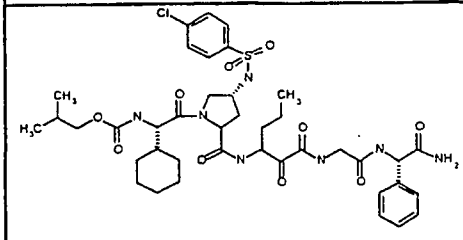
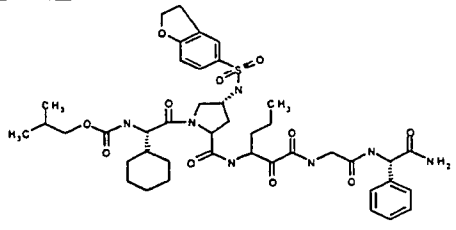
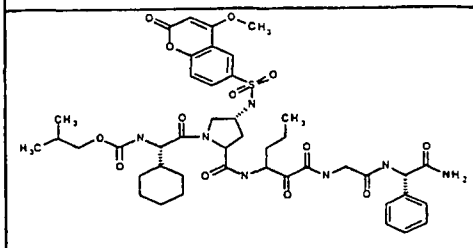
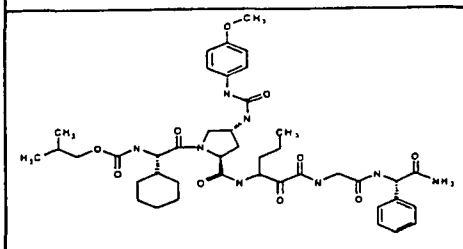
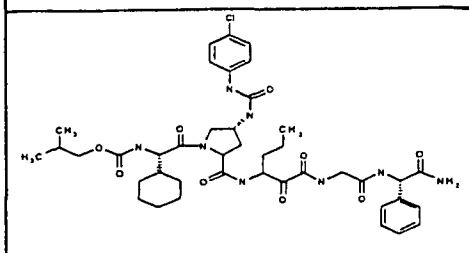
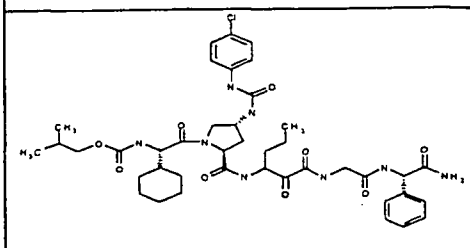
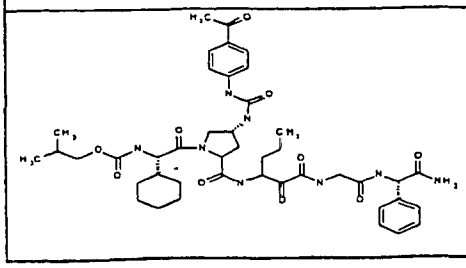
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4t-NHSO2-(4Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-5(2,3-dihydrobenzofuran))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-6(4-OMe)Courmarin)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-Ph(4-OMe))-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Cl))-nV-(CO)-G-G(Ph)-Am	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

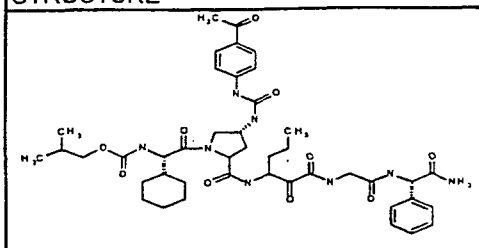
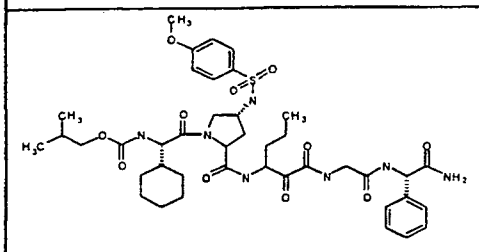
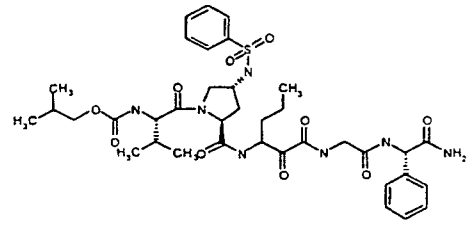
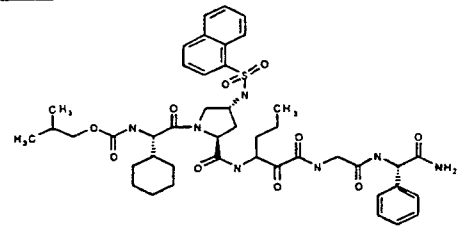
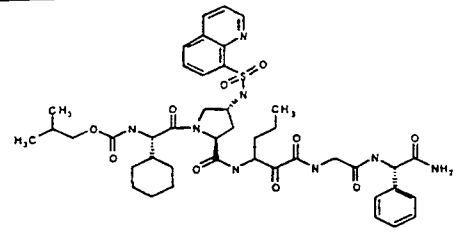
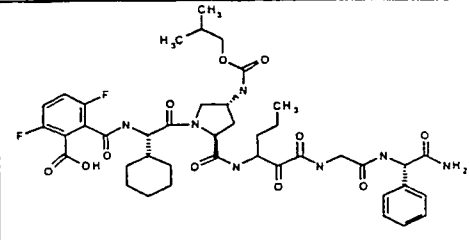
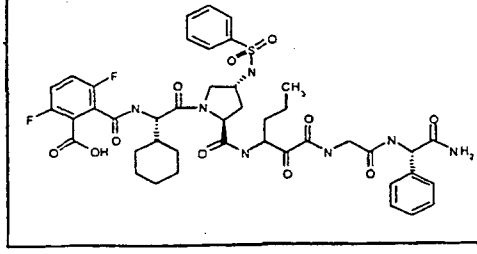
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4t-Urea-Ph(4-Ac))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-Ph(4-OMe))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-V-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-1Np)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-8-Quinoline)-nV-(CO)-G-G(Ph)-Am	B
	(2,5-diF-6-CO2)PhCO-G(Chx)-P(4t-NH-iBoc)-nV-(CO)-G-G(Ph)-Am	A
	(2,5-diF-6-CO2)PhCO-G(Chx)-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	A

Table 4

030186

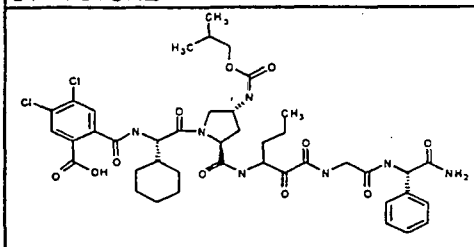
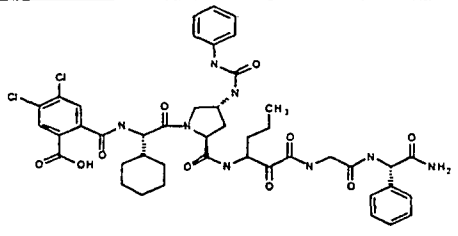
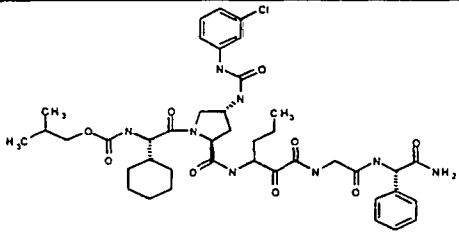
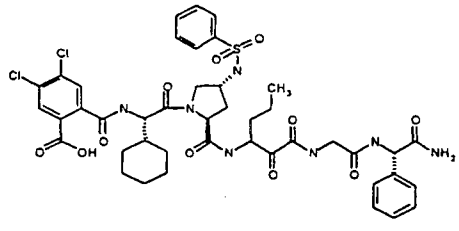
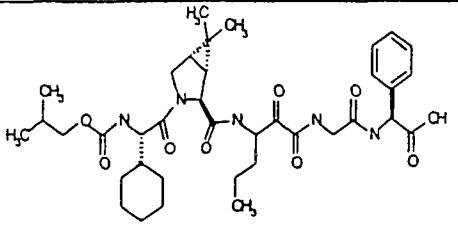
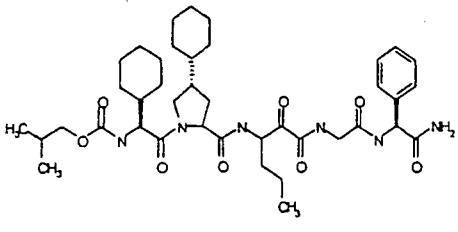
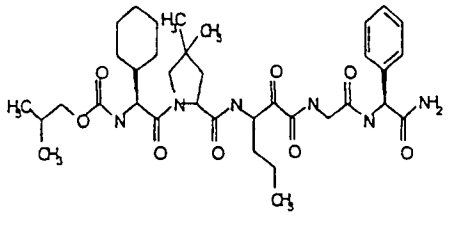
STRUCTURE	NAME	Ki* Range
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-NH-iBoc)-nV-(CO)-G-G(Ph)-Am	A
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-UreaPh)-nV(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-Urea-(3-Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	(3,4-diCl-6-CO2)PhCO-G(Chx)-P(4t-NHSO2-Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(3,4-iPr)-nV-(CO)-G-G(Ph)-OH	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

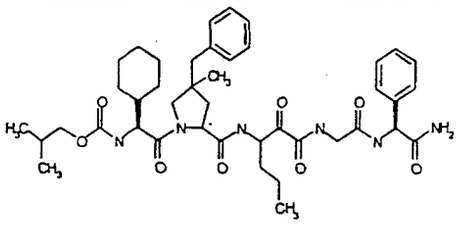
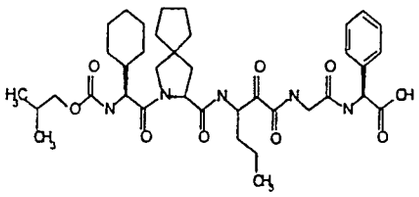
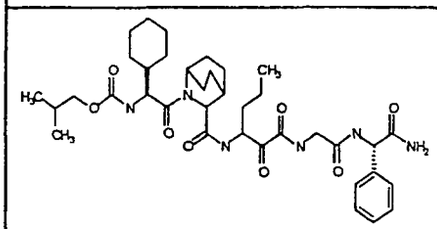
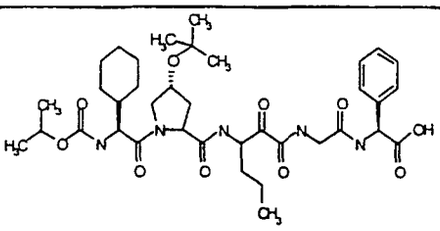
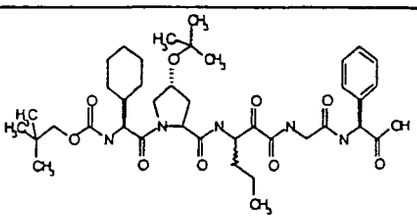
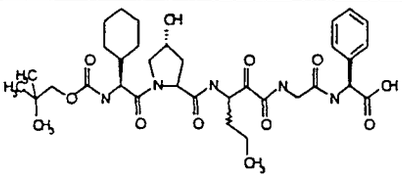
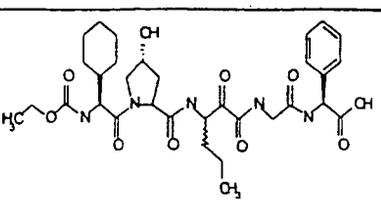
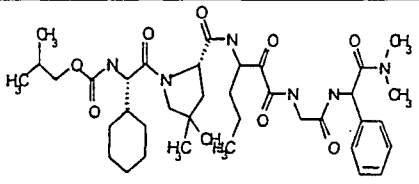
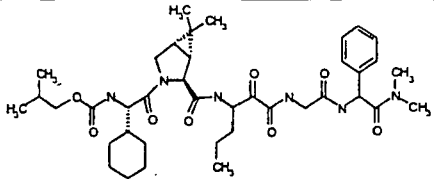
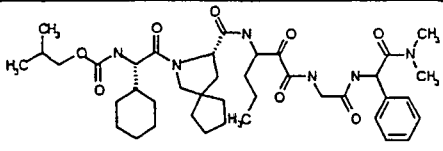
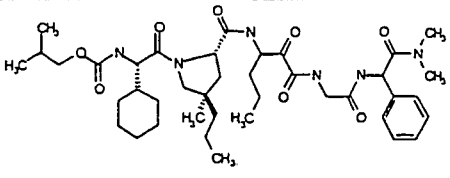
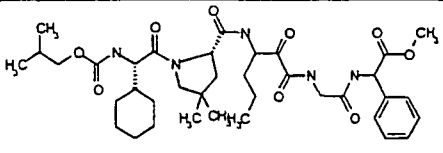
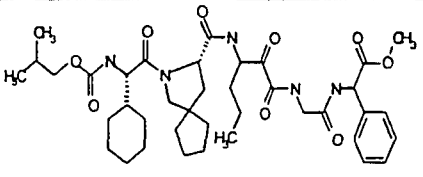
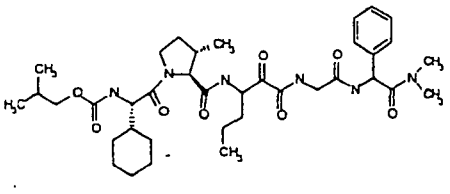
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4-Bn,4-Me)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4-spirocyclopentane)-nV-(CO)-G-G(Ph)-OH	A
	iBoc-G(Chx)-2-Azabicyclo[2.2.2]octane-3-CO-nV-(CO)-G-G(Ph)-Am	B
	iPrOCO-G(Chx)-P(4-OtBu)-nV-(CO)-G-G(Ph)-OH	A
	Neopentoxy(CO)-G(Chx)-P(4-OtBu)-nV- (CO)-G-G(Ph)-OH	B
	Neopentoxy(CO)-G(Chx)-P(OH)-nV-(CO)-G- 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

000187

Table 4

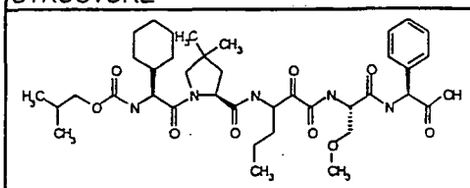
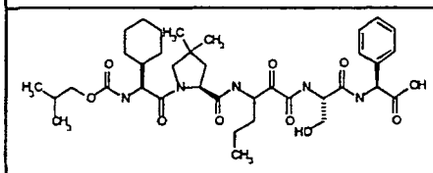
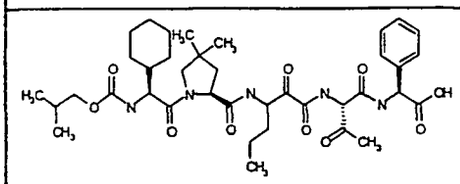
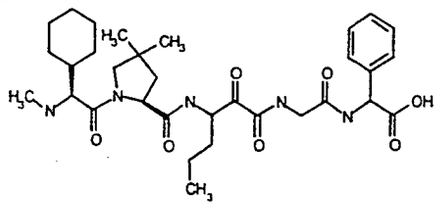
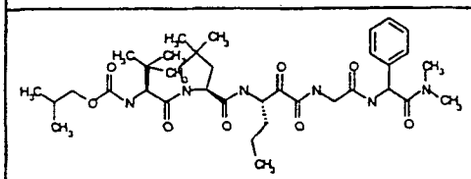
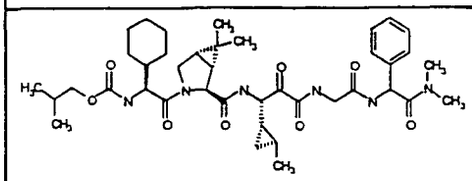
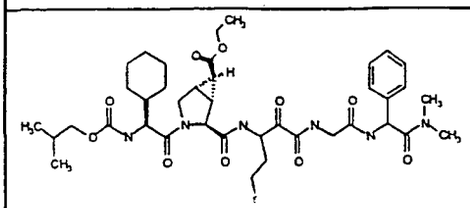
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-P(4,4-diMe)-nV-(CO)-S(Me)-G(Ph)-OH	A
	iBoc-G(Chx)-P(4,4-diMe)-nV-(CO)-S-G(Ph)-OH	B
	iBoc-G(Chx)-P(4,4-diMe)-nV-(CO)-G(Ac)-G(Ph)-OH	C
	N-Me-G(Chx)-P(4,4-diMe)-nV-(CO)-G- G(Ph)-CO2H	C
	iBoc-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4-(diMe-cyclopropyl))-G((S,S)-Me-cyclopropyl)-(CO)-G-G(Ph)-N(Me)	A
	iBoc-G(Chx)-P(6S-CEM)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

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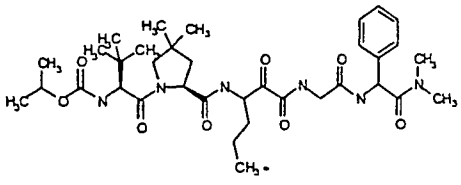
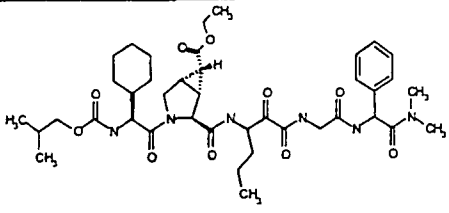
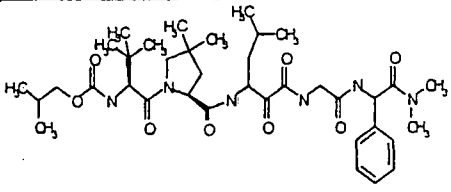
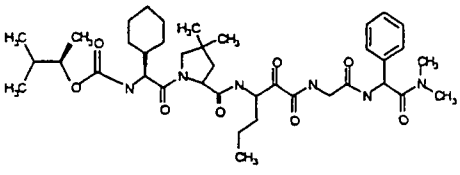
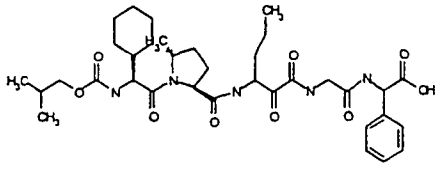
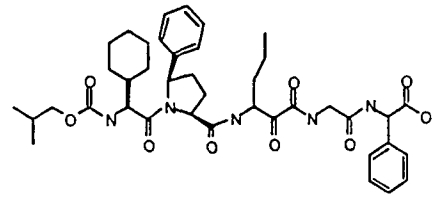
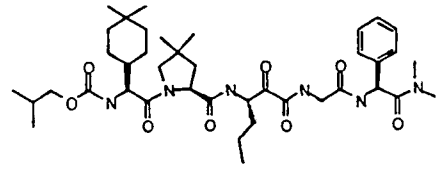
STRUCTURE	NAME	Ki* Range
	iPoc-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(6R-CEM)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(4,4-diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me-iBoc)-G(Chx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(5-c/t-Me)-nV-(CO)-G-G(Ph)-CO2H	A
	iBoc-G(Chx)-P(5-cis-Ph)-nV-(CO)-G-G(Ph)-CO2H	B
	iBoc-G(4,4-diMeChx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

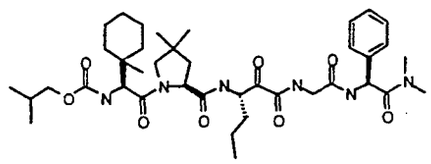
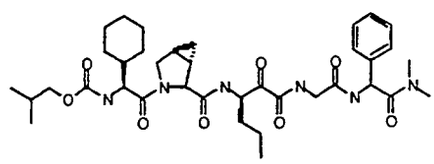
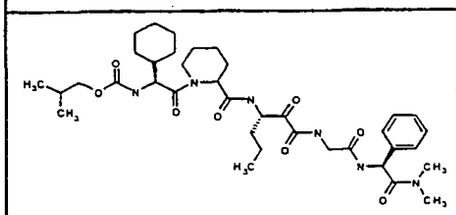
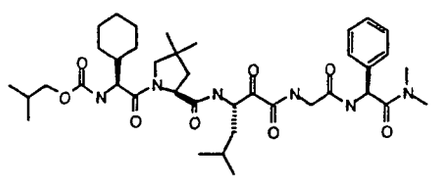
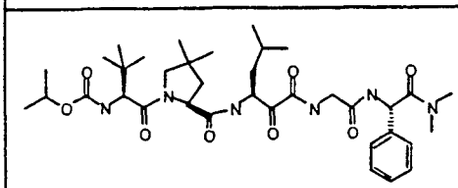
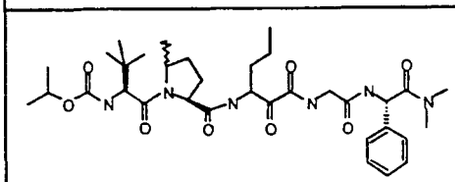
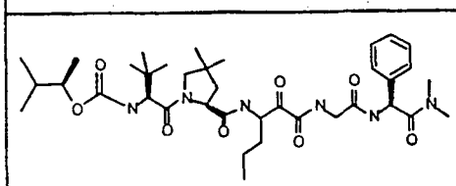
STRUCTURE	NAME	Ki* Range
	iBoc-G(1-MeChx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-Chg-Pip-nV-(CO)-G-G(Ph)-N(Me)2	C
	iBoc-G(Chx)-P(4,4-diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(4,4-diMe)-L-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(5-c/t-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me-iBoc)-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

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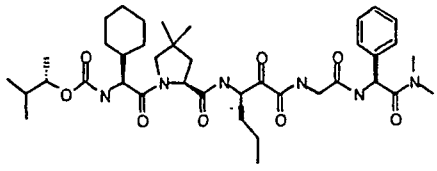
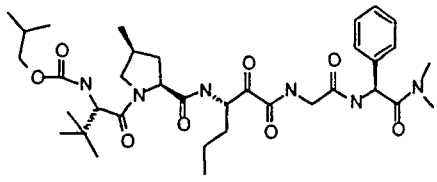
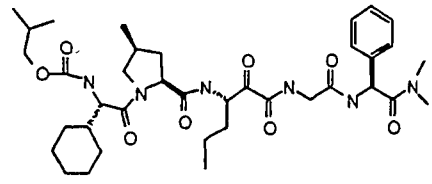
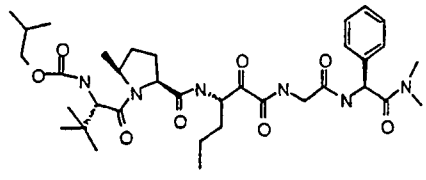
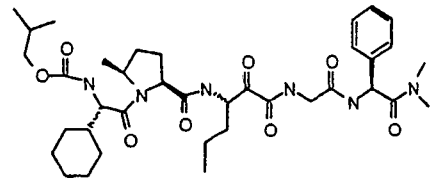
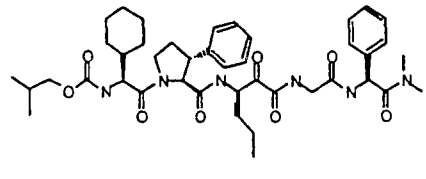
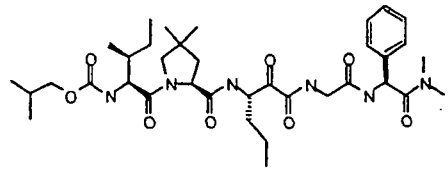
STRUCTURE	NAME	Ki* Range
	(S)-1-MeiBoc-G(Chx)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(4-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(4-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(5-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(5-cis-Me)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(t-3Ph)-nV-(CO)-G-G(Ph)-N(Me)2	B
	iBoc-allo(Ile)-P(4,4diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 4

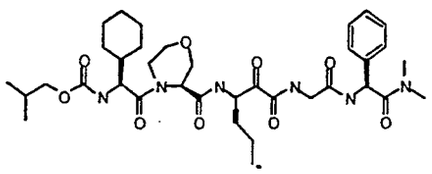
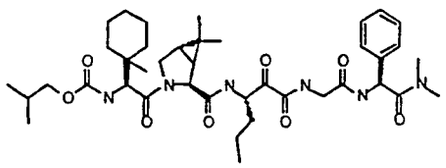
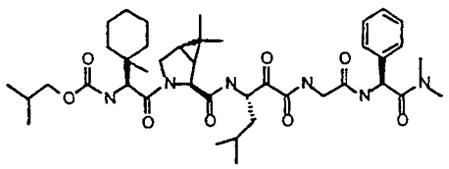
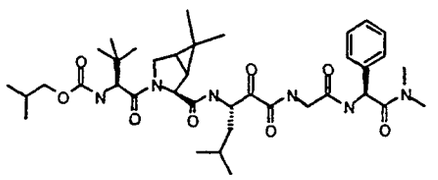
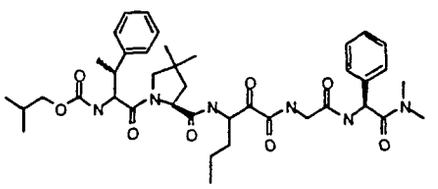
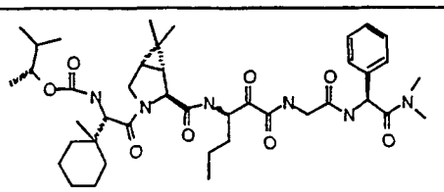
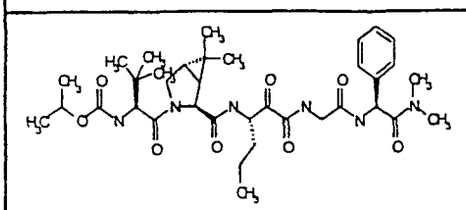
STRUCTURE	NAME	Ki* Range
	iBoc-G(Chx)-Pip(4-morpholino)-nV-(CO)-G-G(Ph)-N(Me)2	B
	iBoc-G(1-MeChx)-P[3,4-(diMe-cyclopropyl)]-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(1-MeChx)-P[3,4-(diMe-cyclopropyl)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P[3,4-(diMe-cyclopropyl)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-erythro-D,L-F(beta-Me)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	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

030190

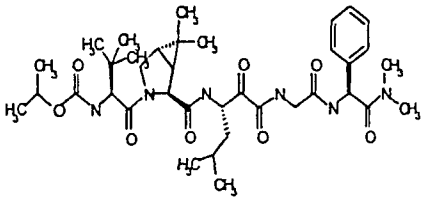
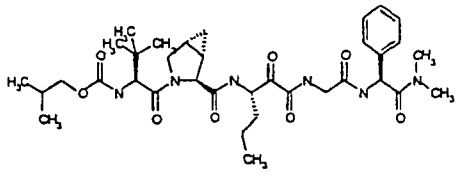
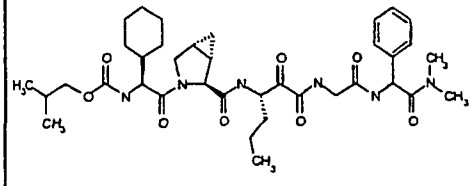
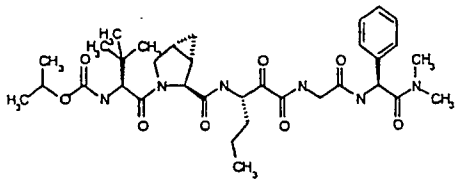
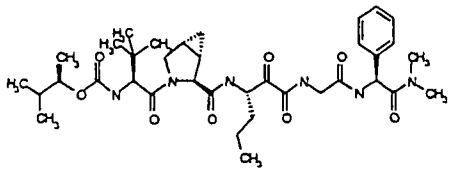
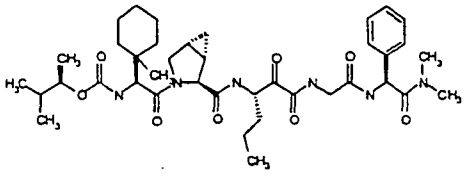
STRUCTURE	NAME	Ki* Range
	iPoc-G(tBu)-P[3,4-(diMe-cyclopropyl)]-L-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(1-MeChx)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A

Table 5

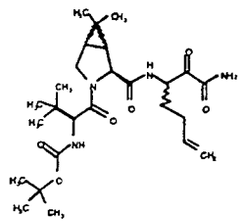
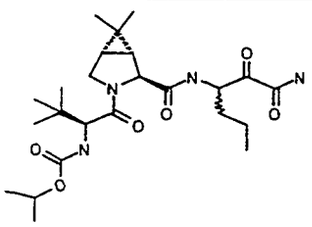
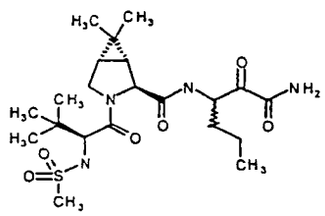
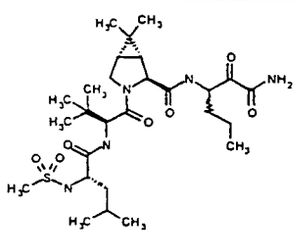
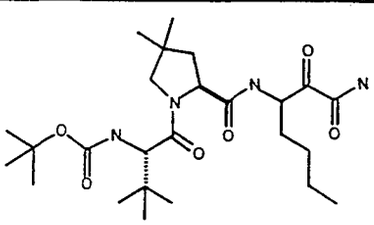
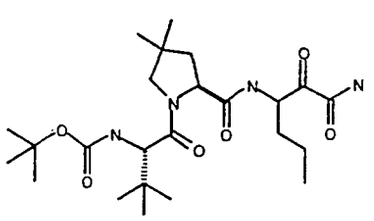
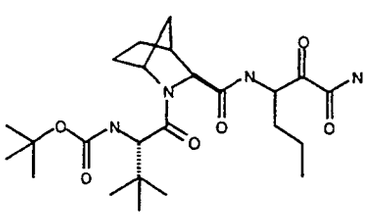
Structure	MW	Ki* range
	507	B
	481	B
	473	C
	586	B
	497	C
	483	C
	481	C

Table 5

000191

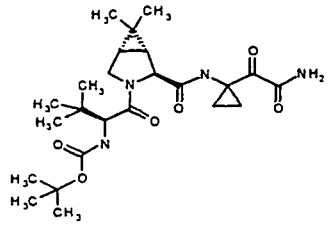
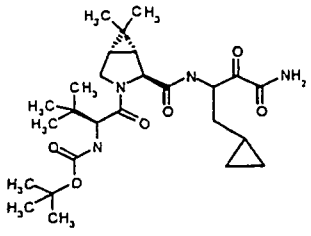
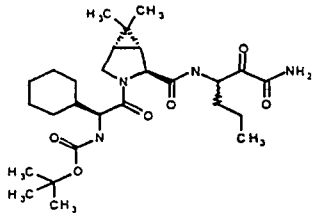
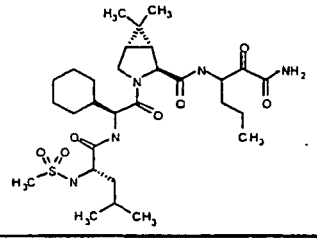
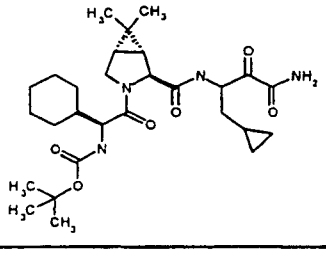
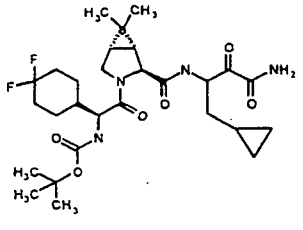
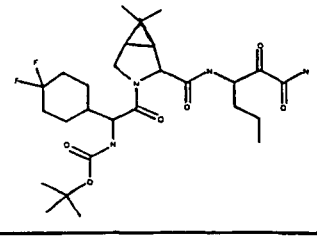
	479	B
	507	A
	521	A
	612	A
	533	A
	569	A
	557	B

Table 5

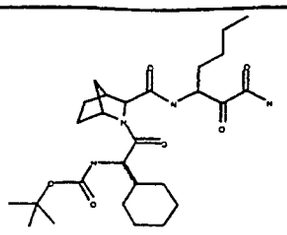
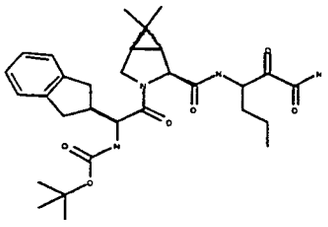
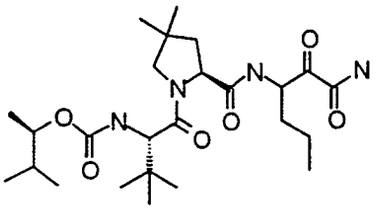
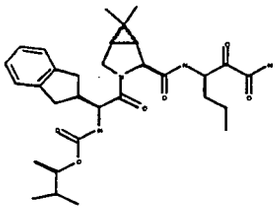
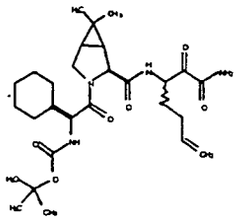
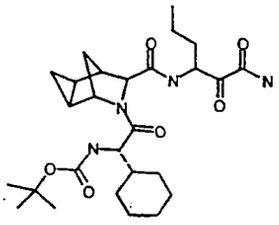
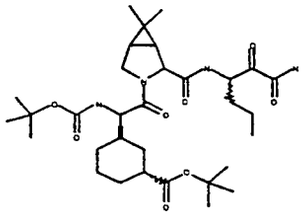
	521	C
	555	A
	497	C
	569	B
	533	B
	519	C
	621	B

Table 5

030192

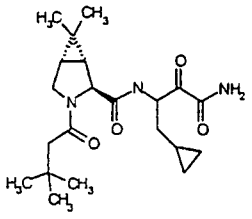
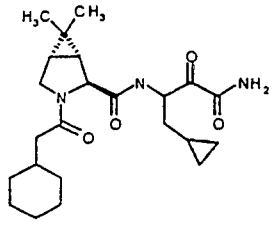
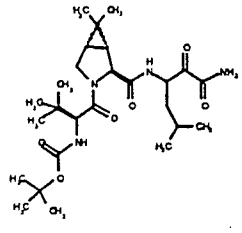
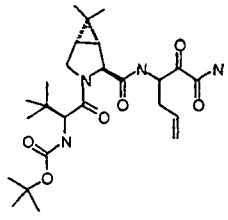
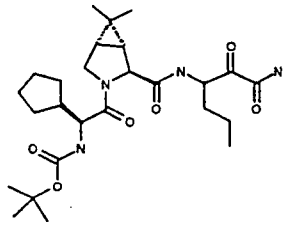
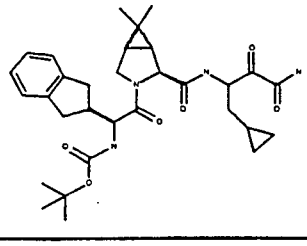
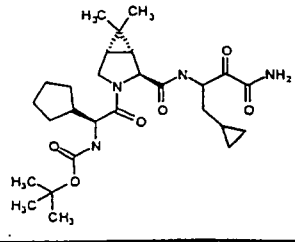
	392	C
	418	C
	509	B
	493	C
	507	B
	567	A
	519	A

Table 5

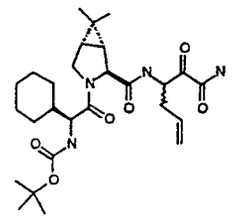
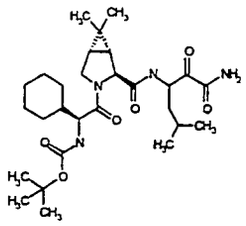
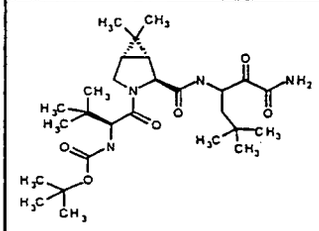
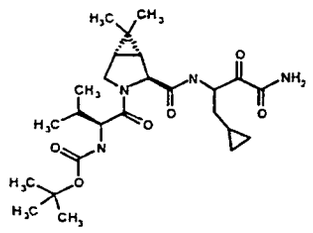
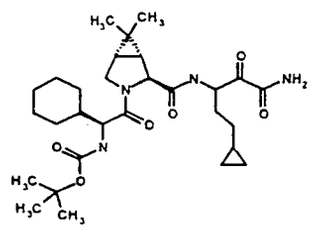
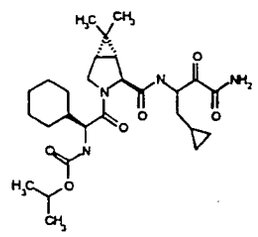
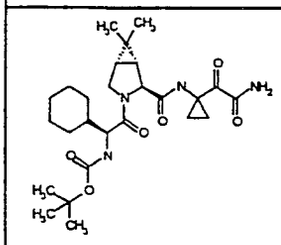
	519	B
	535	B
	523	C
	493	B
	547	B
	519	A
	505	C

Table 5

030193

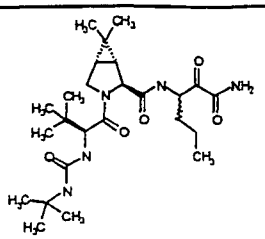
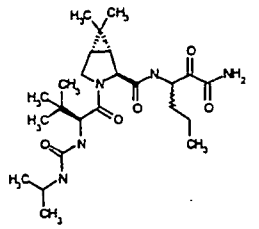
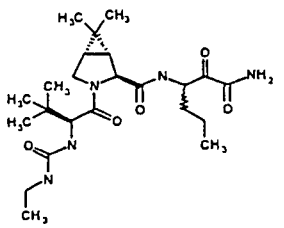
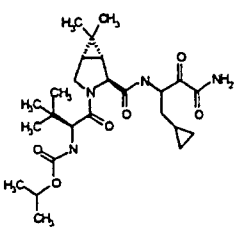
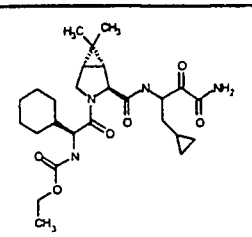
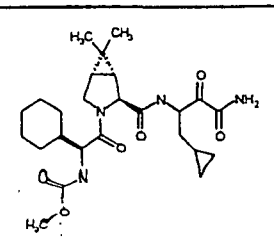
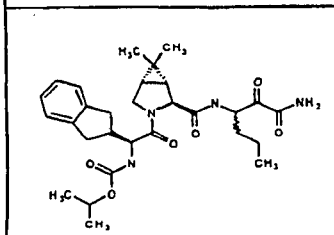
	494	B
	480	B
	466	C
	493	B
	505	B
	491	B
	541	B

Table 5

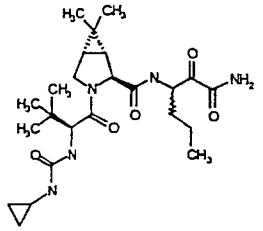
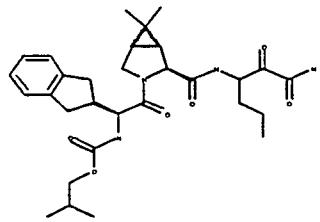
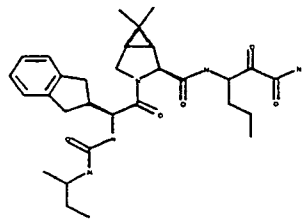
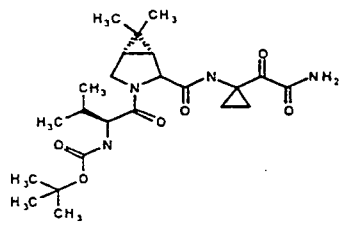
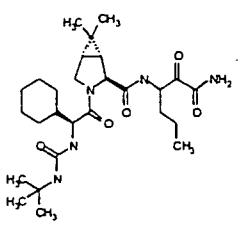
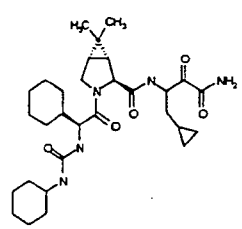
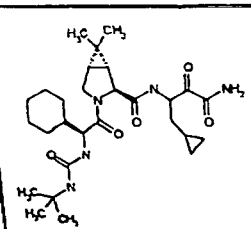
	478	C
	555	B
	554	B
	465	C
	520	A
	558	A
	532	A

Table 5

030194

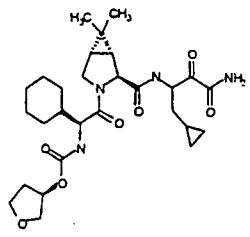
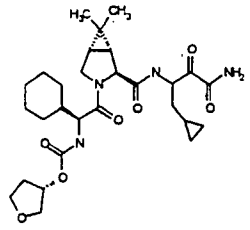
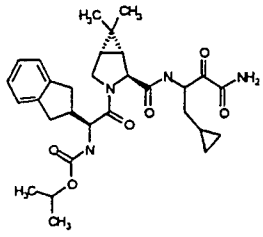
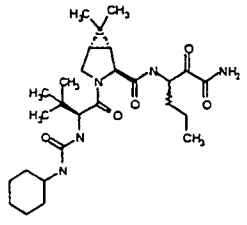
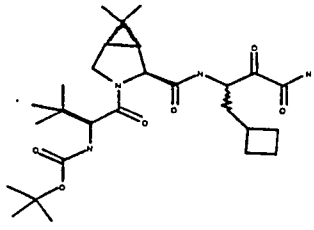
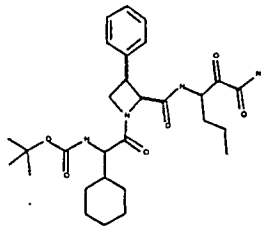
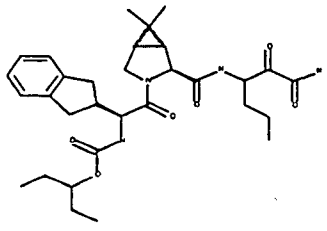
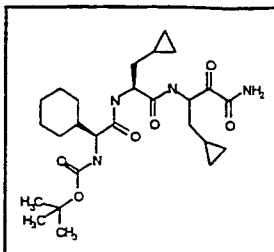
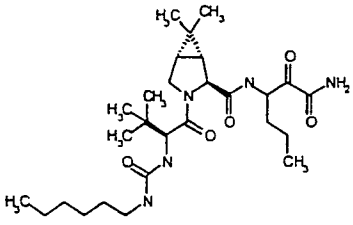
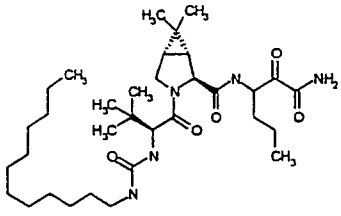
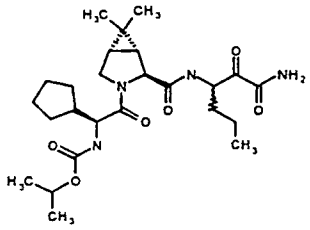
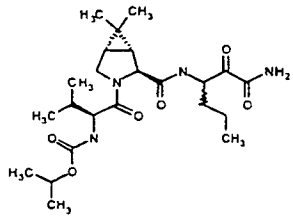
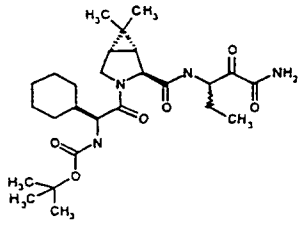
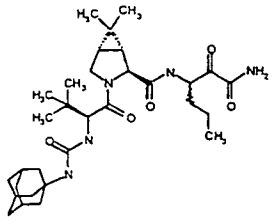
	547	B
	547	B
	553	A
	520	B
	521	A
	543	C
	569	B

Table 5

	507	B
	522	B
	606	C
	493	B
	467	C
	507	B
	572	A

030195

Table 5

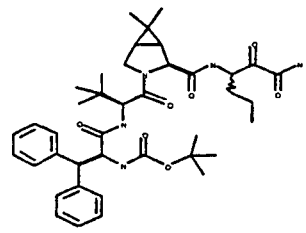
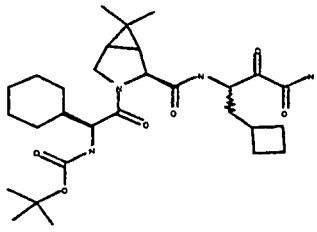
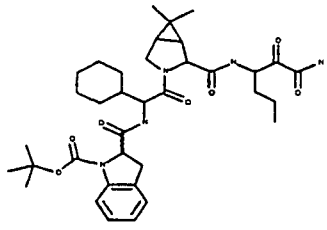
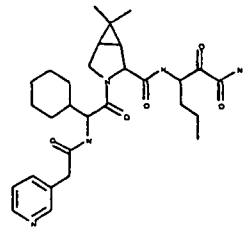
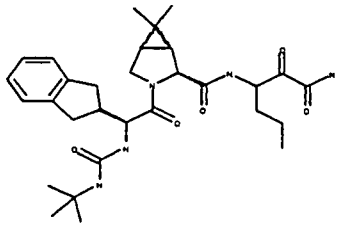
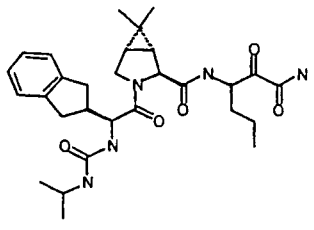
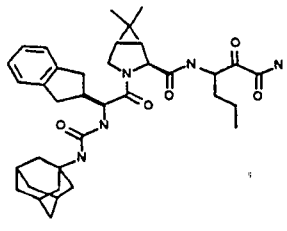
	718	C
	547	A
	666	B
	540	C
	554	B
	540	B
	632	B

Table 5

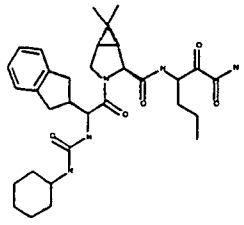
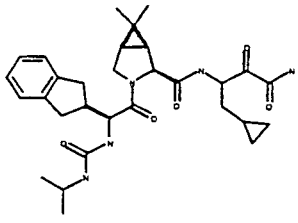
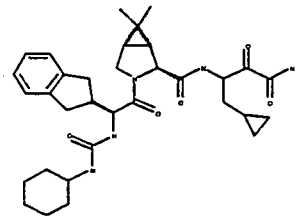
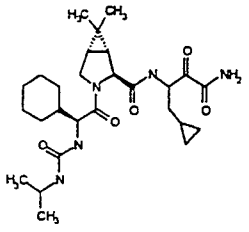
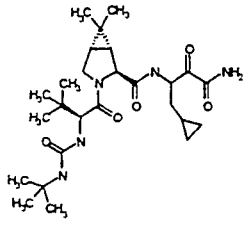
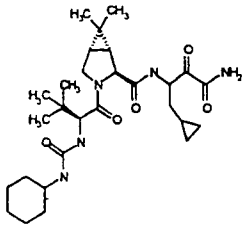
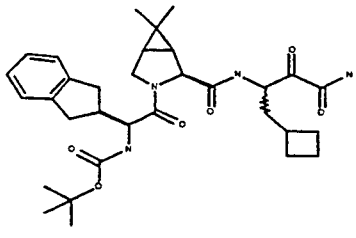
	580	B
	552	A
	592	A
	518	A
	506	A
	532	A
	581	B

Table 5

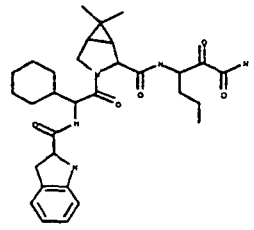
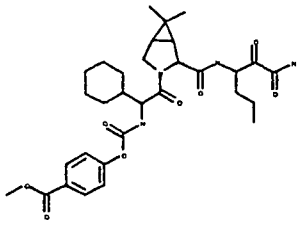
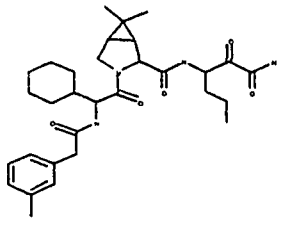
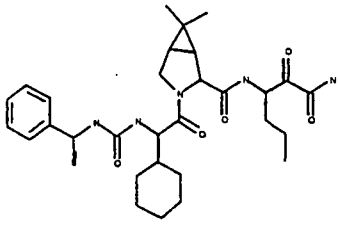
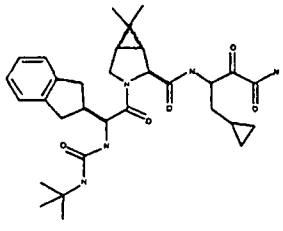
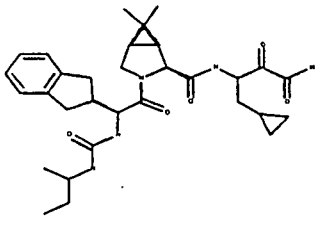
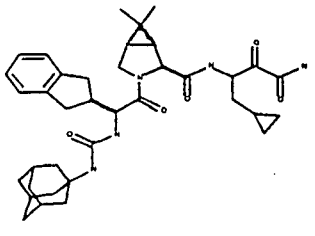
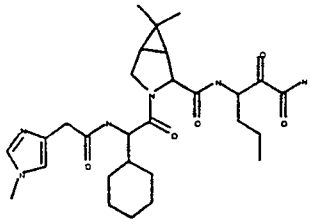
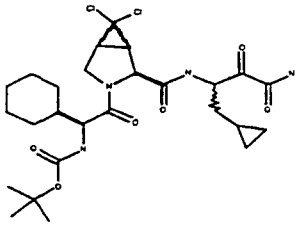
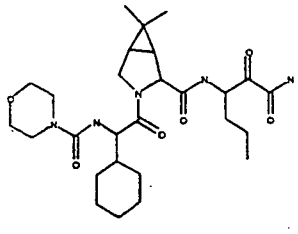
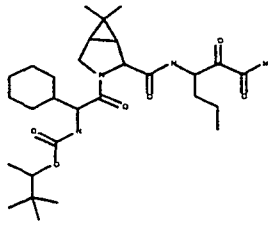
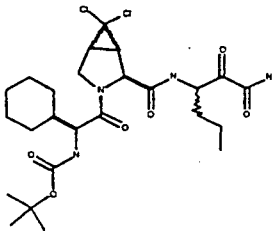
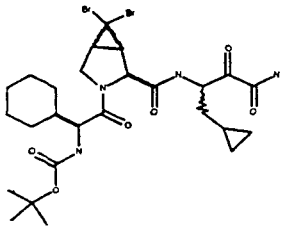
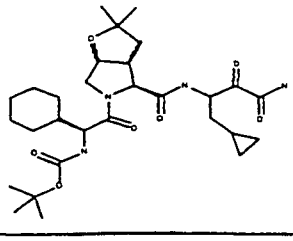
	566	C
	599	B
	553	B
	568	B
	566	A
	566	A
	644	A

Table 5

	543	C
	574	A
	534	C
	549	B
	562	A
	662	A
	563	B

030197

Table 5

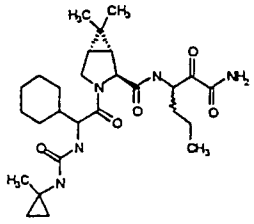
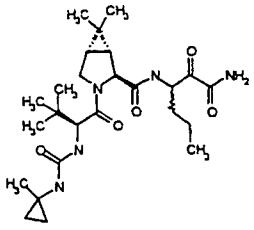
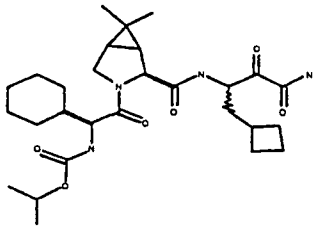
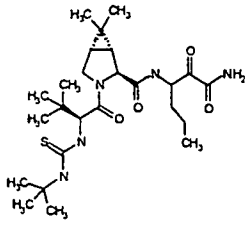
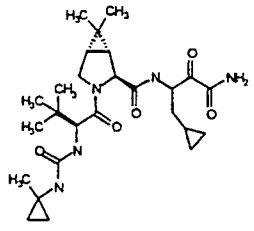
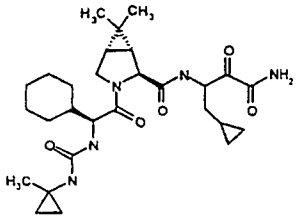
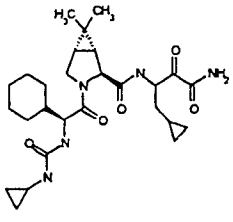
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	533	A
	510	C
	504	A
	530	B
	516	B

Table 5

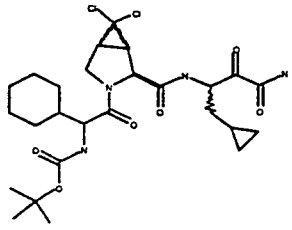
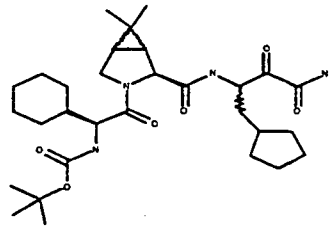
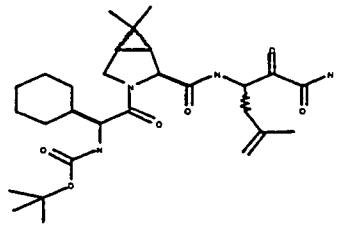
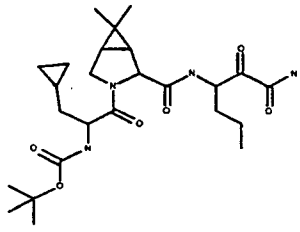
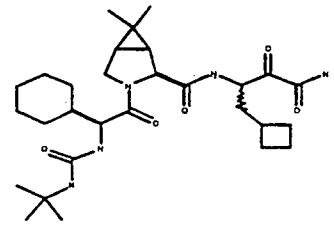
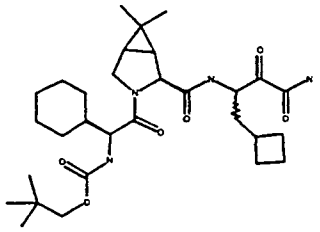
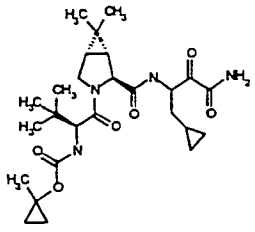
	574	B
	561	B
	533	B
	493	C
	546	A
	561	A
	505	B

Table 5

000198

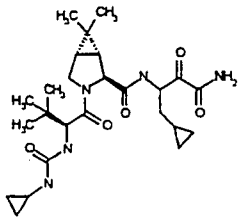
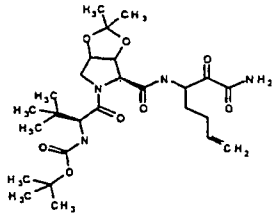
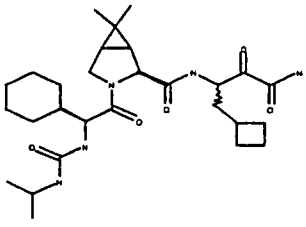
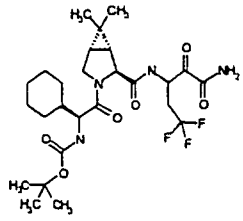
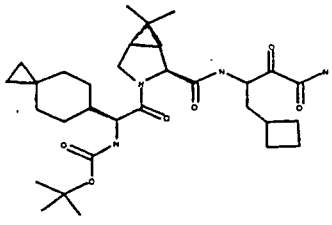
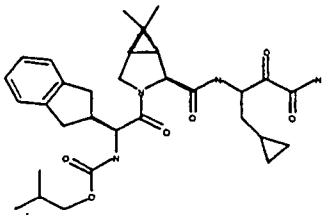
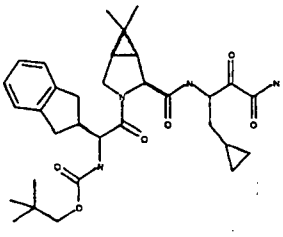
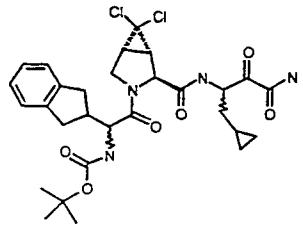
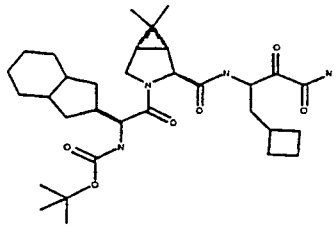
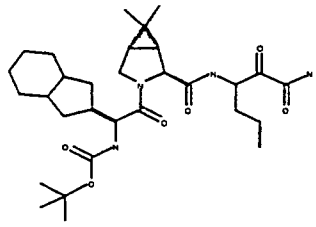
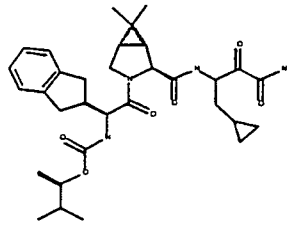
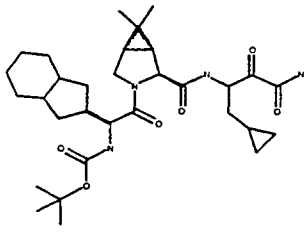
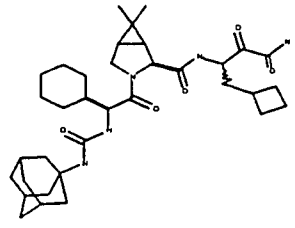
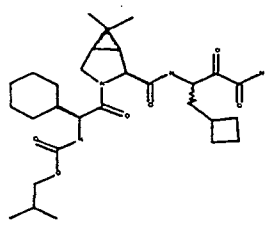
	490	B
	539	C
	532	A
	561	A
	573	A
	567	A
	581	A

Table 5

	608	A
	587	B
	561	B
	581	A
	573	A
	624	A
	547	A

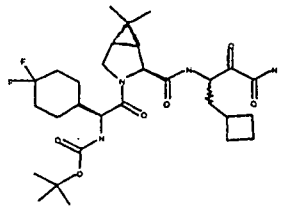
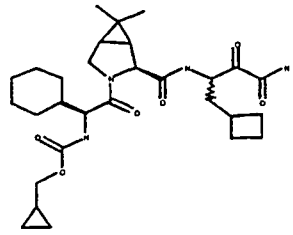
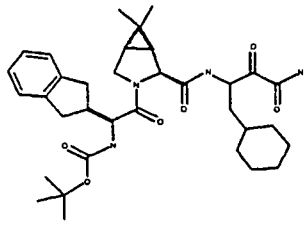
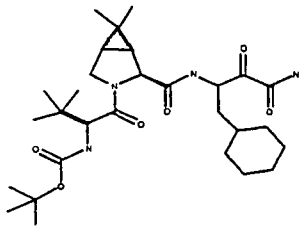
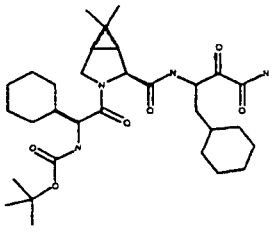
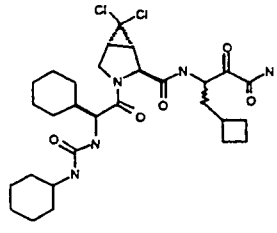
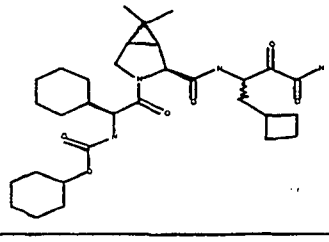
	583	A
	545	B
	609	C
	549	C
	575	C
	613	A
	573	A

Table 5

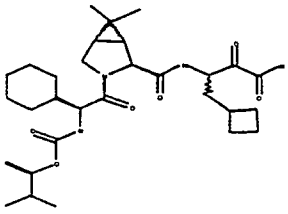
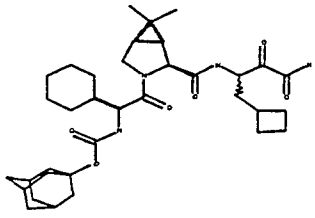
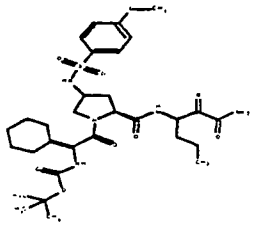
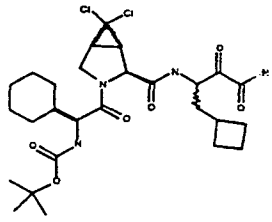
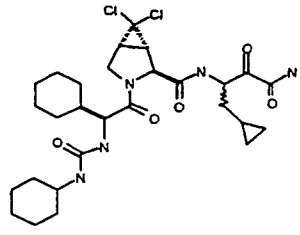
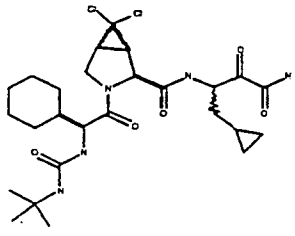
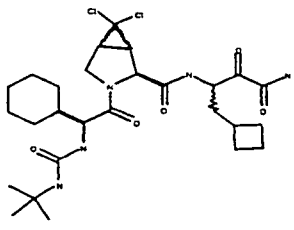
	561	A
	625	A
	666	C
	588	A
	599	A
	573	A
	587	A

Table 5

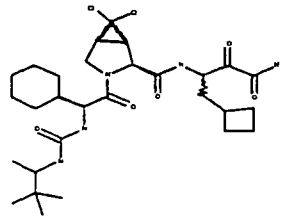
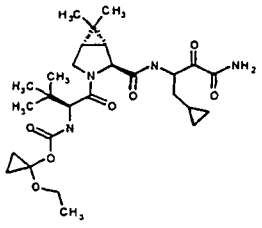
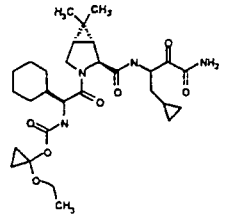
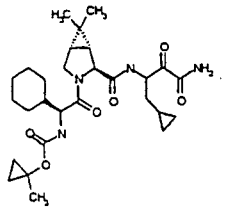
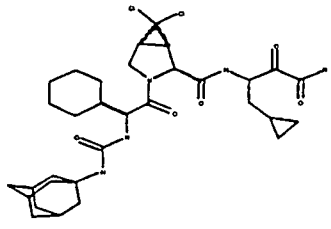
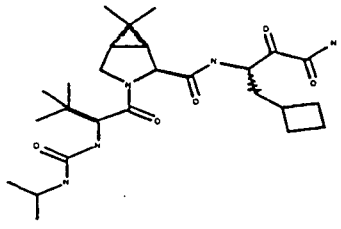
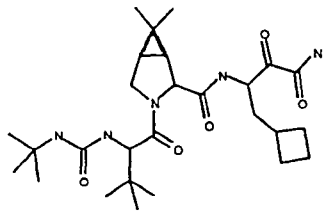
	615	A
	535	B
	561	A
	531	A
	651	A
	506	A
	520	A

Table 5

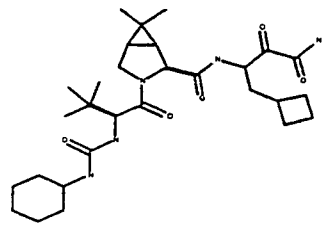
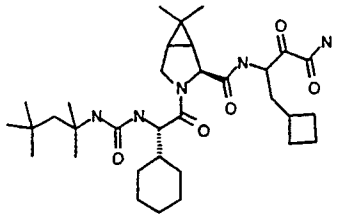
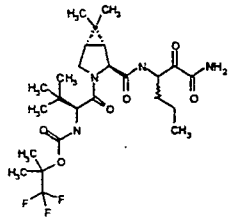
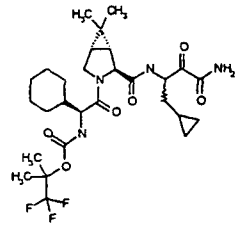
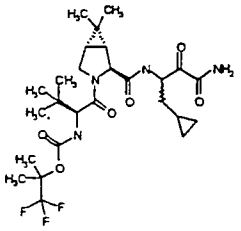
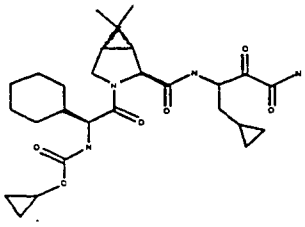
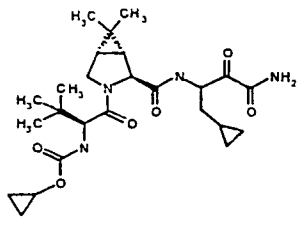
	546	A
	602	A
	549	B
	587	A
	561	A
	517	B
	491	B

Table 5

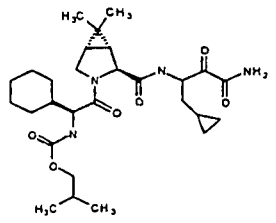
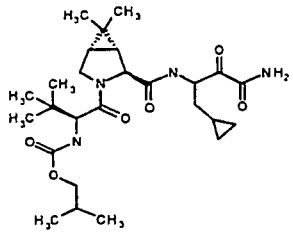
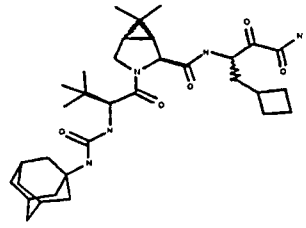
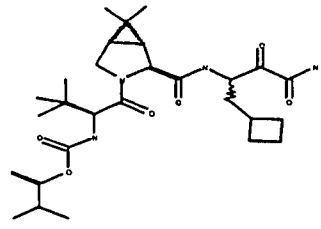
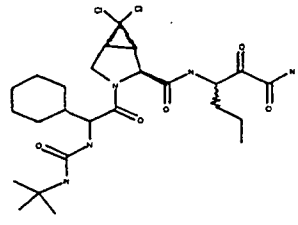
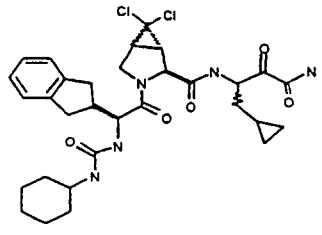
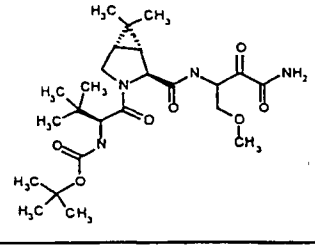
	533	B
	507	A
	598	A
	535	A
	561	A
	633	A
	497	C

Table 5

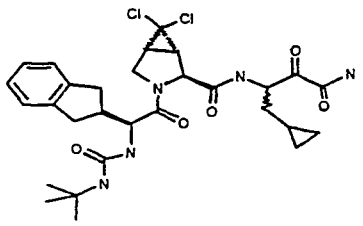
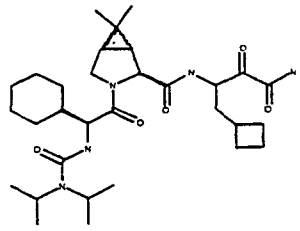
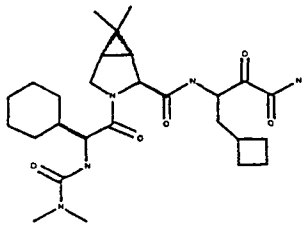
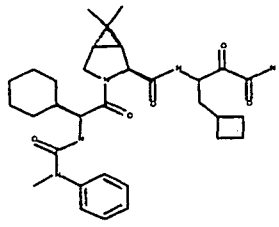
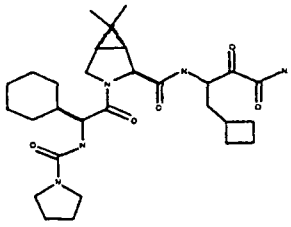
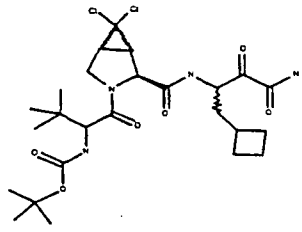
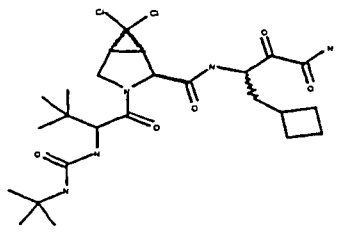
	607	A
	574	B
	518	B
	580	C
	544	B
	562	A
	561	A

Table 5

000202

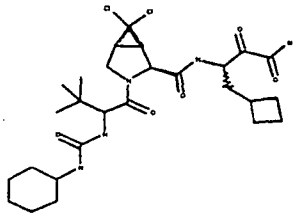
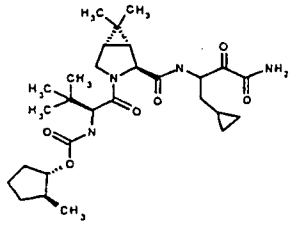
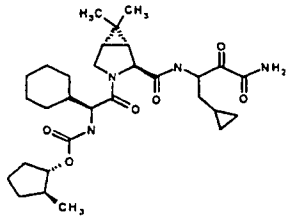
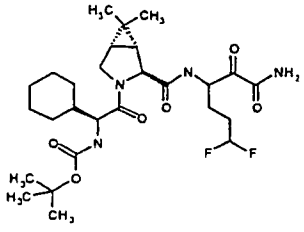
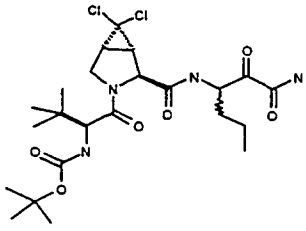
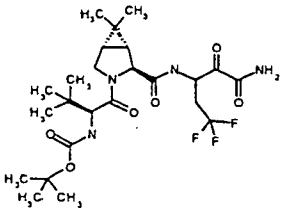
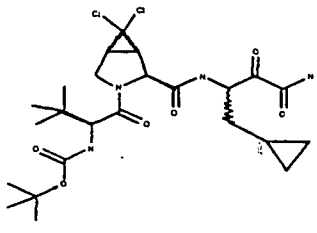
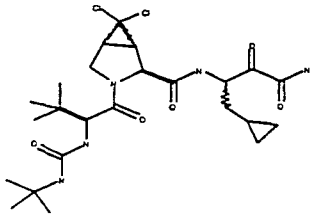
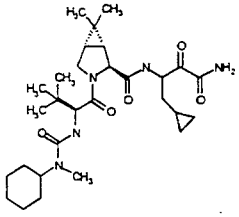
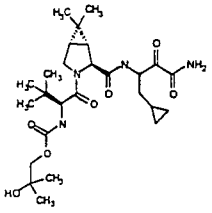
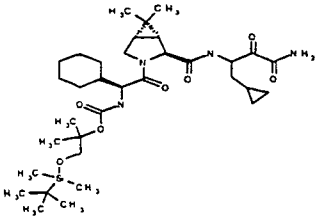
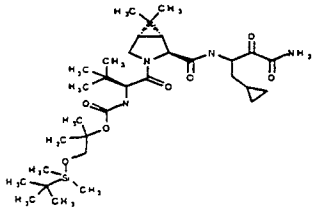
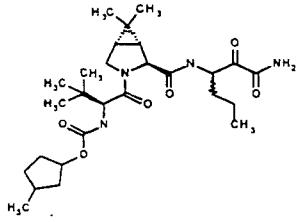
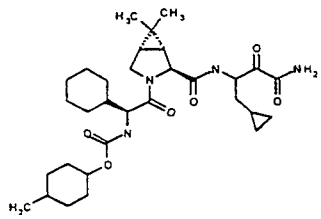
	587	A
	533	A
	559	A
	557	C
	535	A
	535	B
	547	A

Table 5

	546	A
	546	B
	523	B
	663	C
	637	C
	521	B
	573	B

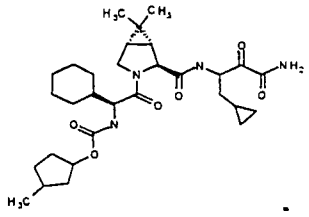
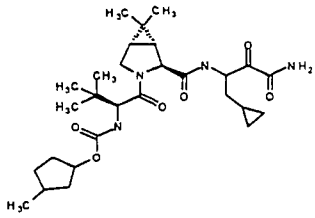
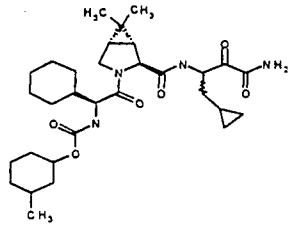
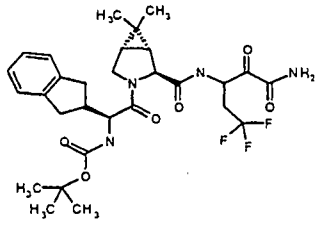
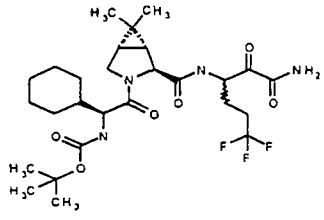
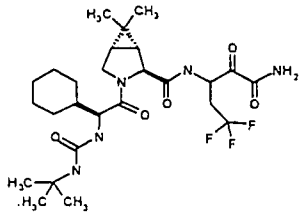
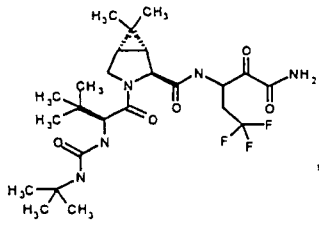
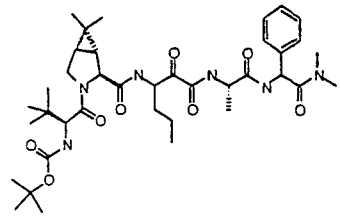
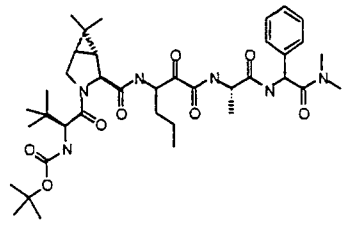
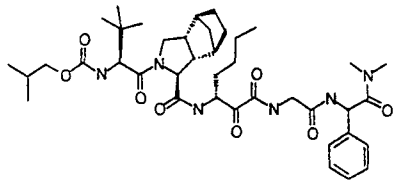
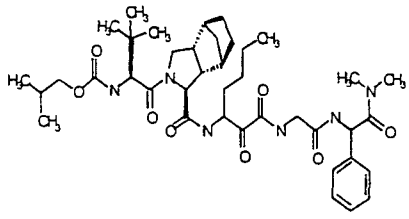
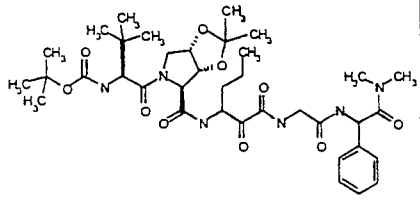
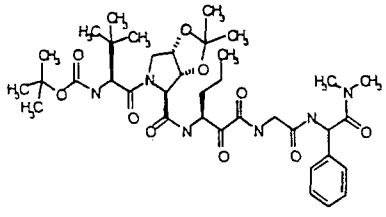
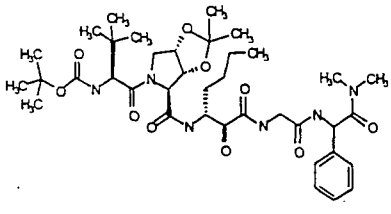
	559	A
	533	A
	573	B
	595	B
	575	A
	560	B
	534	C

Table 5

Structure	MW	Ki* Range
	727	A
	727	A
	753	C
	753	B
	745	A
	745	A
	759	C

030204 Table 5

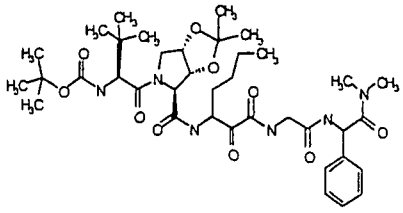
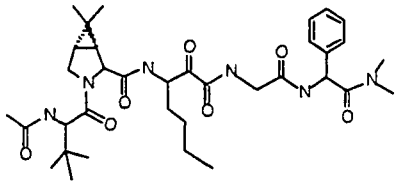
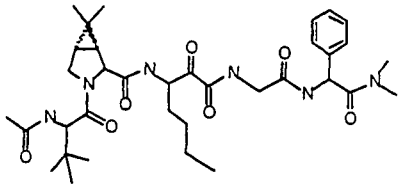
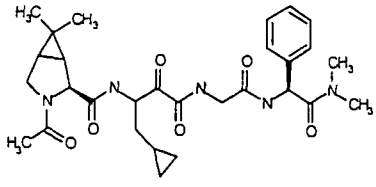
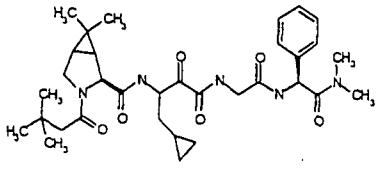
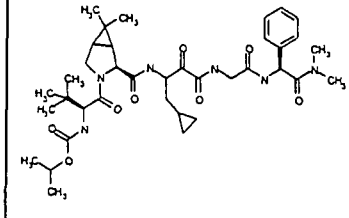
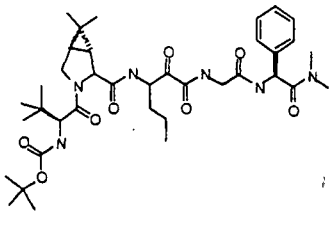
	759	B
	669	B
	669	A
	554	C
	610	B
	711	A
	713	A

Table 5

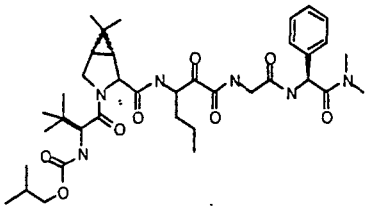
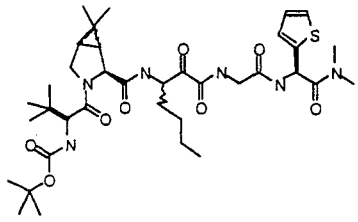
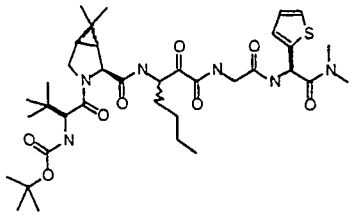
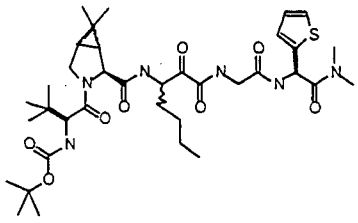
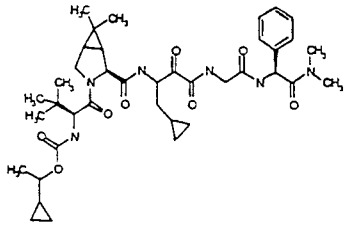
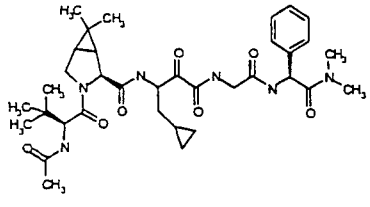
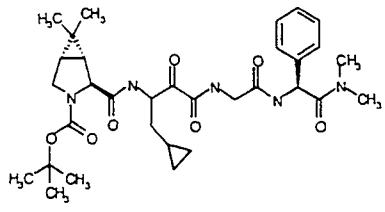
	713	A
	732	A
	733	A
	733	A
	737	A
	667	A
	612	C

Table 5

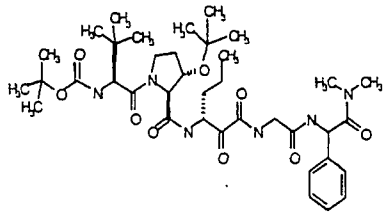
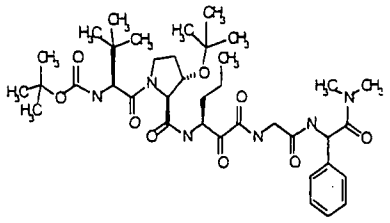
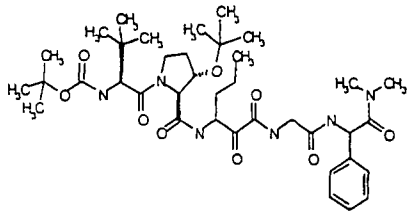
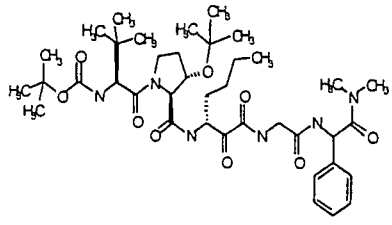
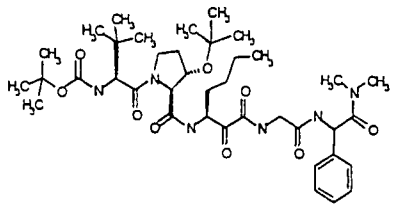
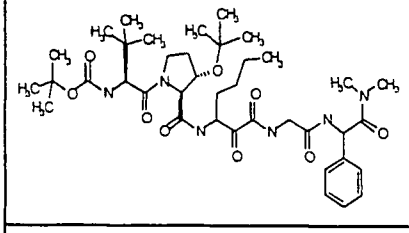
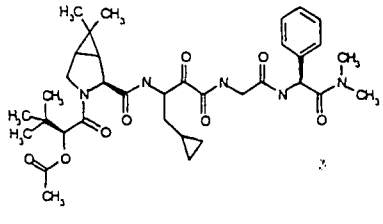
	745	C
	745	C
	745	C
	759	C
	759	C
	759	C
	668	C

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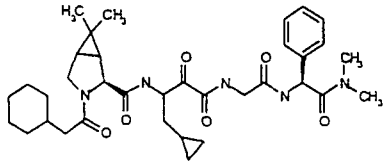
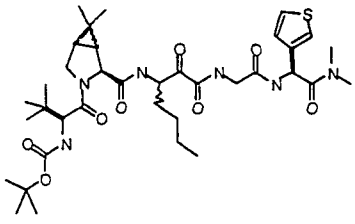
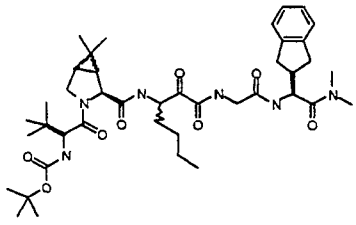
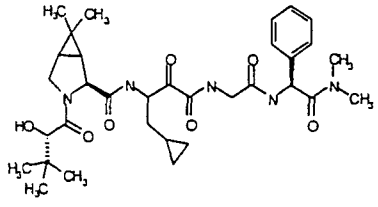
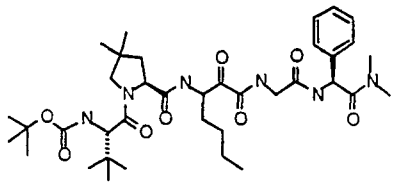
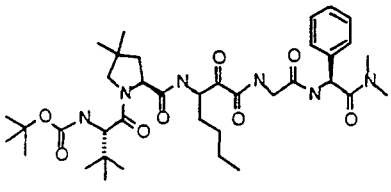
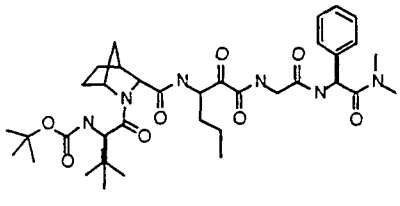
	636	B
	733	A
	767	B
	626	B
	715	C
	715	A
	699	B

Table 5

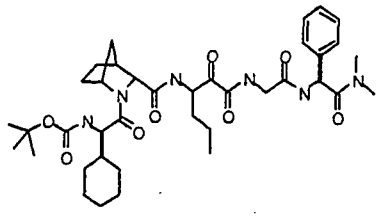
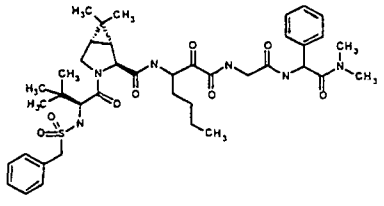
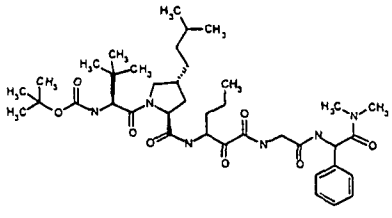
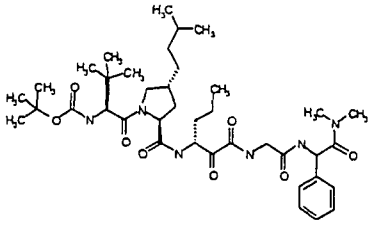
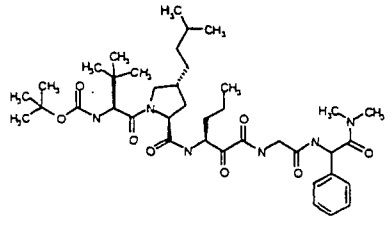
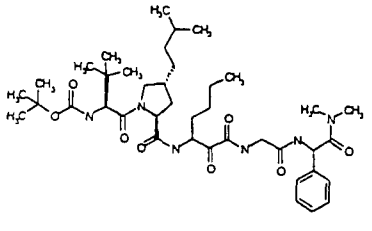
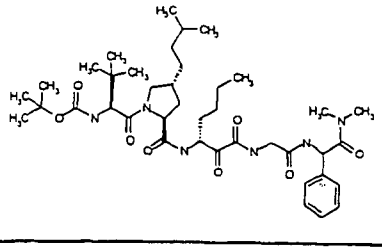
	725	A
	781	B
	743	B
	743	C
	743	A
	757	B
	757	C

Table 5

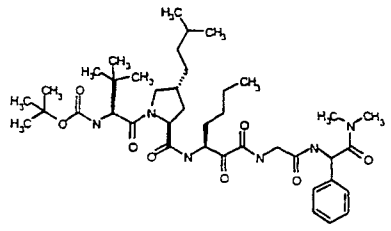
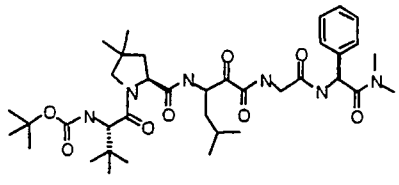
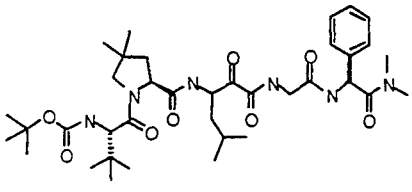
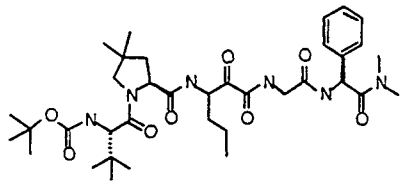
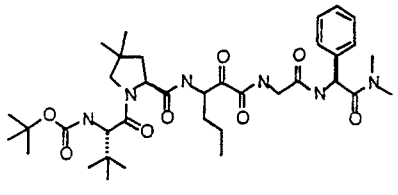
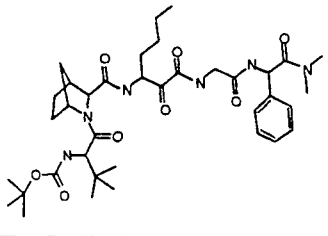
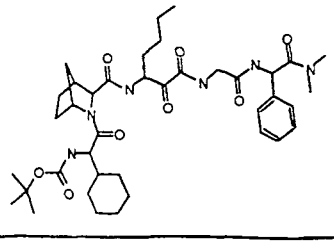
	757	B
	715	A
	715	A
	701	C
	701	A
	713	A
	739	A

Table 5

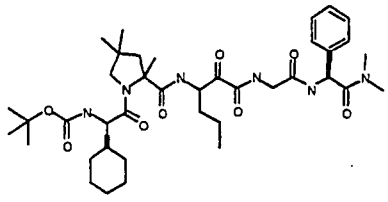
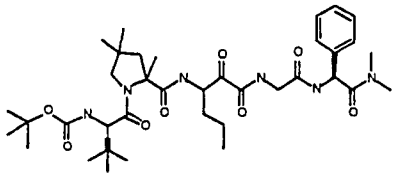
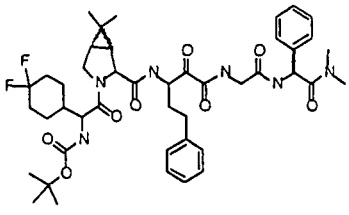
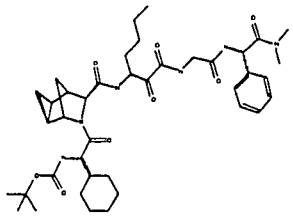
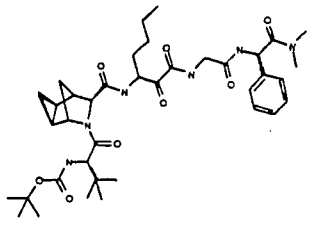
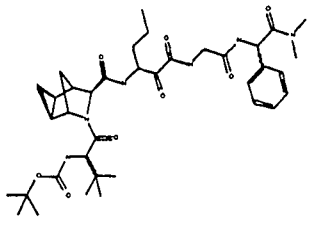
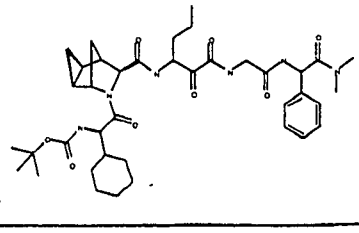
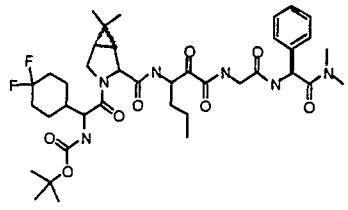
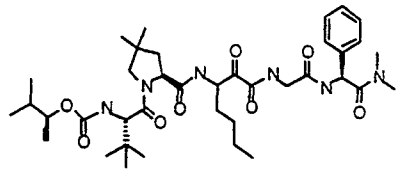
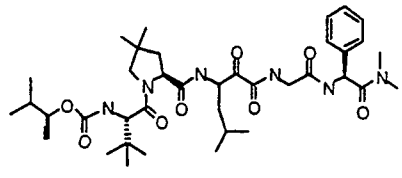
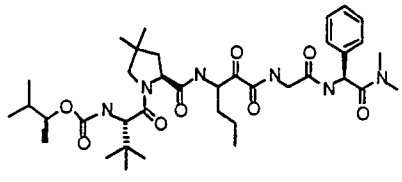
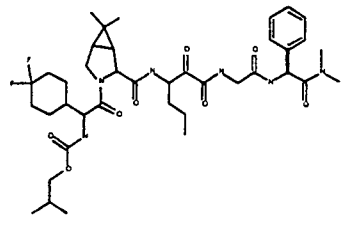
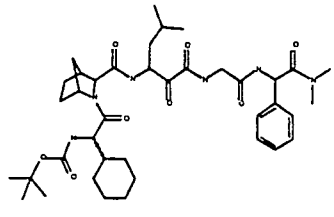
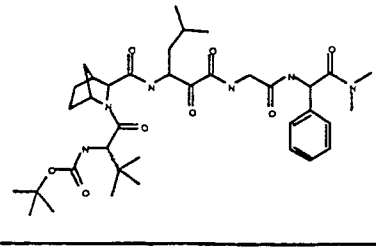
	741	C
	715	C
	837	B
	751	A
	725	C
	711	C
	737	A

Table 5

	775	A
	729	A
	729	A
	715	A
	775	A
	739	A
	713	A

030208

Table 5

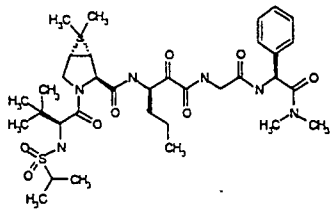
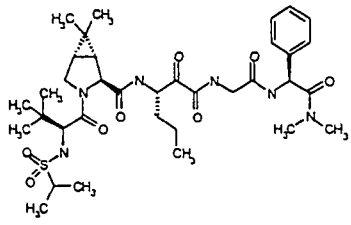
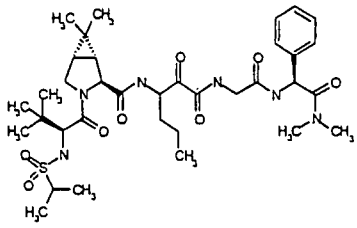
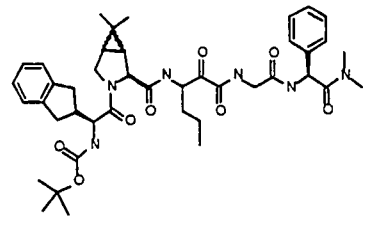
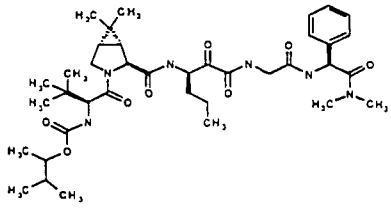
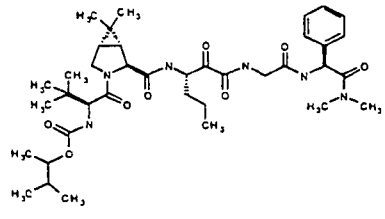
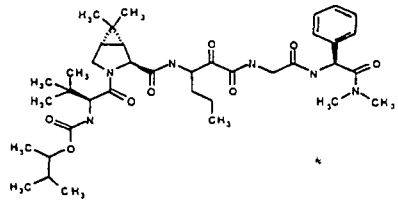
	719	A
	719	A
	719	A
	773	A
	727	A
	727	A
	727	A

Table 5

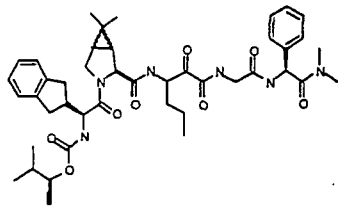
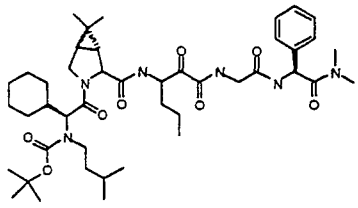
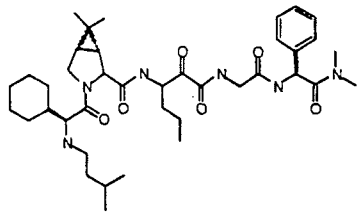
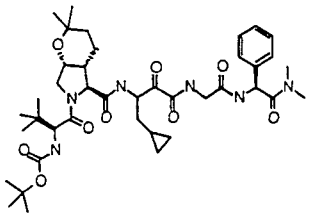
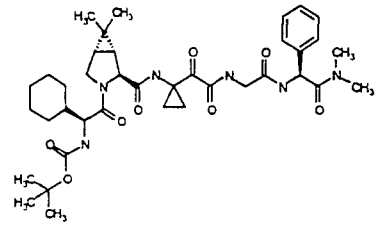
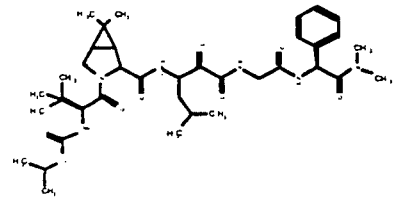
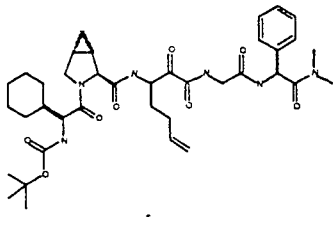
	787	A
	809	C
	709	A
	769	B
	723	C
	713	A
	723	A

Table 5

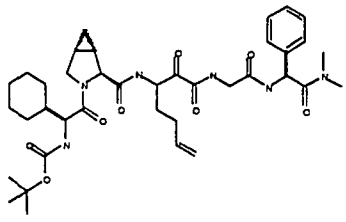
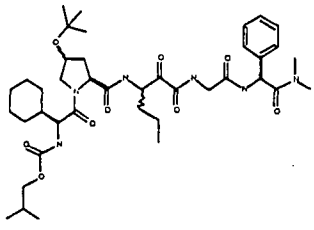
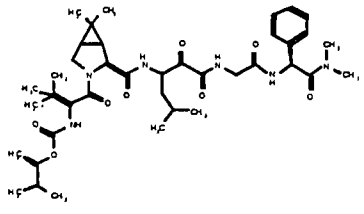
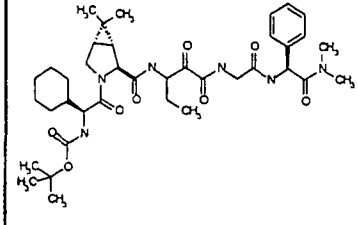
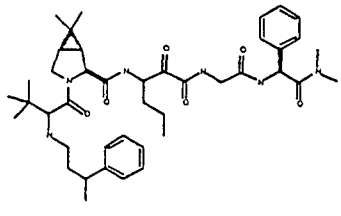
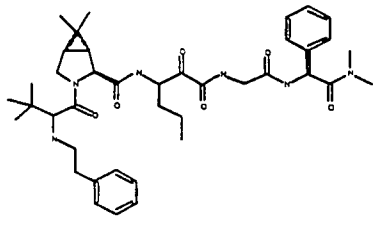
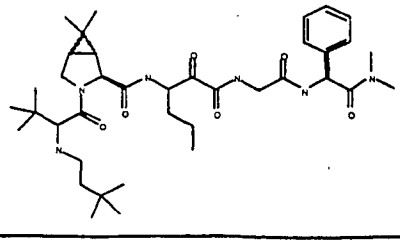
	723	B
	771	C
	741	A
	725	A
	745	A
	716	A
	733	A

Table 5

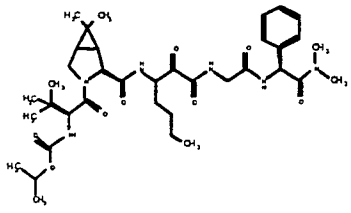
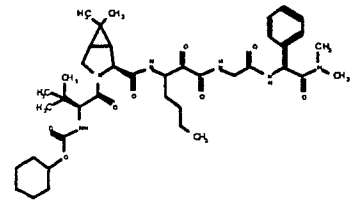
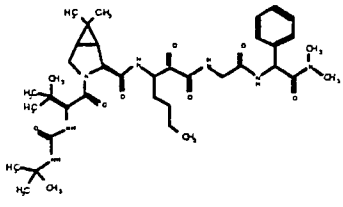
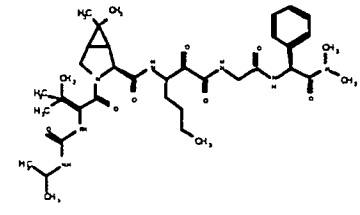
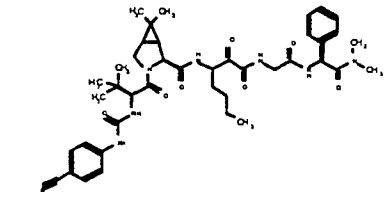
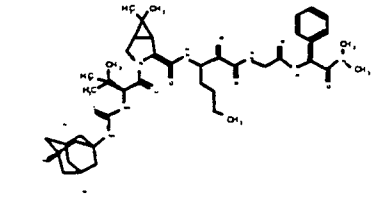
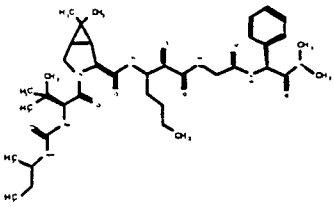
	713	A
	753	A
	726	A
	712	A
	771	B
	804	A
	726	A

Table 5

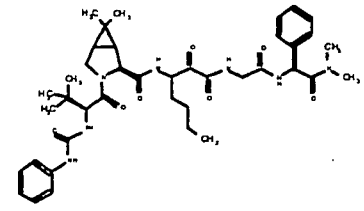
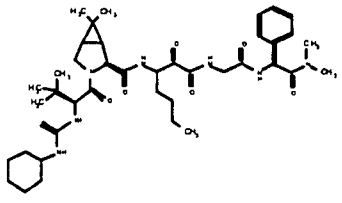
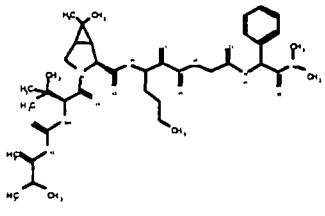
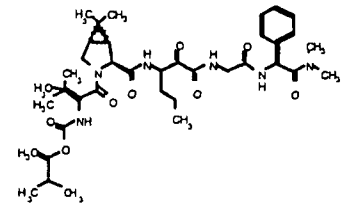
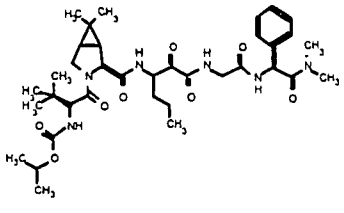
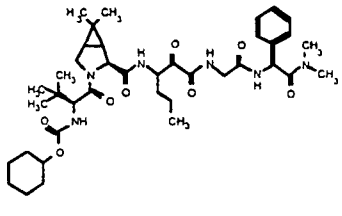
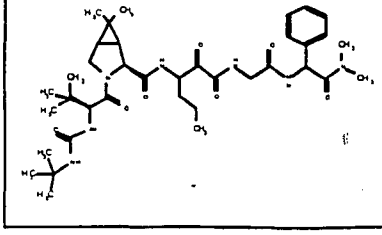
	746	A
	752	A
	741	A
	727	A
	699	A
	739	A
	712	A

Table 5

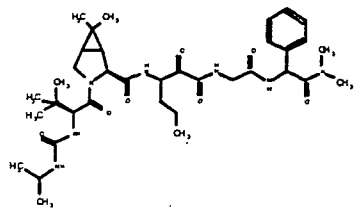
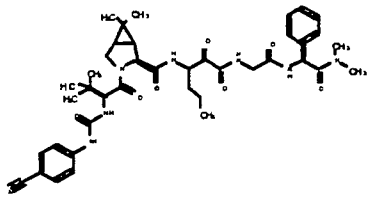
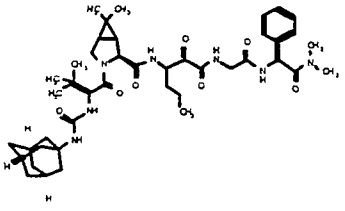
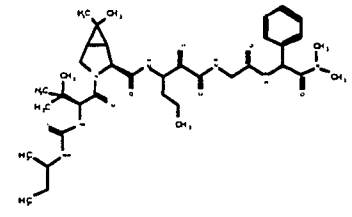
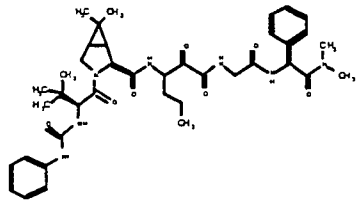
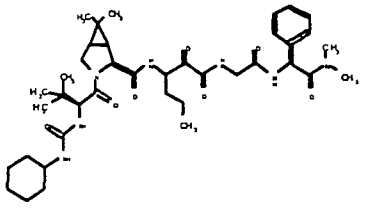
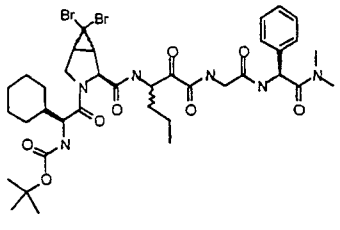
	698	A
	757	B
	790	A
	712	A
	732	A
	738	A
	869	A

Table 5

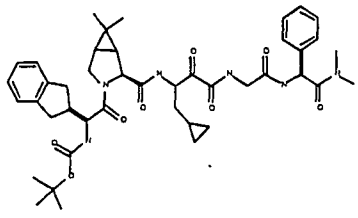
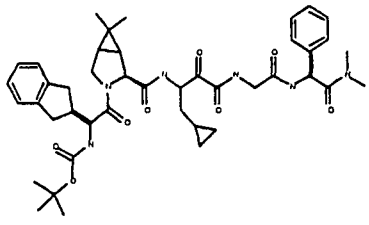
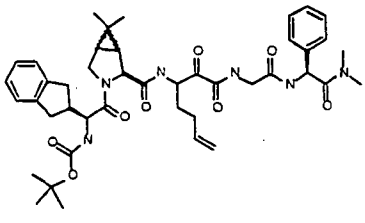
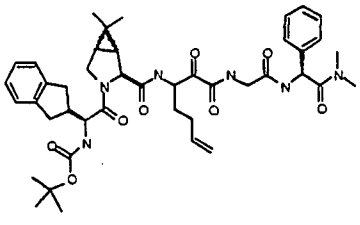
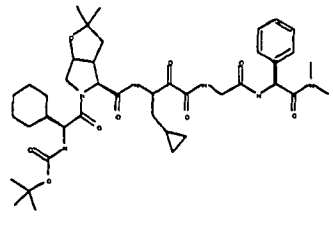
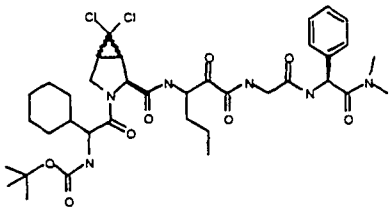
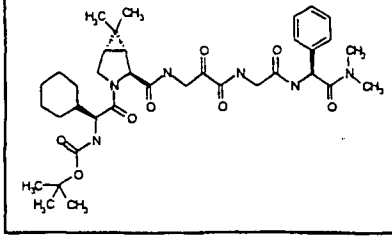
	785	A
	785	A
	785	A
	785	A
	781	A
	780	A
	697	C

Table 5

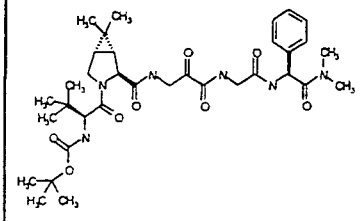
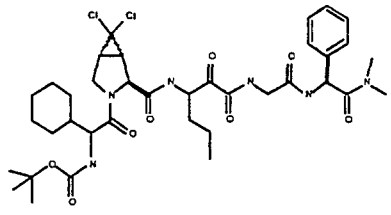
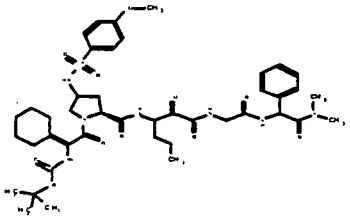
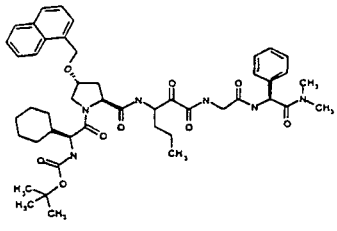
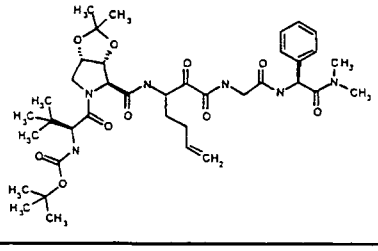
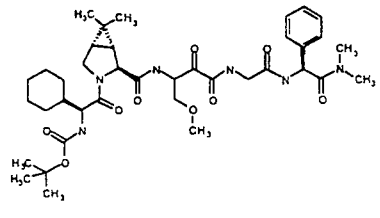
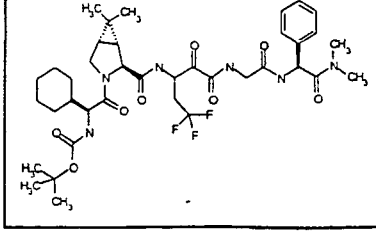
	671	C
	780	A
	884	A
	855	A
	757	B
	741	B
	779	B

Table 5

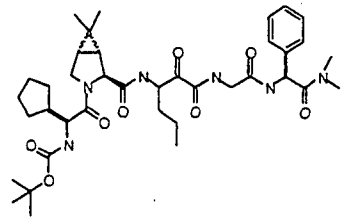
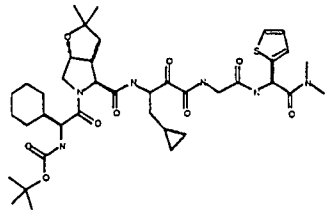
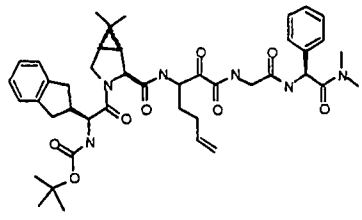
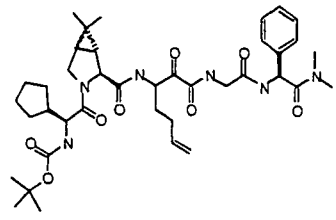
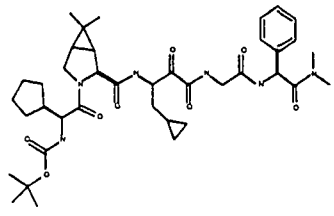
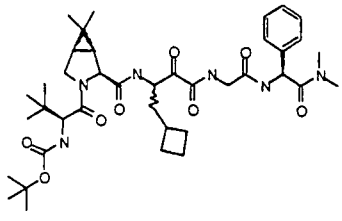
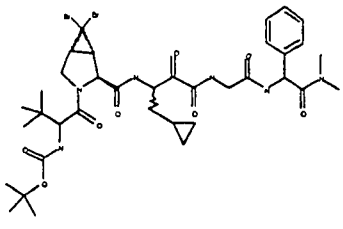
	725	A
	787	A
	785	A
	737	A
	737	A
	739	A
	855	A

Table 5

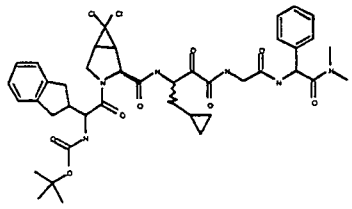
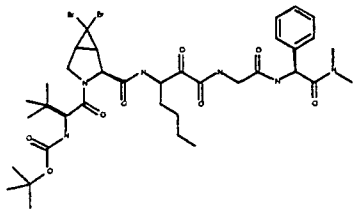
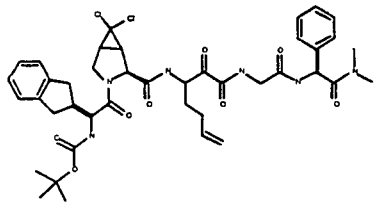
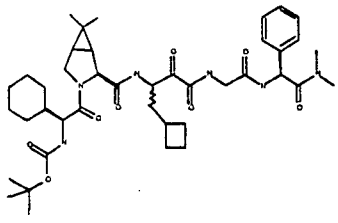
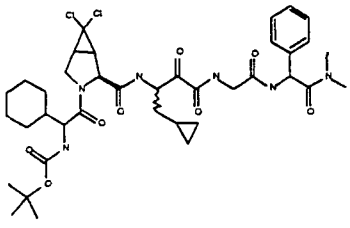
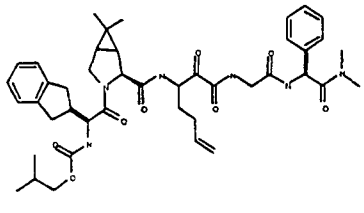
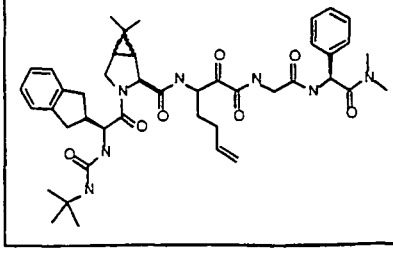
	826	A
	857	A
	826	A
	765	A
	792	A
	799	A
	784	A

Table 5

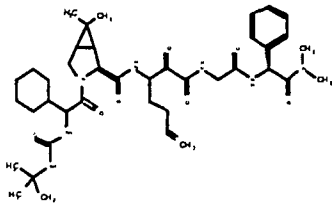
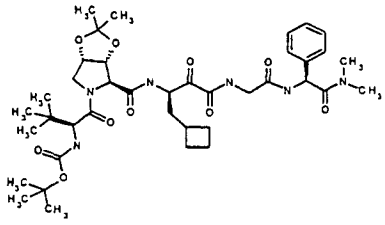
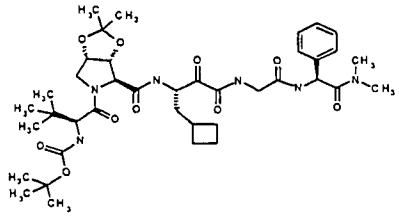
	750	A
	771	A
	771	A

Table 5

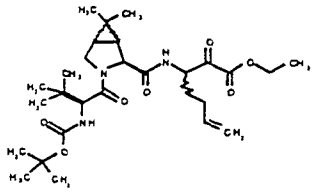
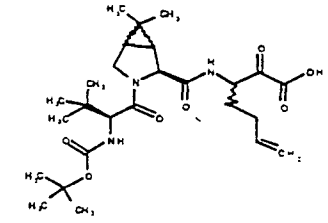
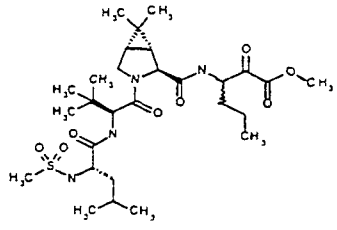
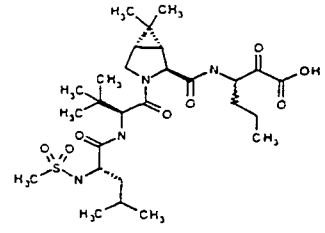
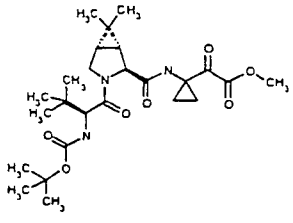
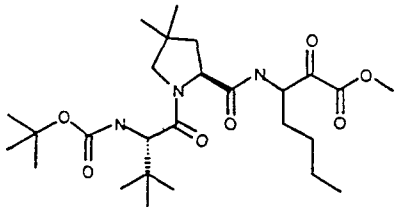
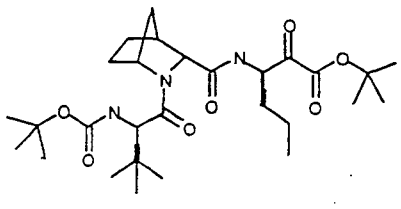
Structure	MW	Ki* range
	536	C
	508	B
	601	C
	587	B
	494	C
	512	C
	538	C

Table 5

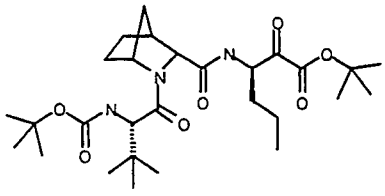
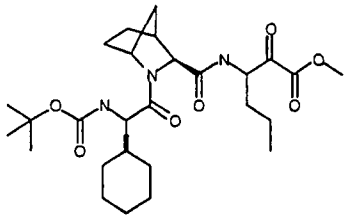
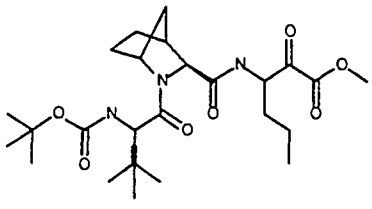
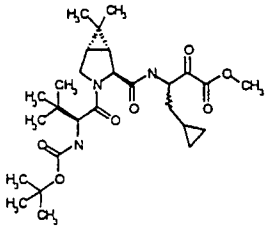
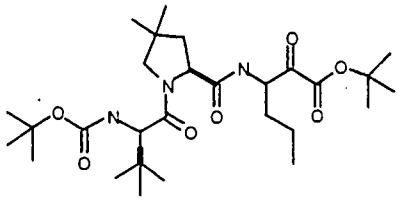
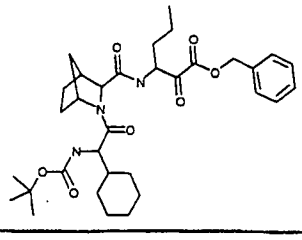
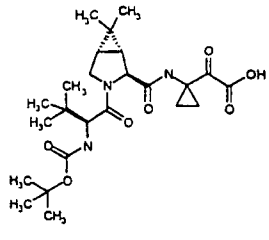
	538	C
	522	C
	496	C
	522	C
	540	C
	598	C
	480	C

Table 5

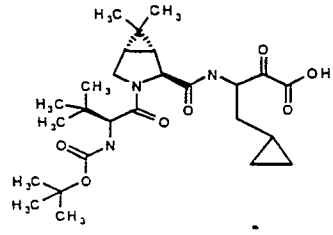
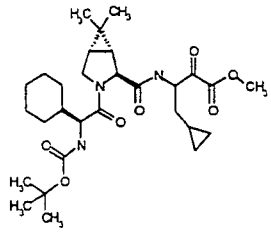
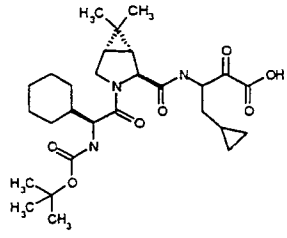
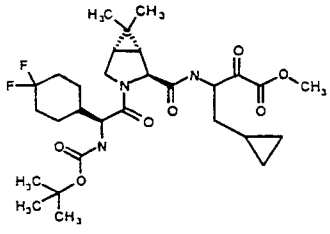
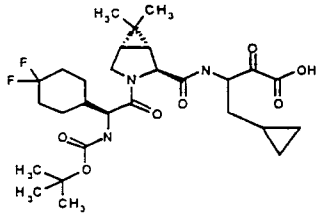
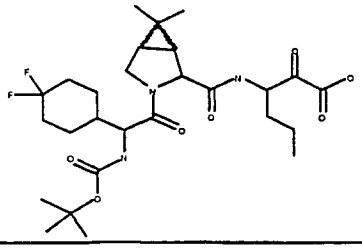
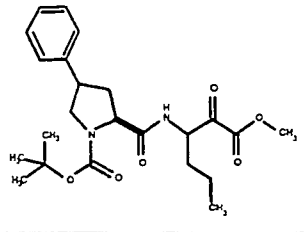
	508	B
	548	C
	534	B
	584	C
	570	B
	558	C
	433	C

Table 5

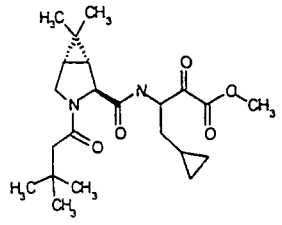
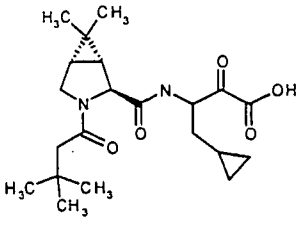
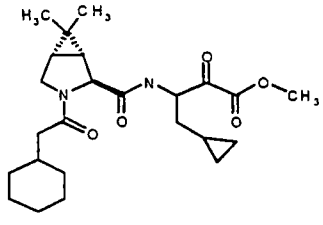
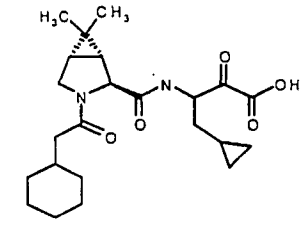
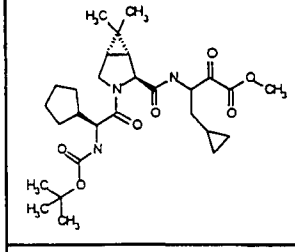
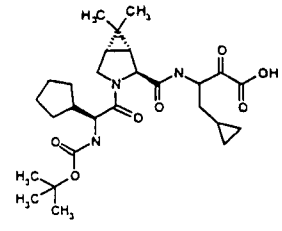
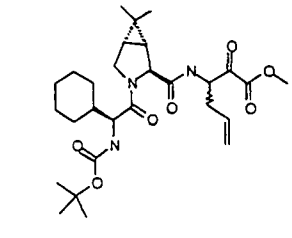
	407	C
	393	C
	433	C
	419	C
	534	C
	520	B
	534	C

Table 5

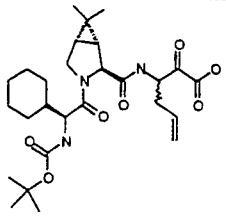
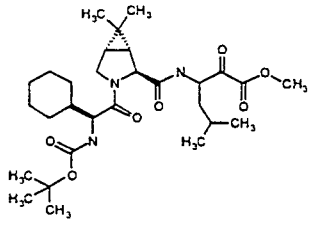
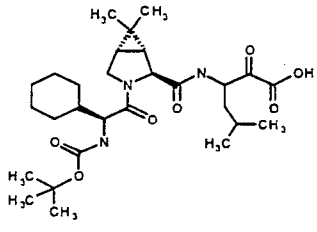
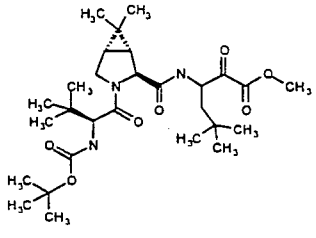
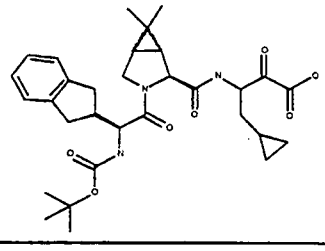
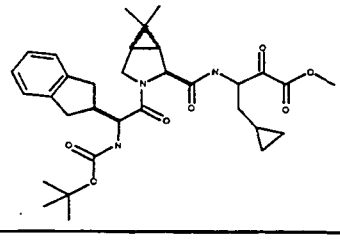
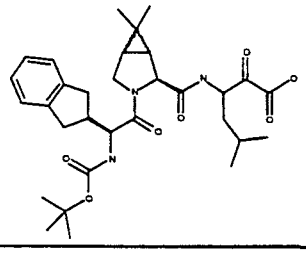
	520	B
	550	C
	536	C
	538	C
	568	B
	582	C
	570	C

Table 5

030216

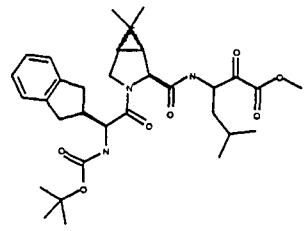
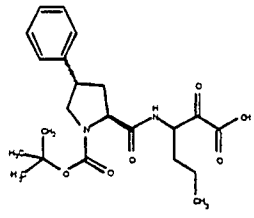
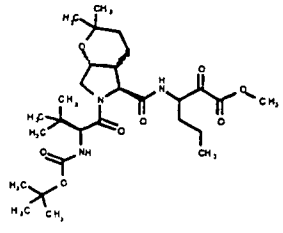
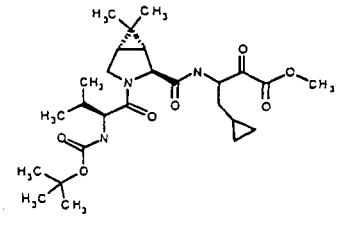
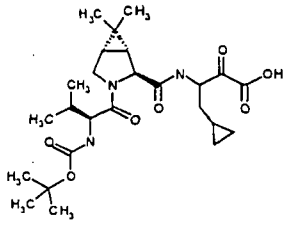
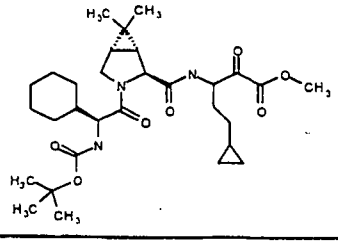
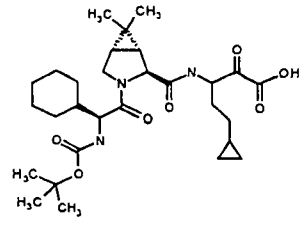
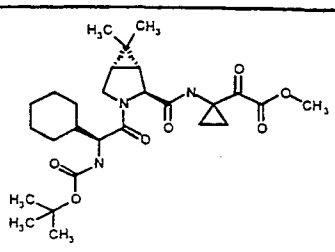
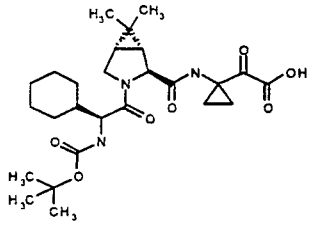
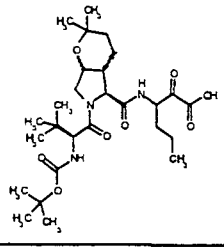
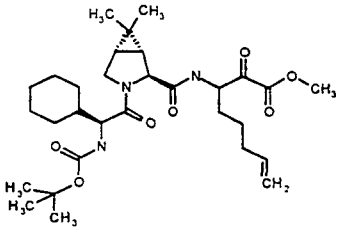
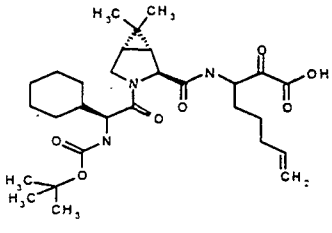
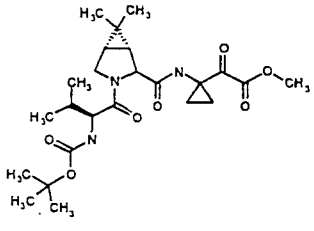
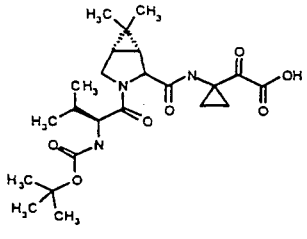
	584	C
	418	C
	554	C
	508	C
	494	B
	562	C
	548	A

Table 5

	520	C
	506	C
	540	C
	562	C
	548	B
	480	C
	466	C

000217

Table 5

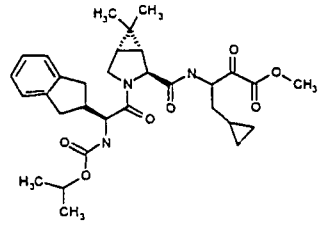
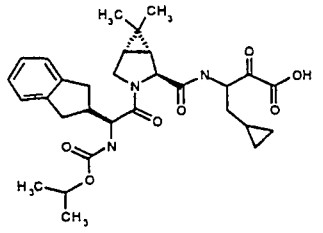
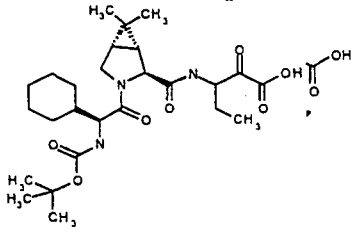
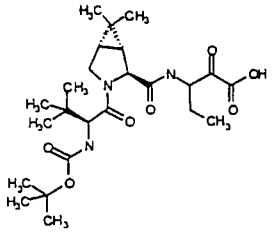
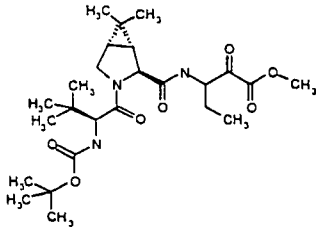
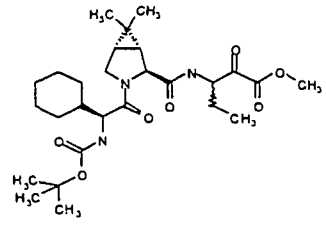
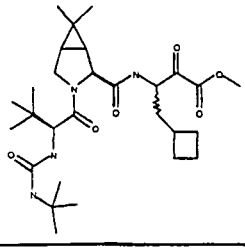
	568	C
	554	B
	508	B
	482	C
	496	C
	522	C
	535	C

Table 5

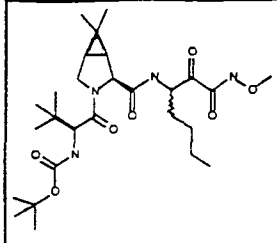
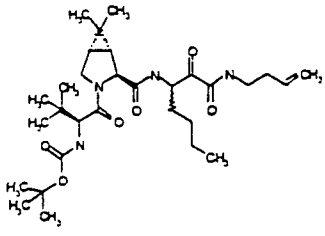
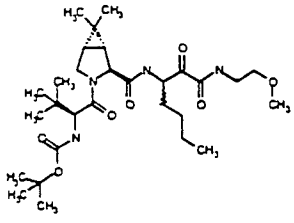
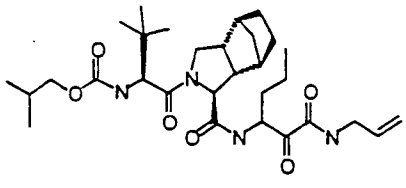
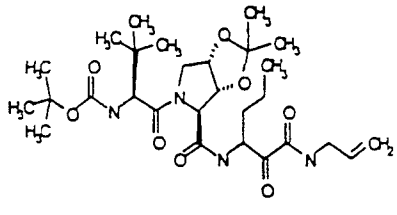
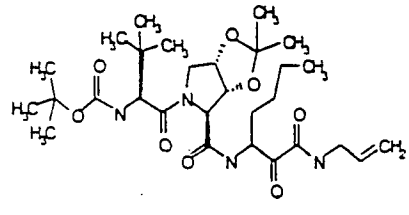
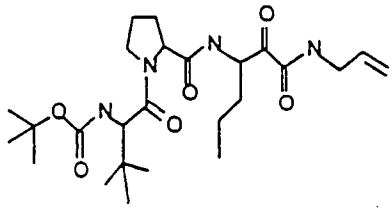
Structure	MW	Ki range
	539	B
	563	B
	567	C
	561	C
	567	C
	581	C
	495	C

Table 5

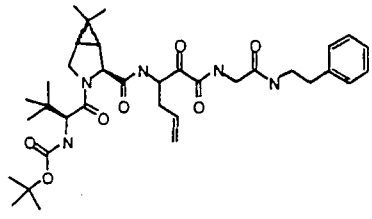
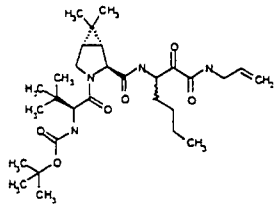
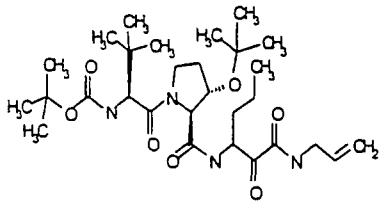
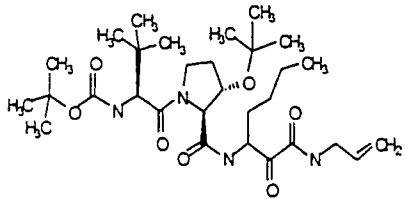
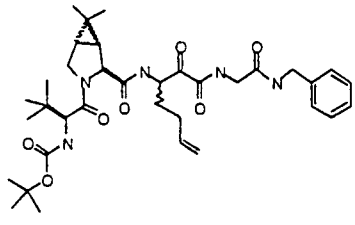
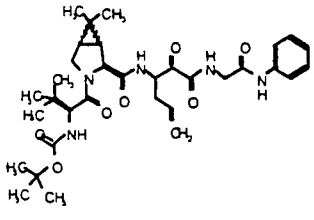
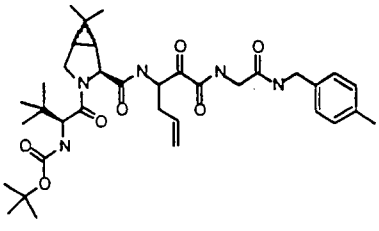
	654	B
	549	C
	567	C
	581	C
	654	C
	626	B
	654	A

Table 5

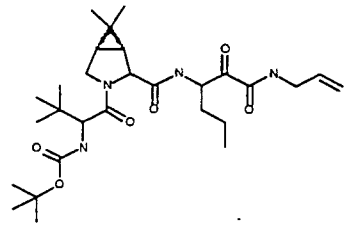
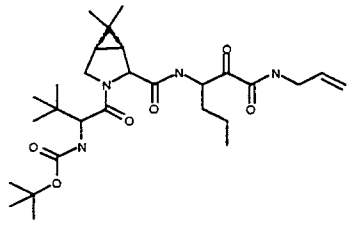
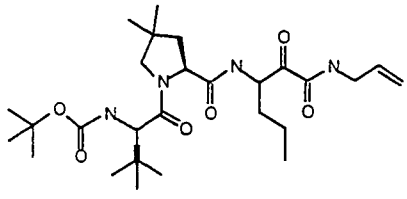
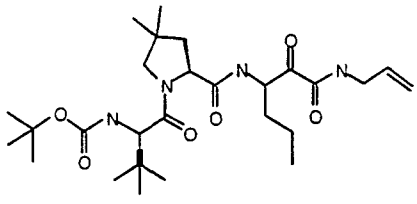
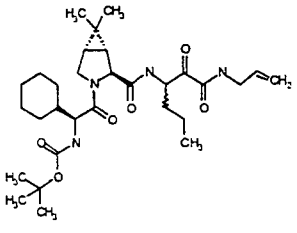
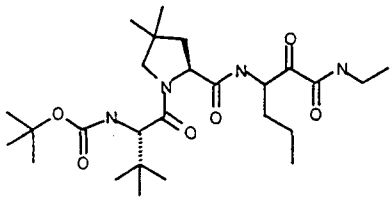
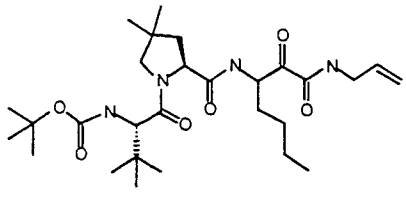
	535	C
	535	B
	523	C
	523	C
	561	B
	511	C
	537	C

Table 5

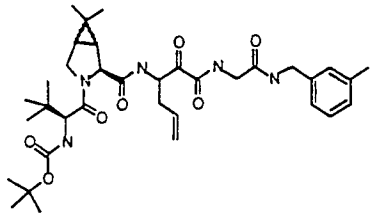
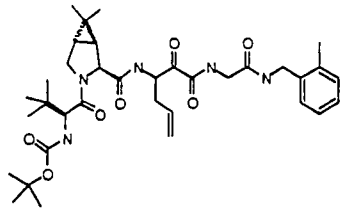
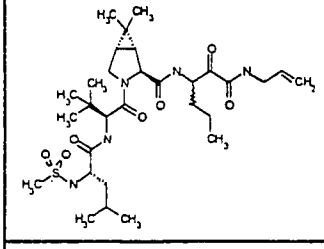
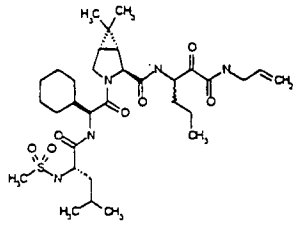
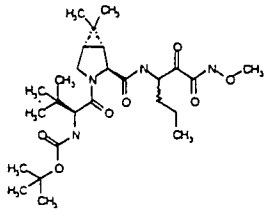
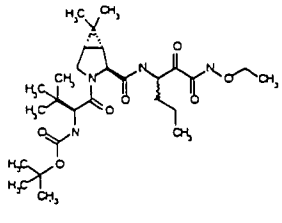
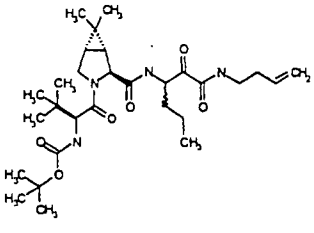
	654	B
	654	A
	626	B
	652	B
	525	C
	539	C
	549	C

Table 5

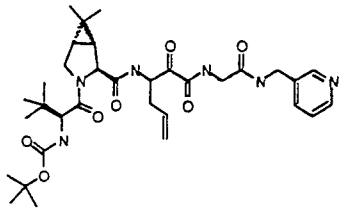
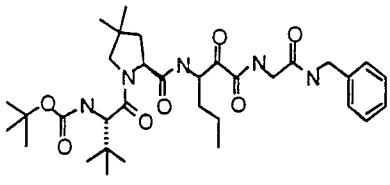
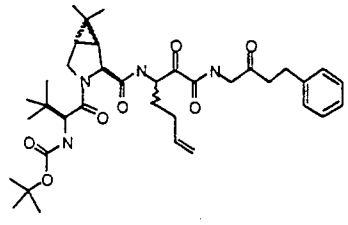
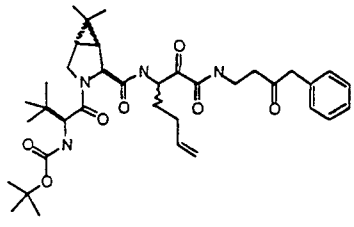
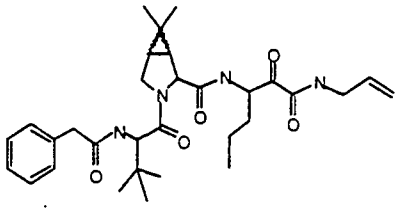
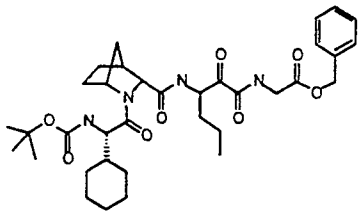
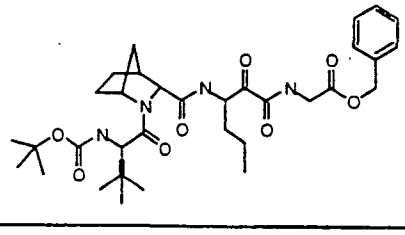
	641	B
	630	C
	653	B
	653	B
	553	C
	655	C
	629	C

Table 5

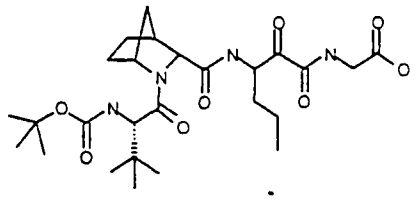
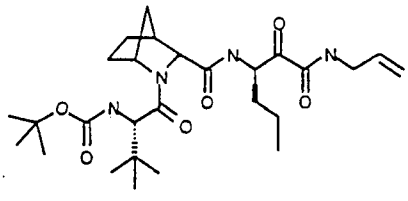
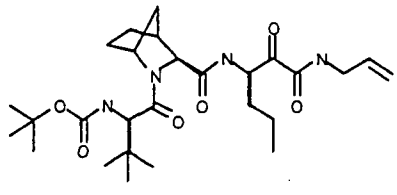
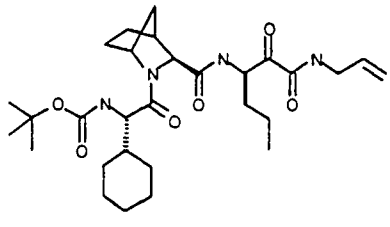
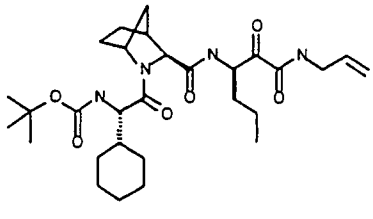
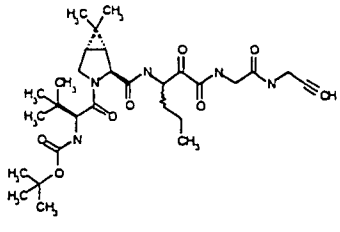
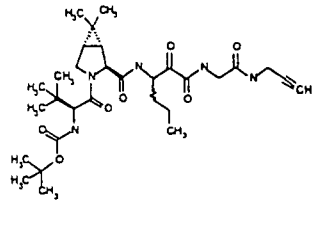
	539	C
	521	C
	521	C
	547	C
	547	C
	590	B
	590	B

Table 5

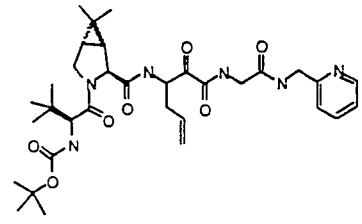
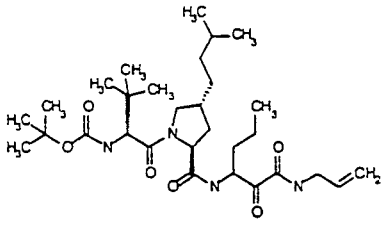
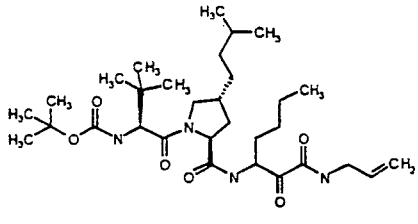
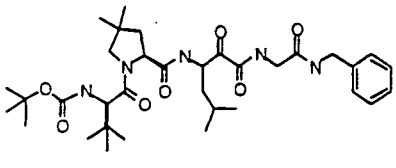
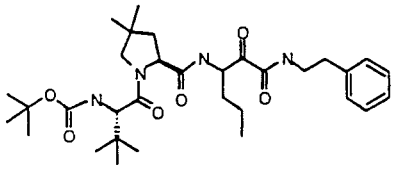
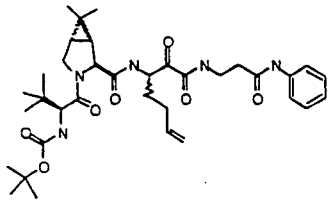
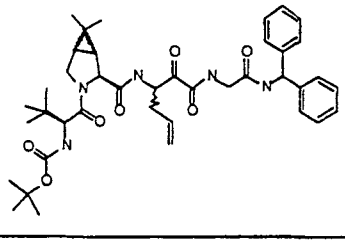
	641	B
	565	C
	579	C
	644	C
	587	C
	654	B
	716	B

Table 5

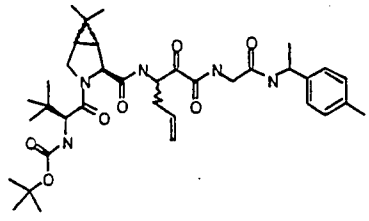
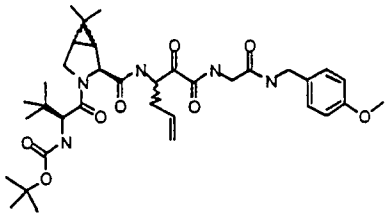
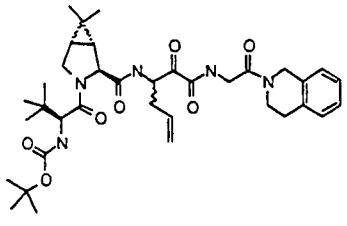
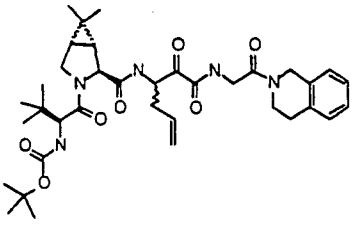
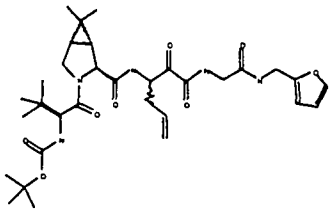
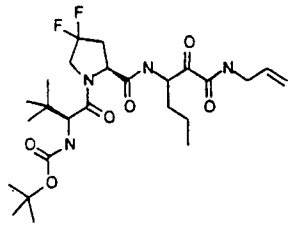
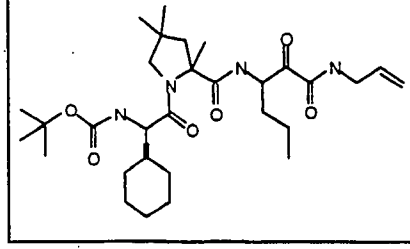
	668	B
	670	A
	666	C
	666	C
	630	B
	531	C
	563	C

Table 5

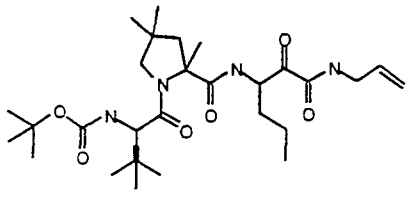
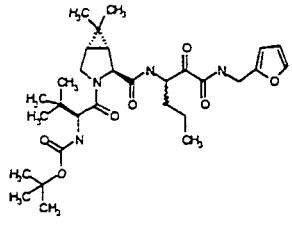
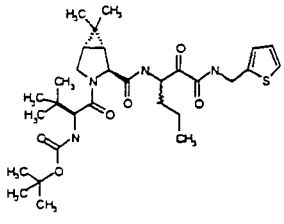
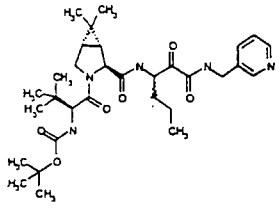
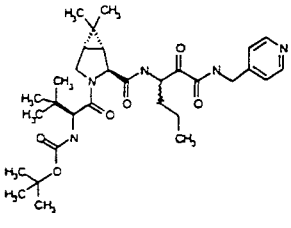
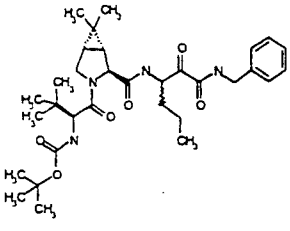
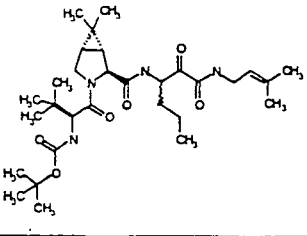
	537	C
	575	B
	591	B
	586	C
	586	C
	585	B
	563	B

Table 5

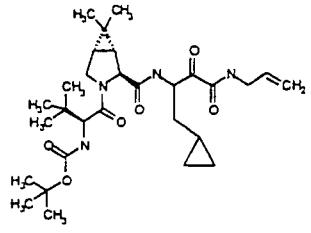
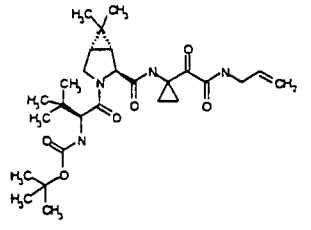
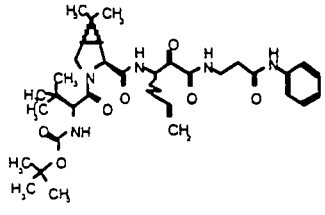
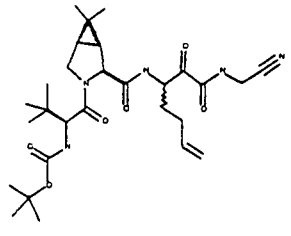
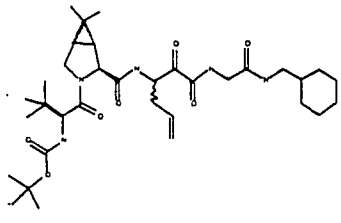
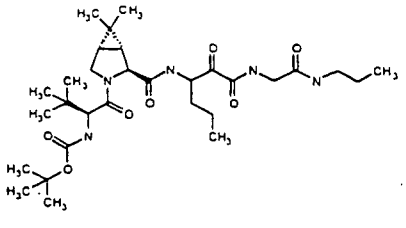
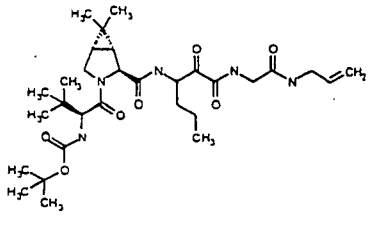
	547	B
	519	C
	640	B
	546	B
	646	B
	594	C
	592	B

Table 5

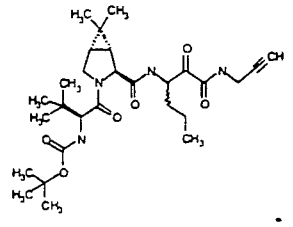
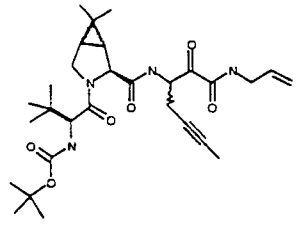
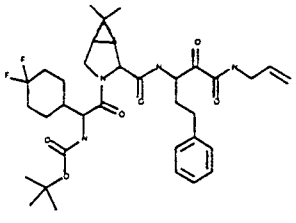
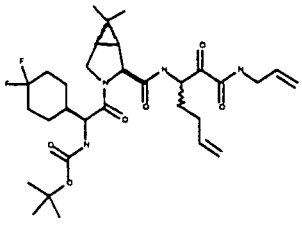
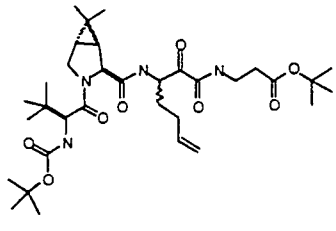
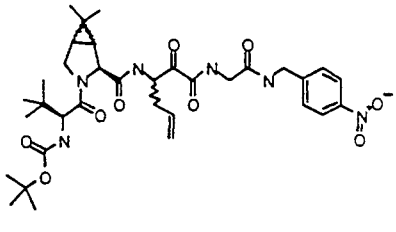
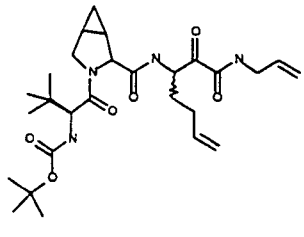
	533	C
	545	C
	659	B
	609	A
	635	B
	685	B
	519	C

Table 5

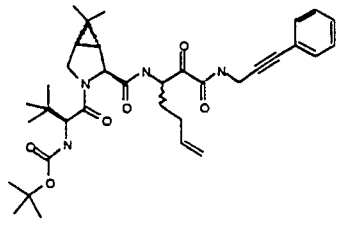
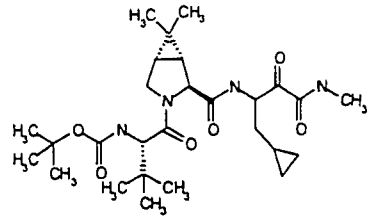
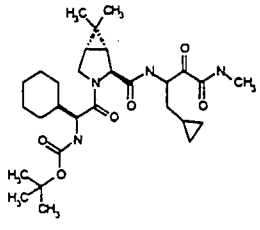
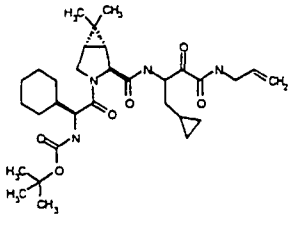
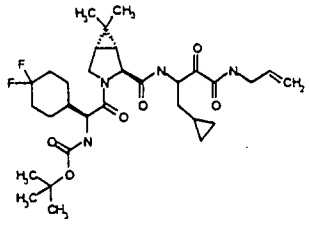
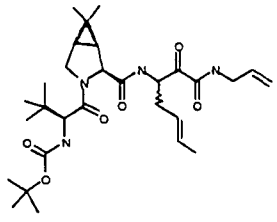
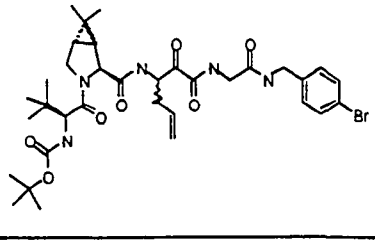
	621	B
	521	B
	547	B
	573	B
	609	B
	547	B
	719	B

Table 5

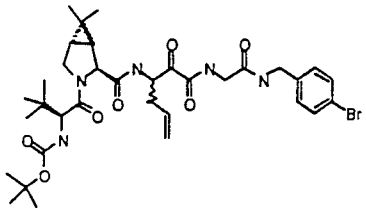
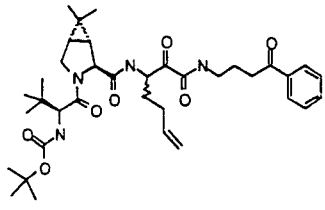
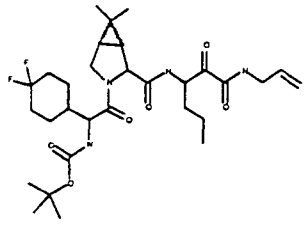
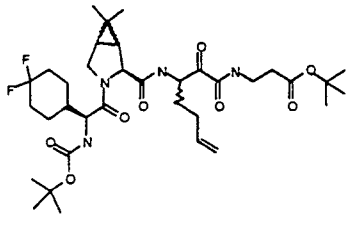
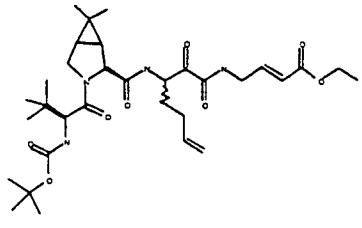
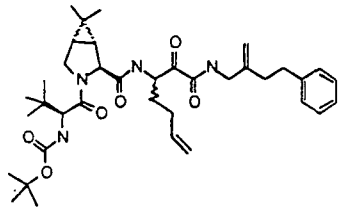
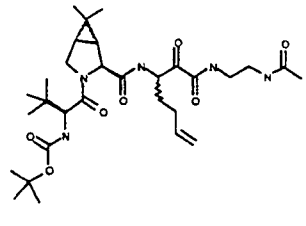
	719	C
	653	B
	597	B
	697	A
	619	B
	651	C
	592	B

Table 5

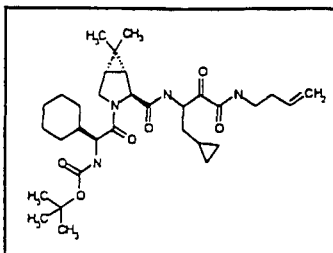
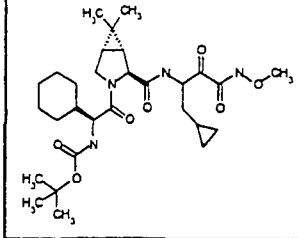
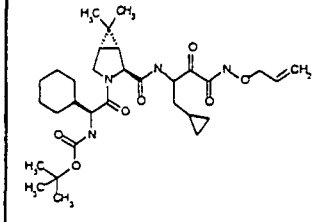
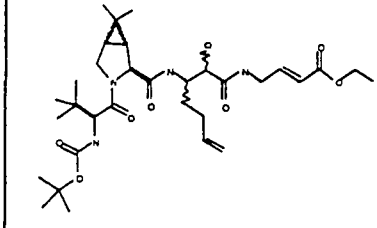
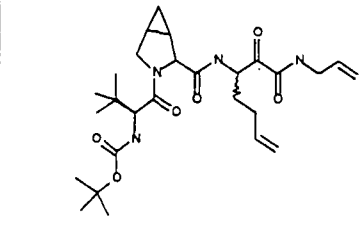
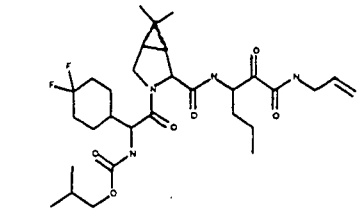
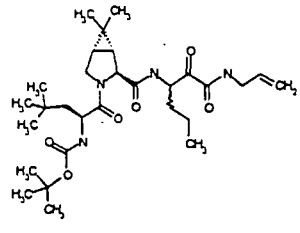
	587	C
	563	B
	589	C
	621	C
	519	C
	597	B
	549	C

Table 5

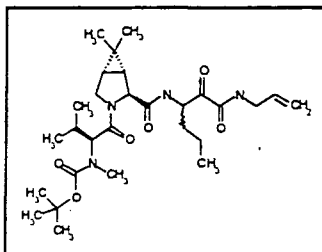
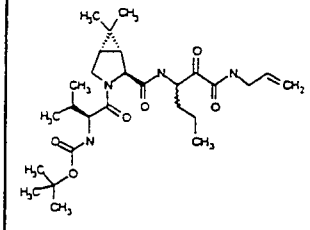
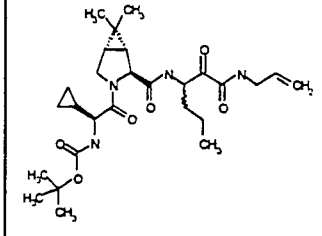
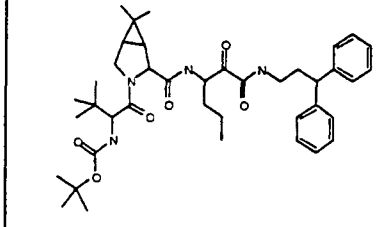
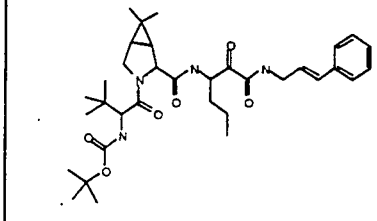
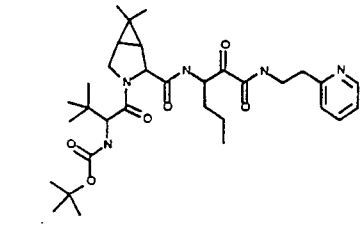
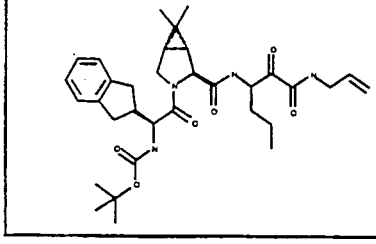
	535	C
	521	B
	519	C
	689	C
	611	C
	600	C
	595	B

Table 5

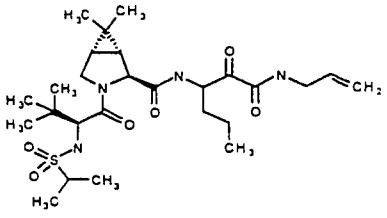
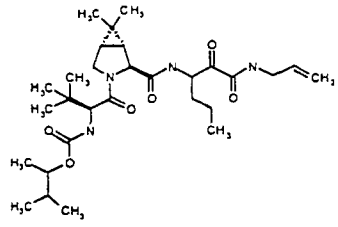
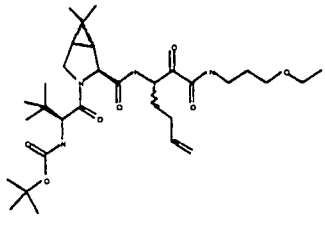
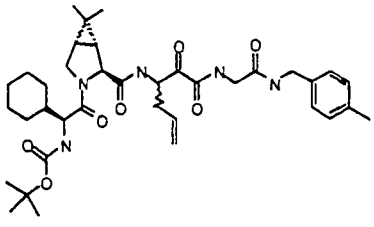
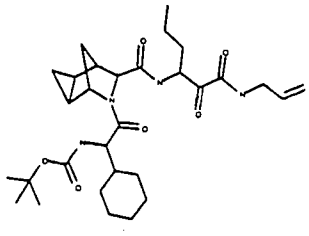
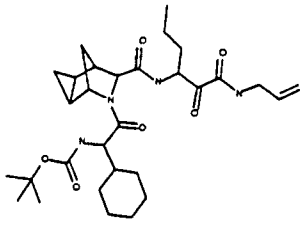
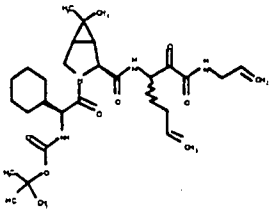
	541	C
	549	B
	593	C
	680	B
	559	C
	559	C
	573	B

Table 5

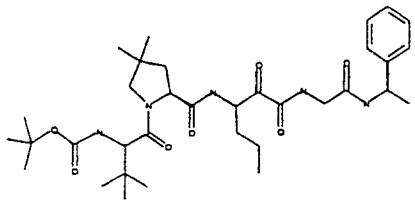
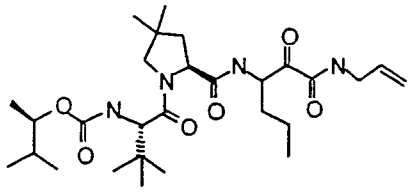
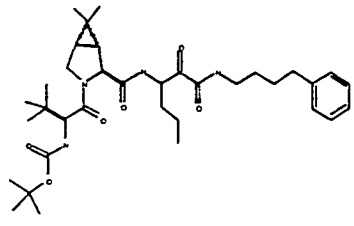
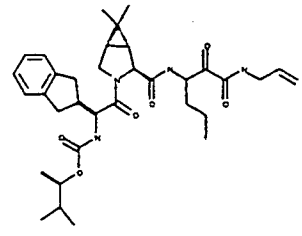
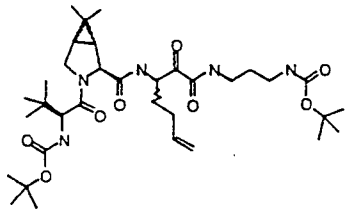
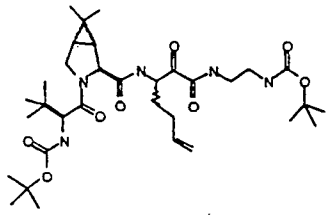
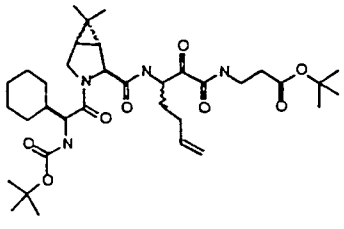
	644	C
	537	C
	627	C
	609	B
	664	B
	650	C
	661	B

Table 5

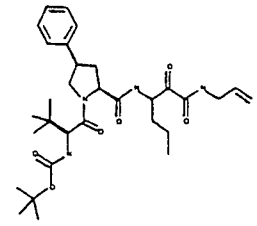
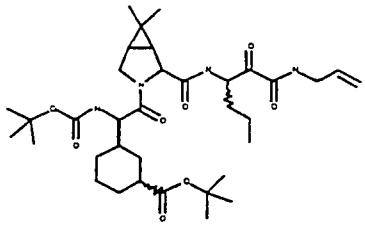
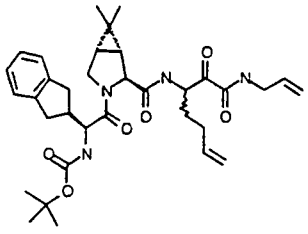
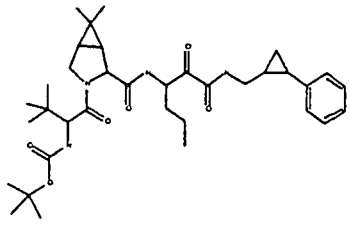
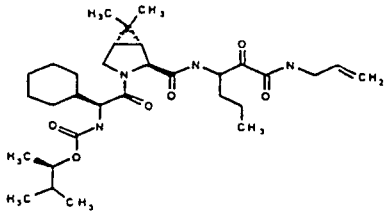
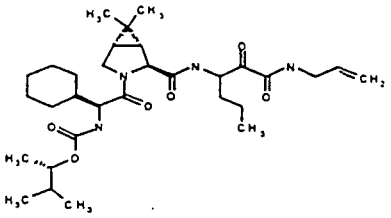
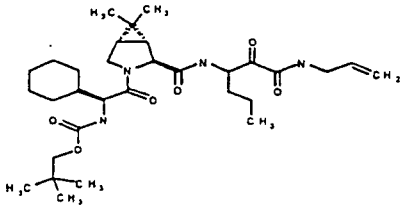
	571	C
	661	B
	607	B
	625	C
	575	B
	575	B
	575	B

Table 5

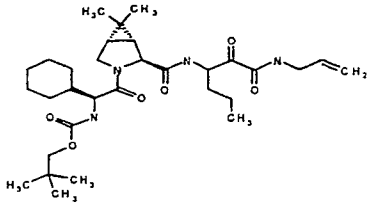
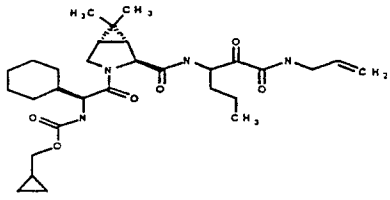
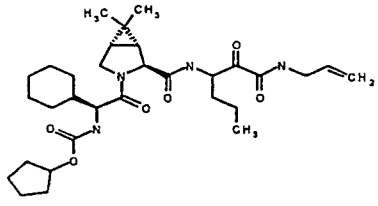
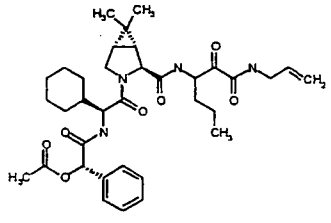
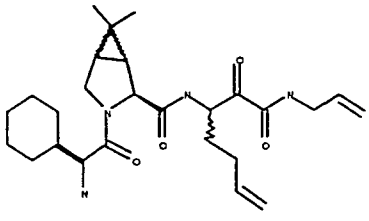
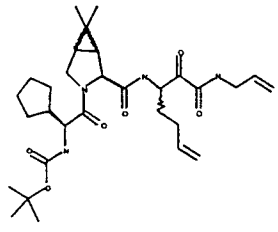
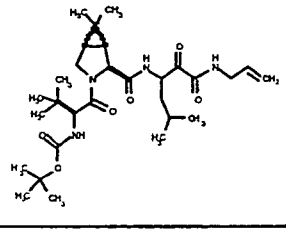
	575	B
	559	B
	573	B
	637	B
	473	C
	559	B
	549	C

Table 5

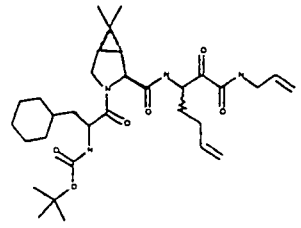
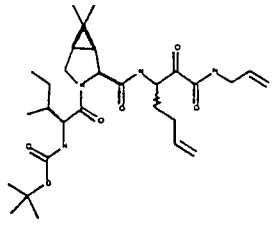
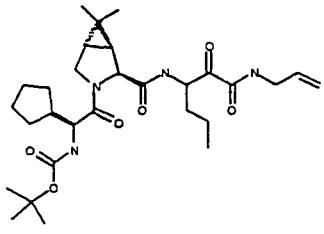
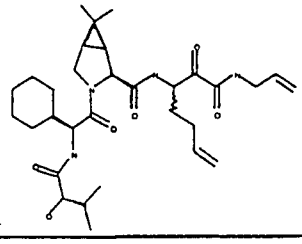
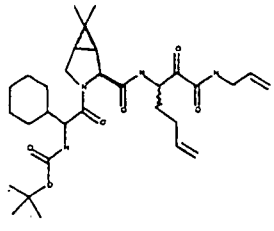
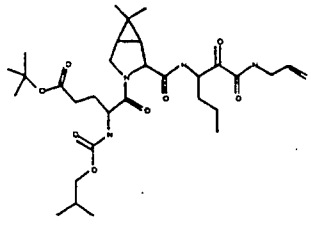
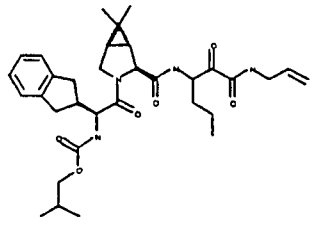
	587	C
	547	C
	547	B
	573	C
	573	C
	607	C
	595	B

Table 5

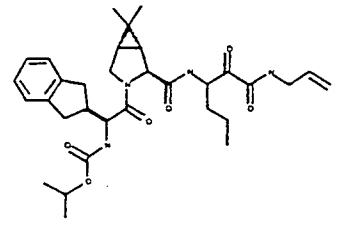
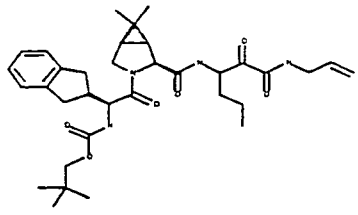
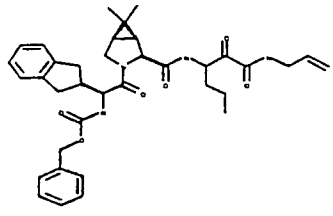
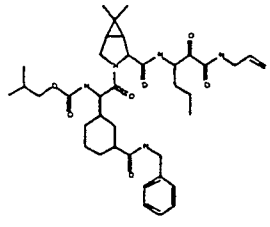
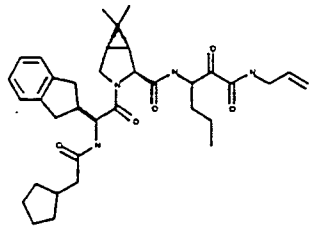
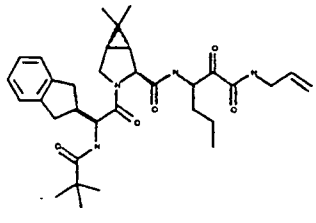
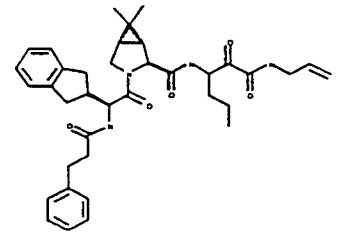
	581	B
	609	B
	629	C
	694	C
	605	C
	579	C
	627	C

Table 5

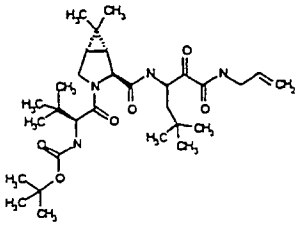
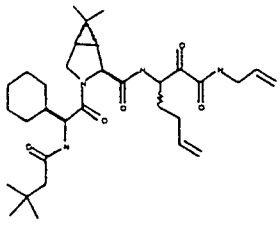
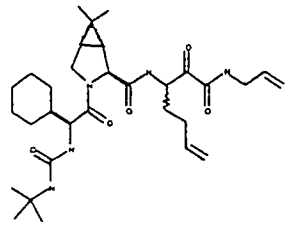
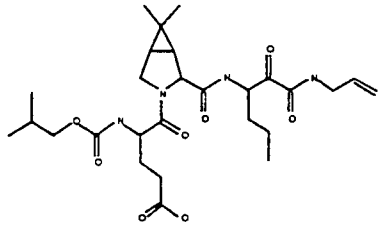
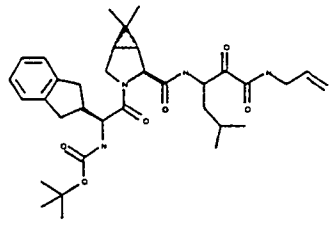
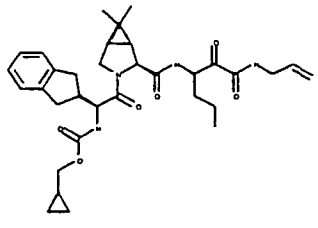
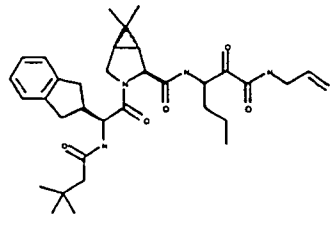
	563	C
	571	C
	572	B
	551	C
	609	C
	593	B
	593	C

Table 5

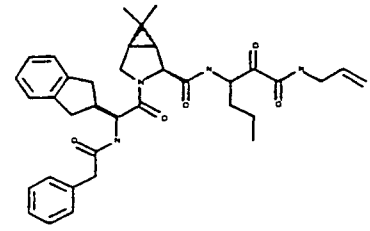
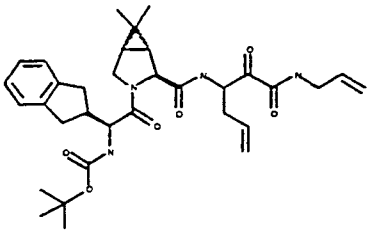
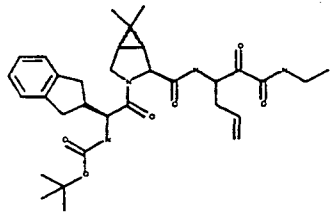
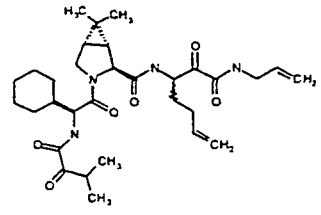
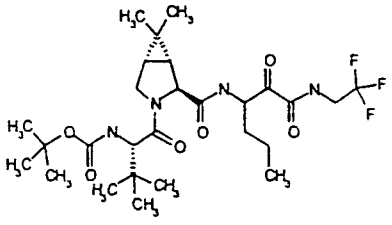
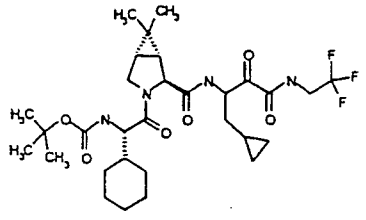
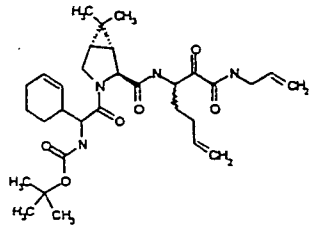
	613	C
	593	B
	581	C
	571	B
	577	C
	615	C
	571	C

Table 5

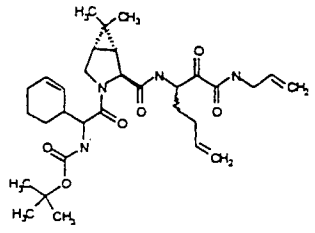
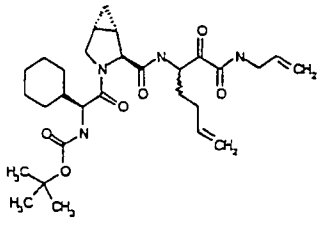
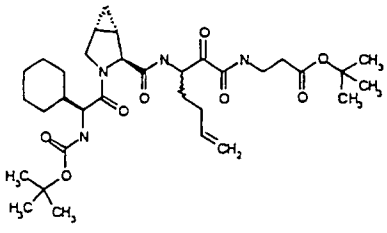
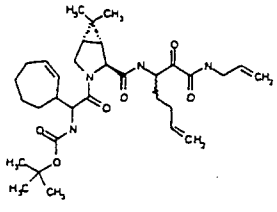
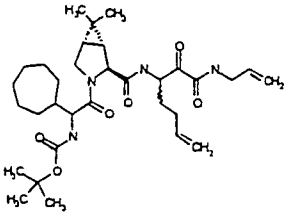
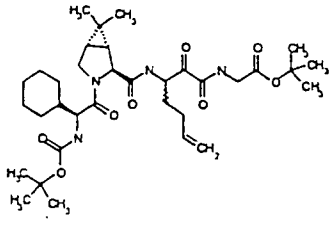
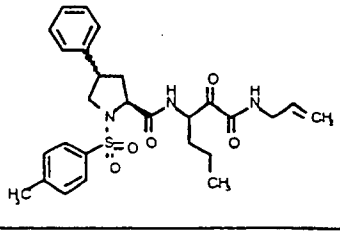
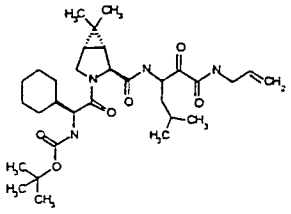
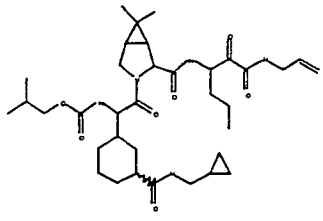
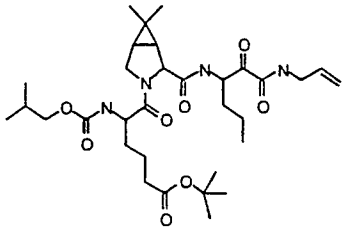
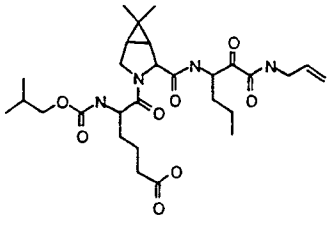
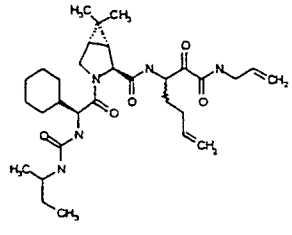
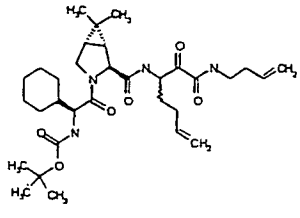
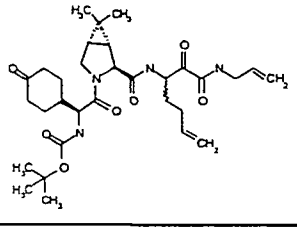
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	633	C
	585	B
	587	B
	647	B
	512	C

Table 5

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	621	C
	565	C
	572	A
	587	A
	587	B

033239

Table 5

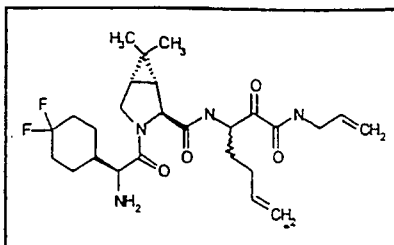
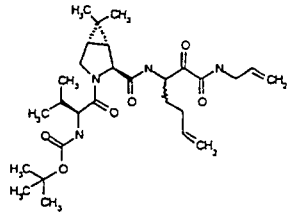
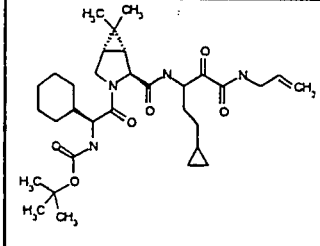
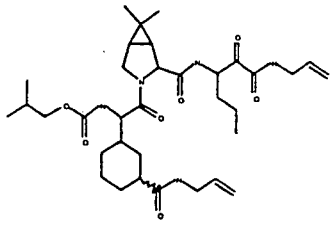
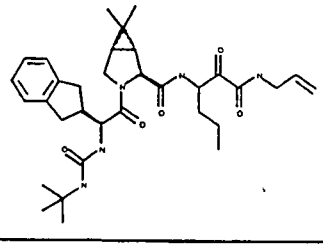
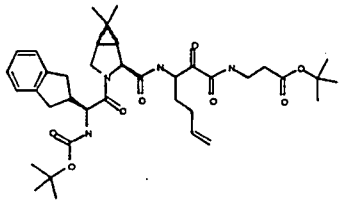
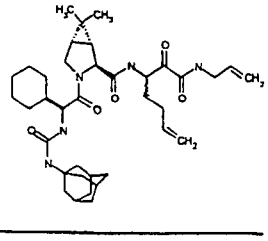
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	587	B
	644	C
	594	B
	695	B
	650	B

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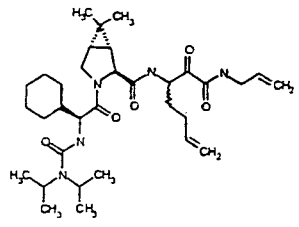
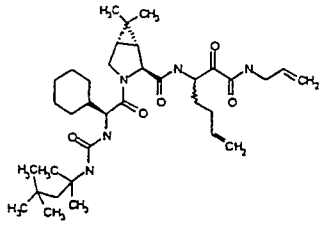
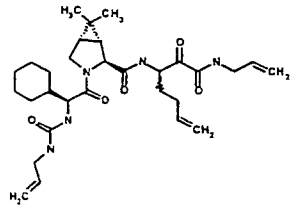
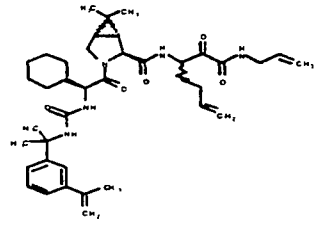
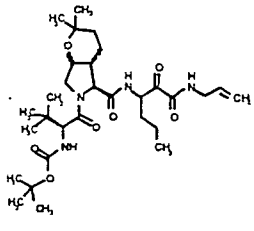
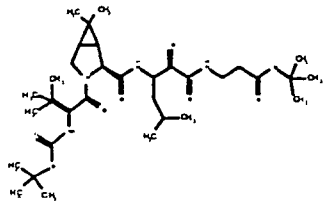
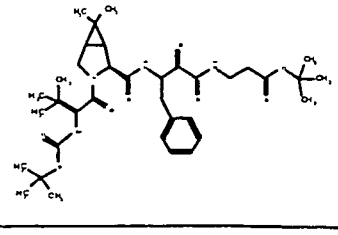
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	556	B
	674	B
	579	C
	637	C
	671	C

Table 5

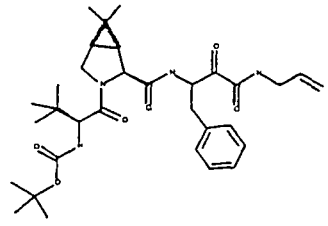
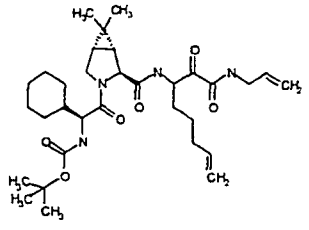
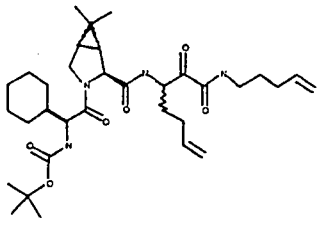
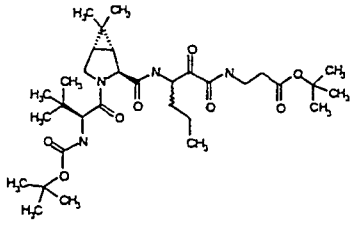
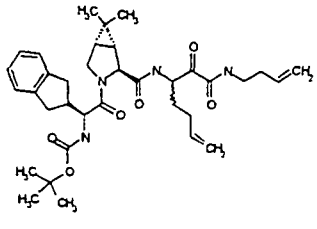
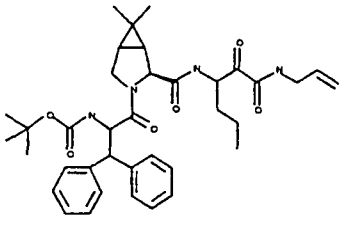
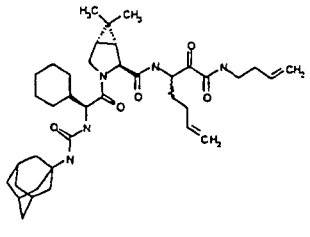
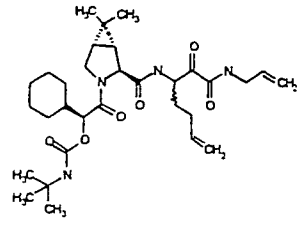
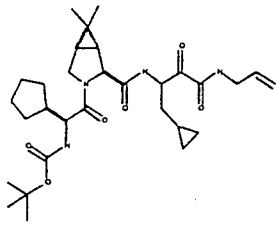
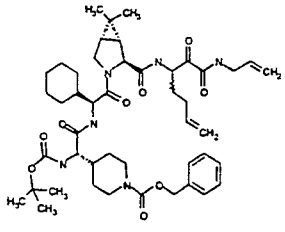
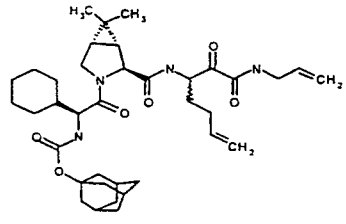
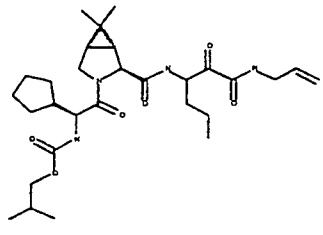
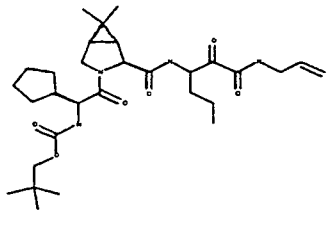
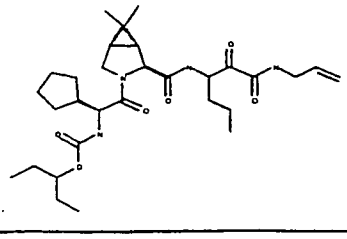
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	587	B
	601	B
	623	B
	621	A
	645	C
	664	B

Table 5

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	559	C
	847	B
	651	B
	547	C
	561	B
	561	B

030232

Table 5

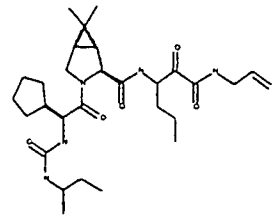
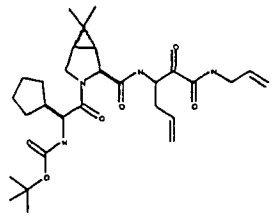
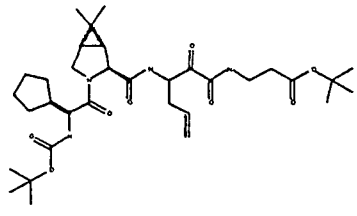
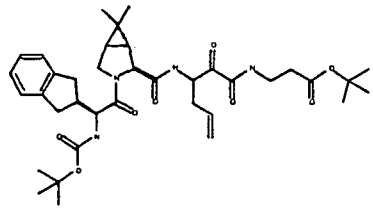
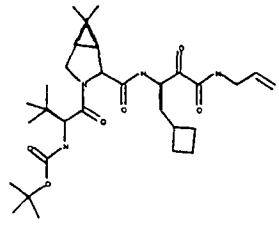
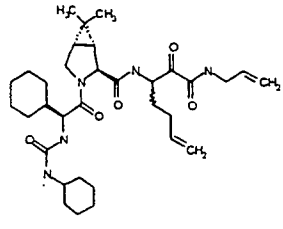
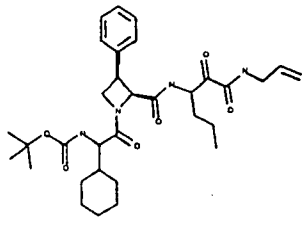
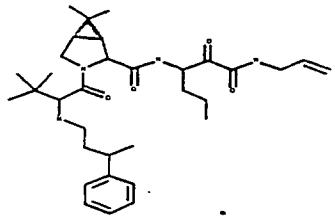
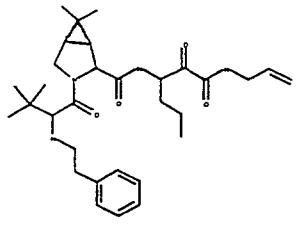
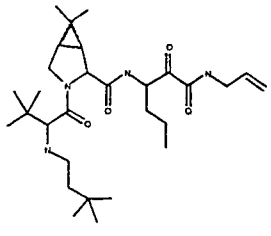
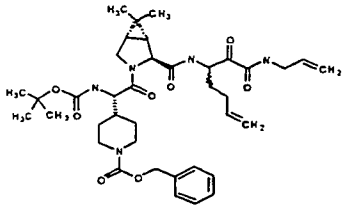
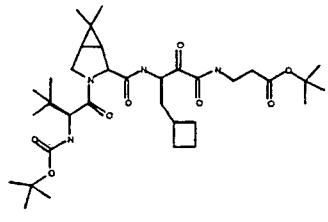
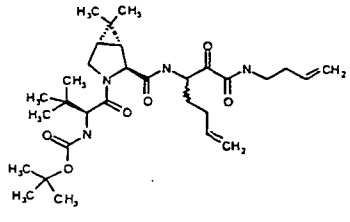
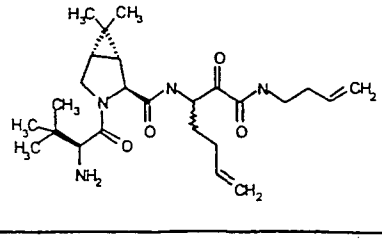
	546	C
	545	C
	633	B
	681	C
	561	C
	598	B
	583	C

Table 5

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	519	C
	708	B
	649	C
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030233

Table 5

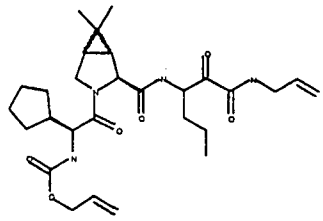
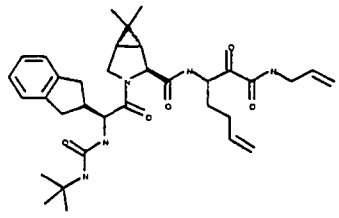
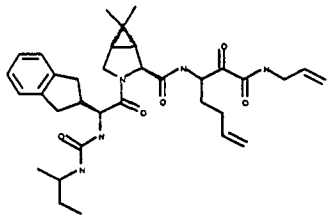
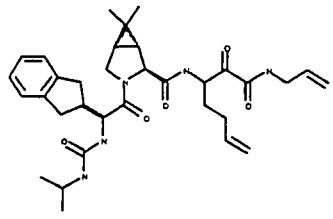
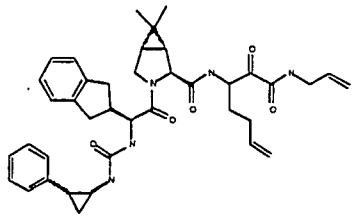
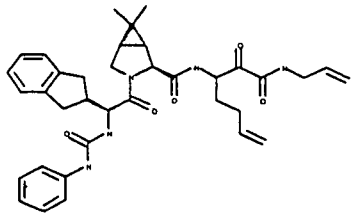
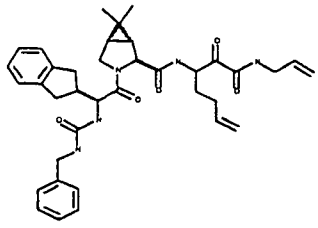
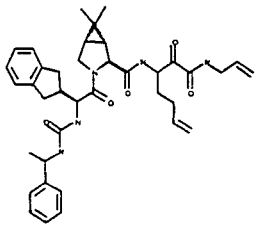
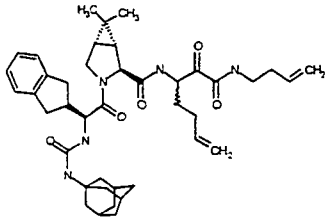
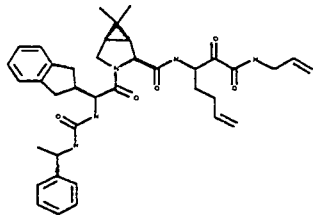
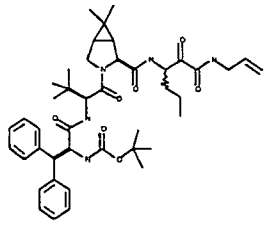
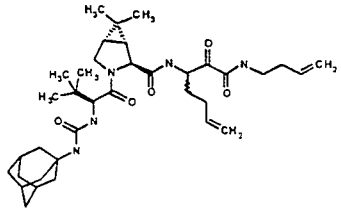
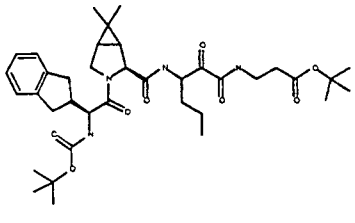
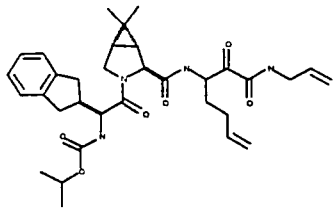
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	606	A
	592	A
	666	C
	626	B
	640	B

Table 5

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	654	B
	758	C
	638	A
	683	B
	593	A

000234

Table 5

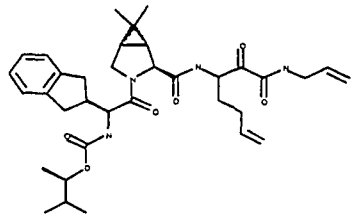
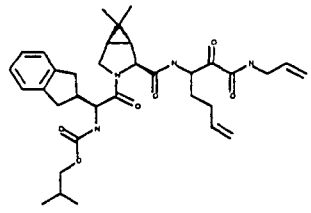
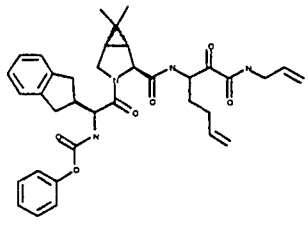
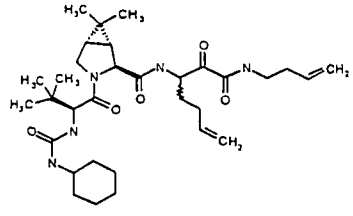
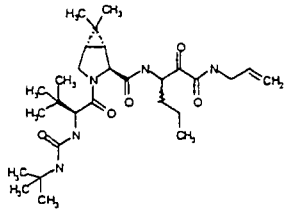
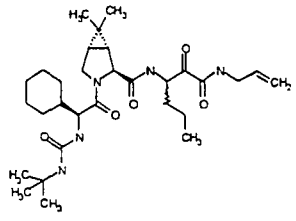
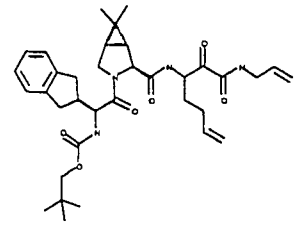
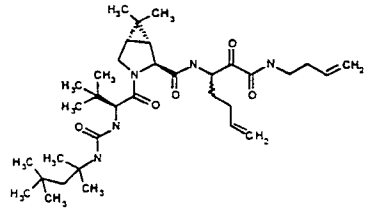
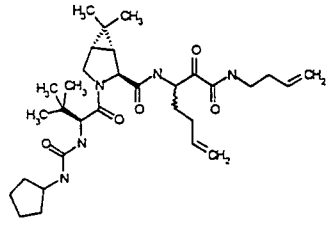
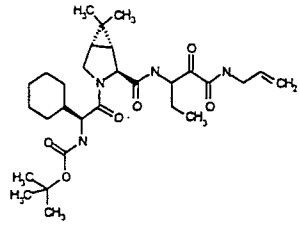
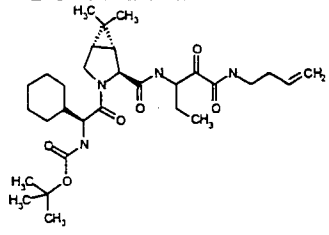
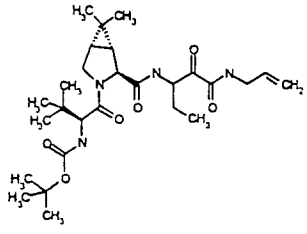
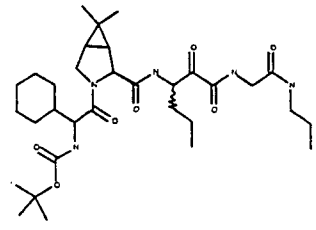
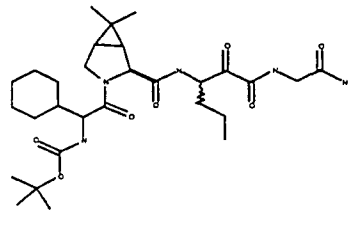
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	607	B
	627	B
	586	A
	534	B
	560	C
	621	A

Table 5

	616	B
	572	A
	547	C
	561	C
	521	C
	620	B
	578	B

000235

Table 5

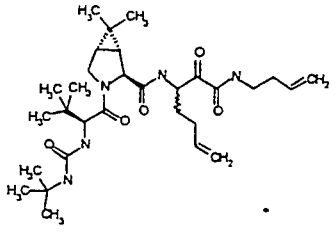
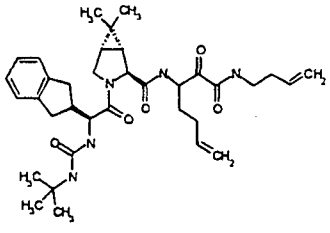
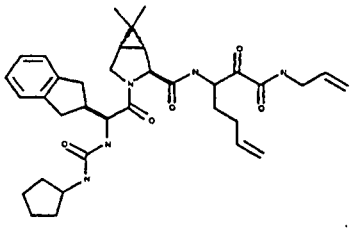
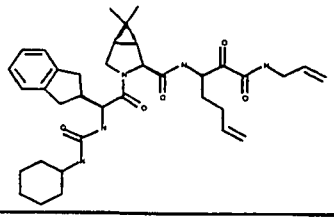
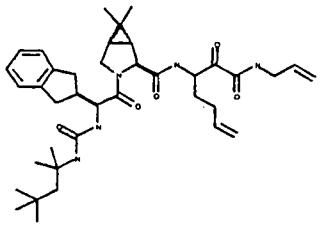
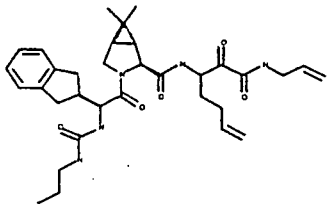
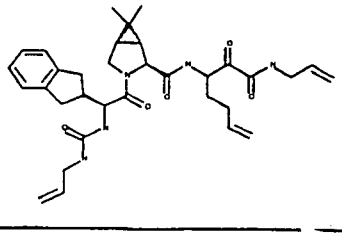
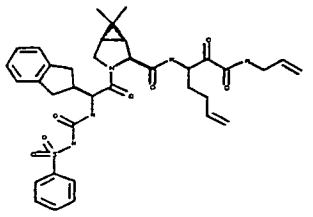
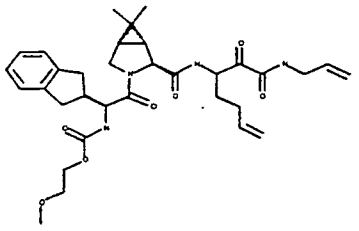
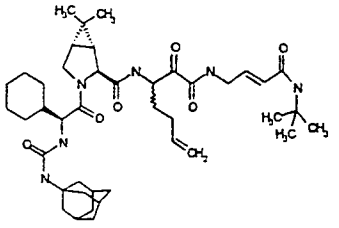
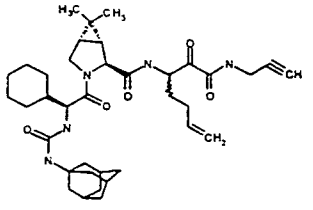
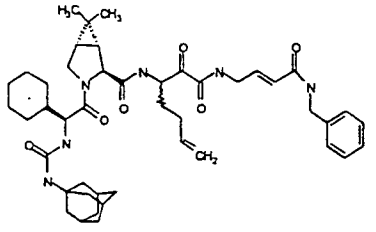
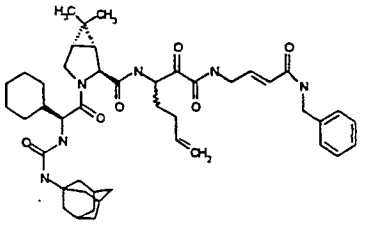
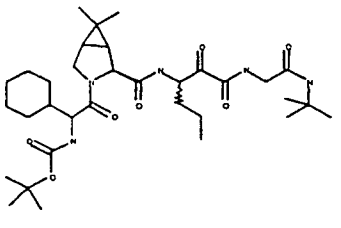
	560	A
	620	A
	618	B
	632	B
	662	B
	592	B
	590	B

Table 5

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	783	B
	783	B
	634	C

000238

Table 5

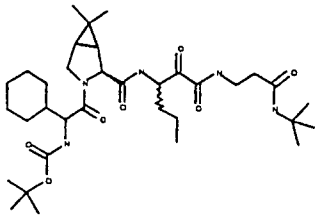
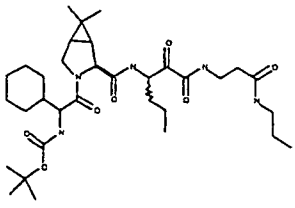
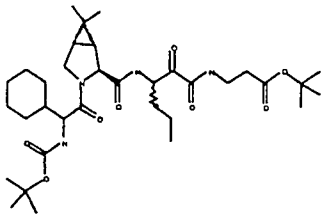
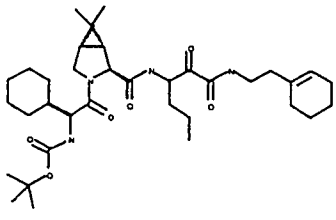
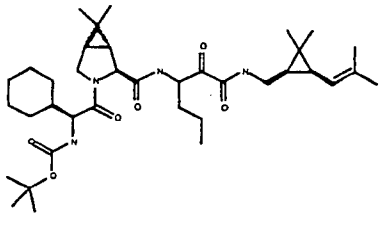
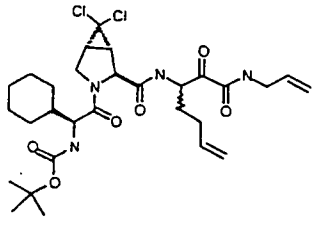
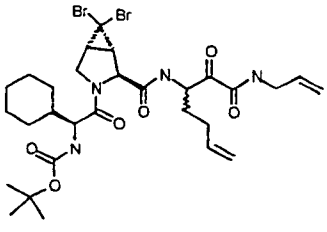
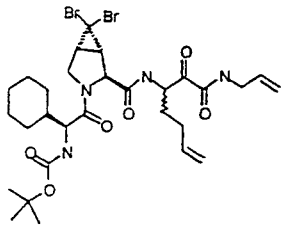
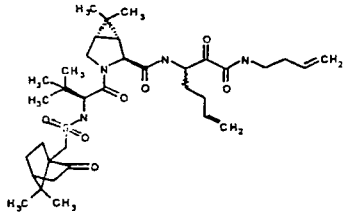
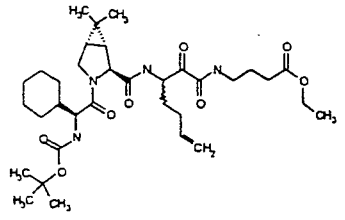
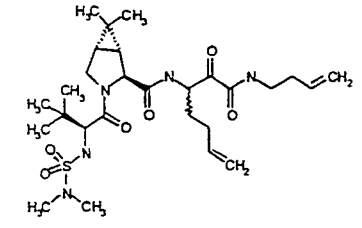
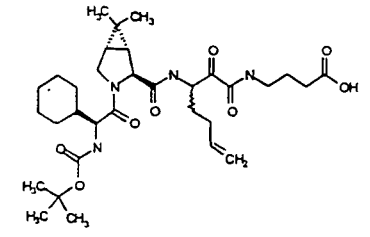
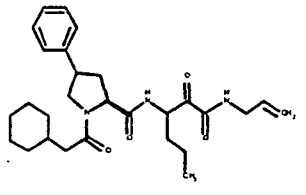
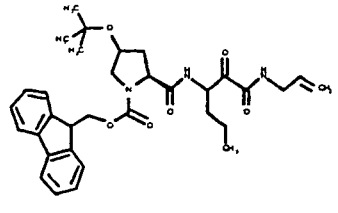
	648	C
	634	C
	649	C
	629	C
	657	C
	614	A
	702	B

Table 5

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	647	B
	568	C
	619	C
	482	C
	576	C

000237

Table 5

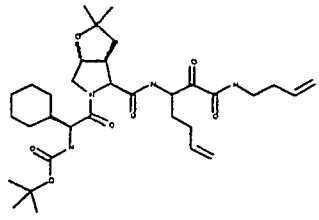
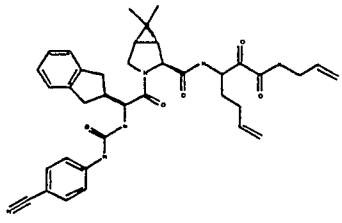
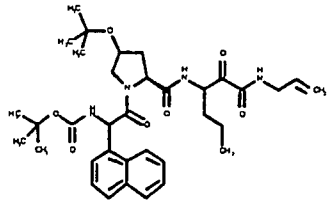
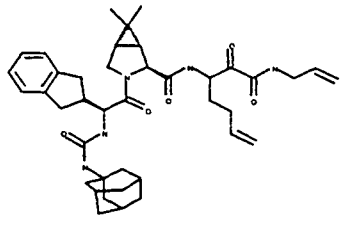
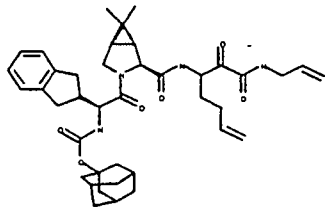
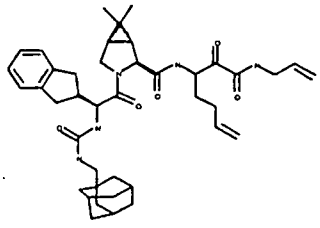
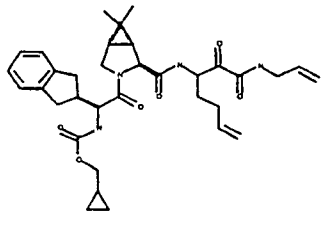
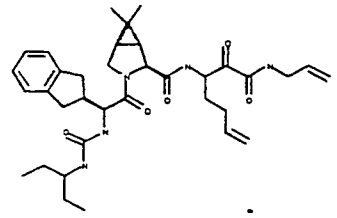
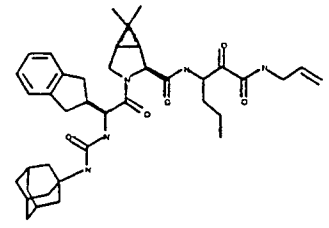
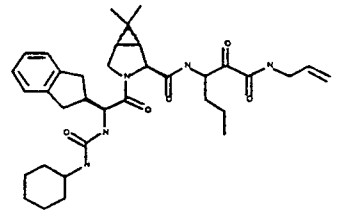
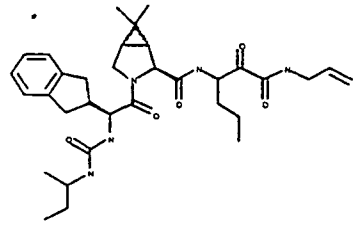
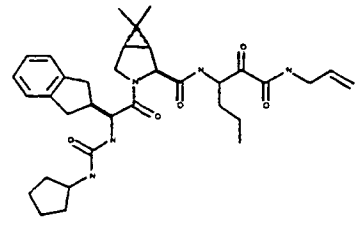
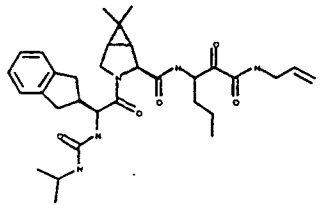
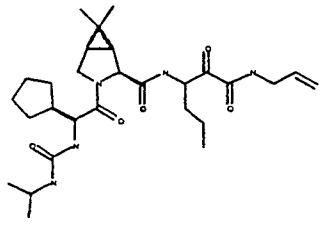
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	698	B
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Table 5

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	580	C
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000238

Table 5

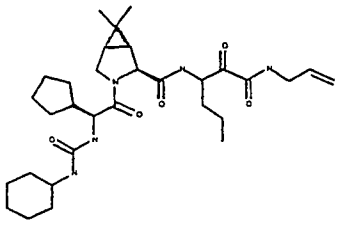
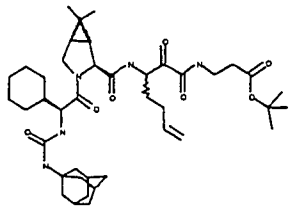
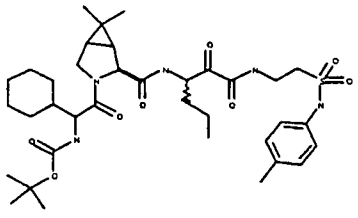
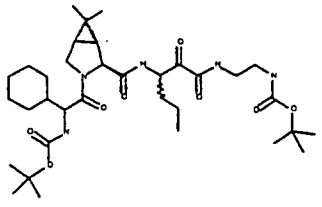
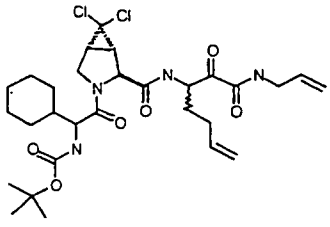
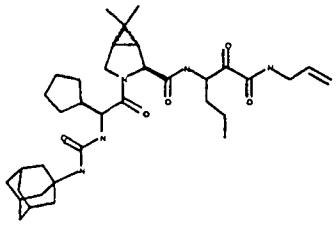
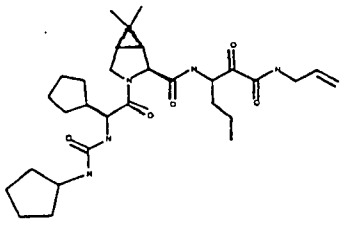
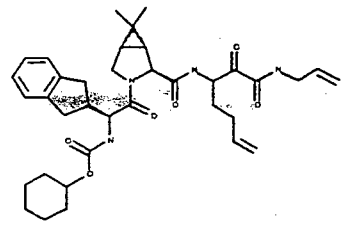
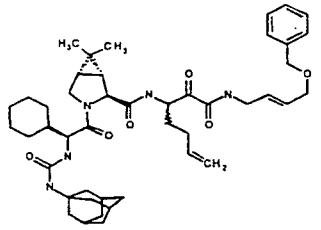
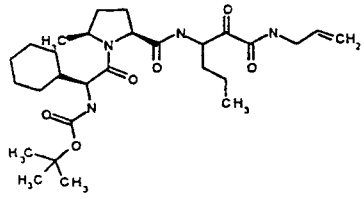
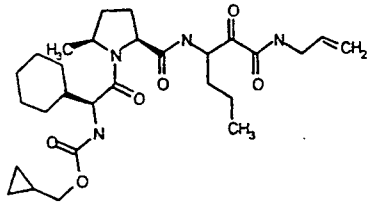
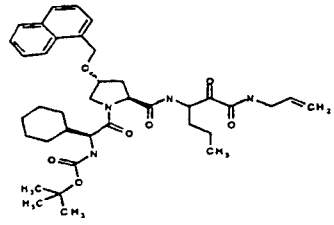
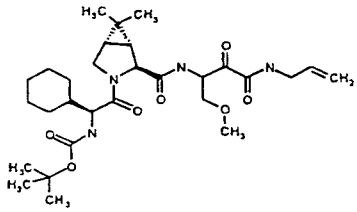
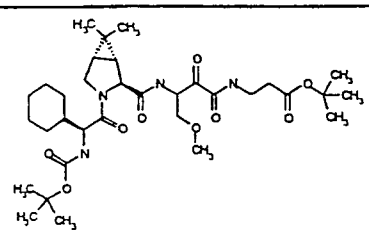
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	614	B
	624	B
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Table 5

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	535	C
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	677	C
	563	B
	651	A

000239

Table 5

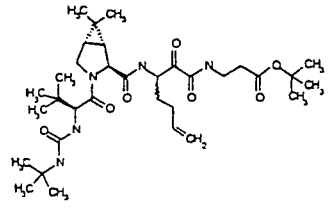
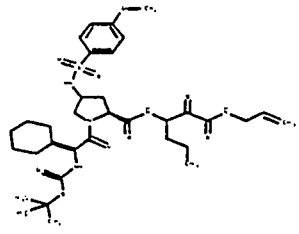
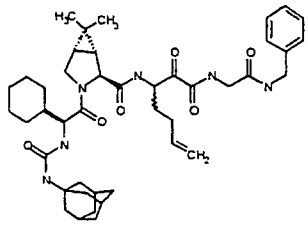
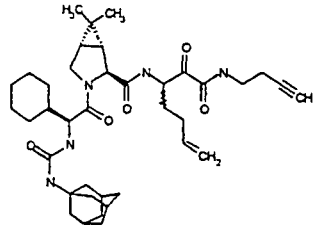
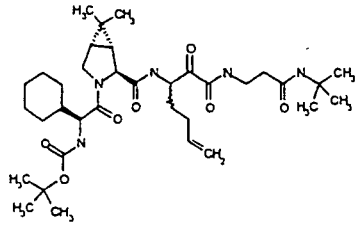
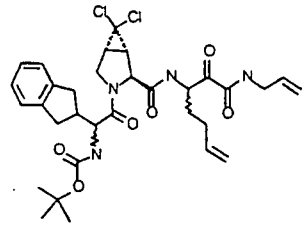
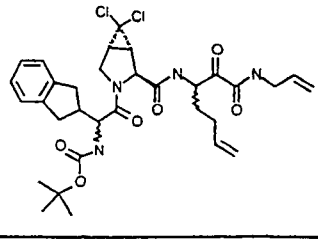
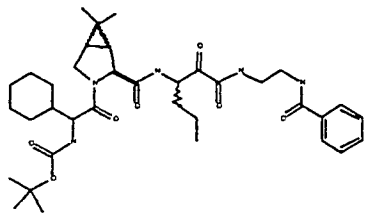
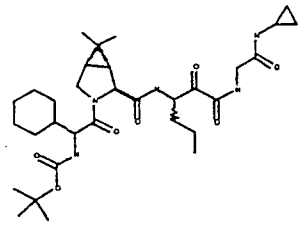
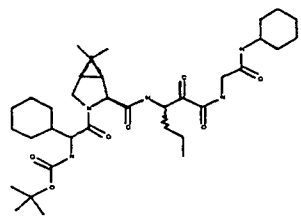
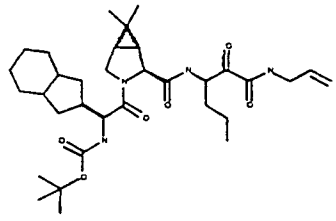
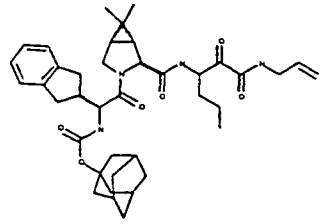
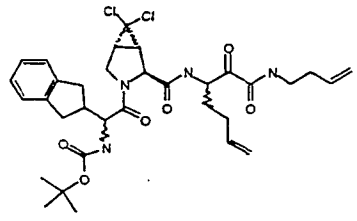
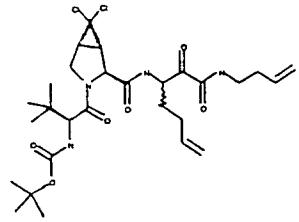
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	757	A
	662	A
	660	A
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	648	C

Table 5

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	673	B
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030240

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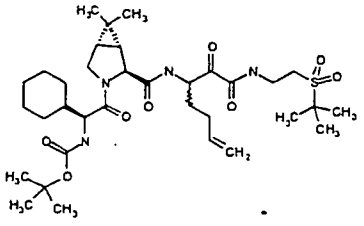
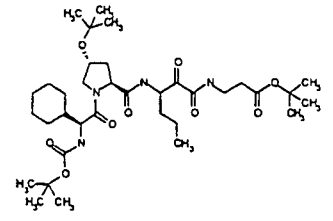
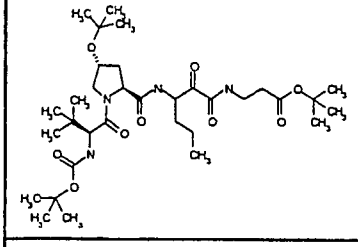
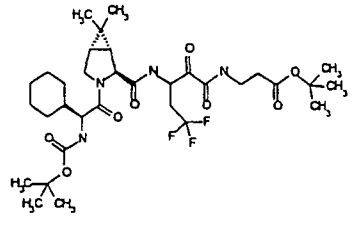
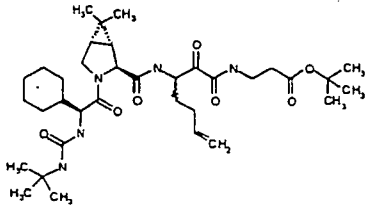
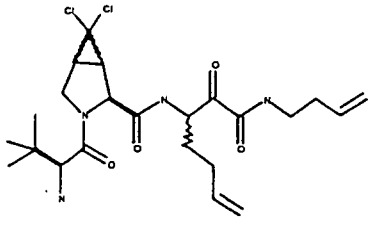
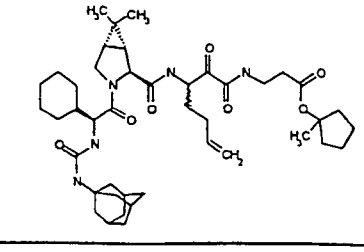
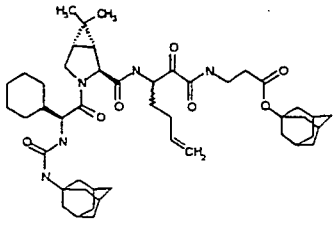
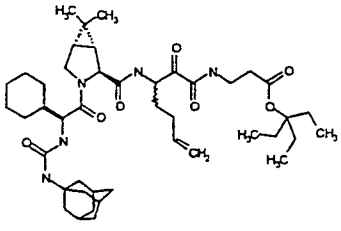
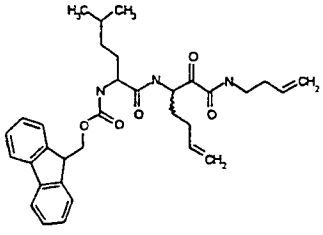
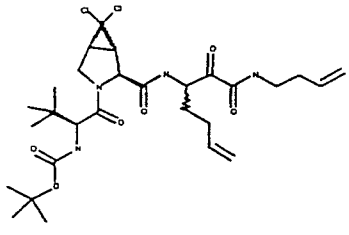
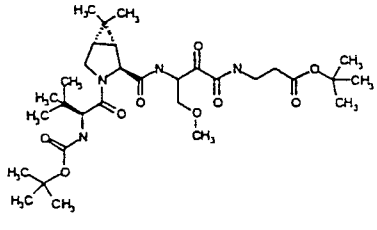
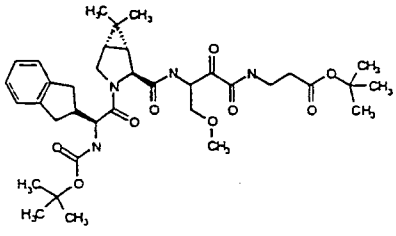
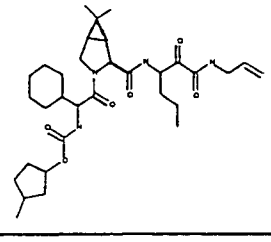
	681	A
	681	C
	655	C
	689	B
	660	A
	538	C
	764	A

Table 5

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	602	C
	625	B
	685	B
	587	A

033241

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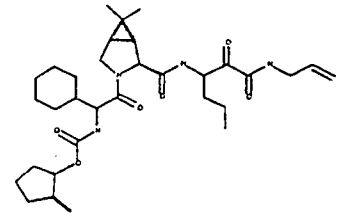
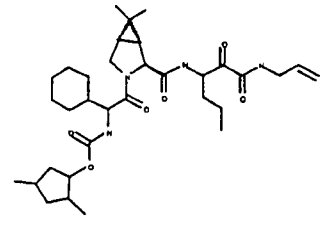
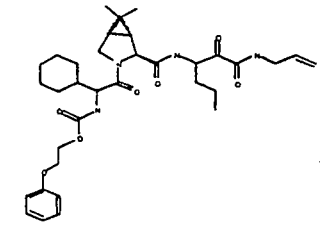
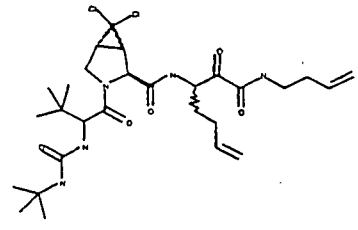
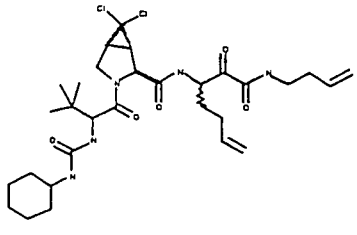
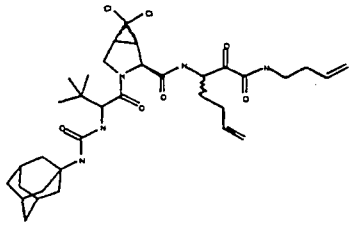
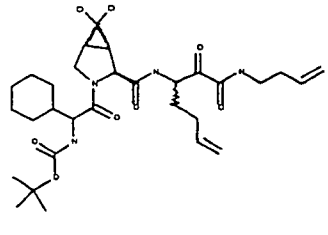
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	625	B
	601	A
	627	B
	679	A
	628	A

Table 5

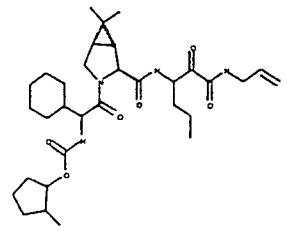
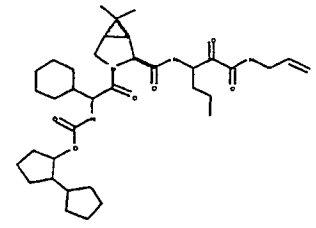
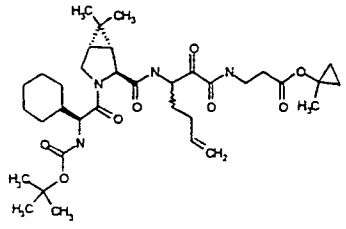
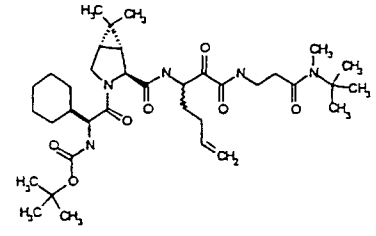
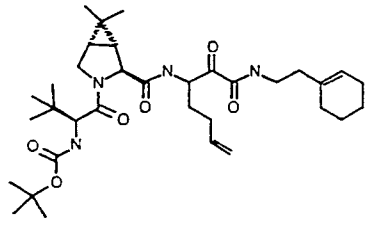
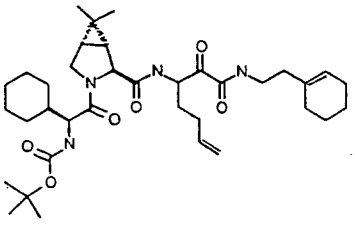
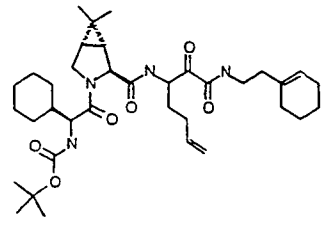
	587	A
	641	A
	659	A
	674	A
	615	B
	641	B
	641	B

Table 5

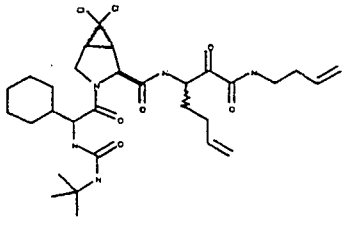
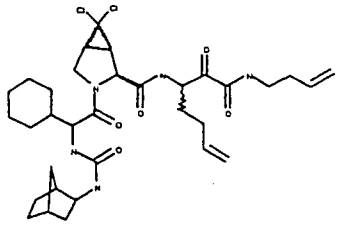
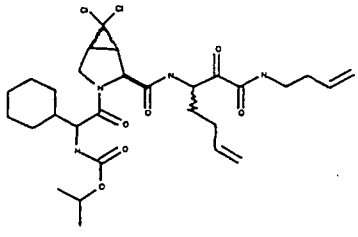
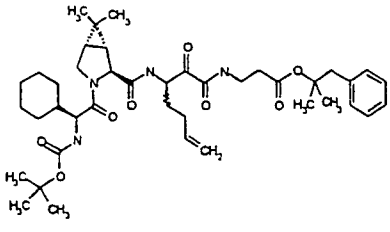
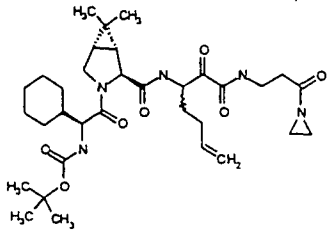
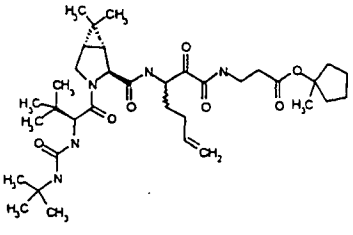
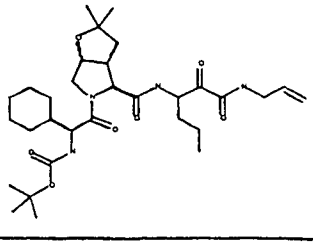
	627	A
	665	A
	614	A
	737	B
	666	A
	660	A
	591	C

Table 5

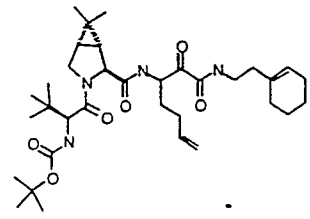
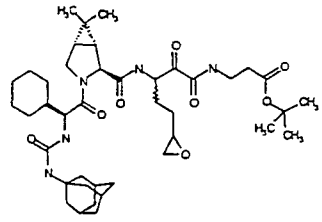
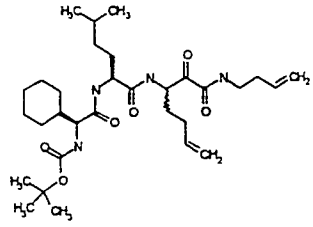
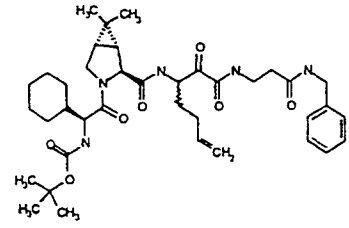
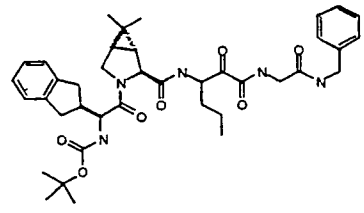
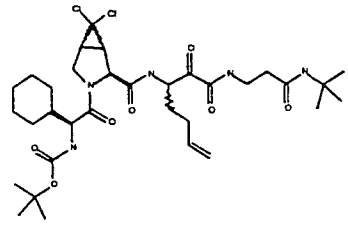
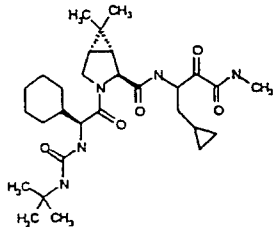
	615	C
	754	B
	577	C
	694	A
	702	A
	701	A
	546	B

Table 5

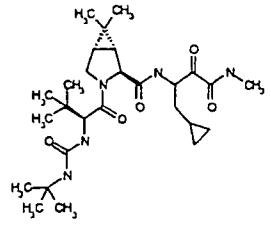
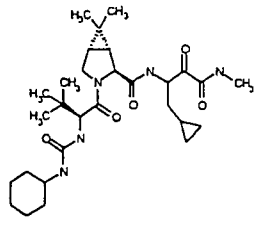
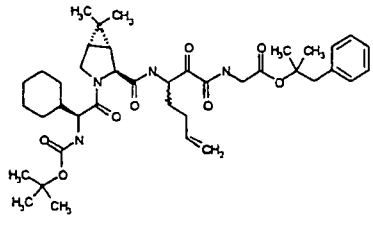
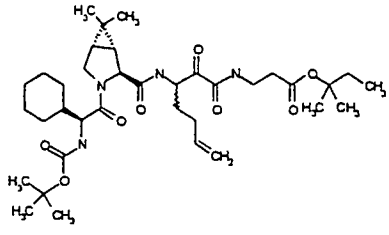
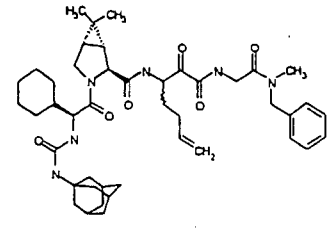
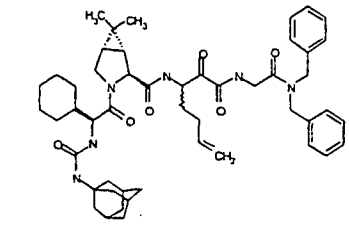
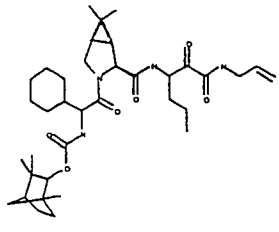
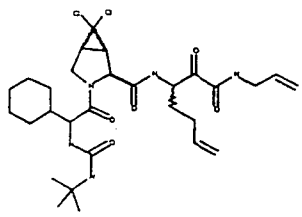
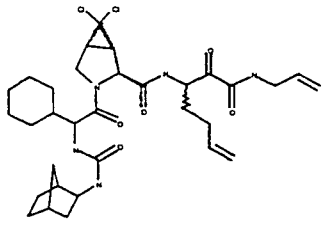
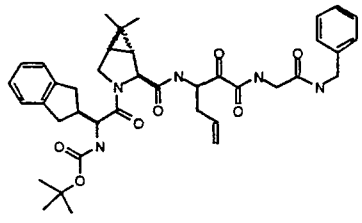
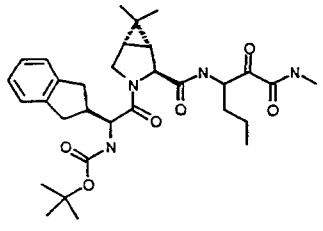
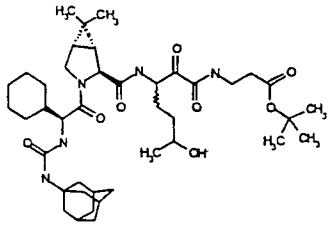
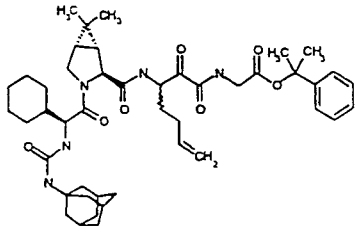
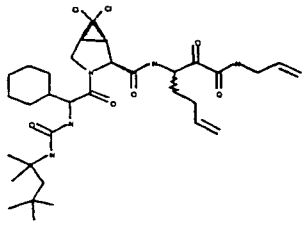
	520	B
	546	B
	723	B
	675	A
	771	B
	847	C
	641	A

Table 5

	613	A
	651	C
	700	A
	569	A
	756	B
	786	A
	669	B

030244

Table 5

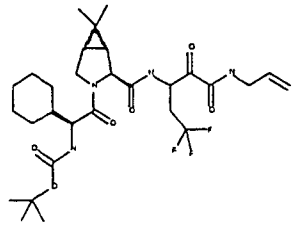
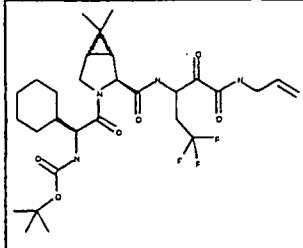
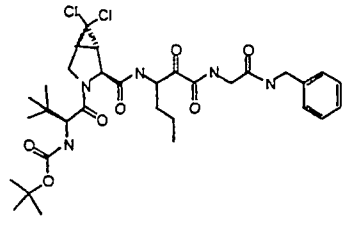
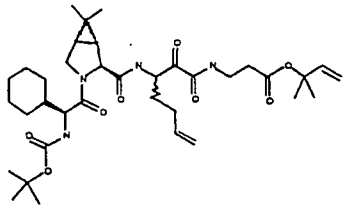
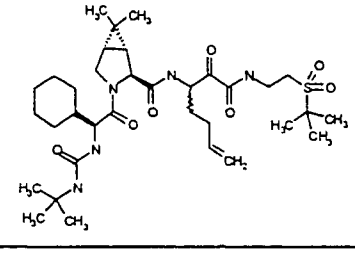
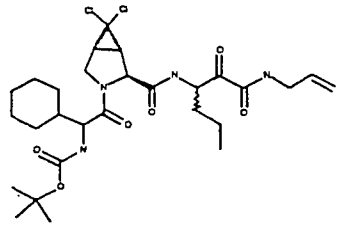
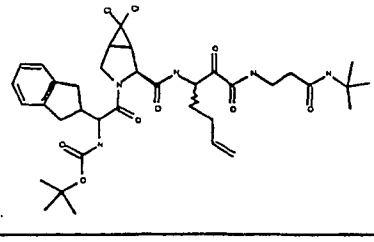
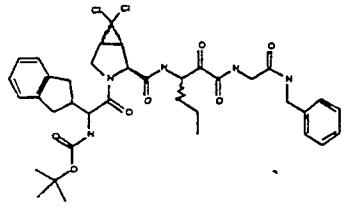
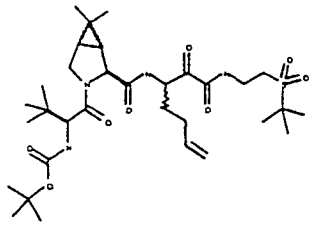
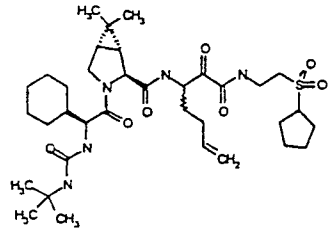
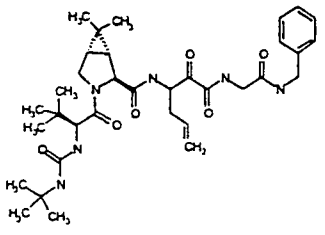
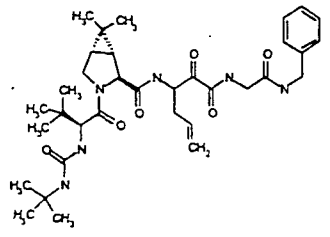
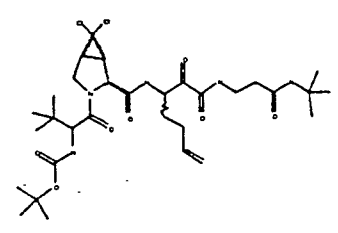
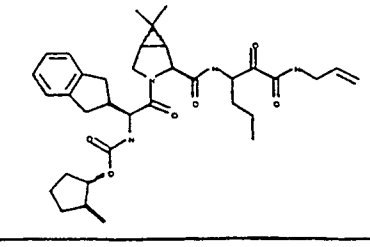
	601	A
	601	B
	683	A
	673	A
	680	A
	602	A
	735	A

Table 5

	743	A
	655	B
	692	A
	639	A
	639	A
	675	A
	621	A

030245

Table 5

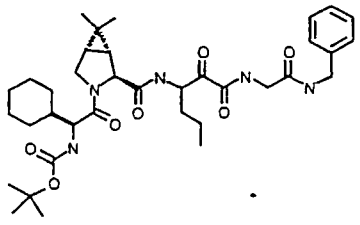
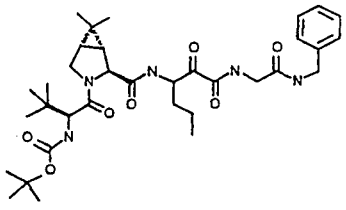
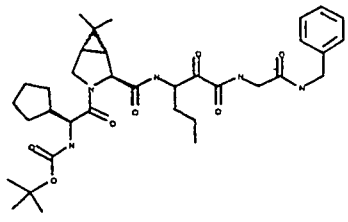
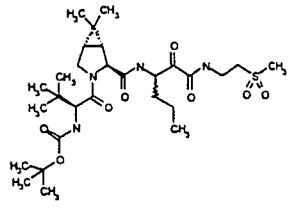
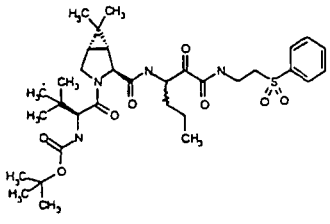
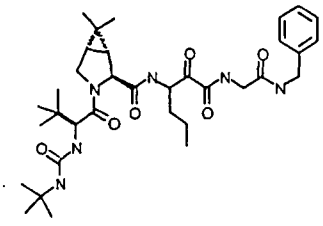
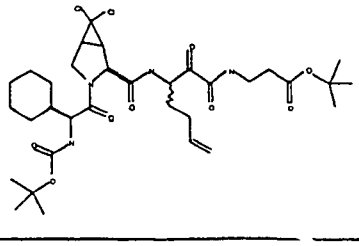
	668	A
	642	A
	654	A
	601	C
	663	B
	641	A
	702	A

Table 5

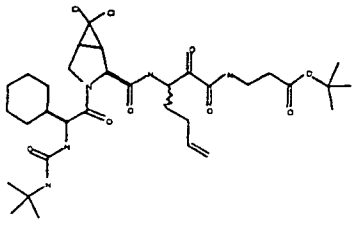
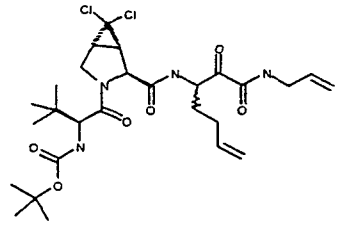
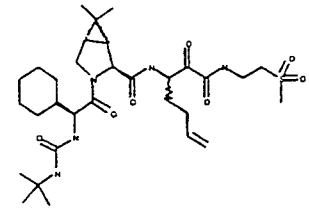
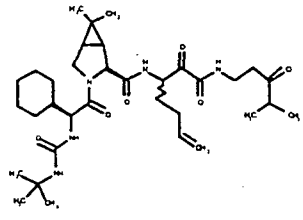
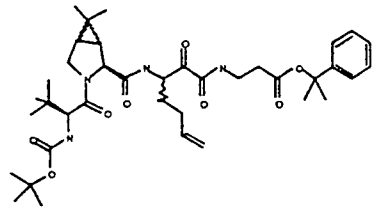
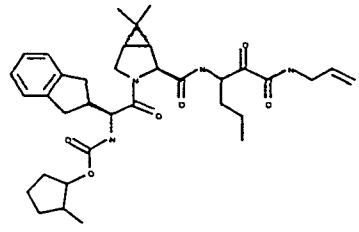
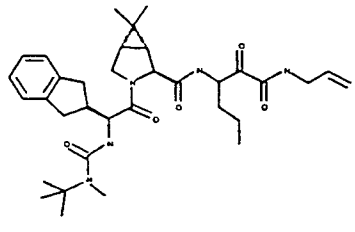
	701	A
	588	B
	638	A
	630	A
	697	A
	621	A
	608	B

Table 5

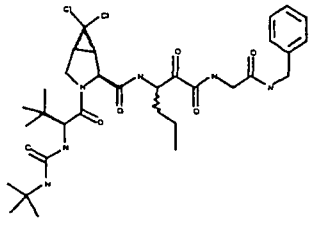
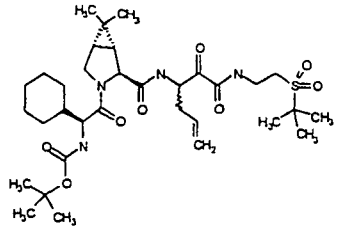
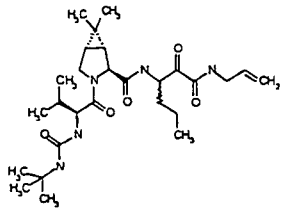
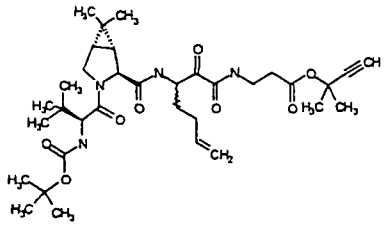
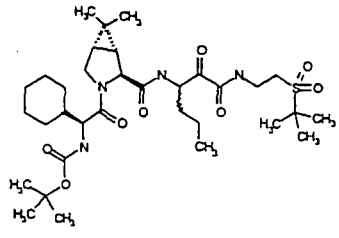
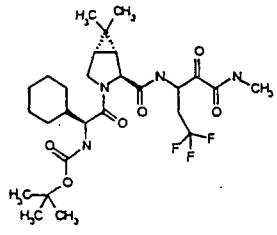
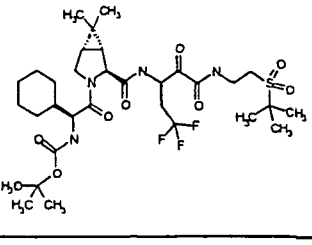
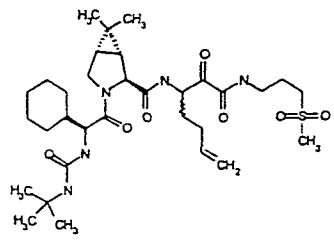
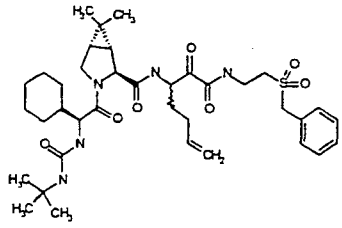
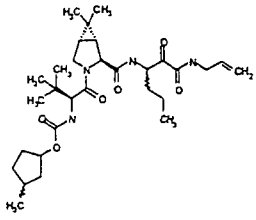
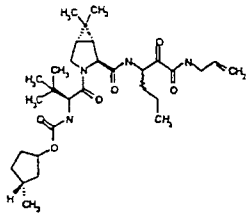
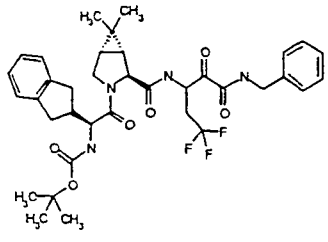
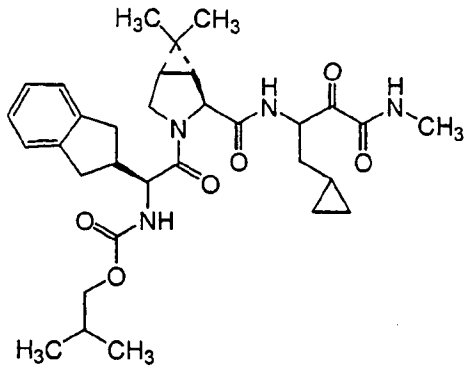
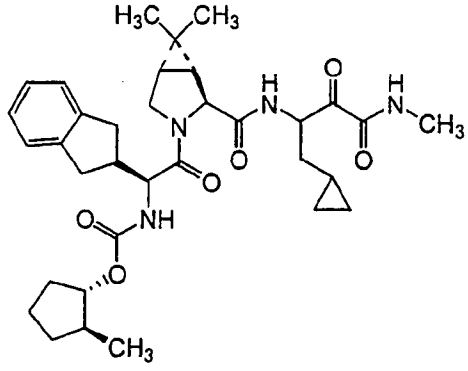
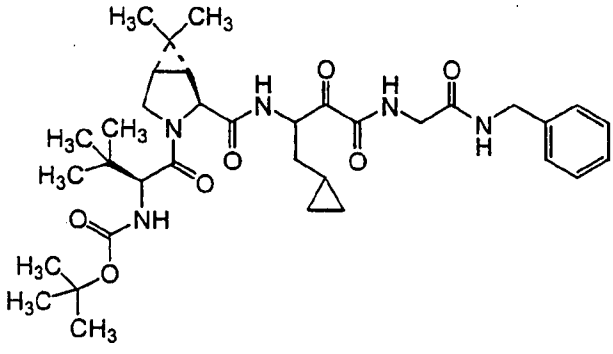
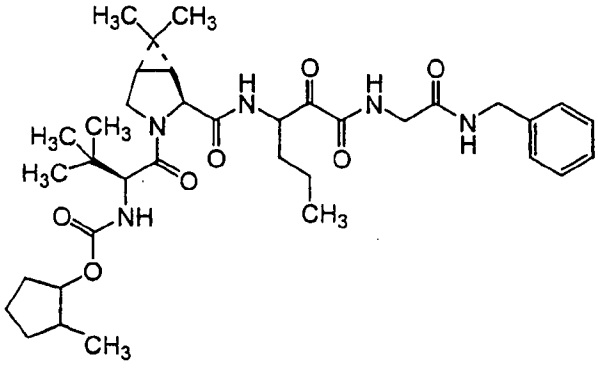
	682	A
	667	B
	520	B
	645	B
	669	C
	575	A
	709	B

Table 5

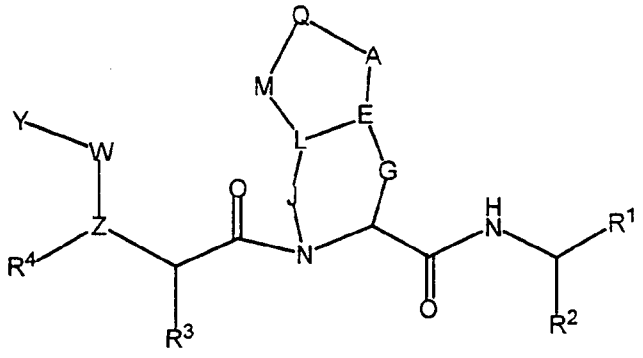
	652	B
	714	A
	561	B
	561	B
	685	B

Structure	MW	Ki* Range
	580	A
	606	A
	653	A
	667	A

Claims

What is claimed is:

1. A compound, including enantiomers, stereoisomers, rotamers, tautomers, racemates and prodrug of said compound, and 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 the following moieties: 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 COR^5 or $B(OR)_2$, wherein R^5 is H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, or COR^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, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pCOR^{11}$, $[CH(R^{1'})]_pCH(OH)R^{11}$, $CH(R^{1'})CONHCH(R^{2'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COO\ R^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO\ R^{11}$ and $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})CONR^{12}R^{13}$, 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, CH or CR;

W maybe present or absent, and if W is present, W is selected from C=O, C=S, C(=N-CN), or SO_2;

Q maybe present or absent, and when Q is present, Q is CH, 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, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_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 $(CRR')_p$, SO_2, NH, NR 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 CH, CR, O, S or NR; 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, SO_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 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;

030249

further wherein said unit N-C-G-E-L-J-N represents a five-membered or 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 COR^5, and R^5 is H, OH, $COOR^8$, $CONR^9R^{10}$.

3. The compound of claim 2, wherein R^1 is $COCONR^9R^{10}$, and R^9 is H, R^{10} is H, R^{14}, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pSO_2N\ R^{12}R^{13}$, $[CH(R^{1'})]_pCOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})\ CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaralkyl.

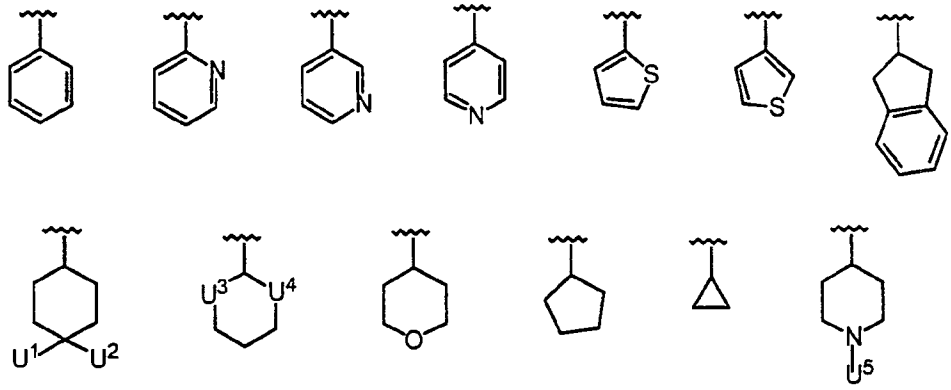
4. The compound of claim 3, wherein R^{10} is H, R^{14}, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})SO_2R^{11}$, $CH(R^{1'})CH(R^{1'})SO_2N\ R^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})COR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})\ CONR^{12}R^{13}$, or $CH(R^{1'})CONHCH(R^{2'})(R')$, wherein $R^{1'}$ is H or alkyl, and $R^{2'}$ is phenyl, substituted phenyl, hetero atom-substituted phenyl, thiophenyl, cycloalkyl, piperidyl or pyridyl.

5. The compound of claim 4, wherein $R^{1'}$ is H.

6. The compound of claim 5, 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 $CH_2CONR^{12}R^{13}$;

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



wherein:

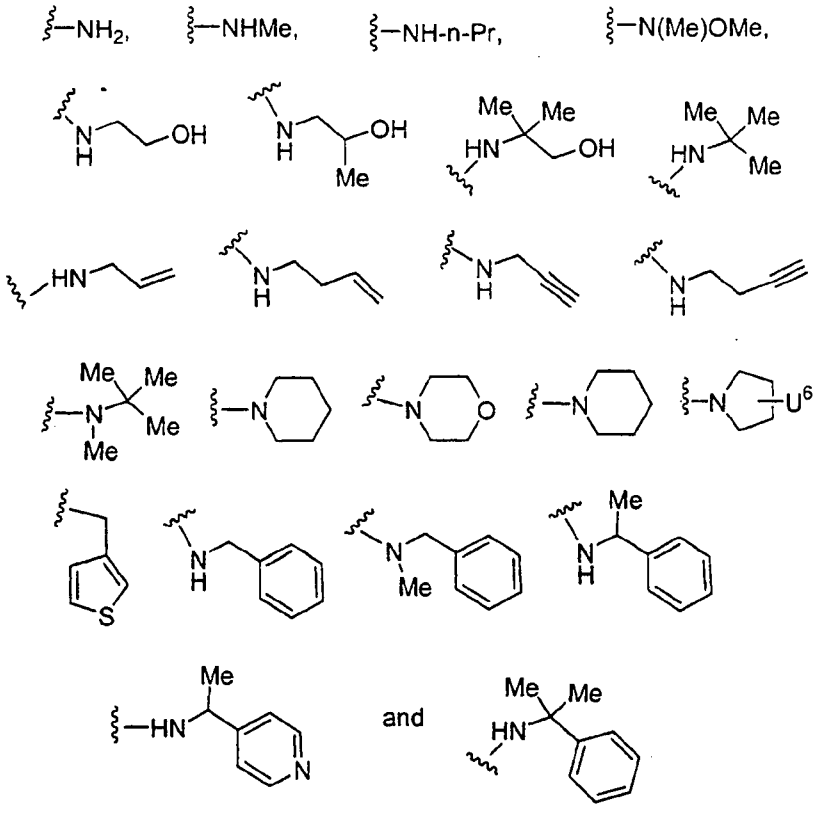
U^1 and U^2 maybe same or different and are selected from H, F, CH_2COOH, CH_2COOMe, CH_2CONH_2, $CH_2CONHMe$, CH_2CONMe_2, azido, amino, hydroxyl, substituted amino, substituted hydroxyl;

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

U^5 is selected from the 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;

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

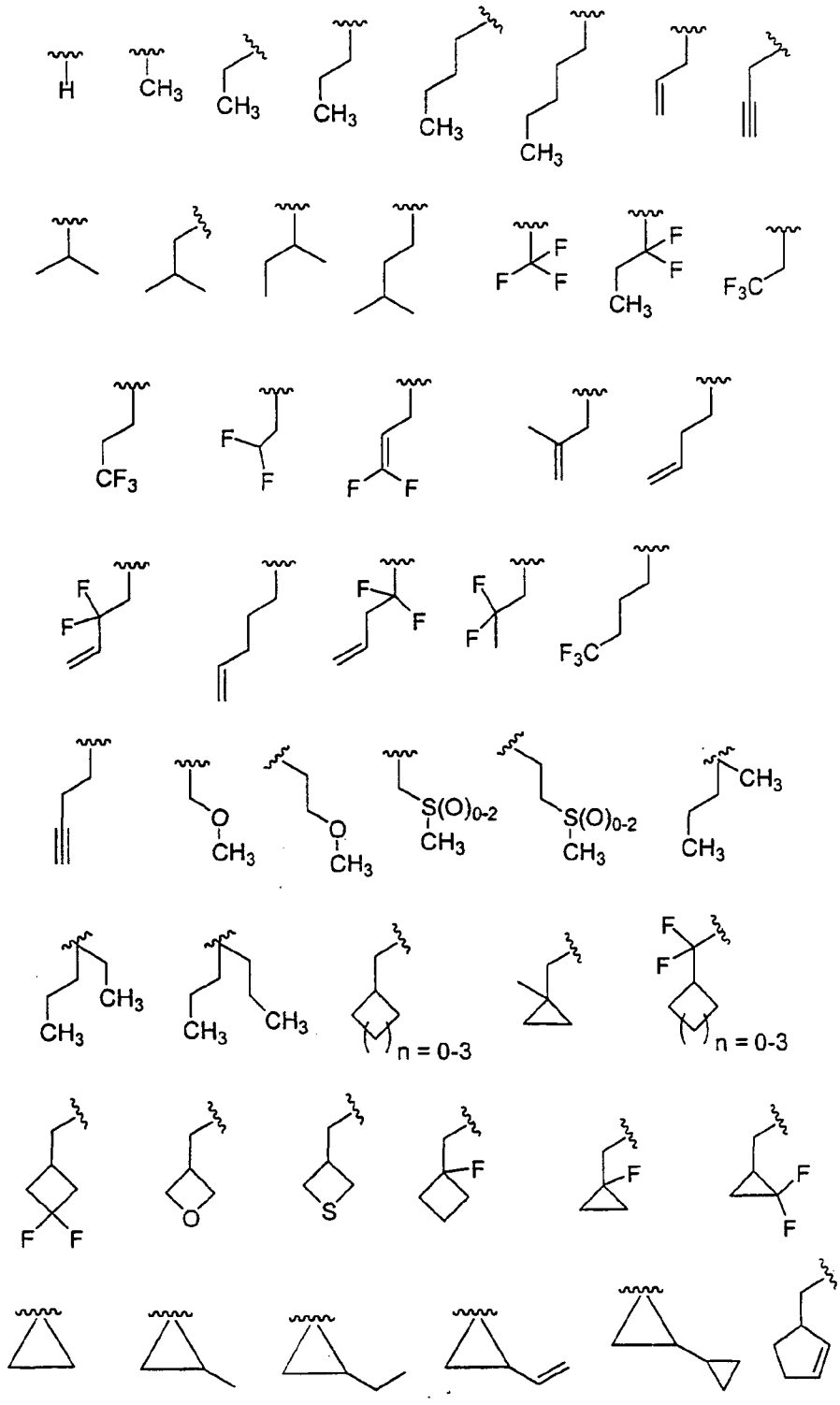
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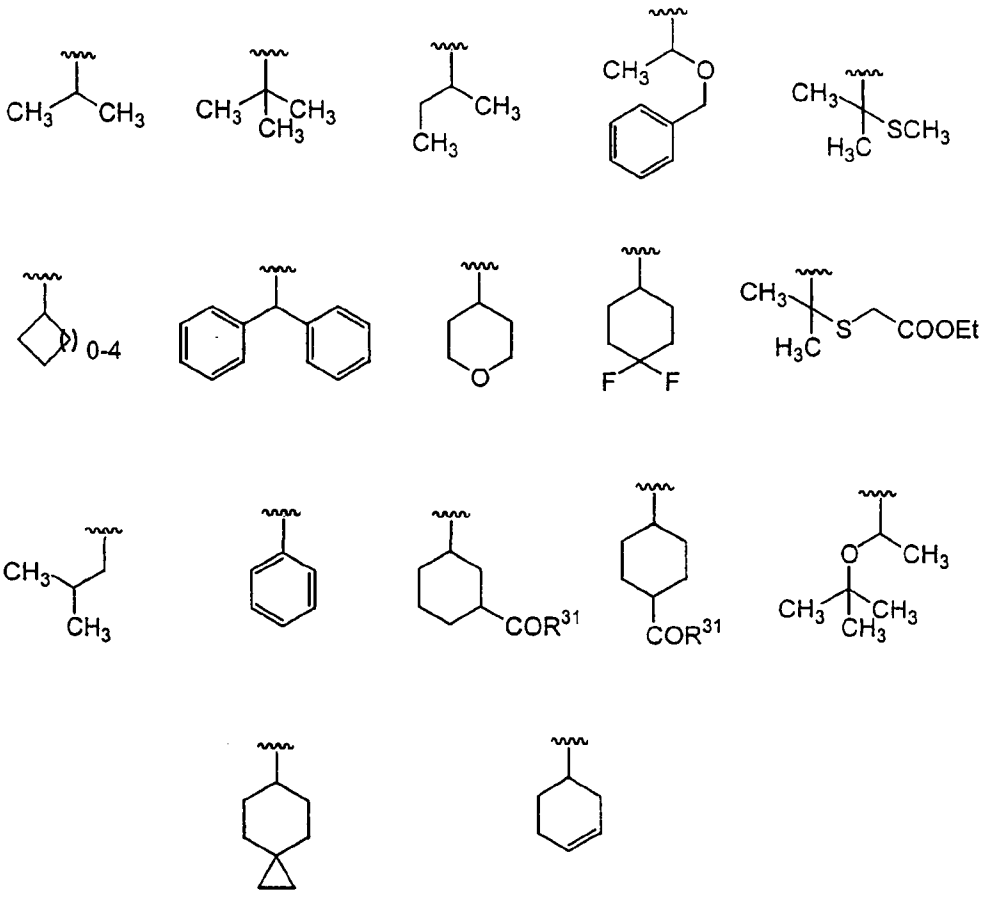
wherein U^6 is H, OH, or CH_2OH, and

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, cyclopropylmethyl.

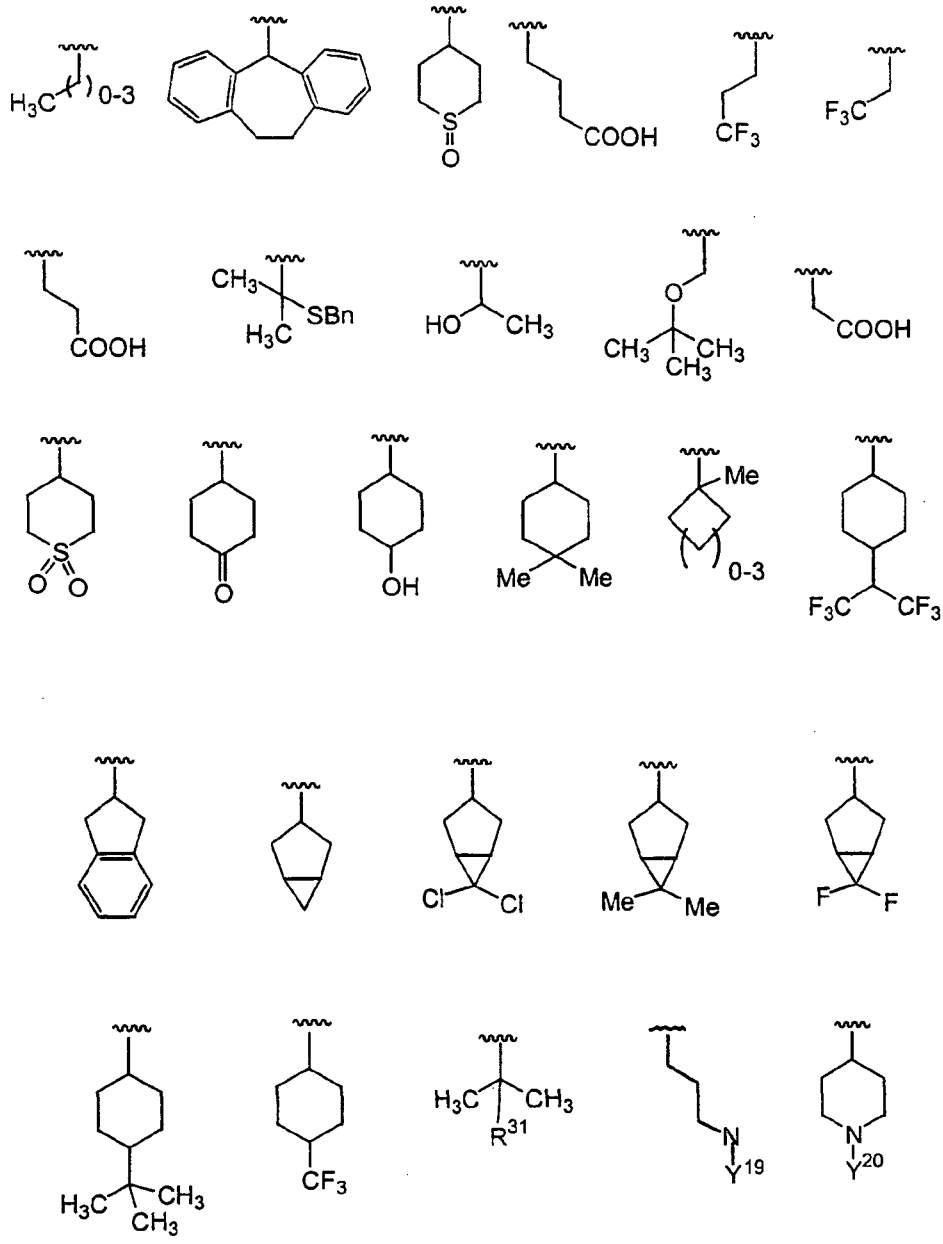
7. The compound of claim 2, wherein R^2 is selected from the group consisting of the following moieties:


H
CH3
CH3
CH3
CH3
CH3
F
F
F
F
F
CH3
F3C
CF3
F
F
F
F
F
F
F
F
F3C
O
CH3
O
CH3
S(O)0-2
CH3
S(O)0-2
CH3
CH3
CH3
CH3
CH3
CH3
n = 0-3
F
F
n = 0-3
F
F
O
S
F
F
F
F
F

8. The compound of claim 7, wherein R^3 is selected from the group consisting of:



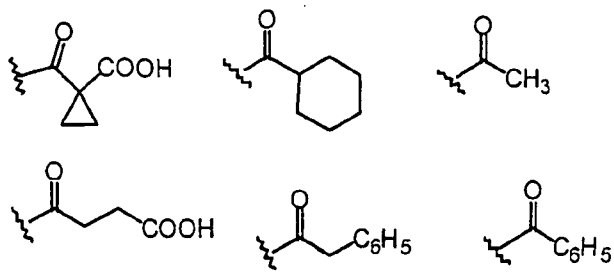
5



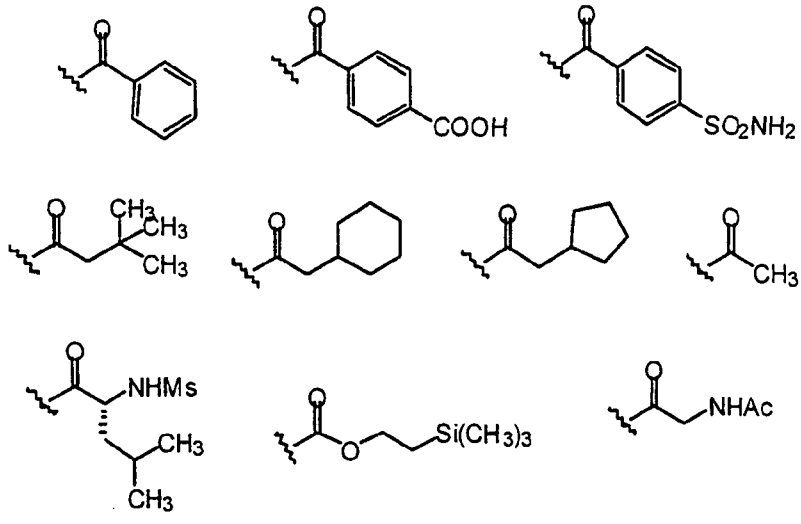
wherein R^{31} = OH or O-alkyl;

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

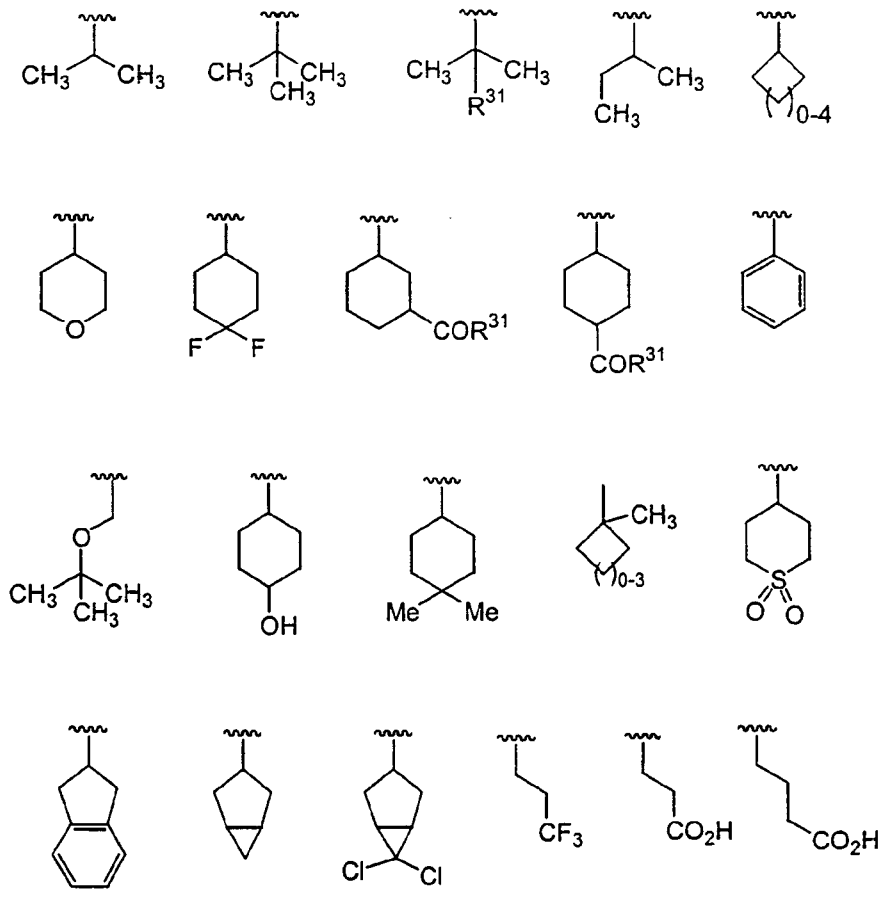
030252



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



9. The compound of claim 8, wherein R^3 is selected from the group consisting of the following moieties:

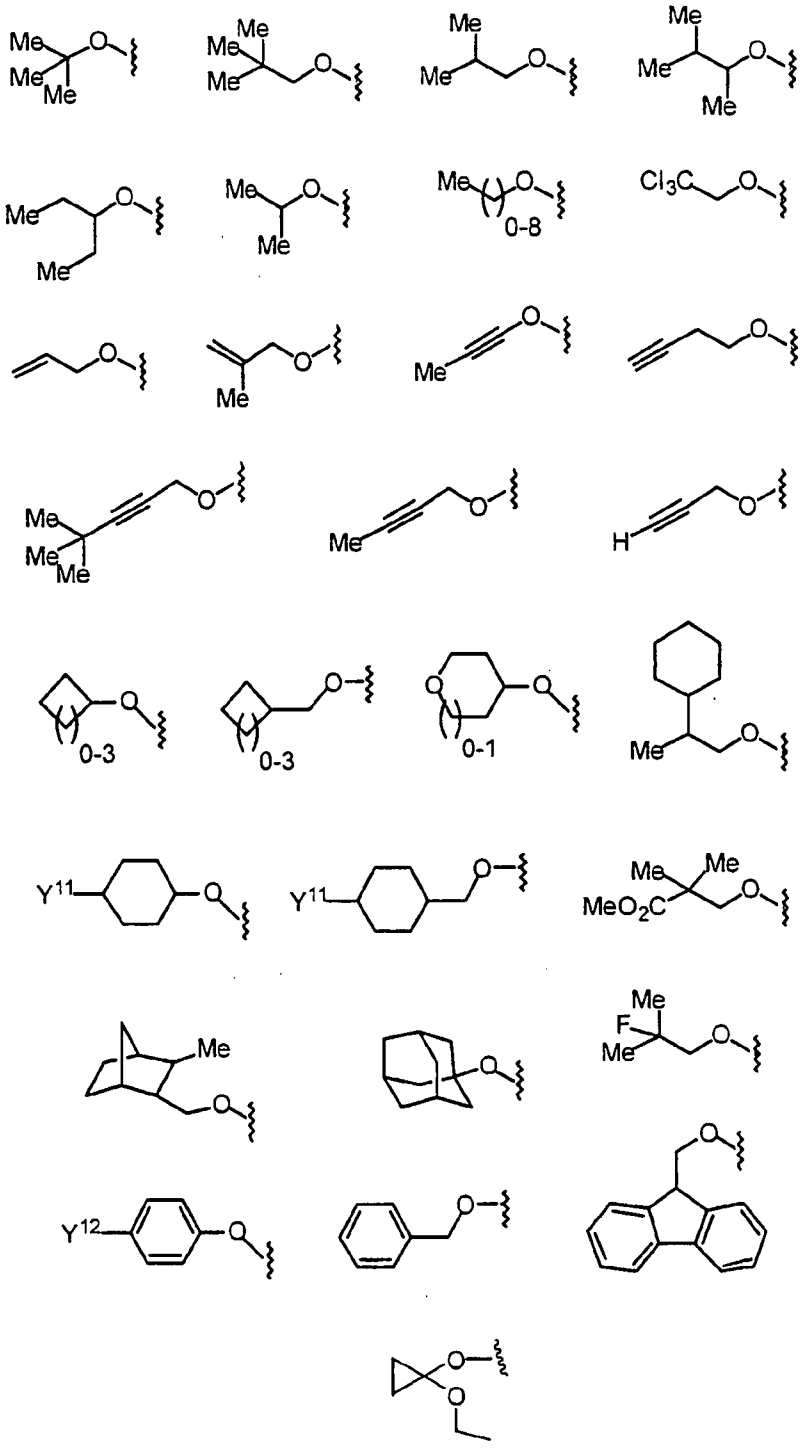


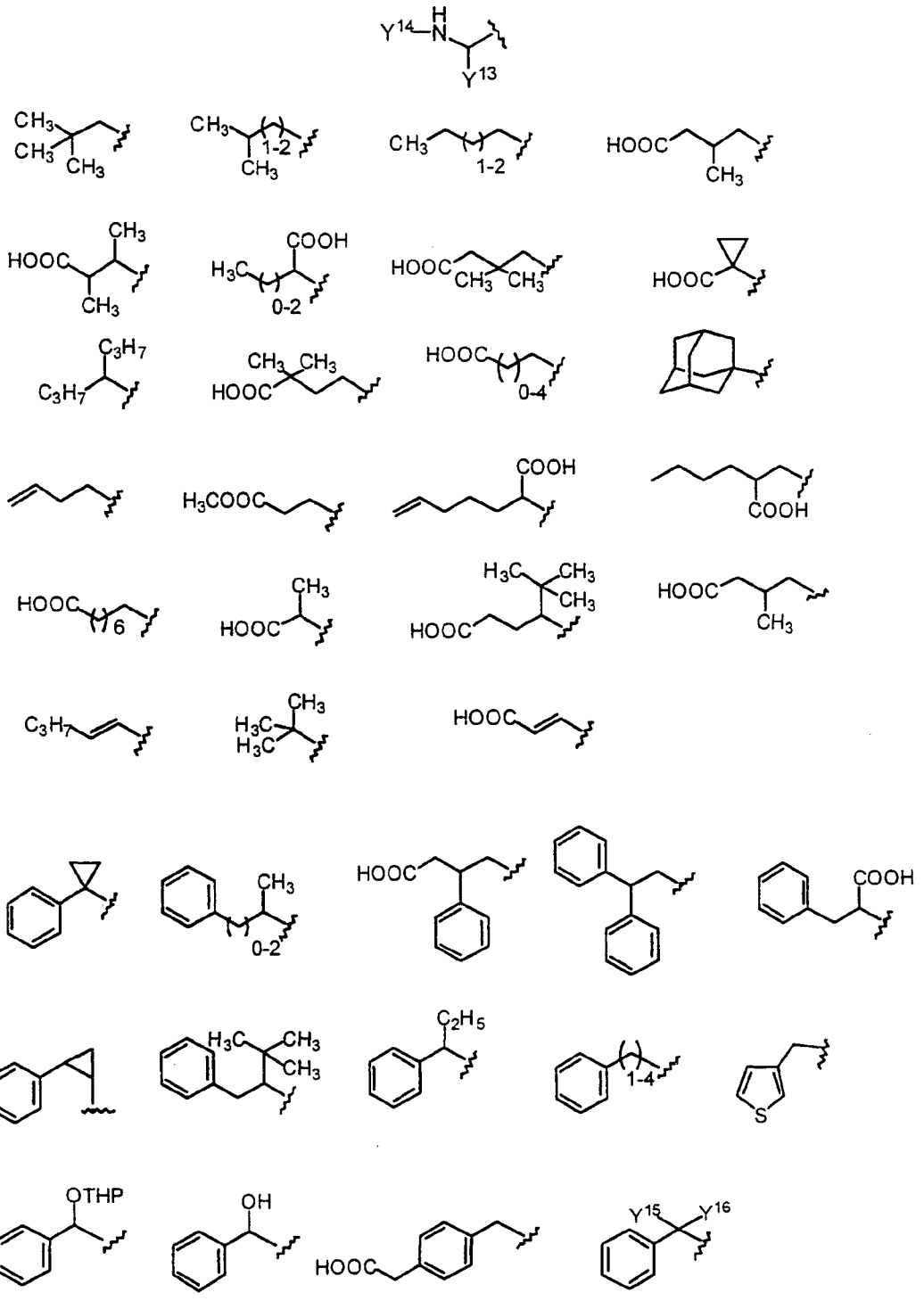
10. The compound of claim 9, wherein Z is N and R^4 is H.

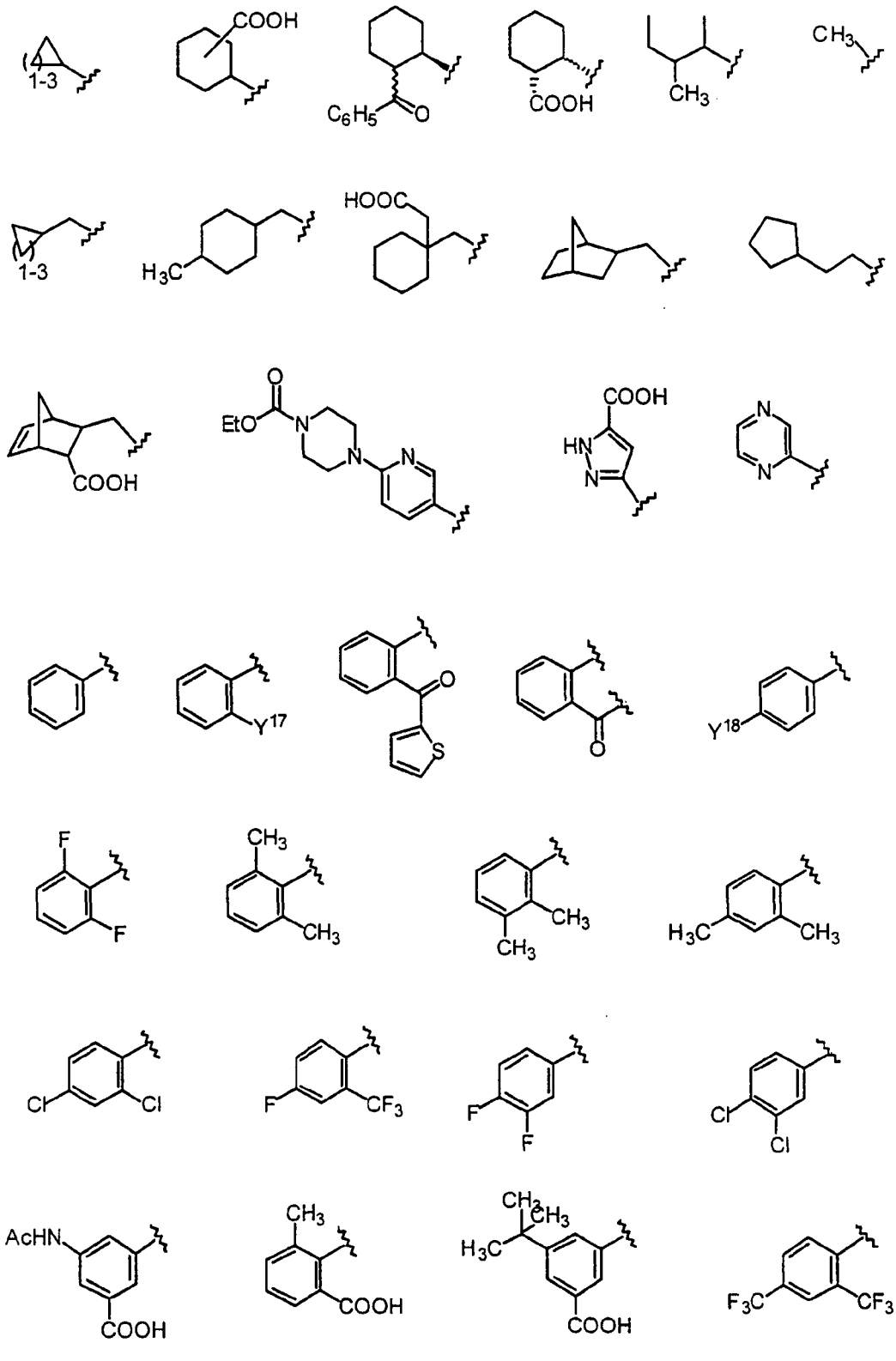
11. The compound of claim 10, wherein W is C=O.

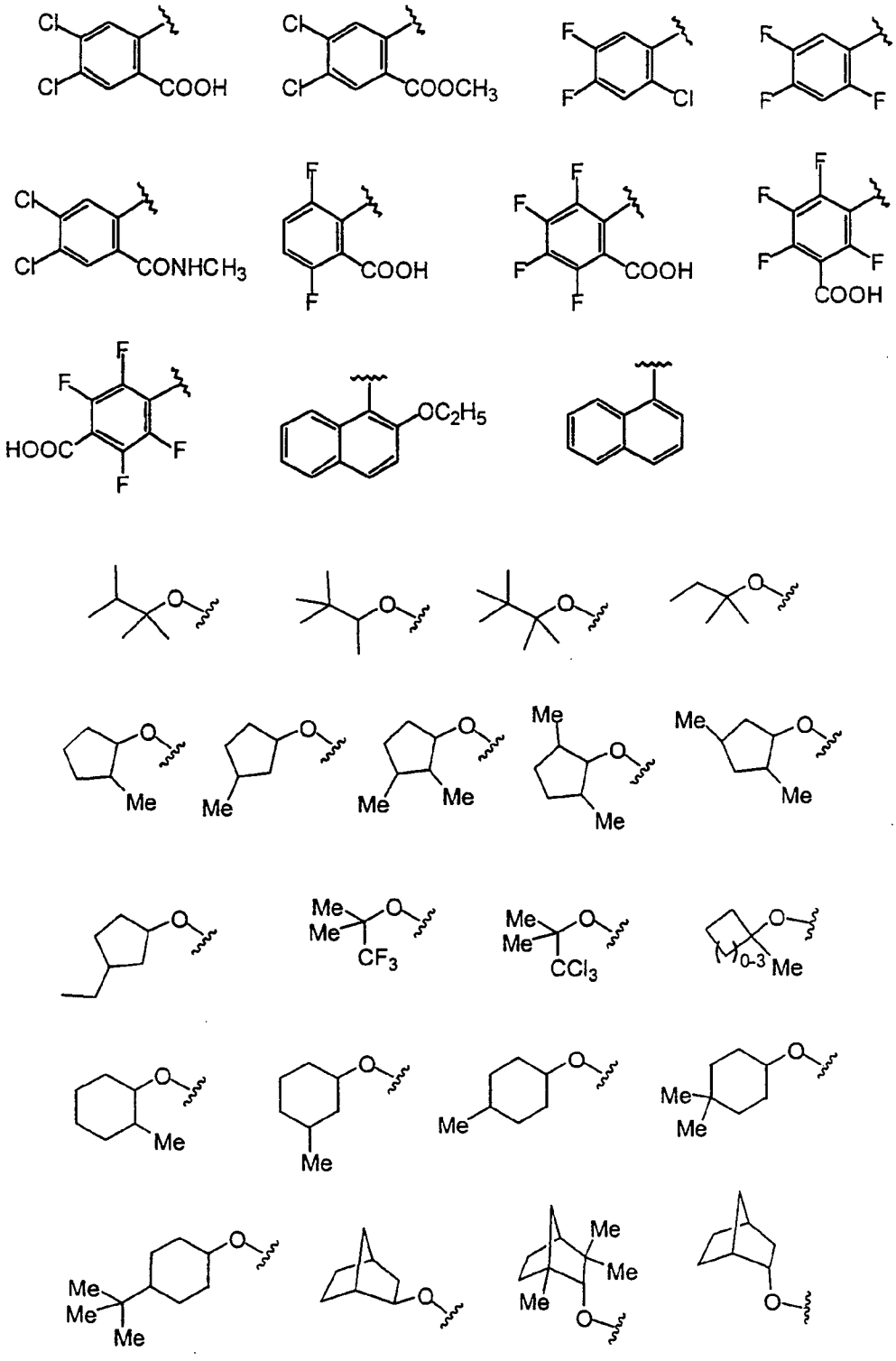
030253

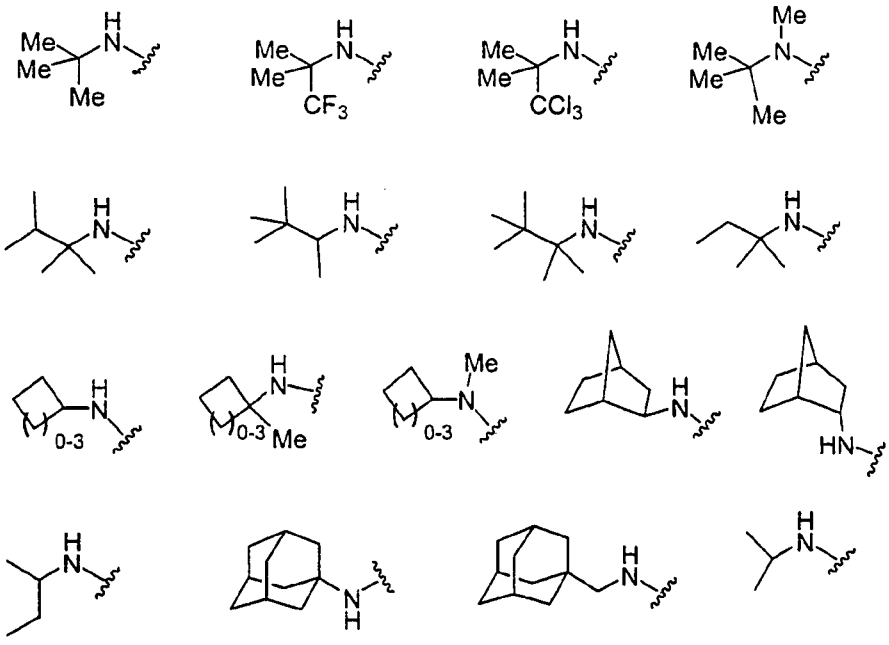
12. The compound of claim 11, wherein Y is selected from the following moieties:




Y14
H
N
Y13
CH3
CH3
CH3
1-2
CH3
CH3
1-2
HOOC
CH3
HOOC
CH3
CH3
CH3
HOOC
H3C
COOH
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
C6H5
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
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
COOH
F
F
F
F
COOH
F
F
HOOC
F
F
OC2H5
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
CF3
Me
Me
CCl3
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Me
Me
Me
Me
Me
O

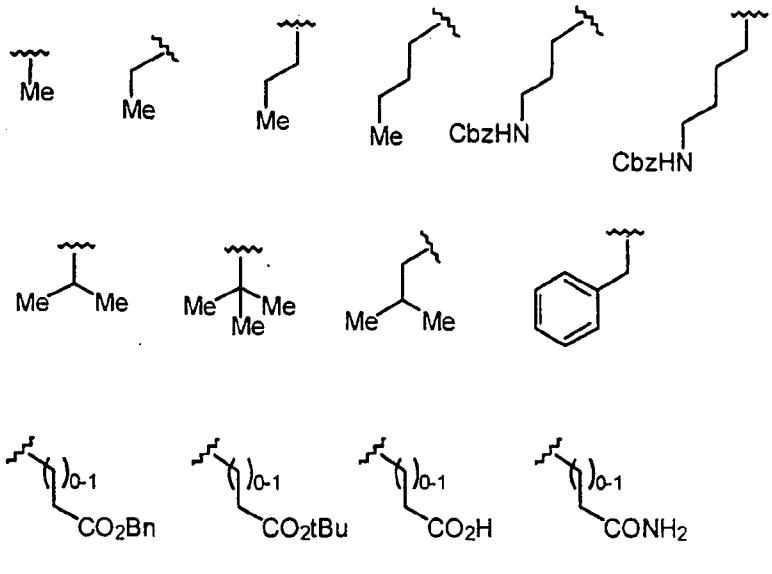


wherein:

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:



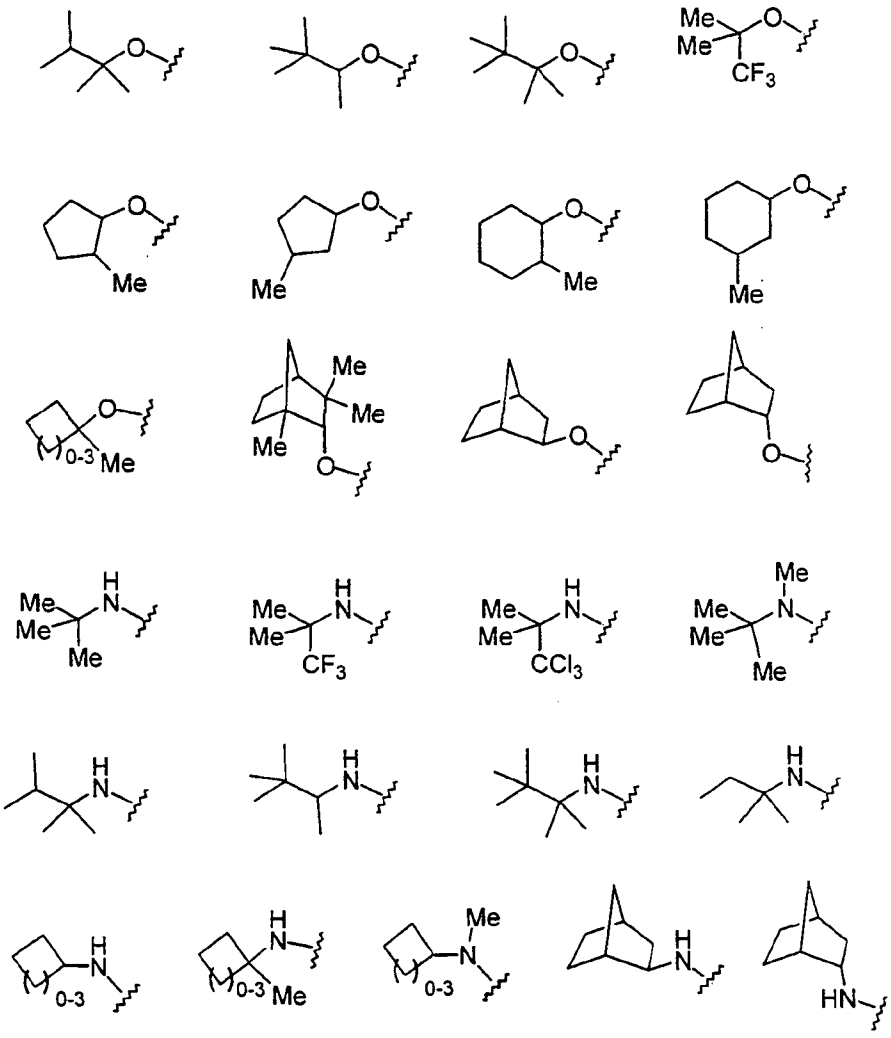
Y^{14} is selected from $MeSO_2$, Ac, Boc, iBoc, Cbz, or Alloc;

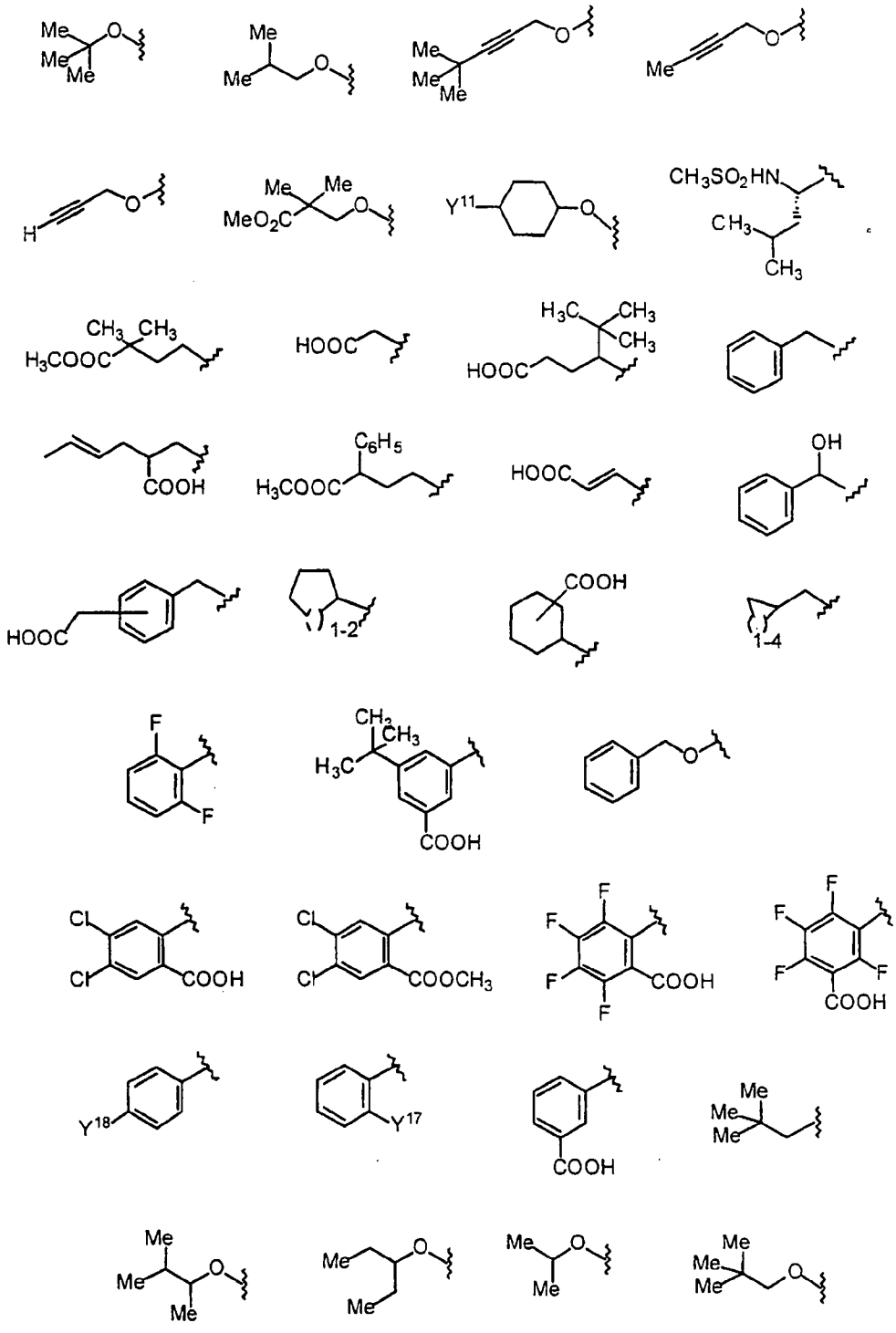
Y^{15} and Y^{16} are independently selected from alkyl, aryl, heteroalkyl, and heteroaryl;

Y^{17} is CF_3, NO_2, $CONH_2$, OH, $COOCH_3$, OCH_3, OC_6H_5, C_6H_5, COC_6H_5, NH_2, or COOH; and

Y^{18} is $COOCH_3$, NO_2, $N(CH_3)_2$, F, OCH_3, CH_2COOH, COOH, SO_2NH_2, or $NHCOCH_3$.

13. The compound of claim 12, wherein Y is selected from the group consisting of:



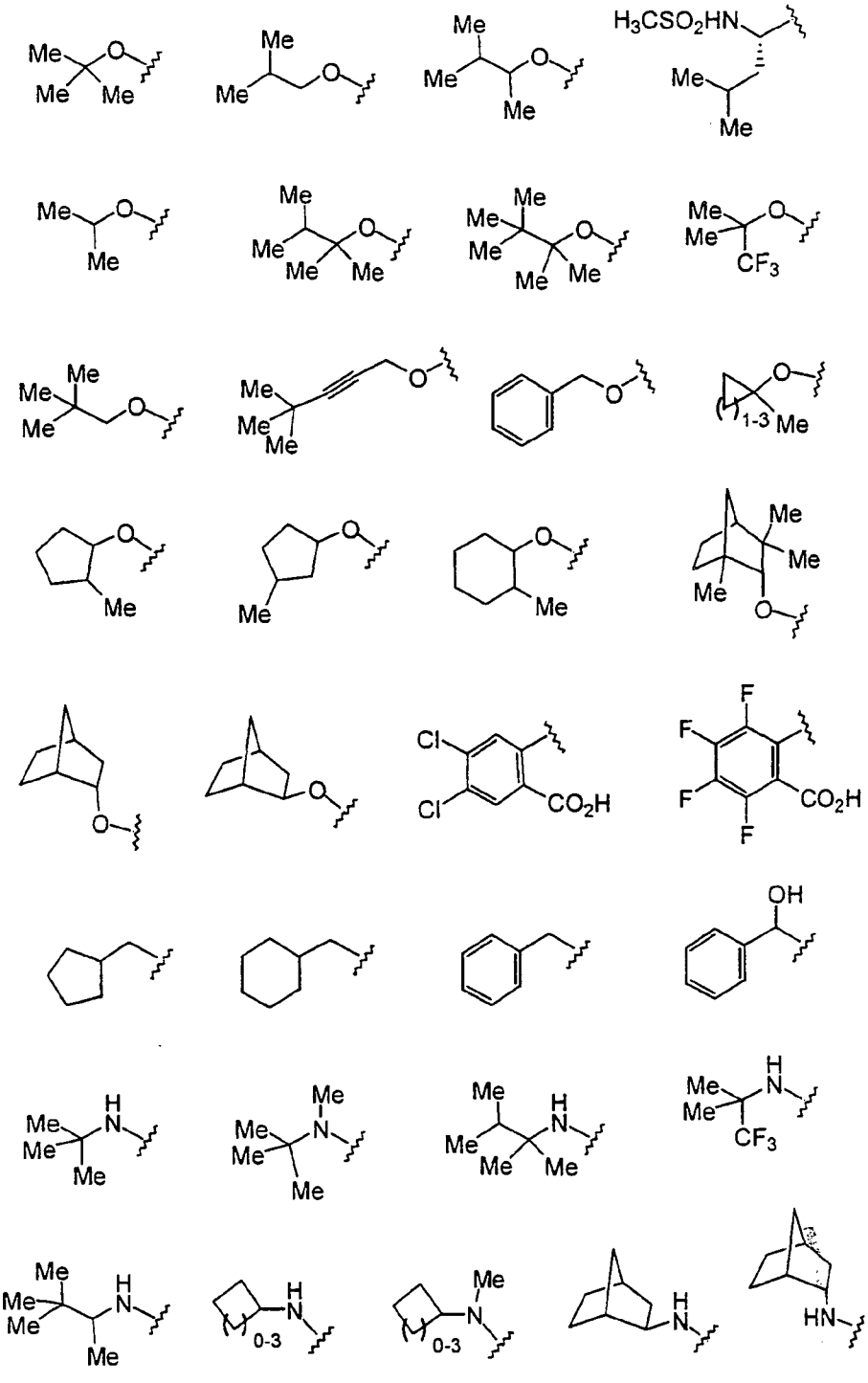


wherein:

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

Y^{18}= F, COOH,

14. The compound of claim 13, wherein Y is selected from the group consisting of:

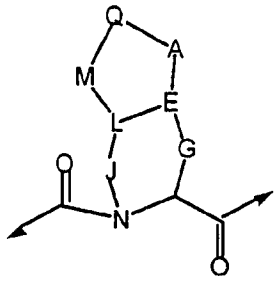


15. The compound of claim 14, wherein L and M are absent, and J is directly linked to E.

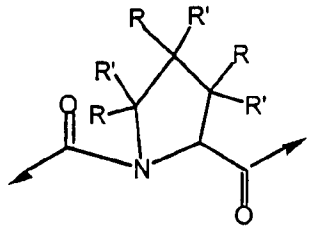
16. The compound of claim 14, wherein L, J and M are absent and E is directly linked to N.

17. The compound of claim 14, wherein G and M are absent.

18. The compound of claim 14, wherein the moiety:

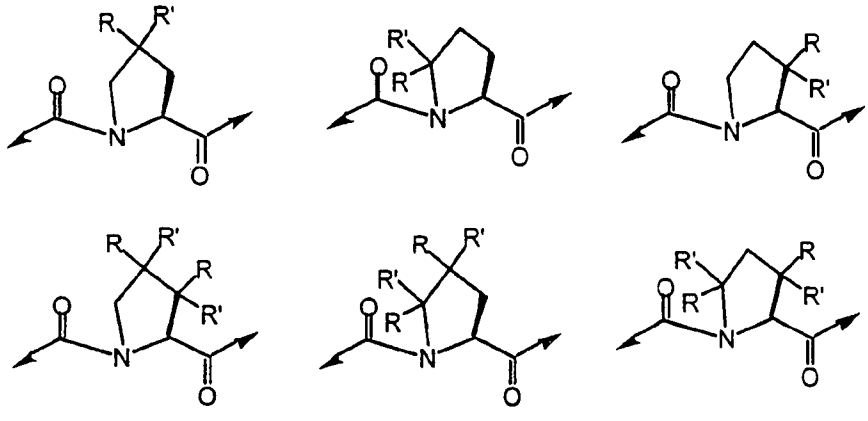


is

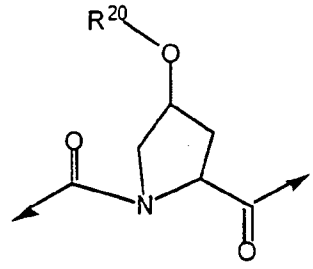


a

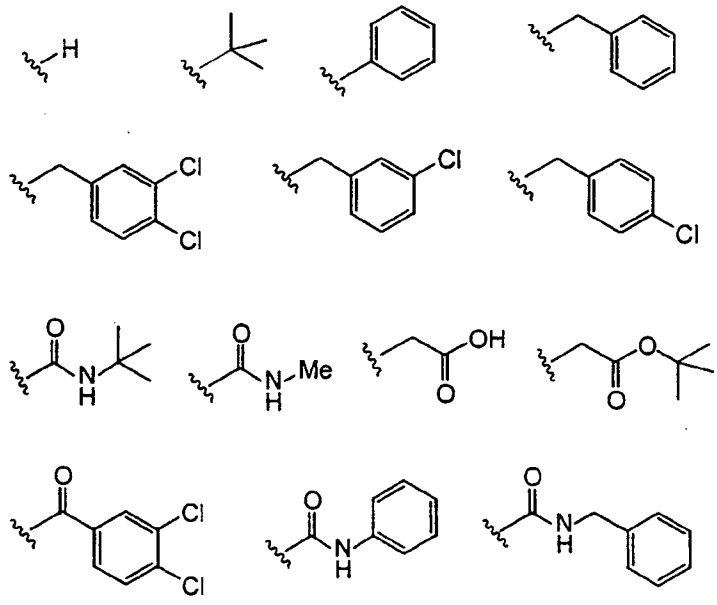
19. The compound of claim 18, wherein structure a is selected from the following structures:



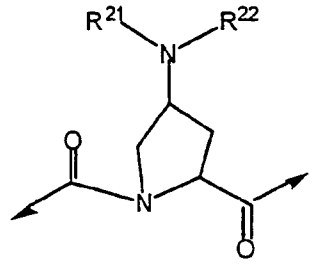
20. The compound of claim 18, wherein structure a is:



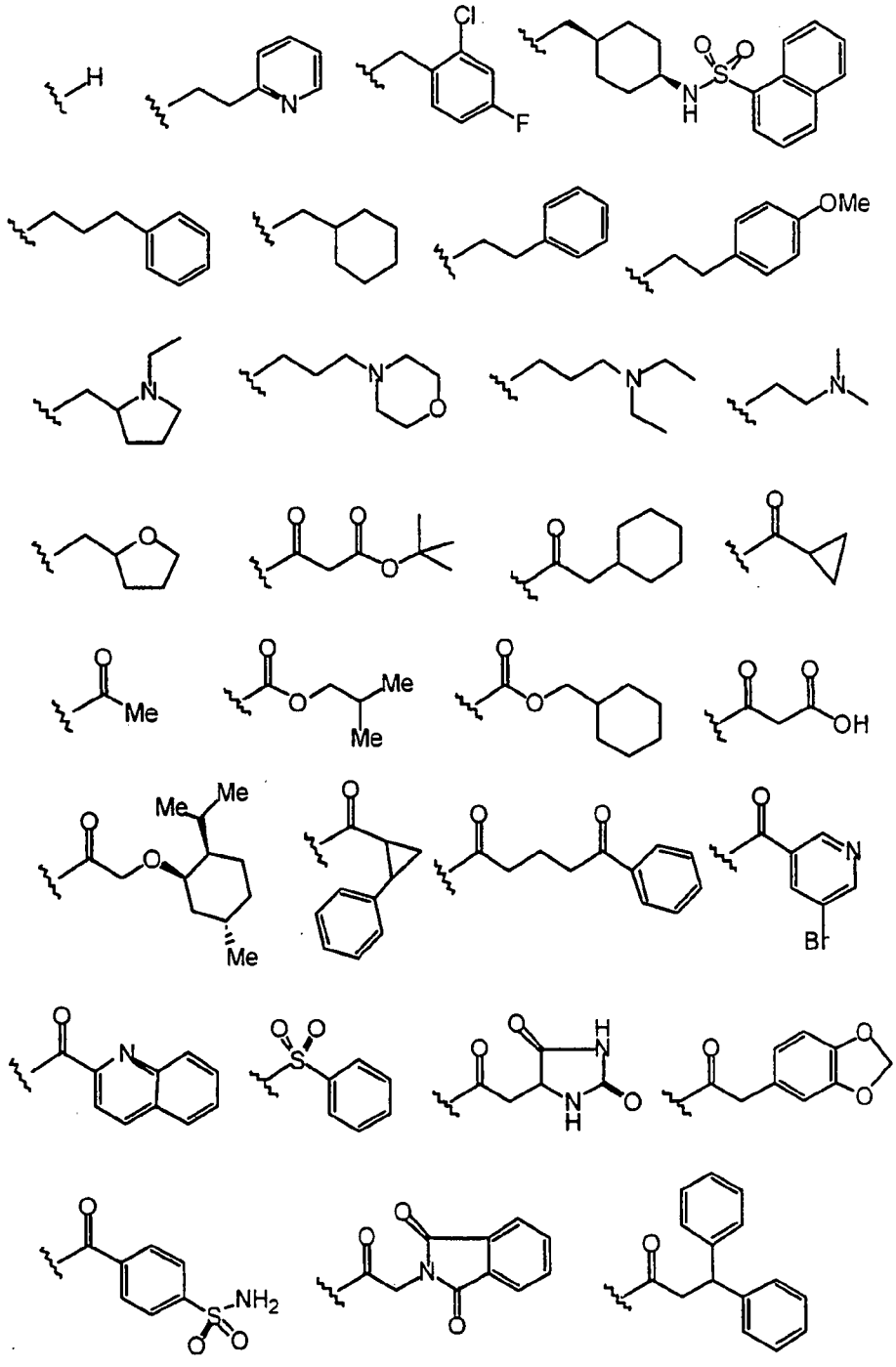
wherein R^{20} is selected from the following structures:



21. The compound of claim 18, wherein structure a is:

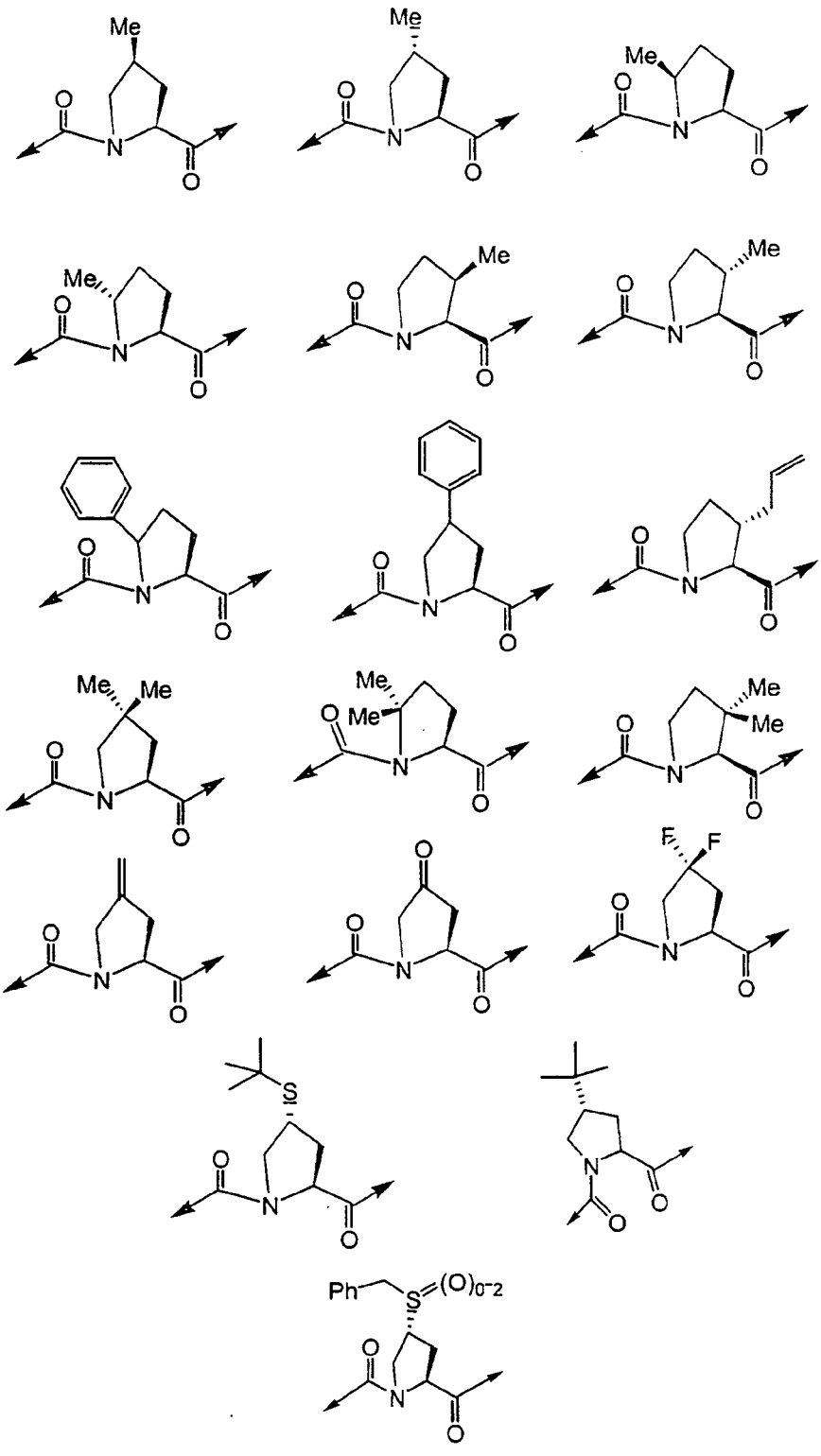


wherein R^{21} and R^{22} may be the same or different and are independently selected from the following structures:

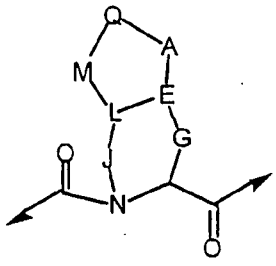


22. The compound of claim 18, wherein structure a is selected from the following structures:

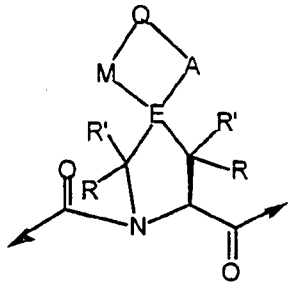
5


Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
F
F
S
Ph
S
(O)0-2

23. The compound of claim 14, wherein:



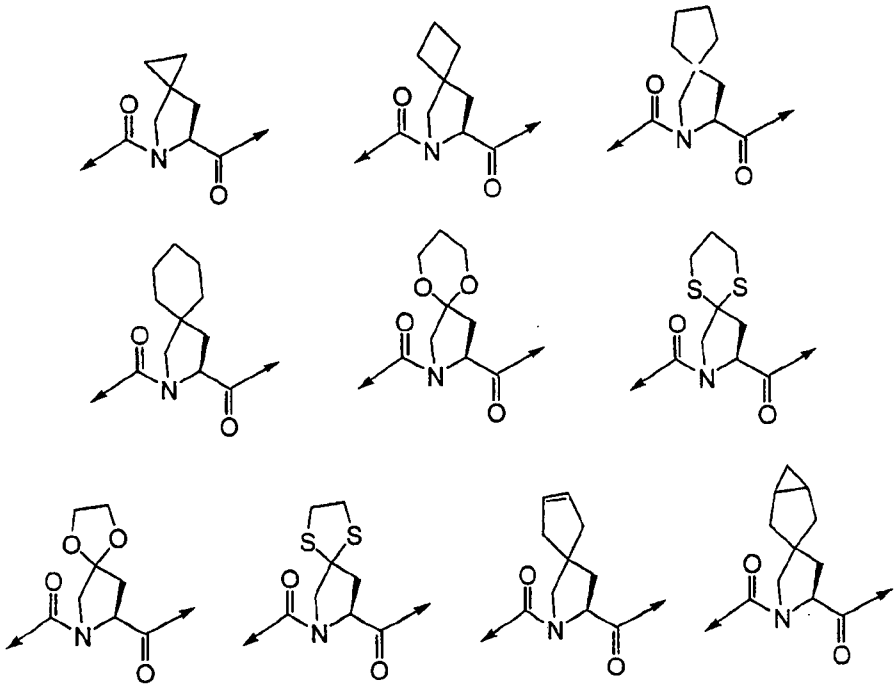
is



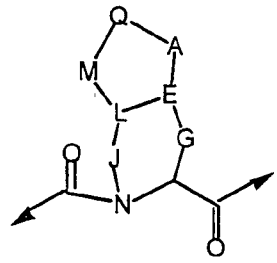
b

wherein Q may be present or absent, and if Q is absent, M is directly linked to A.

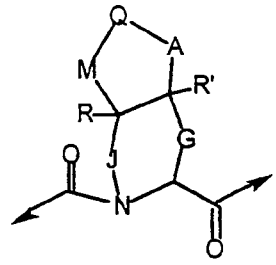
24. The compound of claim 23, wherein structure b is selected from the following structures:



25. The compound of claim 14, wherein:



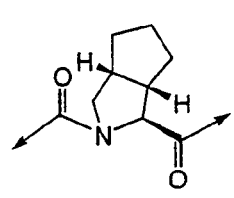
is

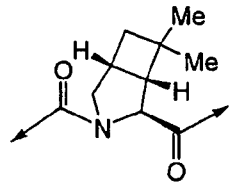


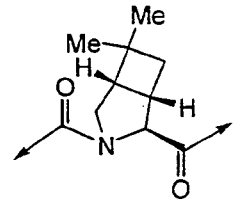
c

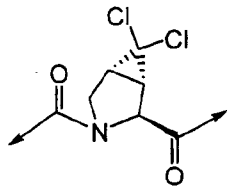
wherein G and J are independently selected from the group consisting of $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; A and M are independently selected from the group consisting of O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$, and $(CRR')_p$; and Q is CH_2, CHR, CRR', NH, NR, O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, and $(CRR')_p$.

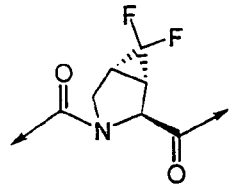
26. The compound of claim 25, wherein structure c is selected from the following structures:

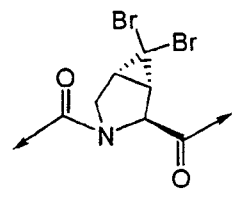




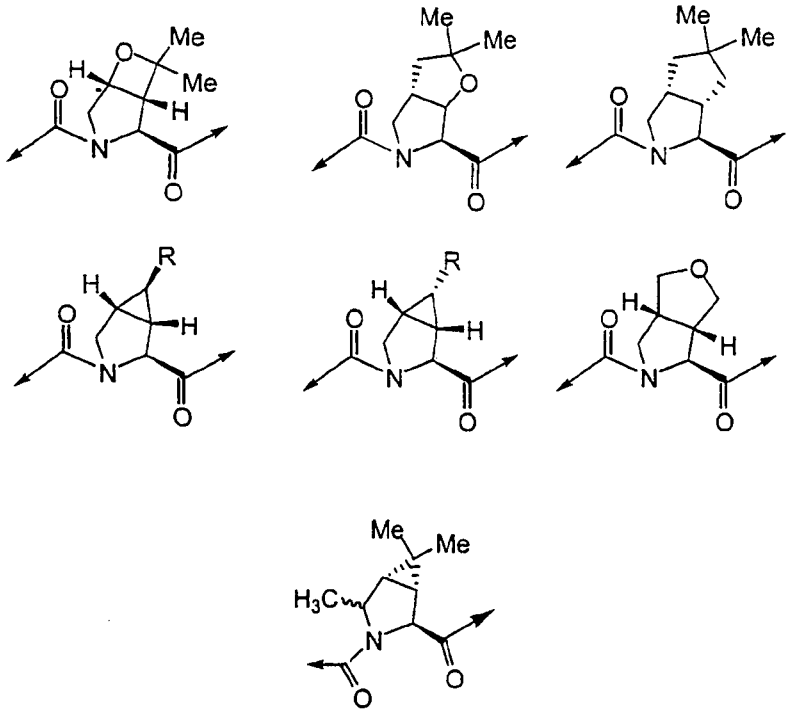


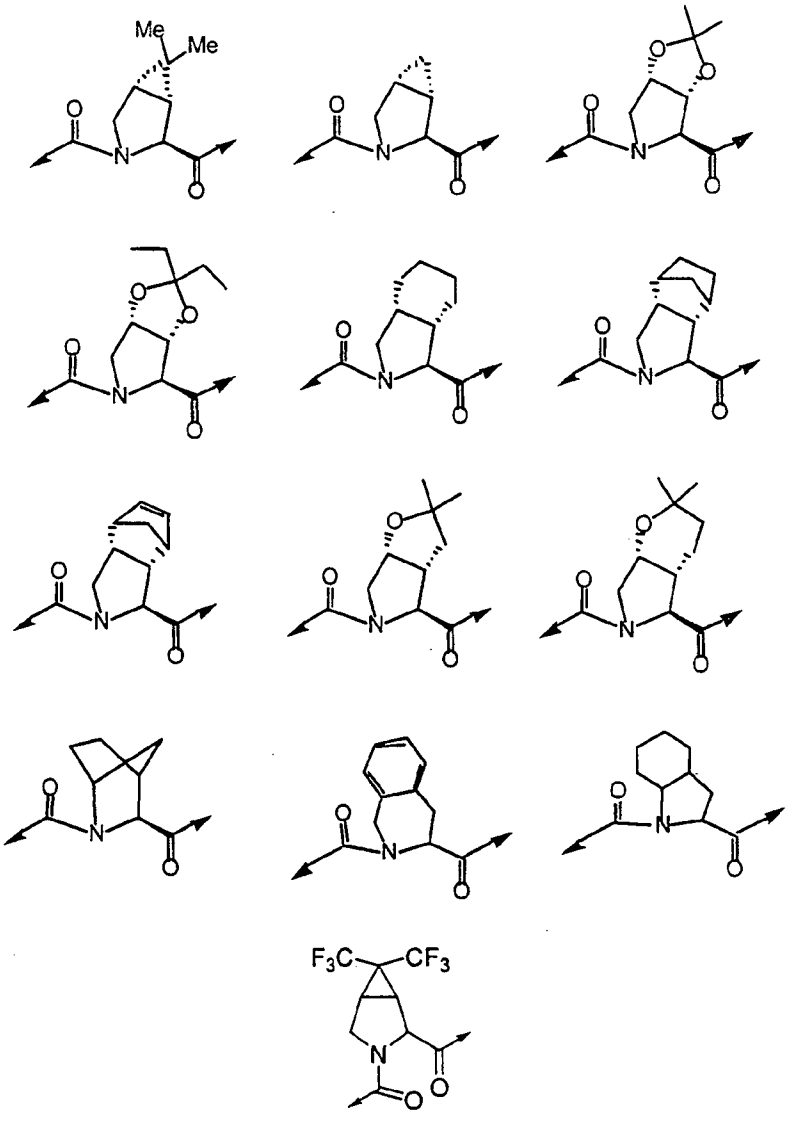




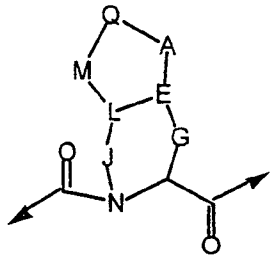


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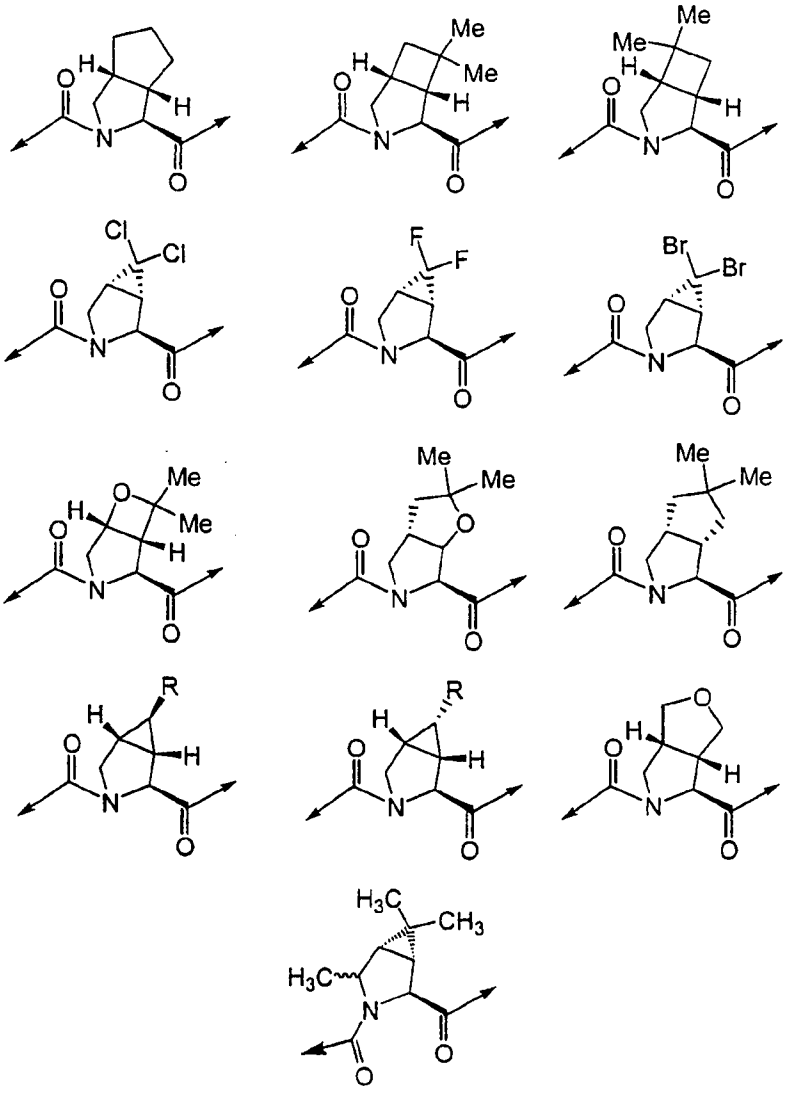

Me
Me
O
H
Me
H
N
O
Me
Me
O
N
O
Me
Me
O
N
O
R
H
O
H
N
O
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N
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O
H
N
O
Me
Me
H3C
N
O
O

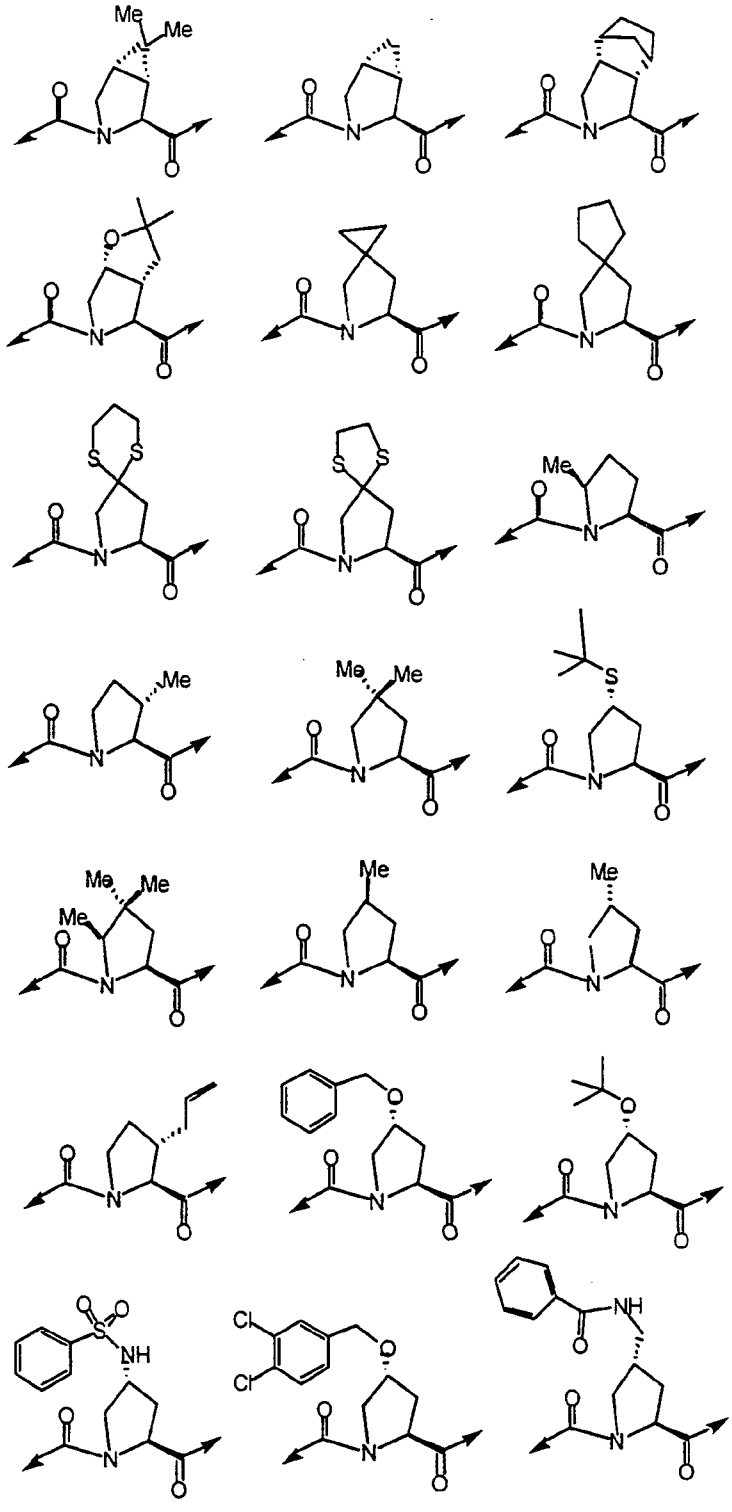


27. The compound of claim 14, wherein:

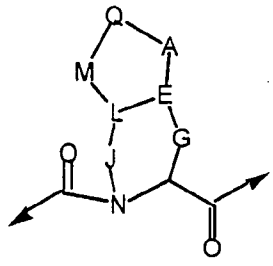


is selected from the following structures:

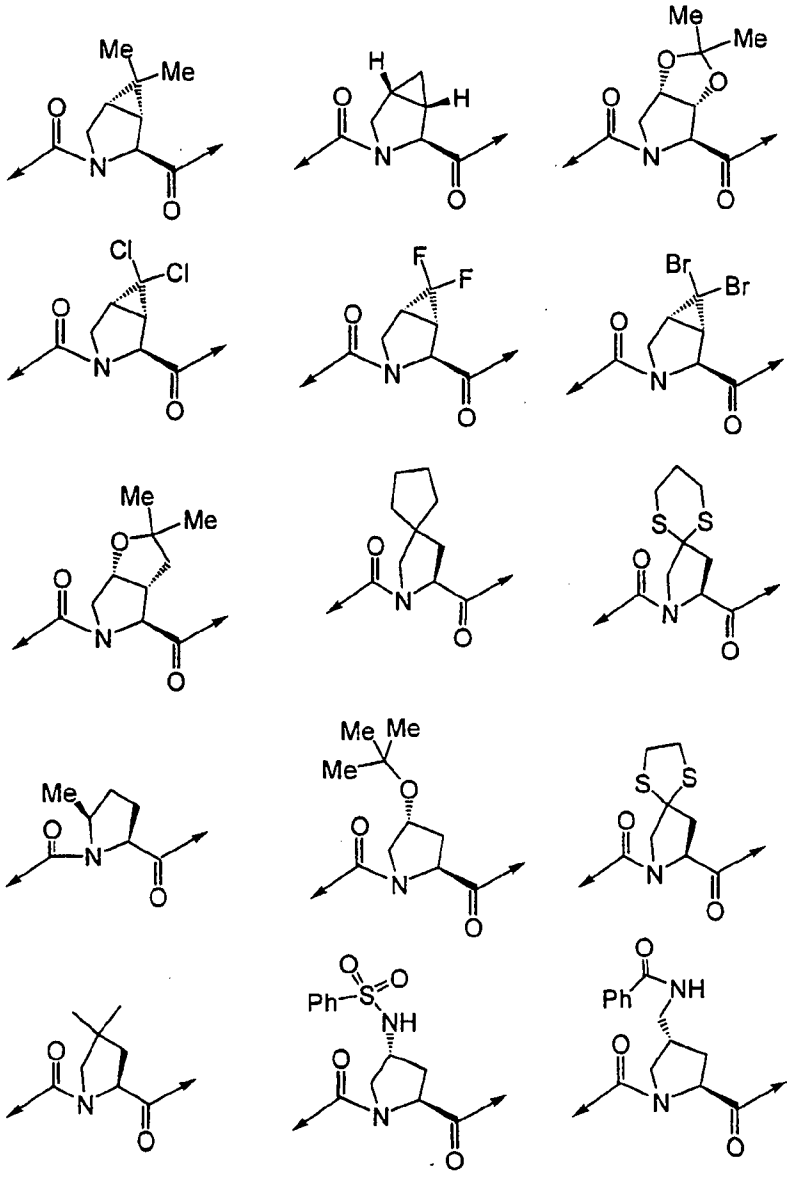




28. The compound of claim 27, wherein:



is selected from the following structures:



29. A pharmaceutical composition comprising as an active ingredient a 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 an 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 a compound of claim 1.

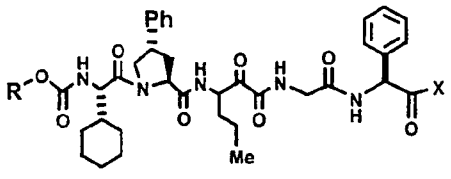
36. The method of claim 35, wherein said administration is oral or subcutaneous.

37. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV.

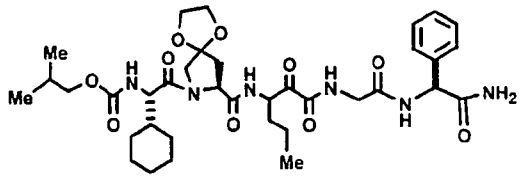
38. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV, said method comprising bringing into intimate contact a compound of claim 1 and a pharmaceutically acceptable carrier.

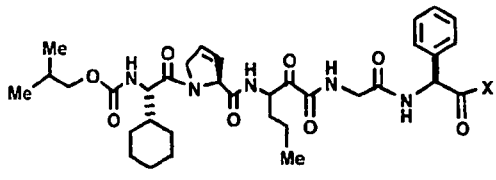
39. A compound exhibiting HCV protease inhibitory activity, including enantiomers, stereoisomers, rotamers, tautomers, racemates and prodrug of said compound, and pharmaceutically acceptable salts or solvates of said compound, or of said prodrug, said compound being selected from the compounds of structures listed below:

030233

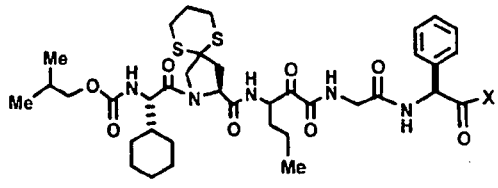


(R = t-butyl, X = NH_2)
(R = Isobutyl, X = NH_2)
(R = t-butyl, X = OH)
(R = Trichloroethyl, X = OH)

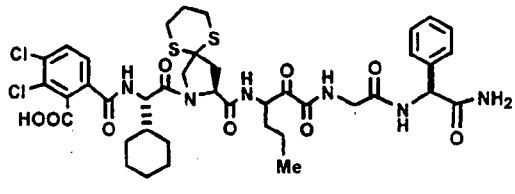


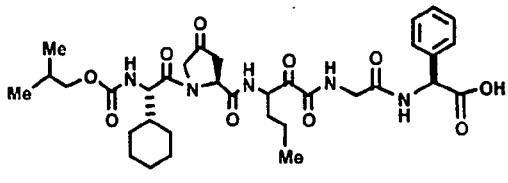


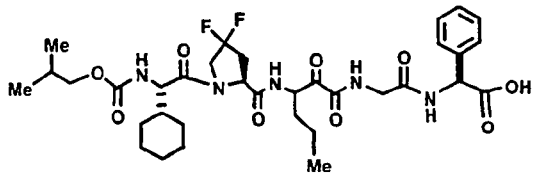
(X = O^{t}Bu)
(X = OH)

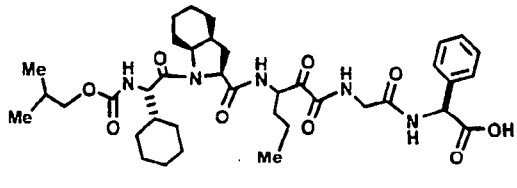


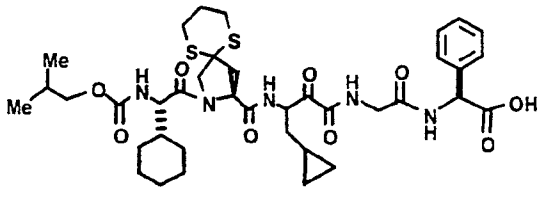
(X = OH)
(X = O^{t}Bu)
(X = NH_2)
(X = NHMe)
(X = NMe_2)

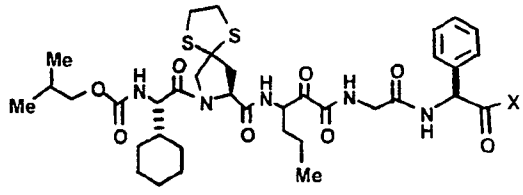




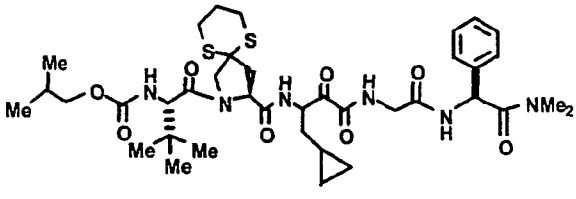


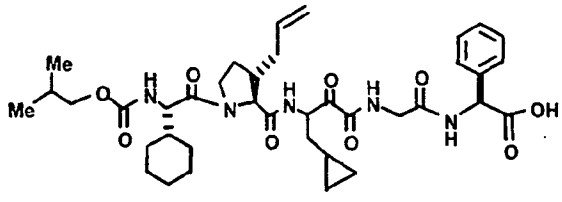


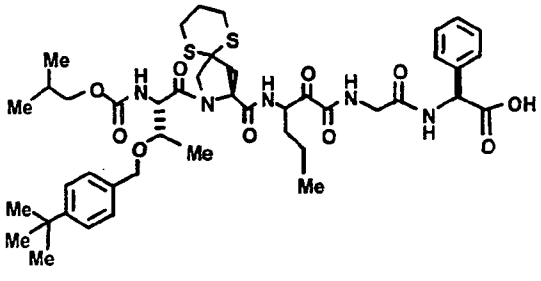


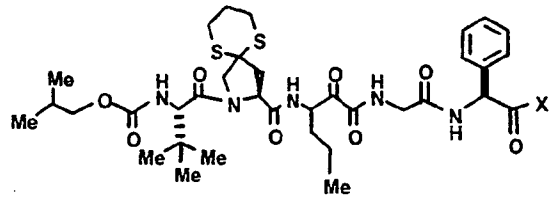


(X = NH_2)
(X = NMe_2)
(X = NHMe)
(X = OH)

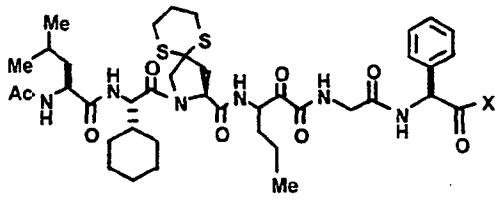




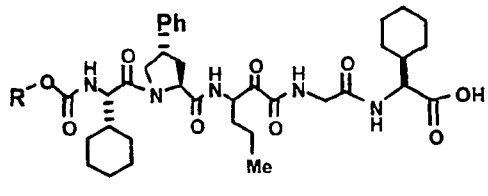




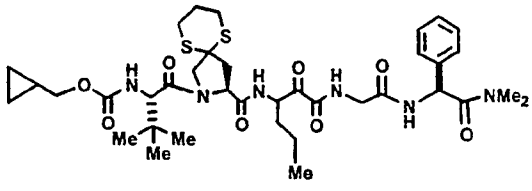
(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)

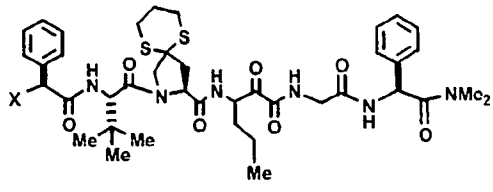


(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)
(X = NMeOMe)

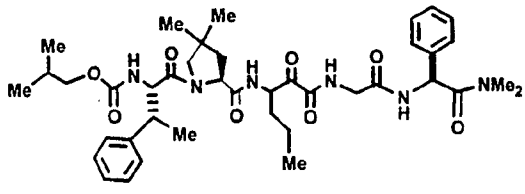


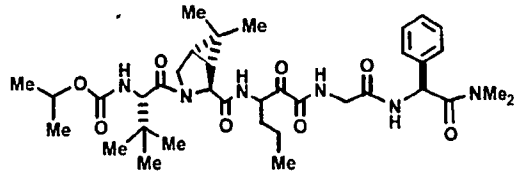
(R = t-butyl)
(R = Isobutyl)

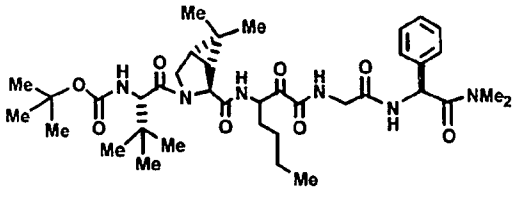


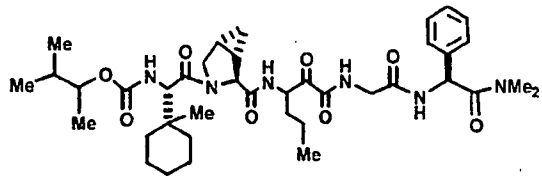


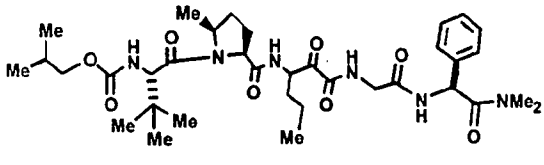
(X = Me, Y = CH_2Me)
(X = OAc, Y = Me)

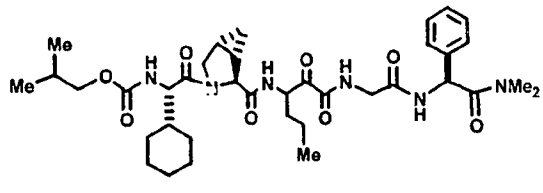


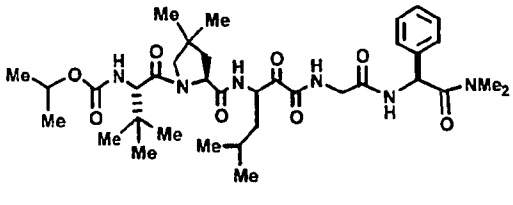


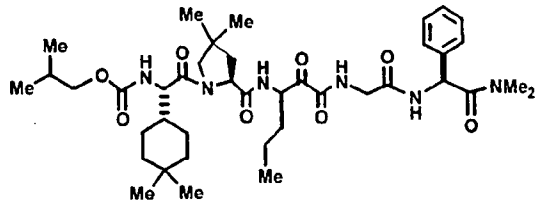


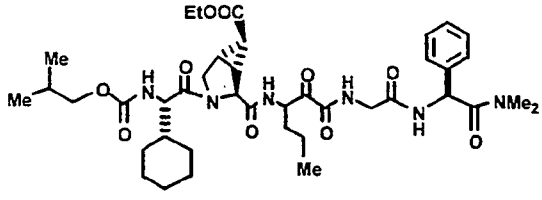


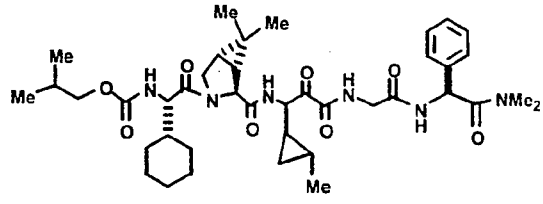


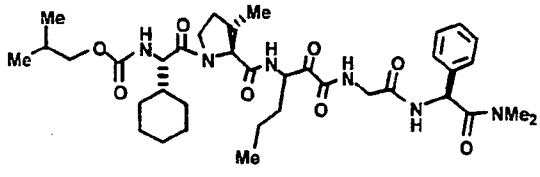


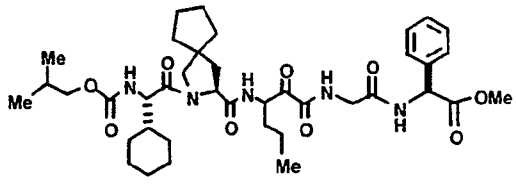


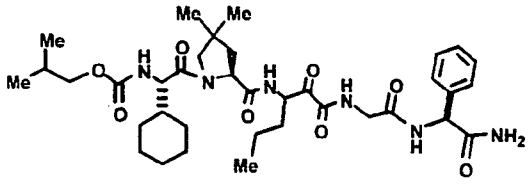


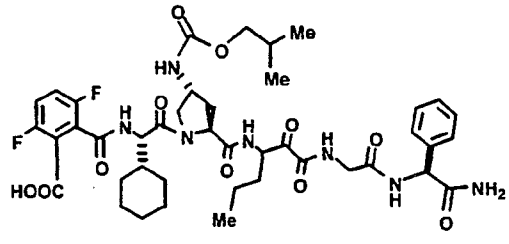


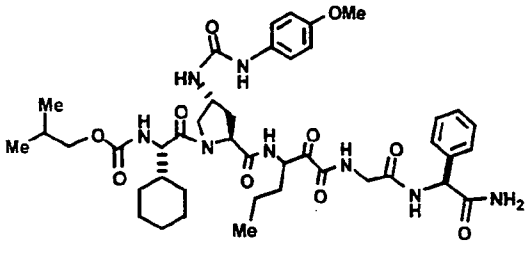


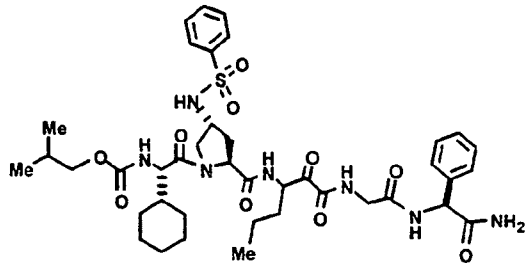


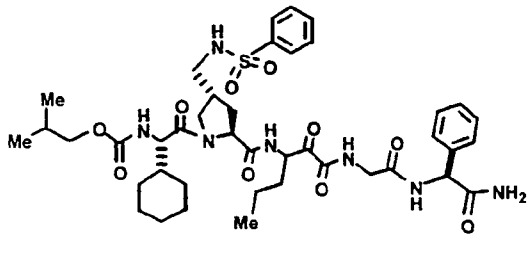


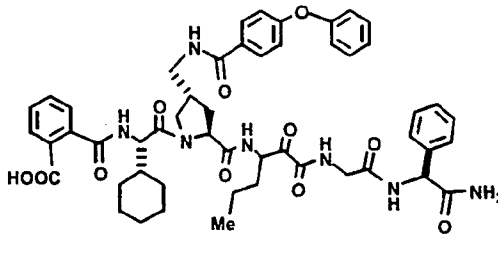


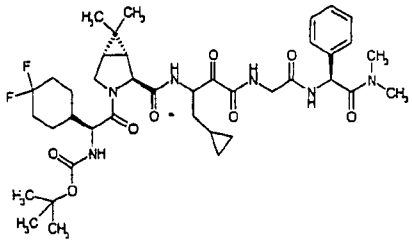


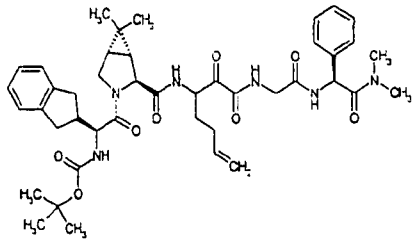


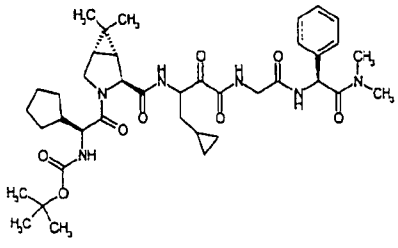


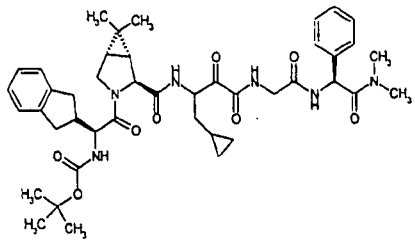


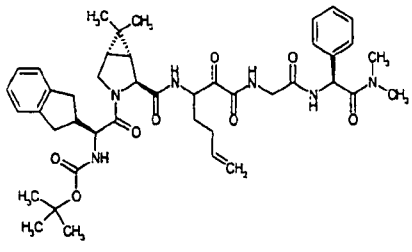


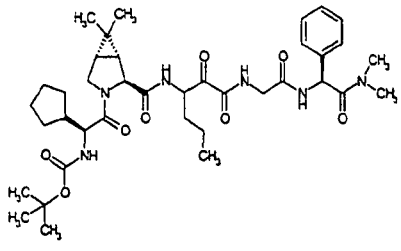


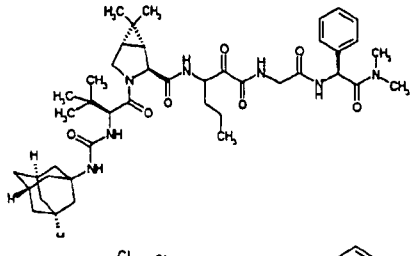


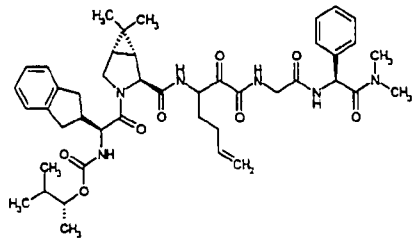


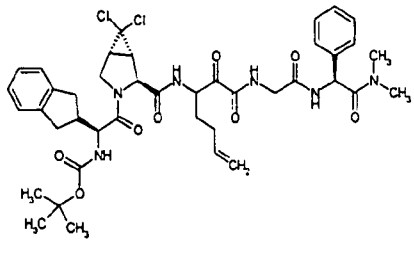


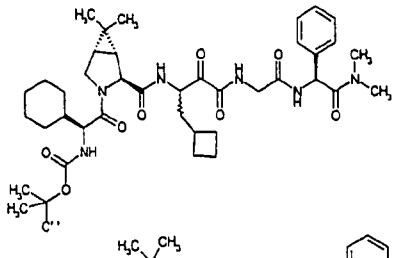


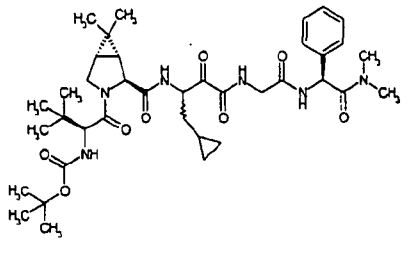


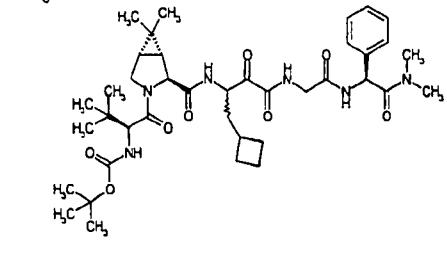


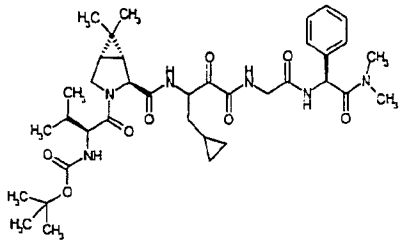


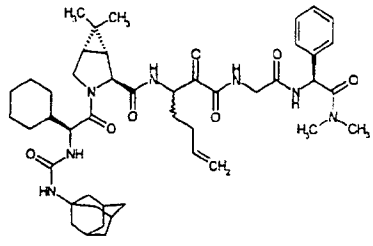


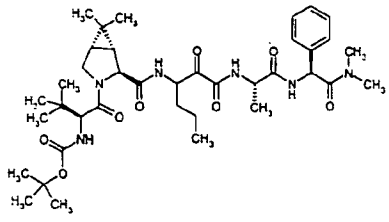


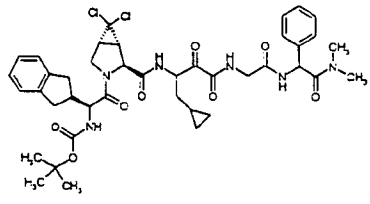


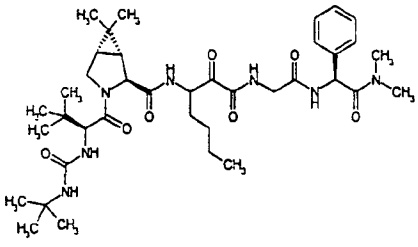


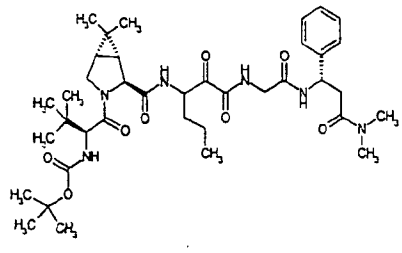


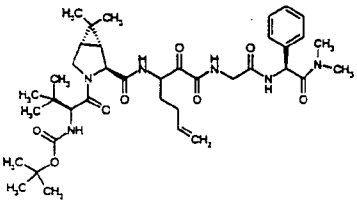


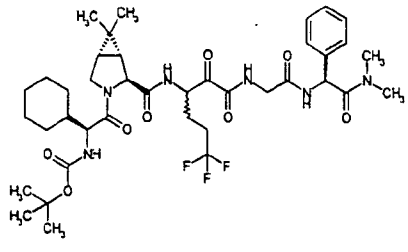


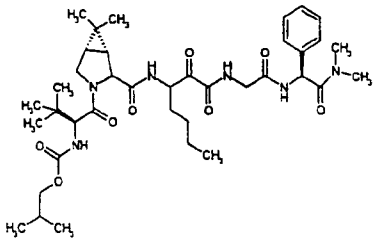


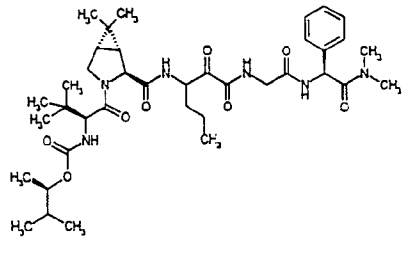


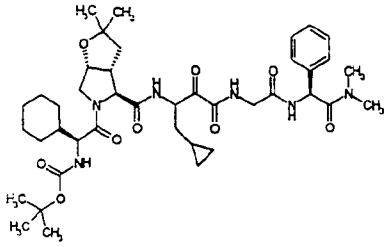


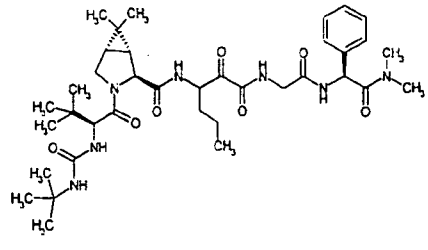


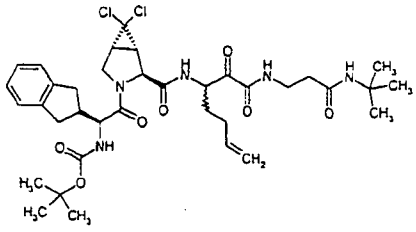


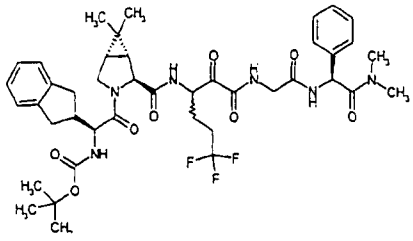


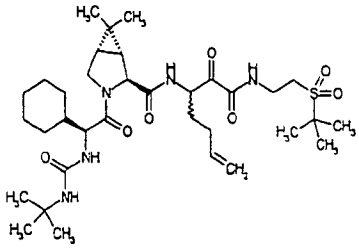


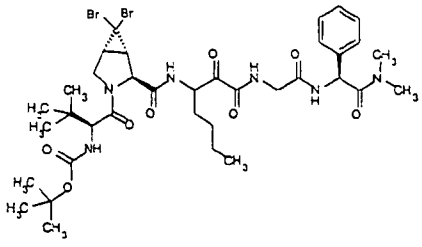


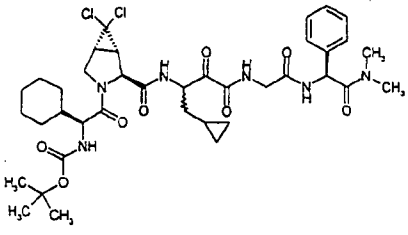


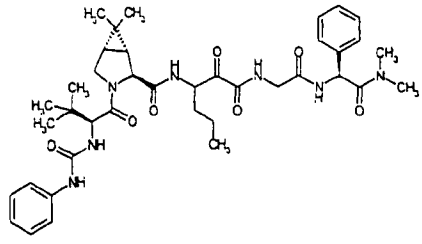


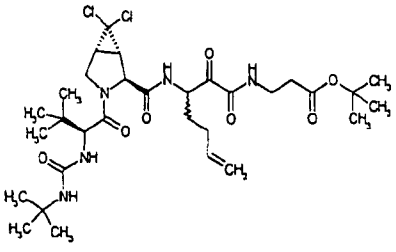


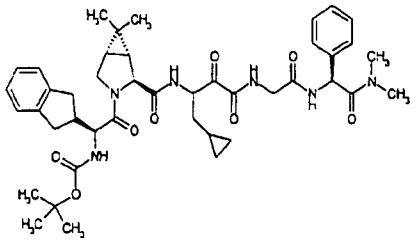


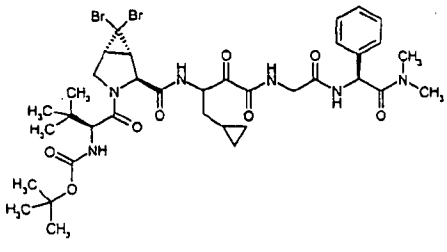


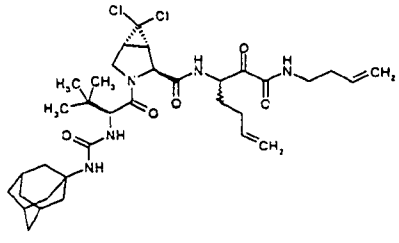


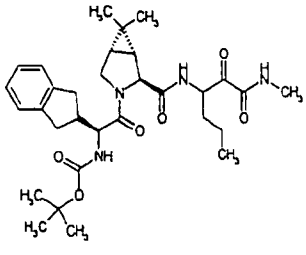


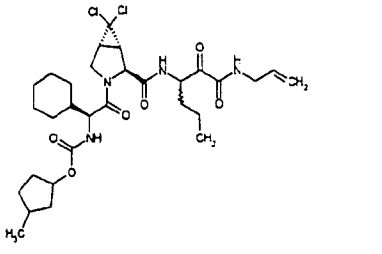


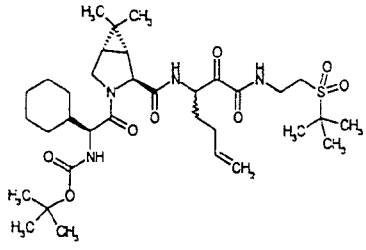


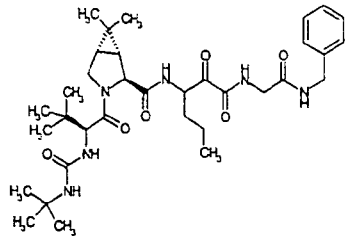


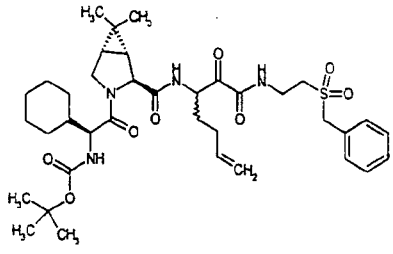


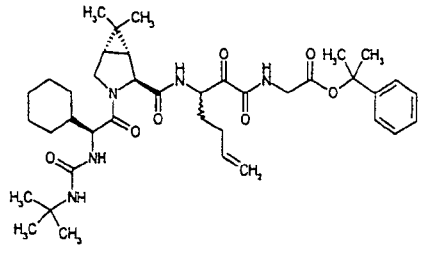


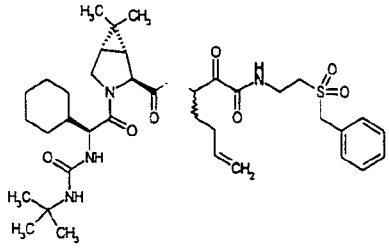


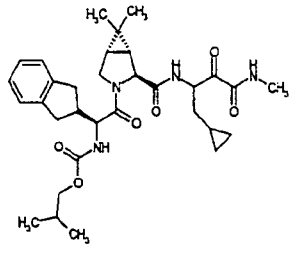


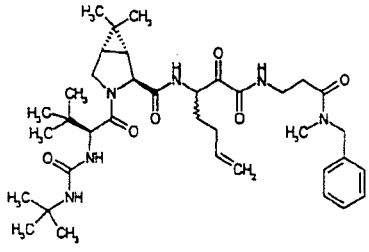


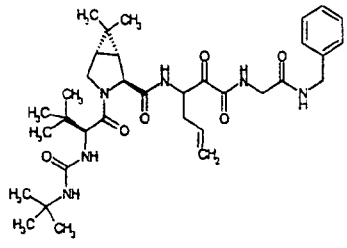


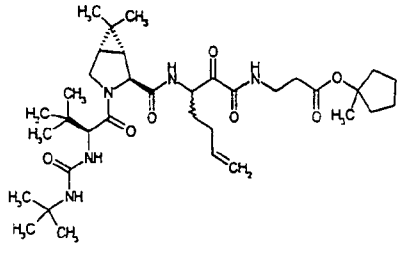


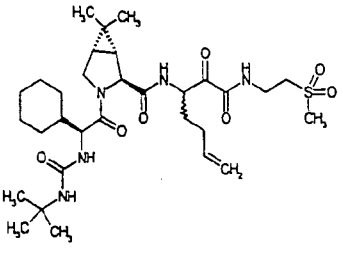


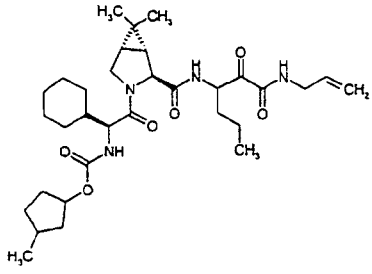


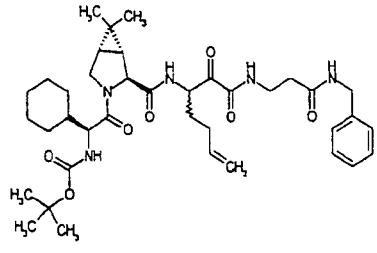


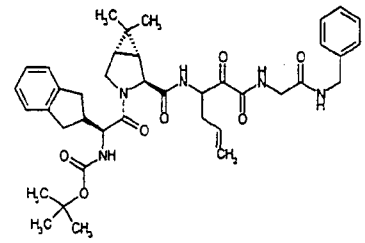
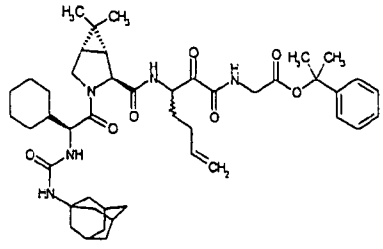
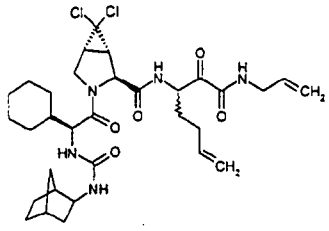
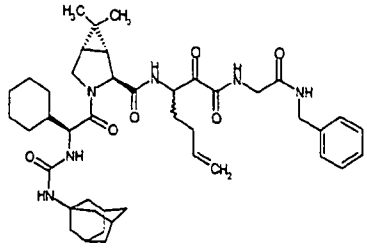
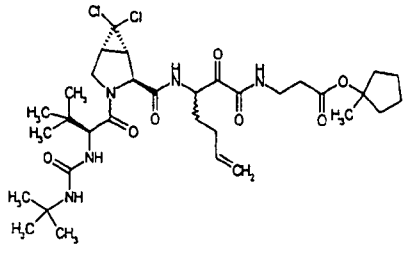
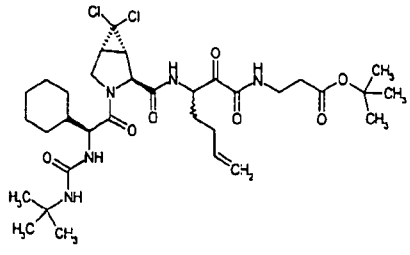
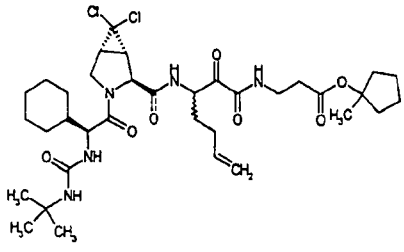
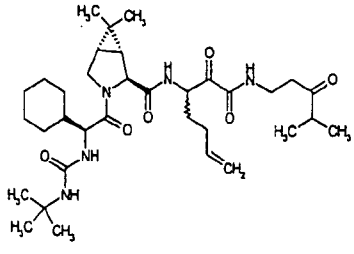
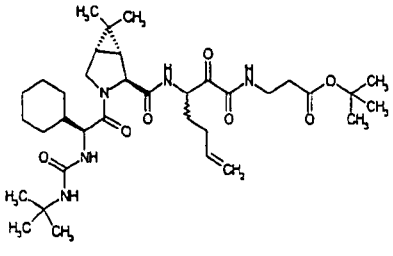
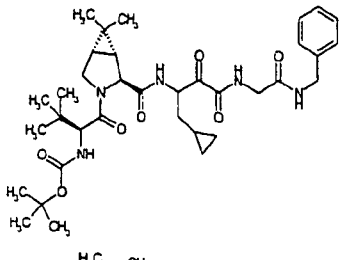
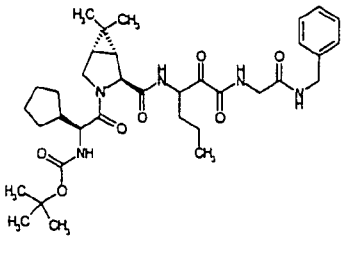
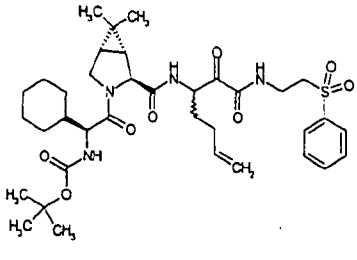


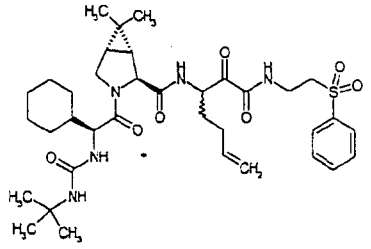


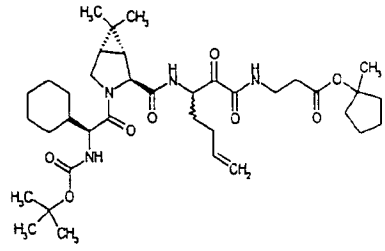


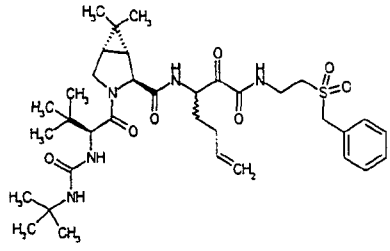


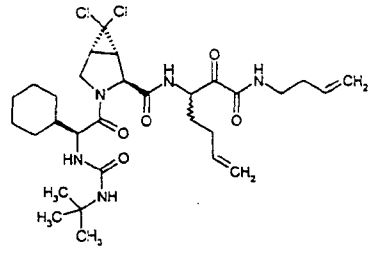


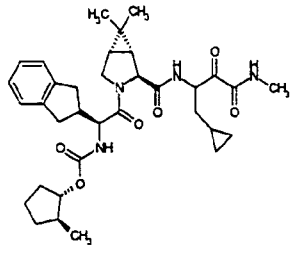













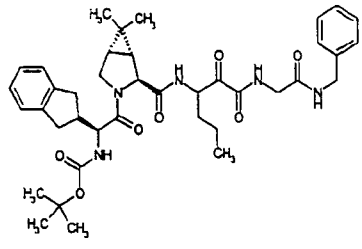


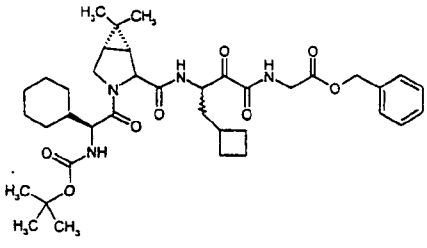


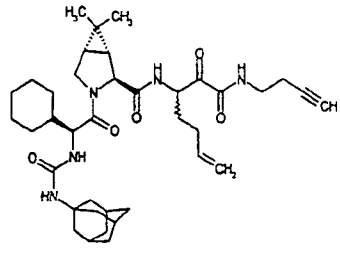


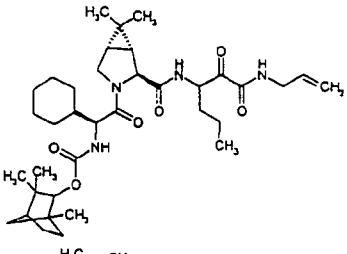


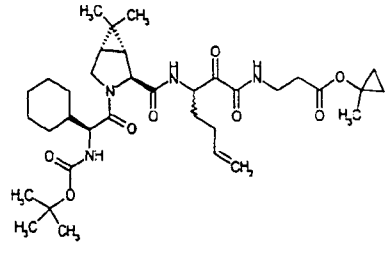


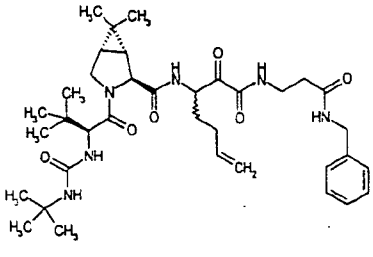


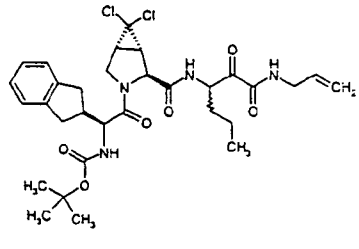


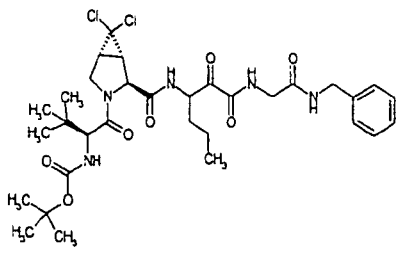


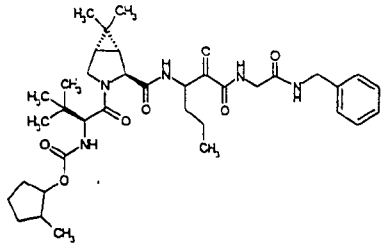


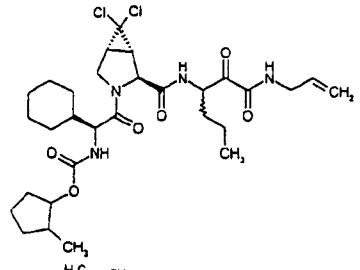


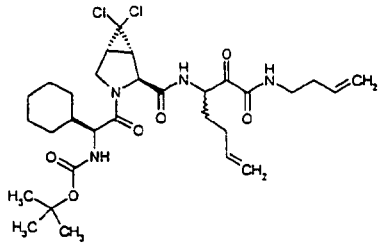


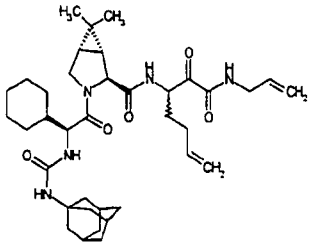


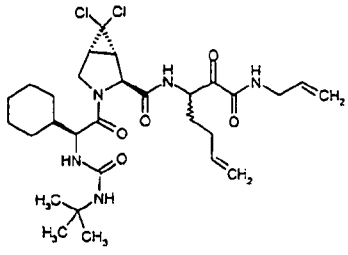


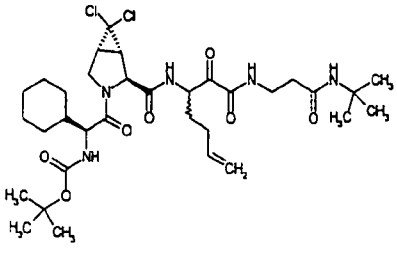


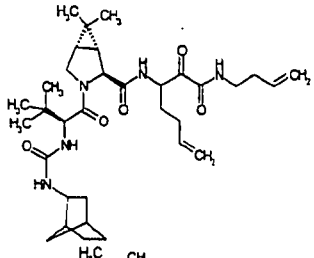


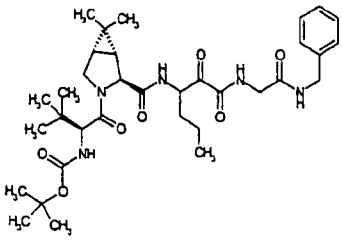


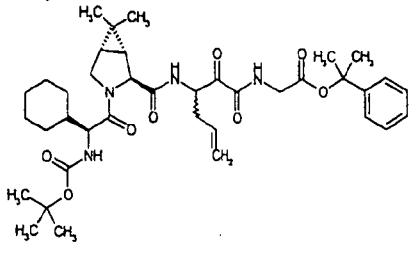


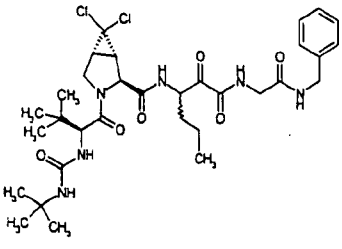


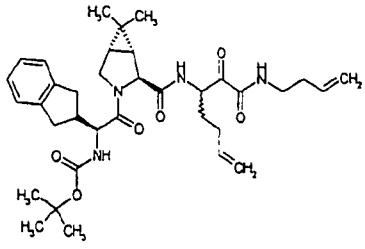


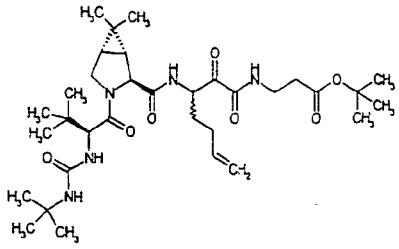


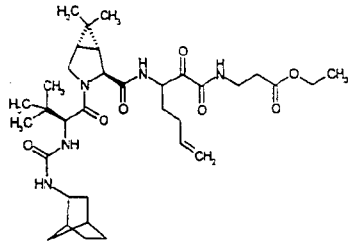


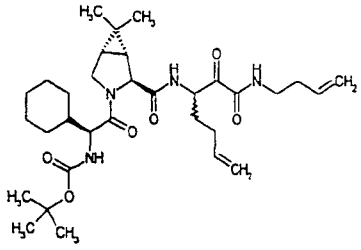


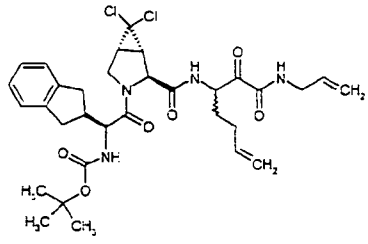


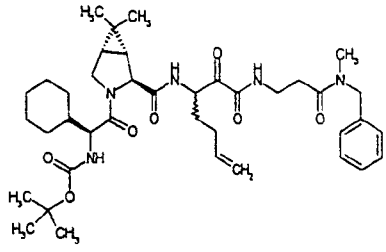


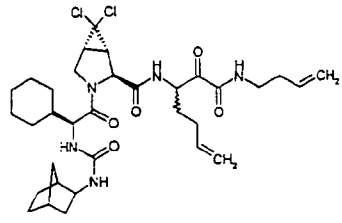


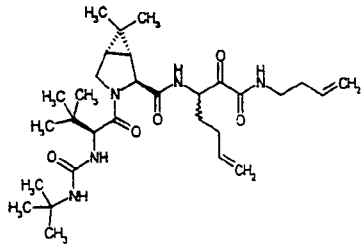


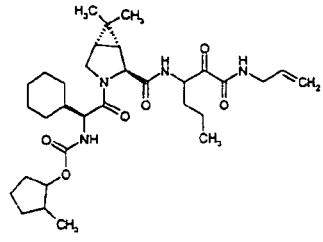


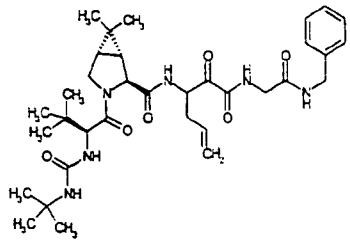


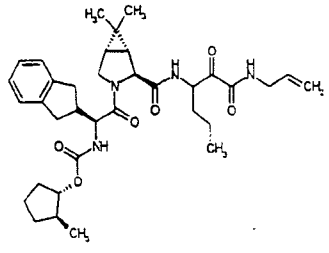


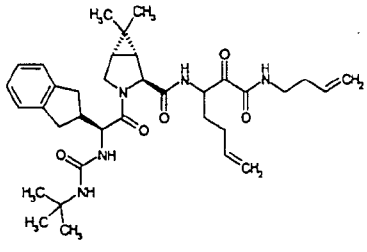


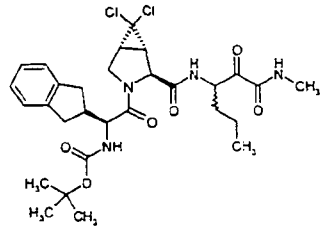


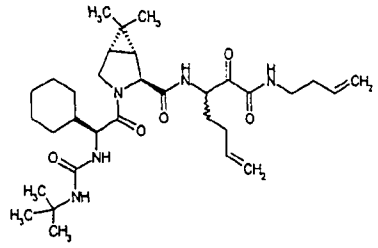


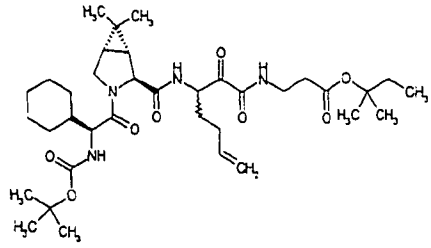


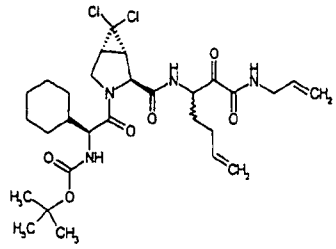


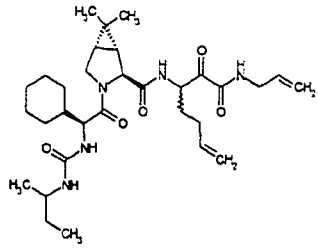


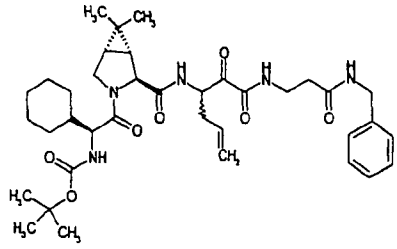


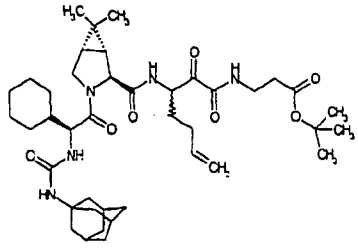


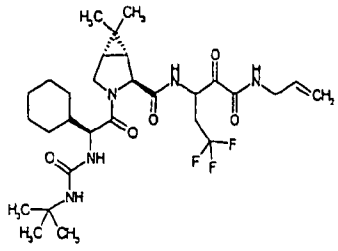


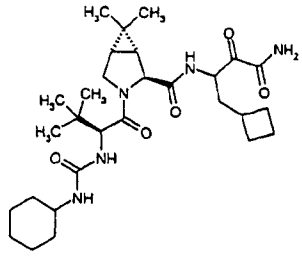


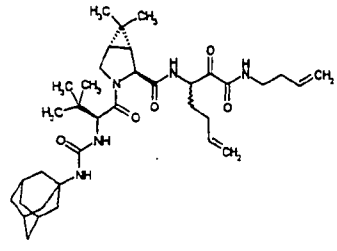


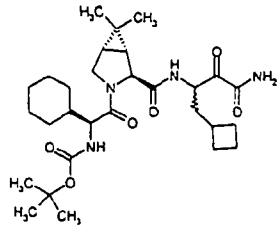


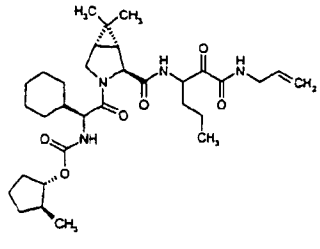


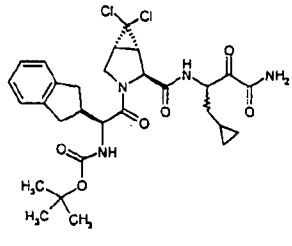


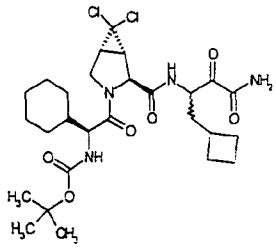


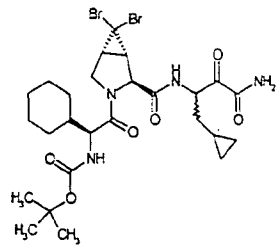


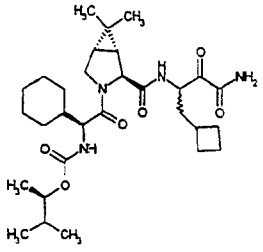


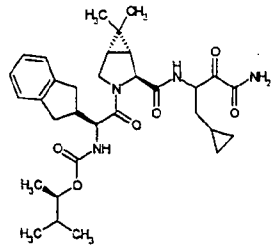


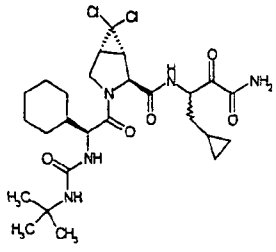


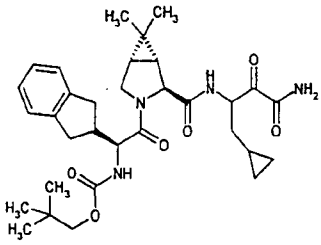


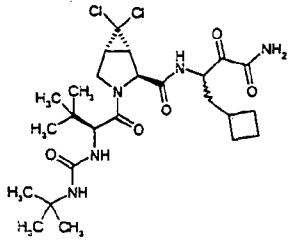


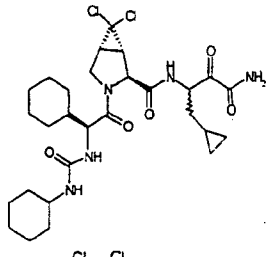


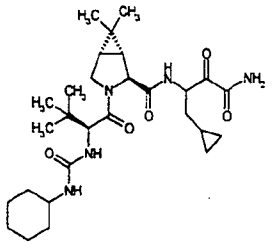


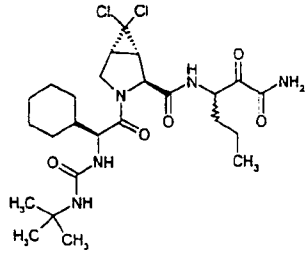


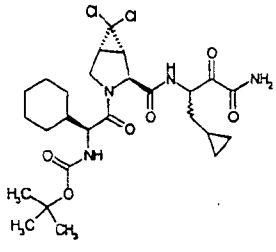


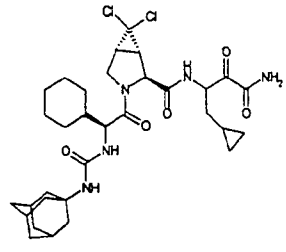






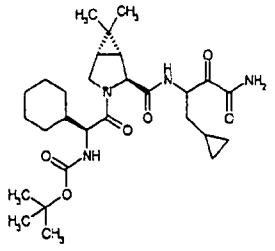


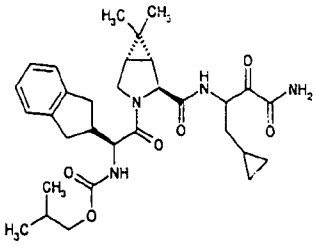


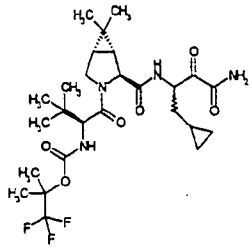


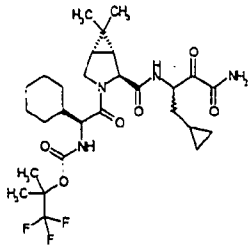
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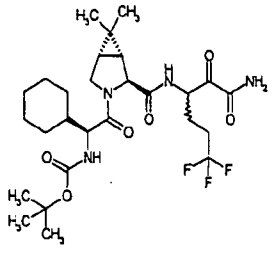
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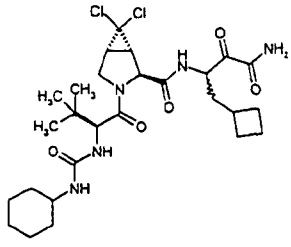


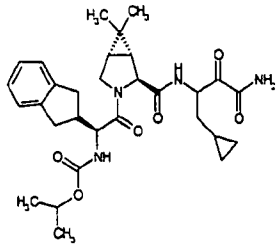


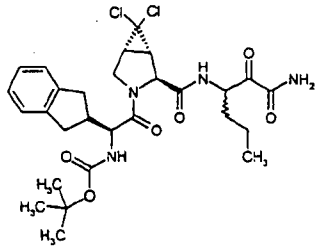


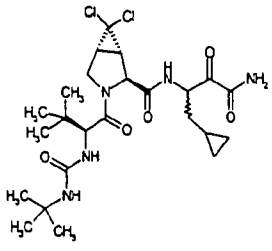


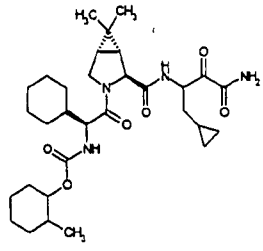


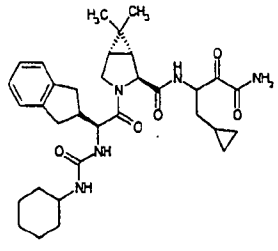


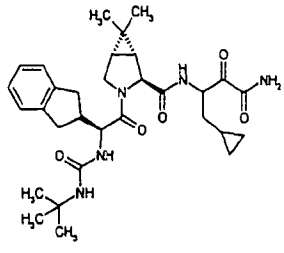


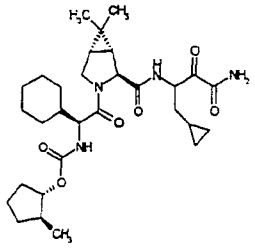


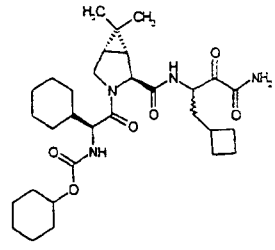


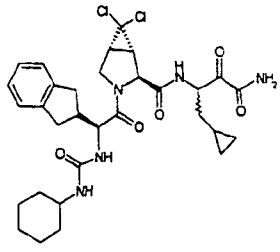


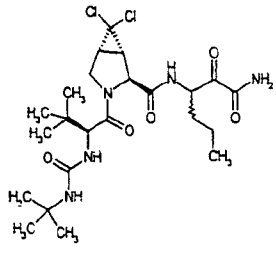


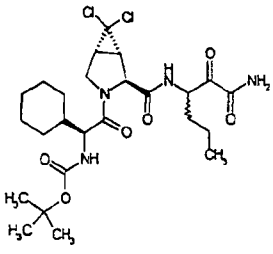


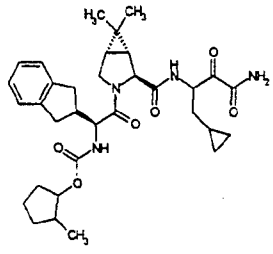


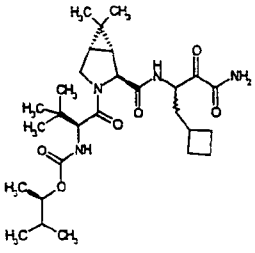


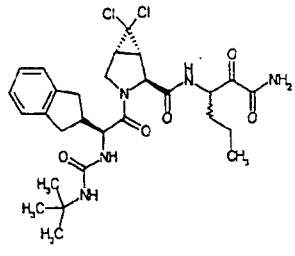


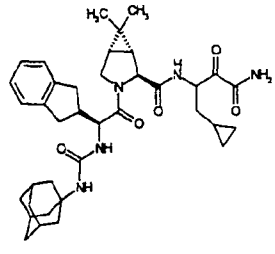


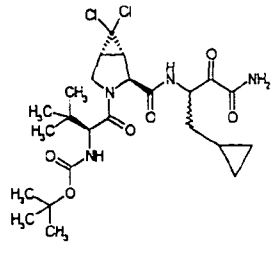


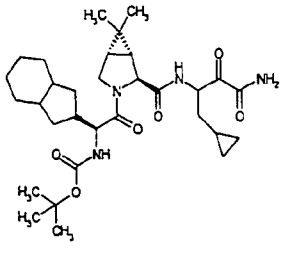


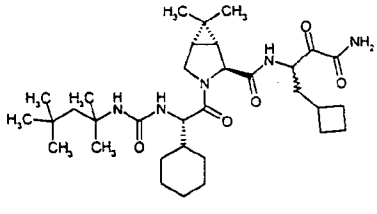




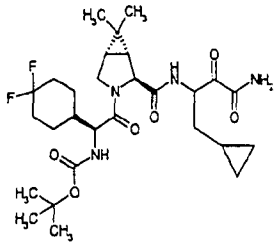


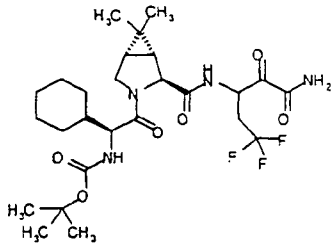


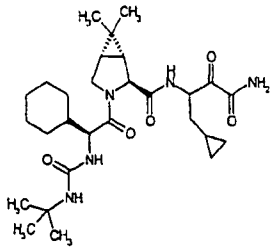


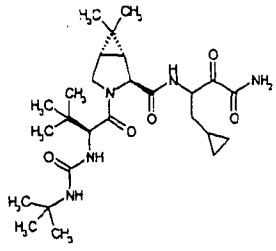


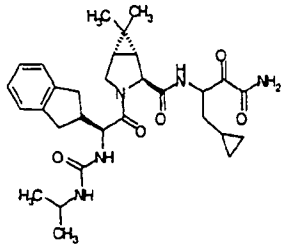
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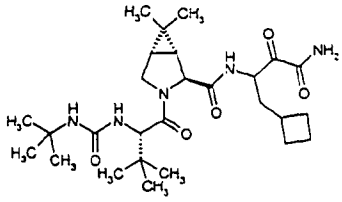


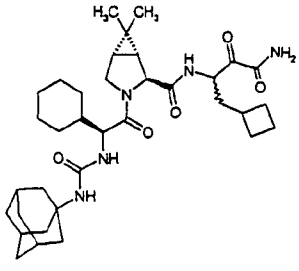


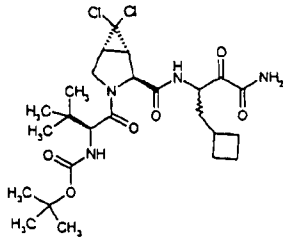


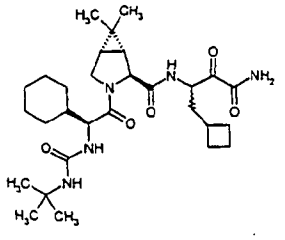


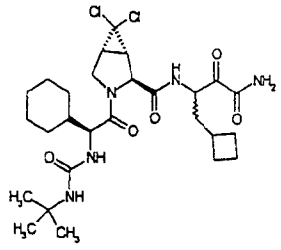


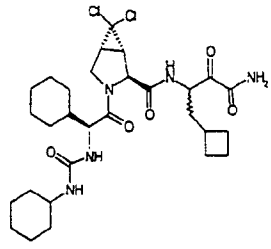


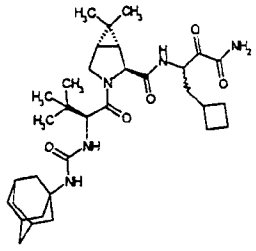


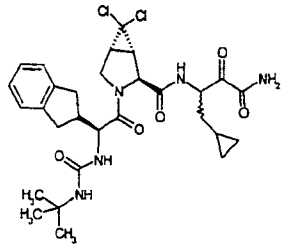


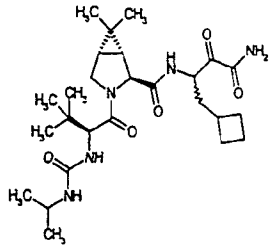


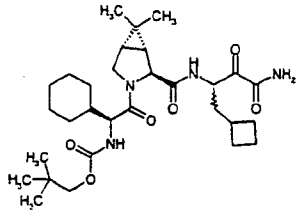


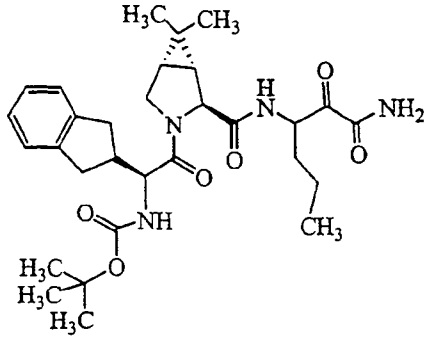


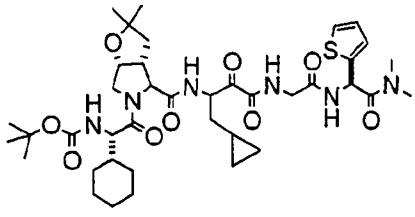


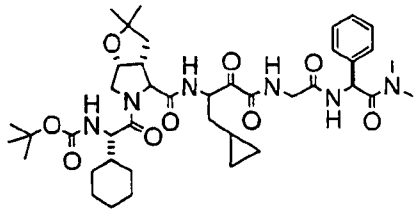


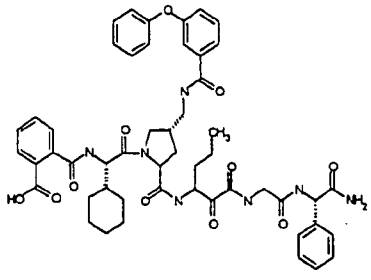


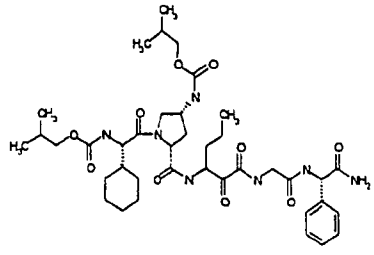


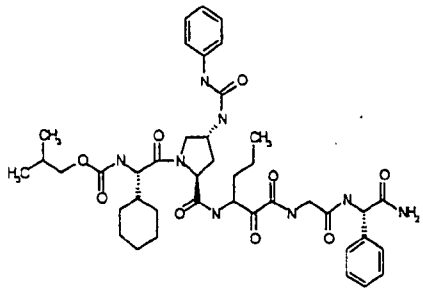


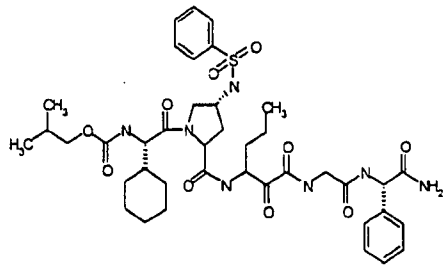


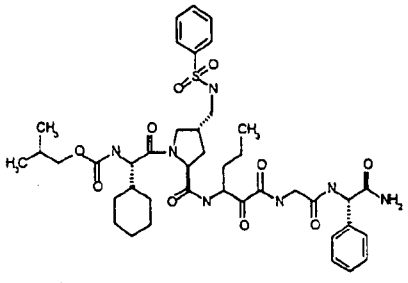


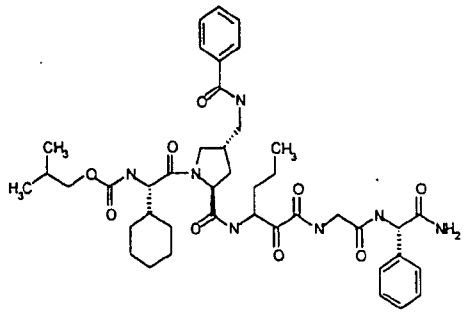


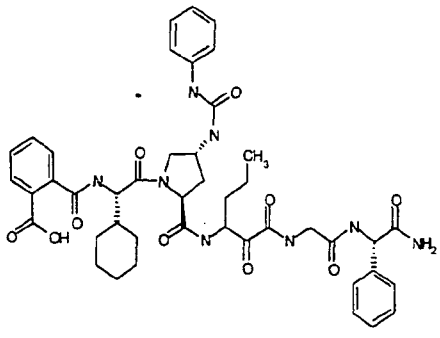


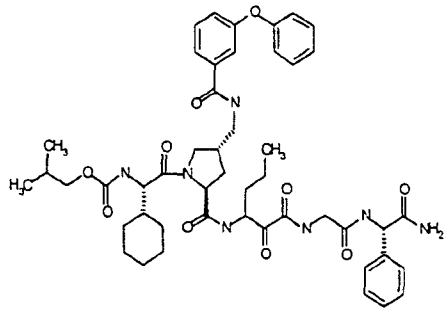


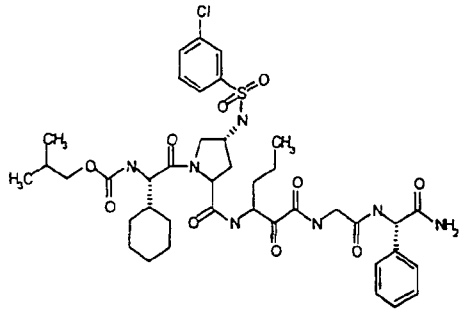


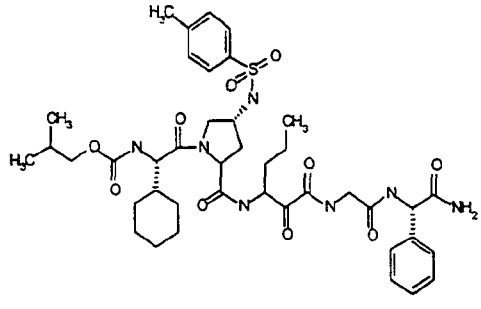


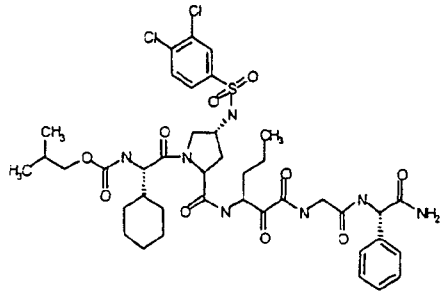




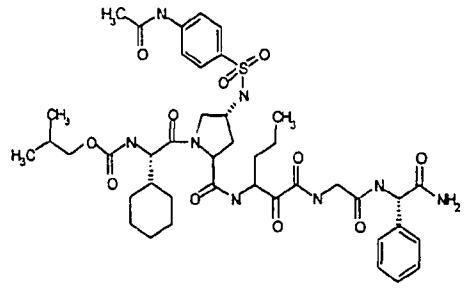


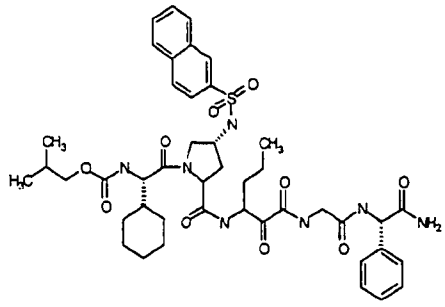


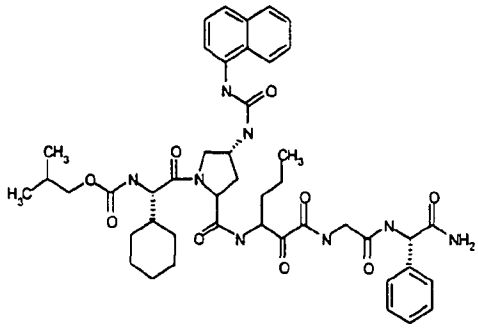




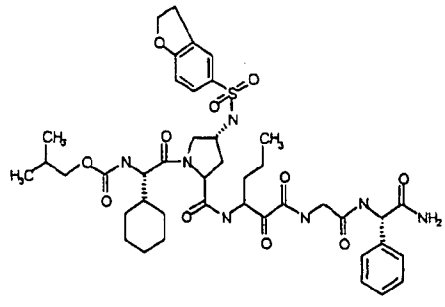
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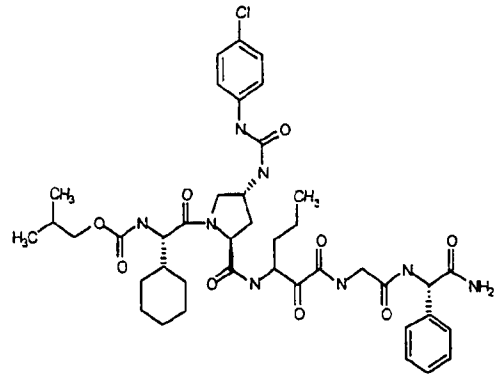


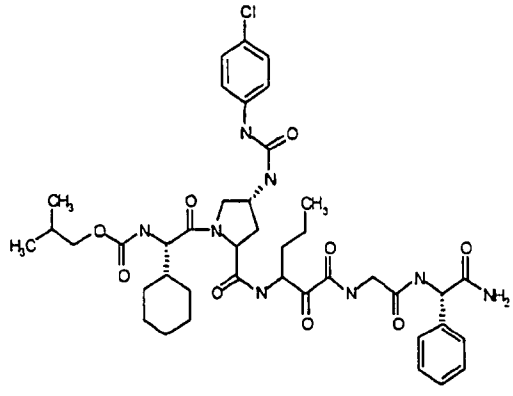


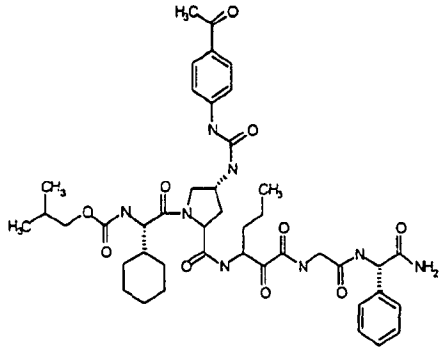


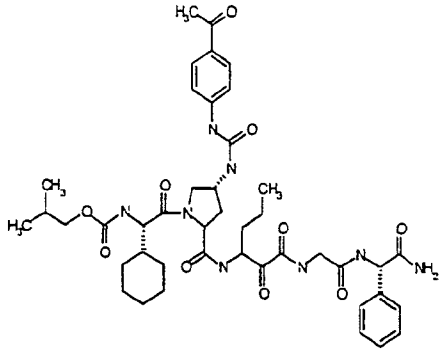
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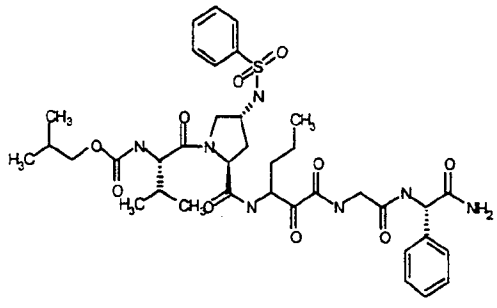


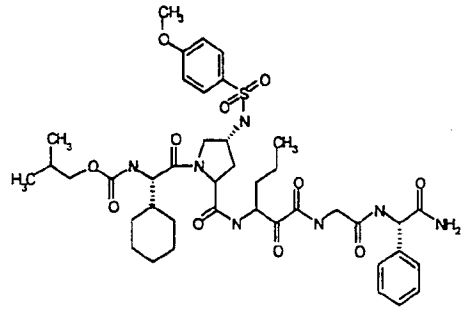


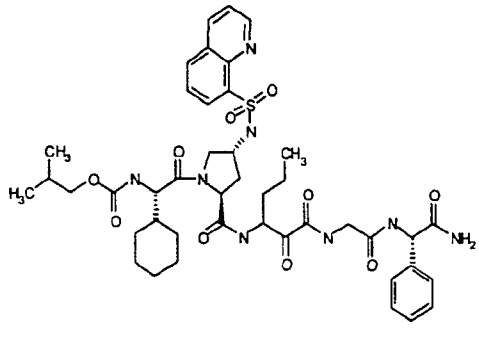


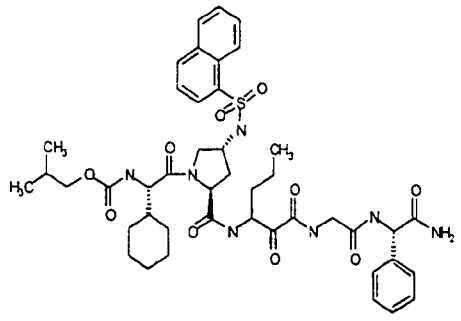


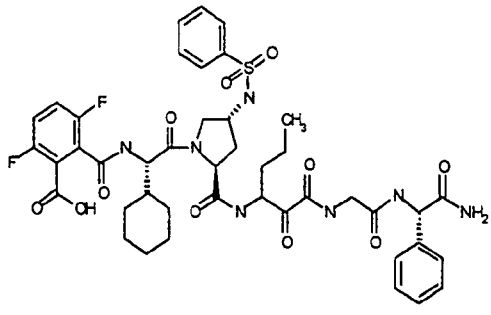


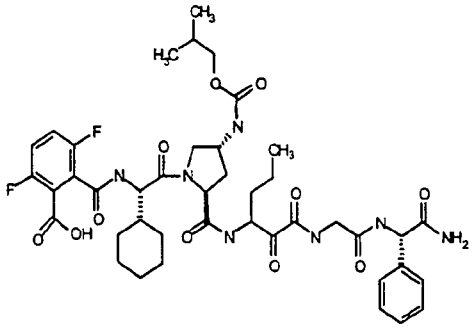


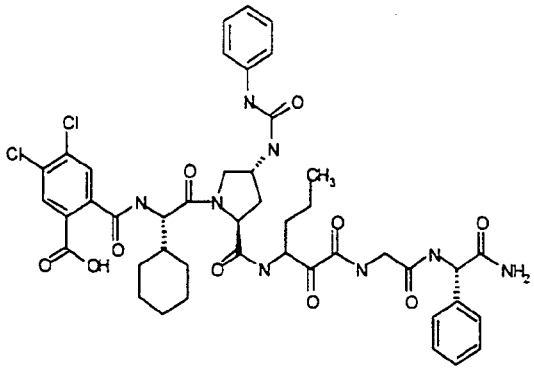


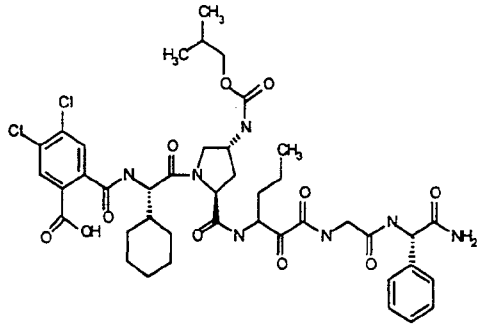


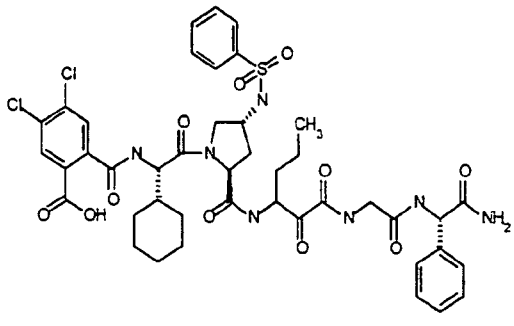


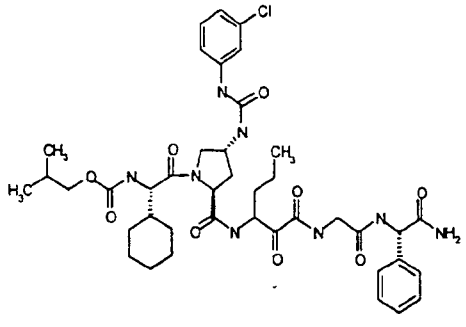




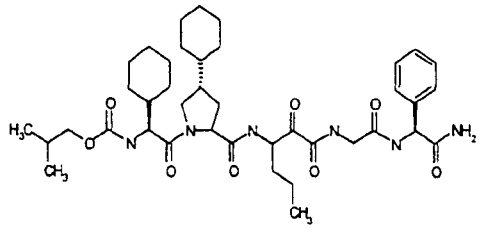


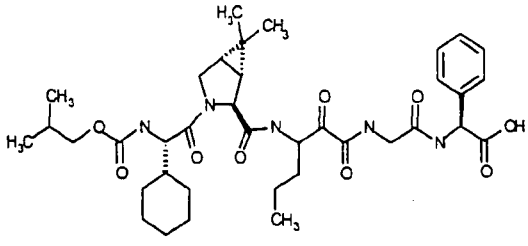


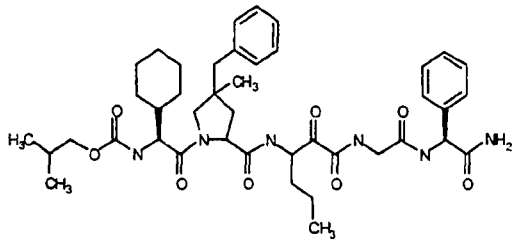


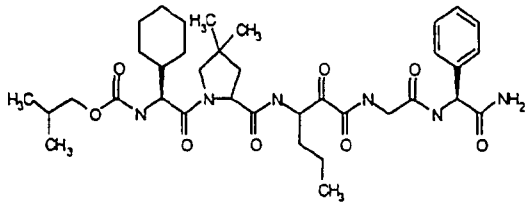


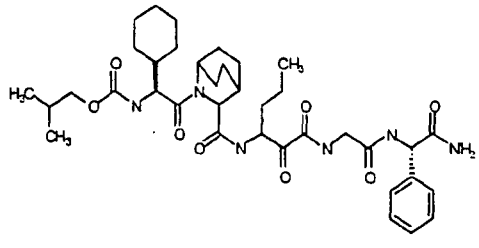
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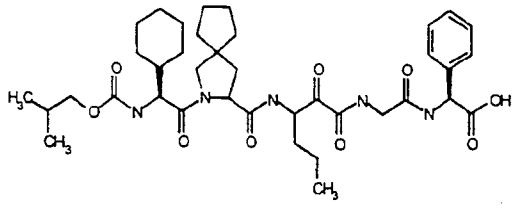


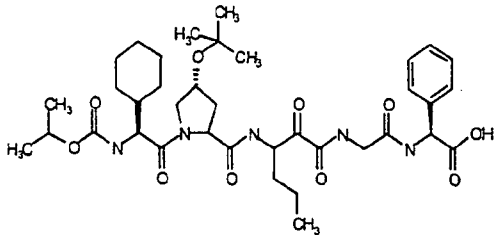


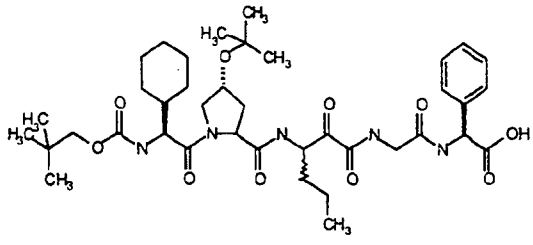


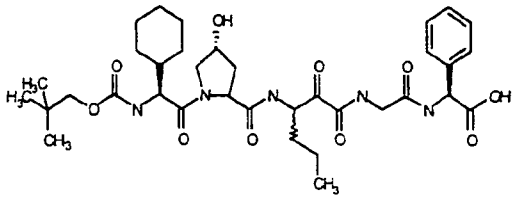


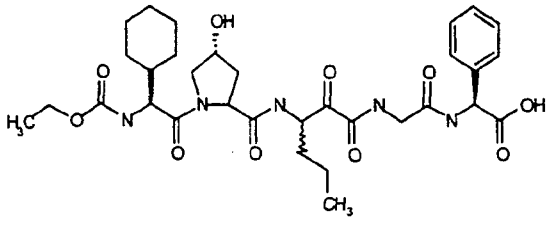
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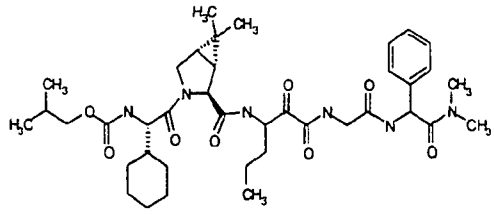


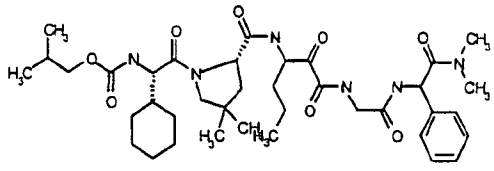


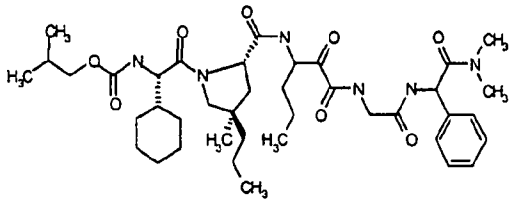


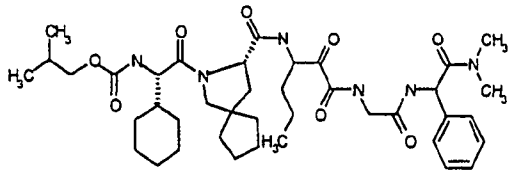


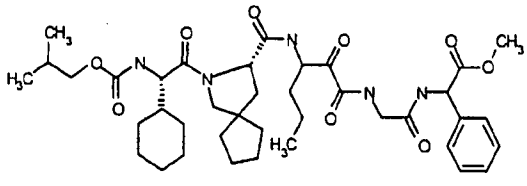
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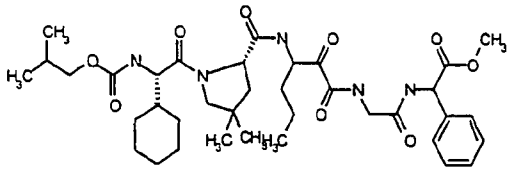


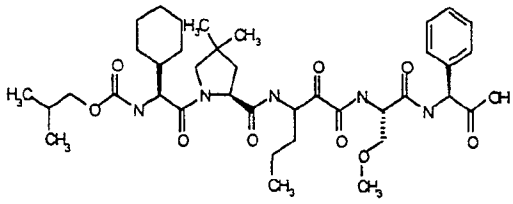


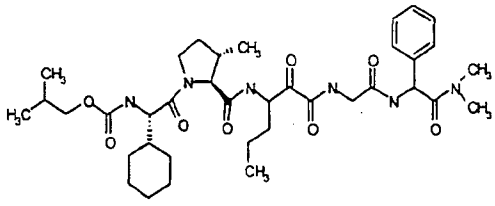


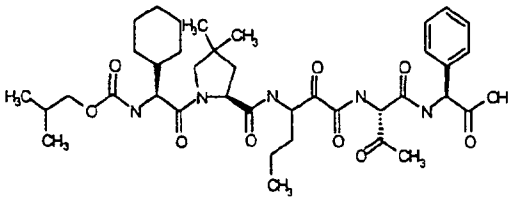


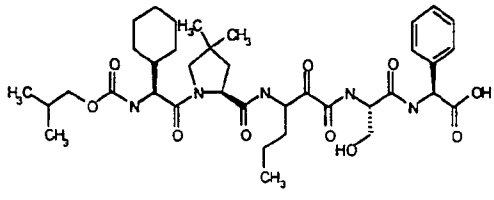


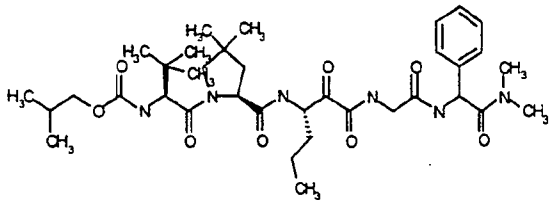


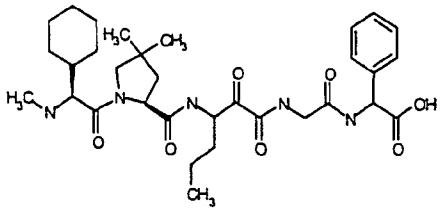




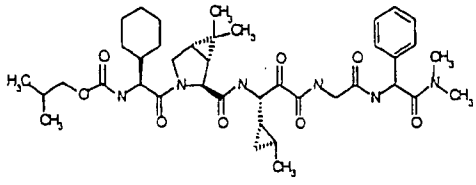


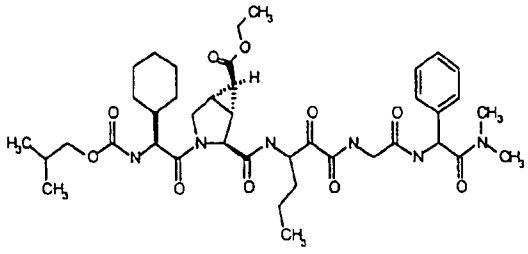


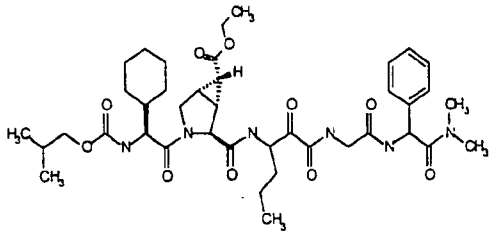


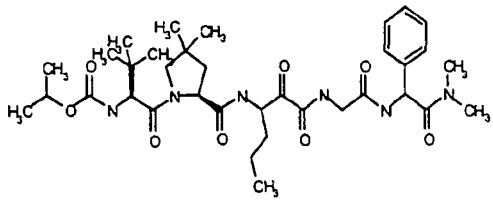


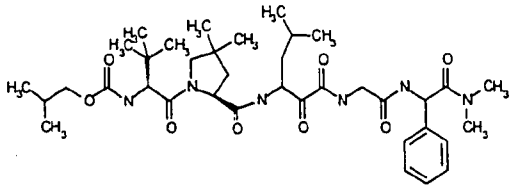
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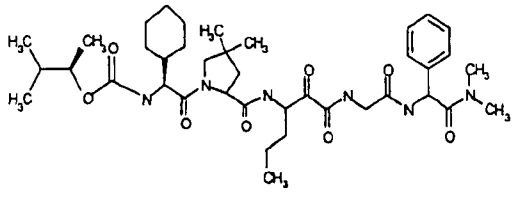


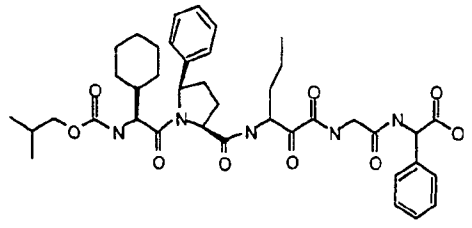


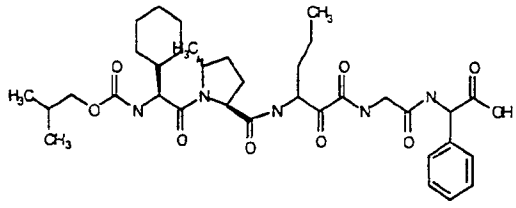


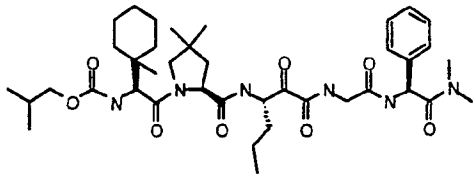


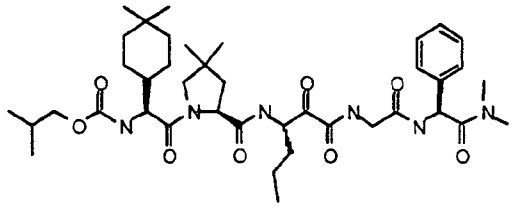


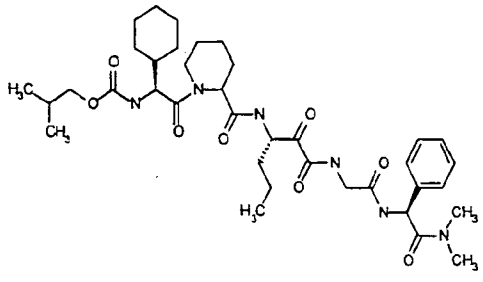




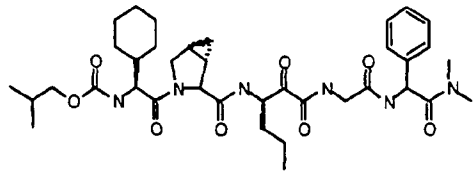


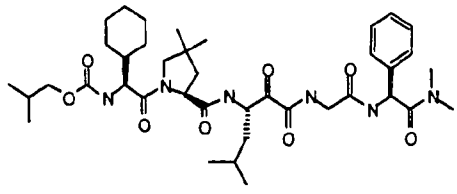


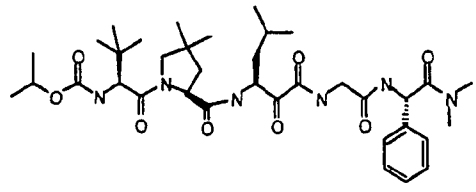


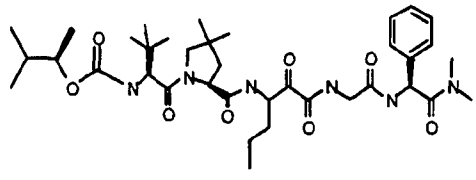


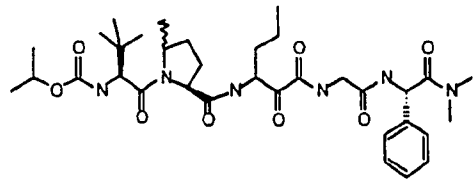
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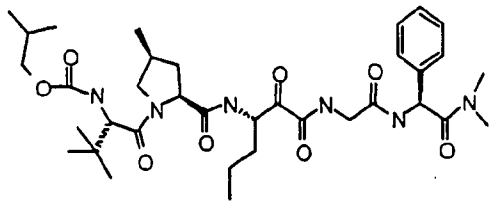


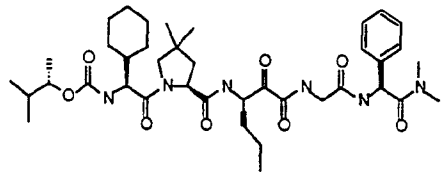


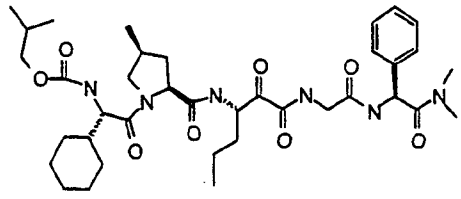


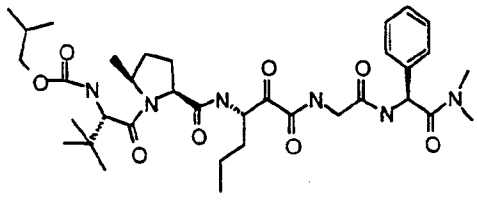


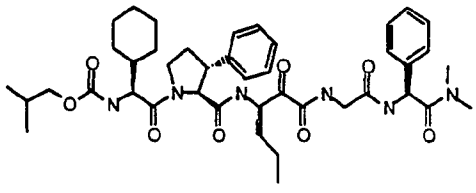


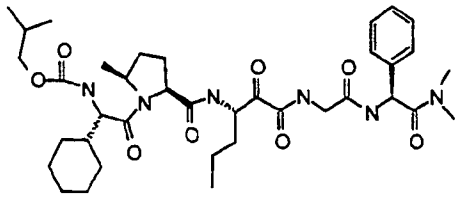


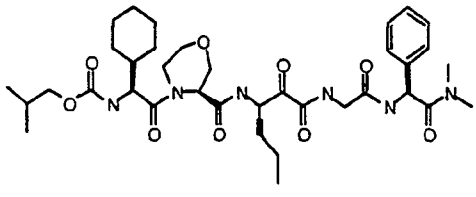




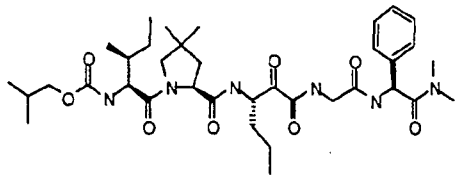


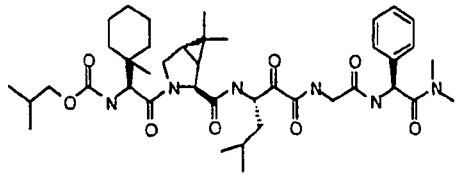


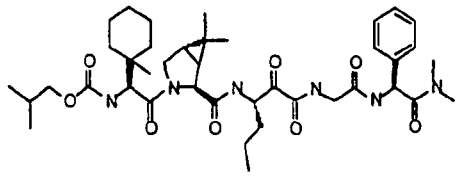


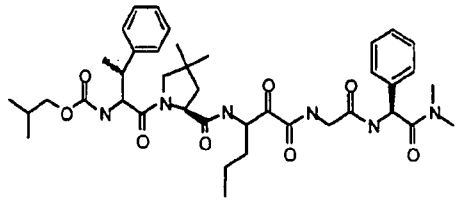


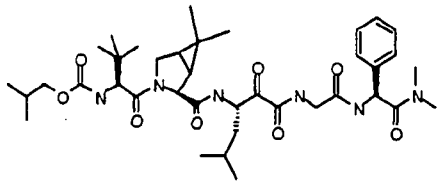
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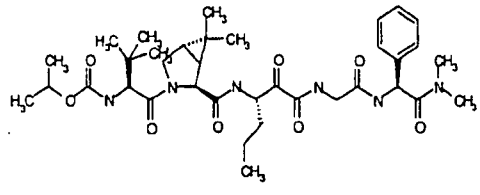


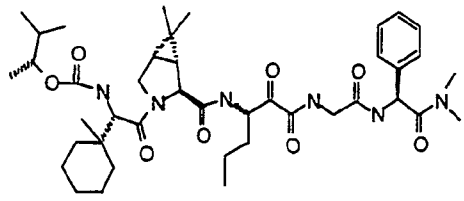


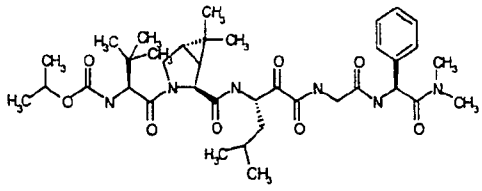


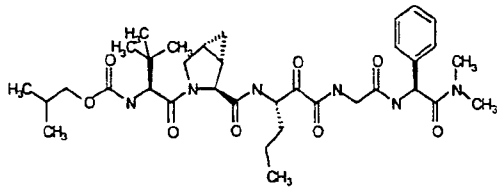


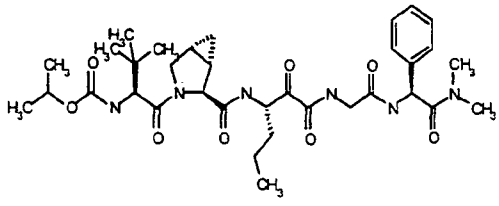


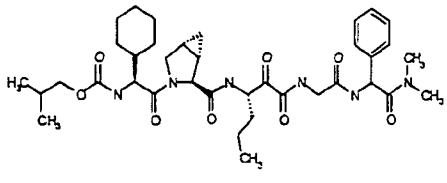


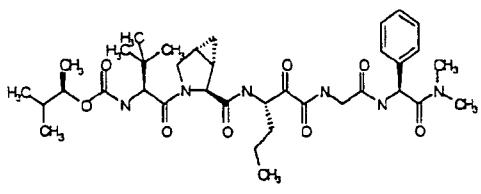




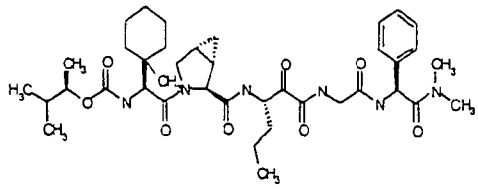








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40. A pharmaceutical composition for treating disorders associated with the HCV, said composition comprising therapeutically effective amount of one or more compounds in claim 39 and a pharmaceutically acceptable carrier.

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 45, wherein the HCV protease is the NS3/NS4a protease.

48. The method of claim 47, 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.

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Memoria Descriptiva

de la

Patente de Invención

Sobre

"NUEVOS PEPTIDOS COMO INHIBIDORES DE PROTEASA SERINA-NS3 DEL VIRUS DE LA HEPATITIS C"

Solicitada por:

*SCHERING CORPORATION * CORVAS INTERNATIONAL, INC., residente en 2000 Galloping Hill Road, Kenilworth, Nueva Jersey 07033-0530 * 3030 Science Park Road, San Diego, California 92121, E. U. DE NORTEAMERICA.*

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NUEVOS PÉPTIDOS COMO INHIBIDORES DE PROTEASA SERINA-NS3 DEL VIRUS DE LA HEPATITIS C

Campo de la Invención

La presente invención se refiere a novedosos inhibidores de 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 para usar dichos inhibidores en el tratamiento de la hepatitis C y trastornos relacionados. Esta invención describe en forma específica nuevos compuestos péptidos como inhibidores de la proteasa serina HCV NS3/NS4a.

Antecedentes de la Invención

El virus de la Hepatitis C es un virus de ARN (+)-sentido, de hebra simple que se ha implicado como el agente causante más importante en la hepatitis no A, no B (NANBH), en particular NANBH asociada con la sangre (BB-NANBH) (Ver, Publicación de la Solicitud de Patente Internacional No. WO 89/04669 y la Publicación de Solicitud de Patente Europea No. EP 381 216). La NANBH debe distinguirse de otros tipos de enfermedades hepáticas inducidas por virus, como el virus de la hepatitis A (HAV), el virus de la hepatitis B (HBV), el virus de la hepatitis delta (HDV), citomegalovirus (CMV) y virus de Epstein-Barr (EBV), como también otras formas de enfermedades hepáticas como la cirrosis biliar primaria y el alcoholismo.

Recientemente, se ha identificado, clonado y expresado una proteasa de HCV para el procesamiento de los polipéptidos y la replicación viral; (ver, por ejemplo, la Patente de los Estados Unidos No. 5.712.145). Esta poliproteína de 3000 amino ácidos contiene, desde la terminal amino a la terminal carboxi, una proteína nucleocápsida (C), proteínas de envoltura (E1 y E2) y varias proteínas no estructurales (NS1, 2, 3, 4a, 5a y 5b). NS3 es una proteína de

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aproximadamente 68 kda, codificada por, aproximadamente, 1893 nucleótidos del genoma de HCV, y tiene dos dominios distintivos (a) un dominio de proteasa serina que consiste de aproximadamente 200 de los amino ácidos N-terminales; y (b) un dominio de ATPasa dependiente del ARN en la terminal C de la proteína. La proteasa NS3 se considera un miembro de la familia de quimiotripsina de similitudes en la secuencia de proteína, estructura tridimensional general y mecanismo de catálisis. Otras enzimas similares a la quimiotripsina son la elactasa, factor Xa, trombina, tripsina, plasmina, urocinasa, tPA y PSA. La proteasa serina HCV NS3 es responsable de la proteólisis del polipéptido (poliproteína) en las uniones NS3/NS4a, NS4a/NS4b, NS4b/NS5a y NS5a/NS5b y es, por tanto, responsable de generar cuatro proteínas virales durante la replicación viral. Esto puede convertir a la proteasa serina HCV NS3 en un objetivo 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 proteasa serina de NS3. La auto disociación de la unión NS3/NS4a mediante la proteasa serina NS3/NS4a ocurre dentro de la molécula (es decir, *cis*) mientras que otros sitios de disociación se procesan dentro de la molécula (por ejemplo, *trans*).

El análisis de los sitios de disociación natural para la proteasa HCV reveló la presencia de cisteína en P1 y serina en P1' y que estos residuos se conservan en forma estricta en las juntas NS4a/NS4b, NS4b/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 para explicar el requerimiento de un procesamiento *cis* en lugar de *trans* en esta unión. Ver, por ejemplo, Pizzi, y sus colaboradores, (1994) Proc. Natl. Acad. Sci (USA) 91: 888-892, Failla, y sus colaboradores, (1996) Folding & Design 1: 35-42. El sitio de disociación NS3/NS4a también es más tolerante de mutagénesis que los otros sitios. Ver,

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por ejemplo, Kollykhalov y sus colaboradores, (1994) J. Virol. 68: 7525-7533. También se encontró que los residuos ácidos en la región ascendente del sitio de disociación se requieren para lograr una disociación eficiente. Ver, por ejemplo, Komoda y sus colaboradores, (1994) J. Virol. 68: 7351-7357.

Los inhibidores de la proteasa HCV que se han reportado incluyen antioxidantes (ver la Publicación de Solicitud de Patente Internacional No. WO 98/14181), ciertos péptidos y análogos de péptidos (ver la Publicación de Solicitud de Patente Internacional No. WO 98/17679, Landro y sus colaboradores, (1997) Biochem. 36: 9340-9348, Ingallinella y sus colaboradores (1998) Biochem. 37: 8906-8914, Llinàs-Brunet y sus colaboradores (1998) Bioorg. Med. Chem. Lett. 8: 1713-1718), inhibidores basados en el polipéptido de 70 amino ácidos eglin c (Martin y sus colaboradores (1998) Biochem. 37: 11459-11468, afinidad por los inhibidores seleccionados del inhibidor de tripsina secretoria pancreática humana (hPSTI-C3) y repertorios de un solo cuerpo (MBip) (Dimasi y sus colaboradores (1997) J. Virol. 71 7461-7469, cV_HE2 (un fragmento de anticuerpo con dominio variable "camelizado") (Martin y sus colaboradores (1997) Protein Eng. 10: 607-614), y α1-antiquimiotripsina (ACT) Elzouki y sus colaboradores) (1997) J. Hepat. 27: 42-28). Recientemente se describió una rebozima diseñada para destruir en forma selectiva el ARN del virus de la hepatitis C (ver *BioWorld Today* 9(217): 4 (10 de noviembre de 1988)).

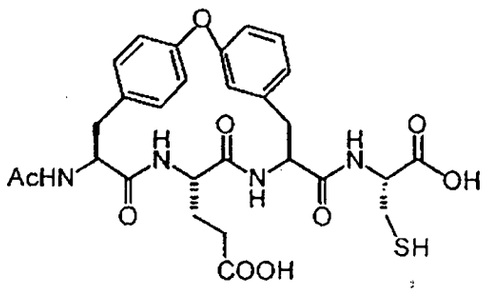
También se hace referencia a las publicaciones de PCT No. WO 98/17679, publicada el 30 de abril de 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, publicada el 28 de mayo de 1998 (F. Hoffmann-La Roche AG); y WO 99/07734, publicada el 18 de febrero de 1999 (Boehringer Ingelheim Canada Ltd.).

El HCV se ha implicado en la cirrosis hepática y en la inducción del carcinoma hepatocelular. La prognosis de los pacientes que sufren de infección

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de HCV es, actualmente, escasa. La infección con HCV es más difícil de tratar que otras formas de hepatitis, debido a la falta de inmunidad o remisión asociadas con la infección de HCV. Los datos actuales indican una tasa de supervivencia inferior al 50% cuatro años después del diagnóstico de cirrosis. Los pacientes diagnosticados con carcinoma hepatocelular extirpable localizado tienen una tasa de supervivencia en 5 años del 10-30%, mientras que aquellos con carcinoma hepatocelular localizado no extirpable tienen una tasa de supervivencia en cinco años inferior al 1%.

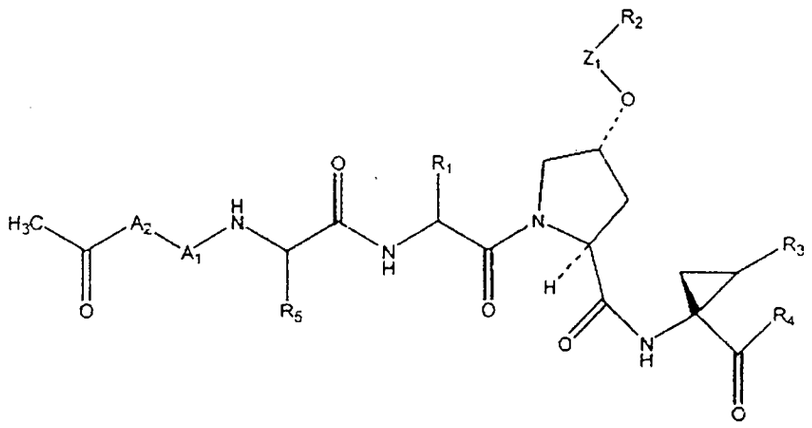
Se hace referencia a A. Marchetti y sus colaboradores, *Synlett*, S1, 1000-1002 (1999) que describe la síntesis de análogos bicíclicos de un inhibidor de la proteasa HCV NS3. Allí se describe un compuesto que tiene la fórmula:



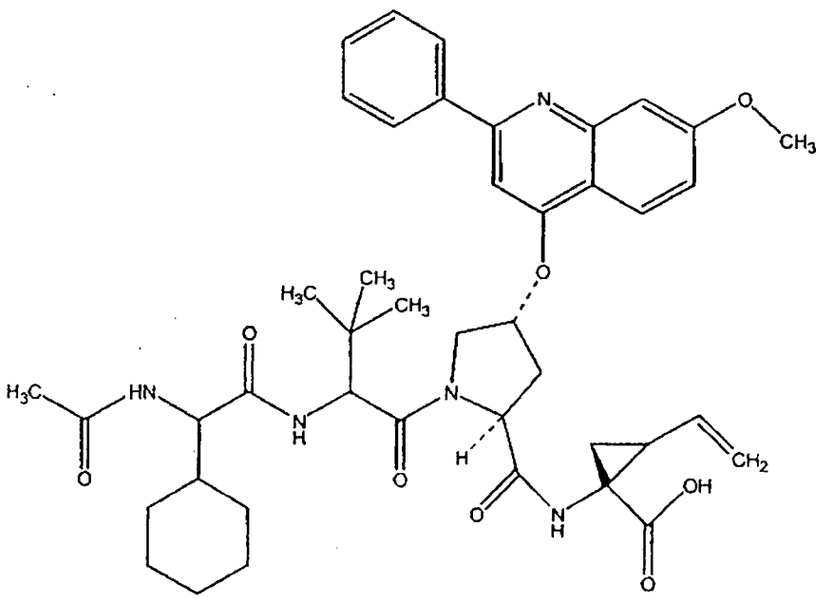
También se hace referencia a W. Han y sus colaboradores, *Bioorganic & Medicinal Chem. Lett,* (2000) 10, 711-713, que describe la preparación de ciertas α-cetoamidas, α-cetoésteres y α-dicetonas que contienen funcionalidades alilo y etilo.

También se hace referencia a la WO 00/09558 (Cesionario: Boehringer Ingelheim Limited; Publicada el 24 de febrero de 2000) que describe derivados de péptidos de la fórmula:

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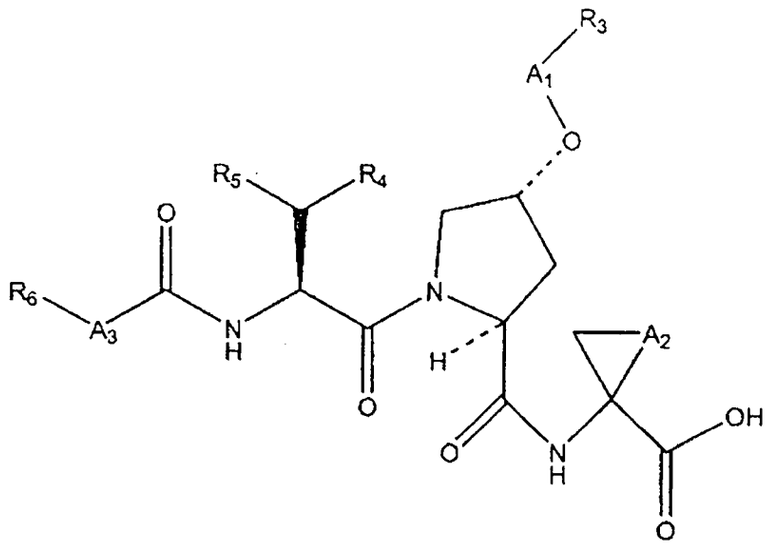


en la cual los diferentes elementos se definen en ella. Un compuesto ilustrativo de esa serie es:

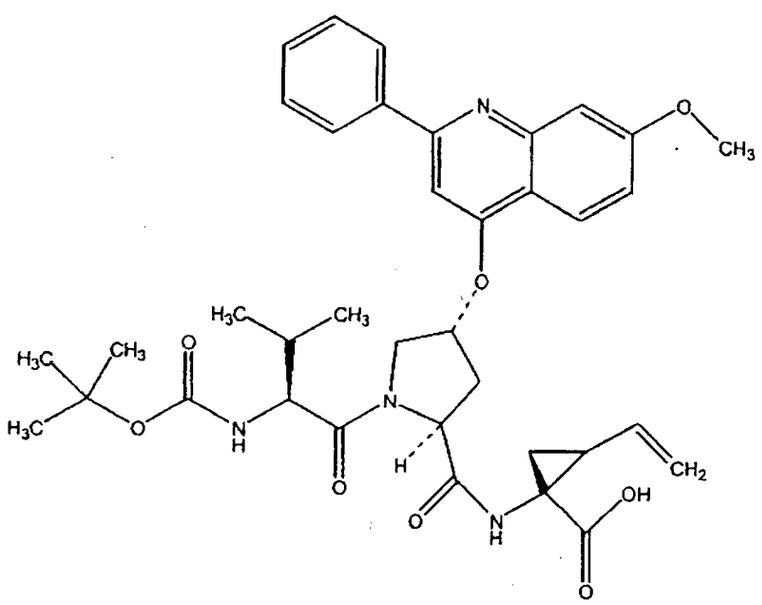


Además, se hace referencia a la WO 00/09543 (Cesionario: Boehringer Ingelheim Limited; Publicada el 24 de febrero de 2000) que describe derivados péptidos de la fórmula:

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donde los diferentes elementos se definen en ella. Un compuesto ilustrativo de esa serie es:



Los tratamientos actuales para la hepatitis C incluyen el interferon-α (INF_{α}) y el tratamiento combinado con ribavirina e interferon. Ver, por ejemplo, Beremguer, y sus colaboradores, (1998) Proc. Assoc. Am. Psysicians 110(2): 98-

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112. Estos tratamientos sufren de una baja tasa de respuesta prolongada y efectos colaterales frecuentes. Ver, por ejemplo, Hoofnagle y sus colaboradores, (1997) N. Engl. J. Med. 336: 347. Actualmente no se encuentra disponible ninguna vacuna para HCV.

Las solicitudes de Patentes 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 proteasa serina NS-3 del virus de la hepatitis C.

Existe una necesidad de nuevos tratamientos y terapias para la infección de HCV. Es, por lo tanto, uno de los objetivos de esta invención, suministrar compuestos útiles en el tratamiento o la prevención o el alivio de uno o más síntomas de la hepatitis C.

Un objetivo adicional es suministrar métodos de tratamiento o prevención o alivio de uno o más síntomas de la hepatitis C.

Un objetivo adicional de la presente invención es suministrar métodos para modular la actividad de las proteasas serina, en particular la proteasa serina NS3/NS4a de HCV, mediante el uso de los compuestos que se suministran aquí.

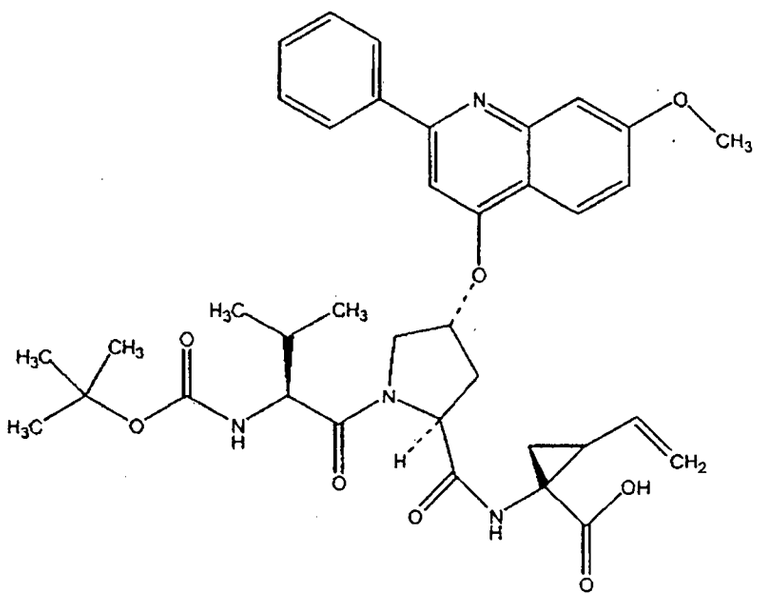
Otro objetivo de la invención es suministrar métodos para modular el procesamiento del polipéptido de HCV con el uso de los compuestos provistos aquí.

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Breve Descripción de la Invención

En sus muchas realizaciones, la presente invención suministra una nueva clase de inhibidores de la proteasa de 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 para el tratamiento, la prevención o el alivio de uno o más de los síntomas de la hepatitis C. También se suministran métodos para modular la interacción de un polipéptido de HCV con la proteasa de HCV. Entre los compuestos que se suministran aquí, los compuestos que inhiben la proteasa serina NS3/NS4a de HCV son los preferidos. La presente solicitud describe un compuesto, que incluye enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos, y prodrogas de dicho compuesto, y las sales y solvatos aceptables para uso

farmacéutico de dicho compuesto o dicha prodroga, dicho compuesto tiene la estructura general que se observa en la Fórmula I:



Fórmula I

en la cual:

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Y se selecciona del grupo que consiste de los siguientes grupos funcionales: 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 condición de que Y puede ser 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 condición de que X^{11} puede sustituirse 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, arilureído, halógeno, ciano, o nitro, con la condición de que dicho alquilo, alcoxi, y arilo pueden sustituirse en forma opcional con grupos funcionales seleccionados en forma independiente de X^{12};

R^1 es COR^5 o $B(OR)_2$, en los cuales R^5 es H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, o COR^7 en el cual R^7 es H, OH, ORB, CHR^9R^{10}, o NR^9R^{10}, en el cual R^6, R^8, R^9 y R^{10} se seleccionan en forma independiente del grupo que consiste de H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, cicloalquilo; arilalquilo, heteroarilalquilo, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pCOR^{11}$, $[CH(R^{1'})]_pCH(OH)R^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$,

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$CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO\ R^{11}$ y $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})\ CONR^{12}R^{13}$, en las cuales $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, y R', se seleccionan en forma independiente del grupo que consiste de H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo y heteroaralquilo;

Z se selecciona de O, N, CH o CR;

W puede estar presente o ausente, y si W está presente, W se selecciona de C=O, C=S, C(=N-CN), o SO_2;

Q puede estar presente o ausente, y cuando Q está presente, Q es CH, 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 se enlaza directamente a L;

A es O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_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 1 como G está enlazado a;

J puede estar presente o ausente, y cuando J está presente, J es $(CH_2)_p$, $(CHR)_p$, o $(CRR')_p$, SO_2, NH, NR u O; y cuando J está ausente, G está presente y E está enlazado directamente a N que se muestra en la Fórmula I enlazado a J;

L puede estar presente o ausente, y cuando L está presente, L es CH, CR, O, S o NR; y cuando L está ausente, entonces M puede estar presente o ausente; y si M está presente cuando L está ausente, entonces M se enlaza en

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forma directa e independiente a E, y J se enlaza directa e independientemente a E;

M puede estar presente o ausente, y cuando M está presente, M es O, NR, S, SO_2, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, o $(CRR')_p$; p es un número de 0 a 6; y

R, R', R^2, R^3 y R^4 se seleccionan en forma independiente del grupo que consiste de H; alquilo de C_1-C_{10}; alquenilo de C_2-C_{10}; cicloalquilo de C_3-C_8; heterocicloaiquilo de C_3-C_4, 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 a ocho átomos de carbono, y de cero a seis átomos de oxígeno, nitrógeno, sulfuro o fósforo, y dicho alquilo es de uno a seis átomos de carbono; arilo; heteroarilo; alquil-arilo; y alquil-heteroarilo; donde dichos grupos funcionales alquilo, heteroalquilo, alquenilo, heteroalquenilo, arilo, heteroarilo, cicloalquil y heterocicloalquilo pueden sustituirse en forma apropiada para la química, donde dicho término "substituido" se refiere a una sustitución opcional y apropiada para la química de uno o más grupos funcionales seleccionados del grupo que consiste de 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, e hidroxamato; además donde dicha unidad N-C-G-E-L-J-N representa una estructura de anillo cíclico de cinco o seis elementos con la condición de que cuando dicha unidad N-C-G-E-L-J-N representa una estructura de anillo cíclico de cinco elementos, o cuando la estructura de anillo bicíclico de la Fórmula I comprende N, C, G, E, L, J, N, A, Q, y M representa una estructura de anillo cíclico de cinco elementos, entonces la estructura de anillo cíclico de cinco elementos carece de un grupo carbonilo como parte del anillo cíclico.

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Entre las definiciones detalladas anteriormente para los diferentes grupos funcionales de la Fórmula I, los grupos preferidos para los diferentes grupos funcionales son de la siguiente manera: La definición preferida para R^1 es COR^5 donde R^5 es H, OH, $COOR^8$ o $CONR^9R^{10}$, donde R^8, R^9 y R^{10} son como se definieron anteriormente. Aún el grupo funcional preferido para R^1 es $COCONR^9R^{10}$, donde R^9 es H; and R^{10} es H, R^{14}, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pSO_2N\ R^{12}R^{13}$, $[CH(R^{1'})]_pCOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})\ CONR^{12}R^{13}$, o $CH(R^{1'})CONHCH(R^{2'})(R')$, donde R^{14} es H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo, alquenilo, alquinil o heteroaralquil.

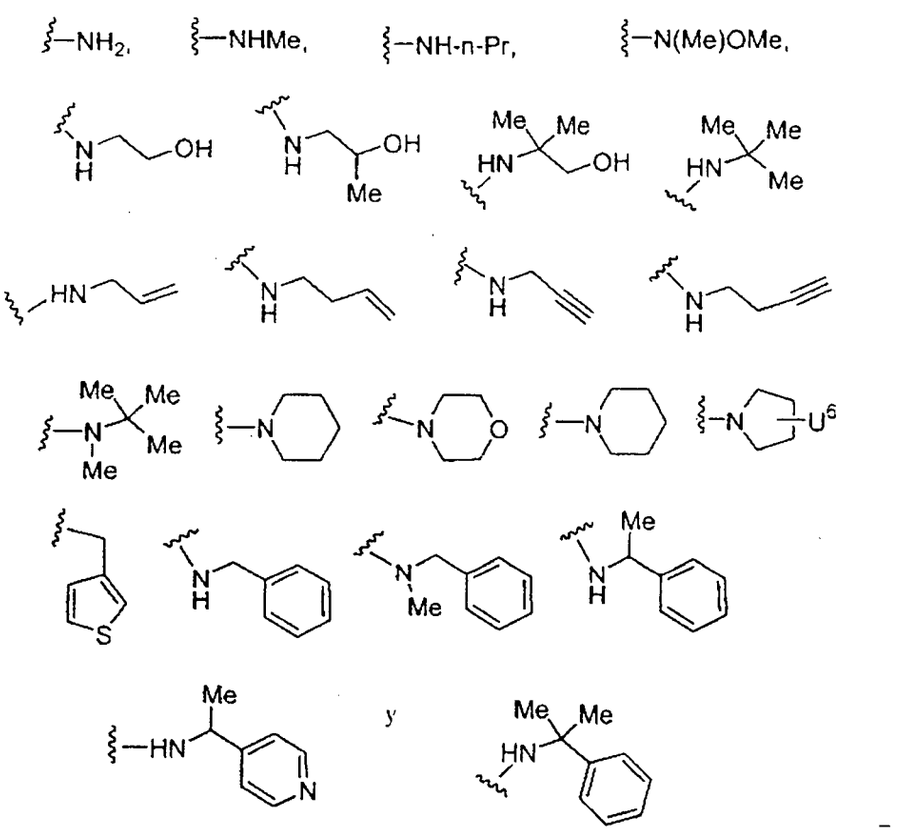
Entre los anteriores, para R^{10}, los grupos funcionales para R^1 are: H, R^{14}, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})SO_2R^{11}$, $CH(R^{1'})CH(R^{1'})SO_2N\ R^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})COR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})\ CONR^{12}R^{13}$, o $CH(R^{1'})CONHCH(R^{2'})(R')$, donde $R^{1'}$ es H o alquilo, y $R^{2'}$ es fenilo, fenilo sustituido, fenilo sustituido por un heteroátomo, tiofenilo, cicloalquilo, piperidilo o piridilo.

Los grupos funcionales más preferidos son: para $R^{1'}$ es H, para R^{11} es H, metilo, etilo, alilo, terbutilo, bencilo, α-metilbencilo, α,α-dimetilbencilo, 1-metilciclopropilo o 1-metilciclopentilo; para

R' es hidroximetilo o $CH_2CONR^{12}R^{13}$

donde $NR^{12}R^{13}$ se selecciona del grupo que consiste de:

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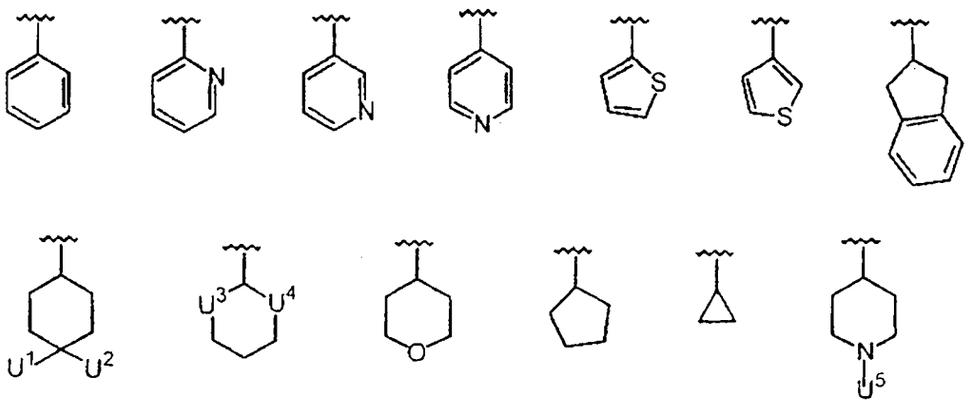


donde U^6 es H, OH o CH_2OH;

R^{14} se selecciona, con preferencia, del grupo que consiste de: H, Me, Et, *n*-propilo, metoxi, ciclopropilo, *n*-butilo, 1-but-3-inilo, bencilo, α-metilbencilo, fenetilo, alilo, 1-but-3-enilo, OMe, ciclopropilmetilo;

y $R^{2'}$ se selecciona, con preferencia, en forma independiente del grupo que consiste de:

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en el cual

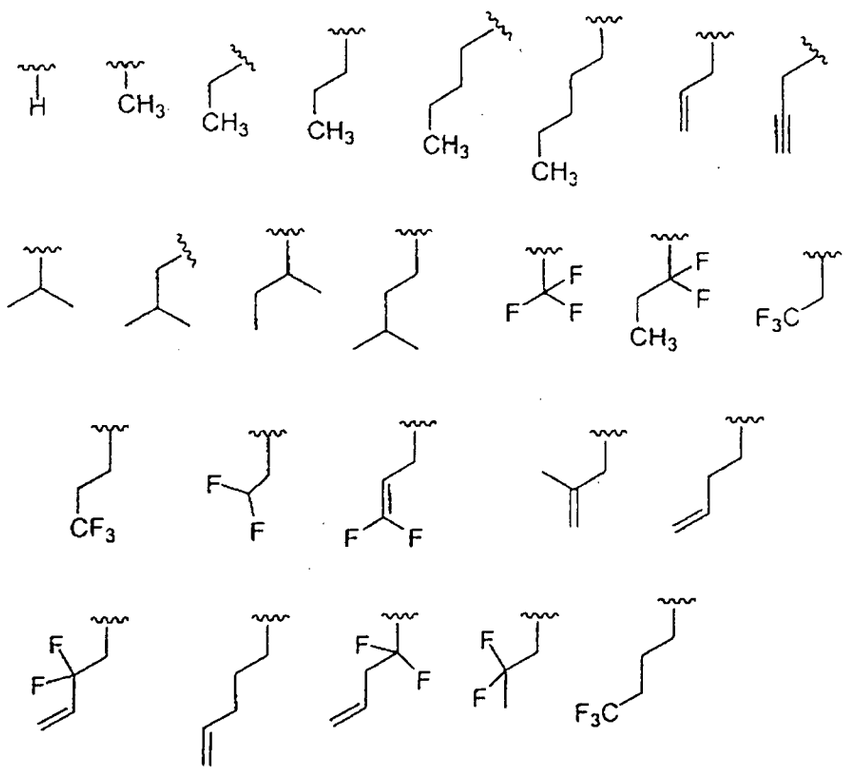
U^1 y U^2 pueden ser iguales o diferentes y se seleccionan de H, F, CH_2COOH, CH_2COOMe, CH_2CONH_2, $CH_2CONHMe$, CH_2CONMe_2, azido, amino, hidroxilo, amino sustituido, hidroxilo sustituido;

U^3 y U^4 pueden ser iguales o diferentes y se seleccionan de O y S;

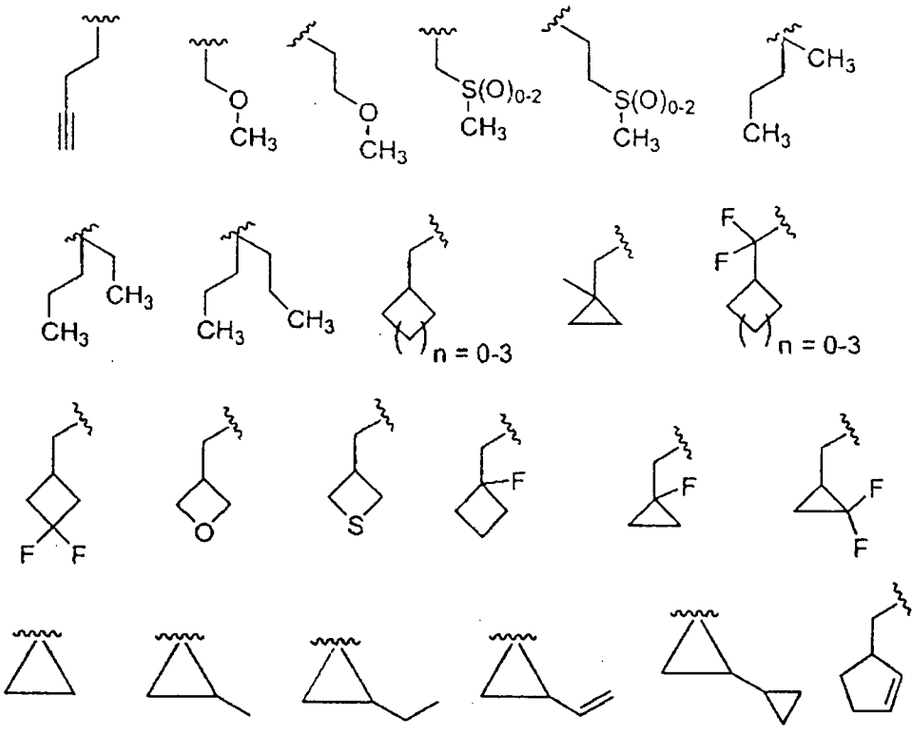
U^5 se selecciona de los grupos funcionales que consisten de alquilo, sulfonilo, aril-sulfonilo, heteroalquil sulfonilo, heteroaril sulfonilo, alquil carbonilo, aril carbonilo, heteroalquil carbonilo, heteroaril carbonilo, alcoxicarbonilo, ariloxicarbonilo, heteroariloxicarbonilo, alquilaminocarbonilo, arilaminocarbonilo, heteroarilaminocarbonilo, o una combinación de estos.

Los grupos funcionales preferidos para R^2 son:

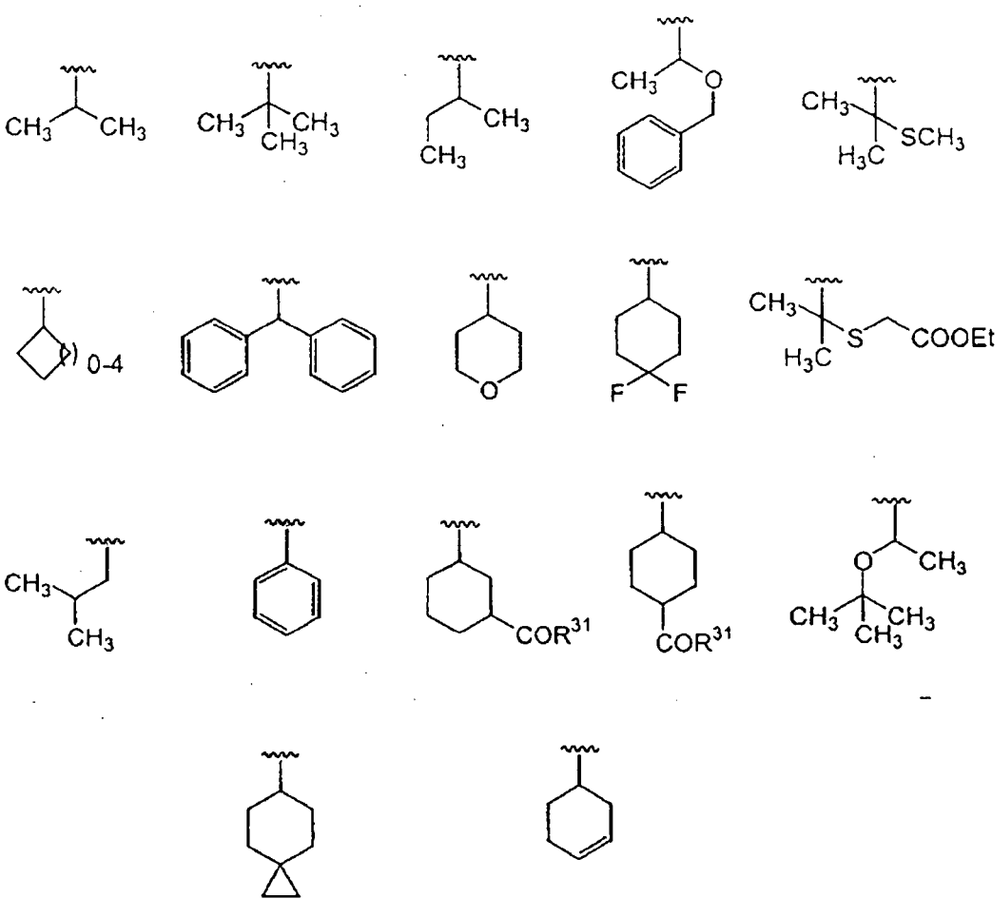
033297



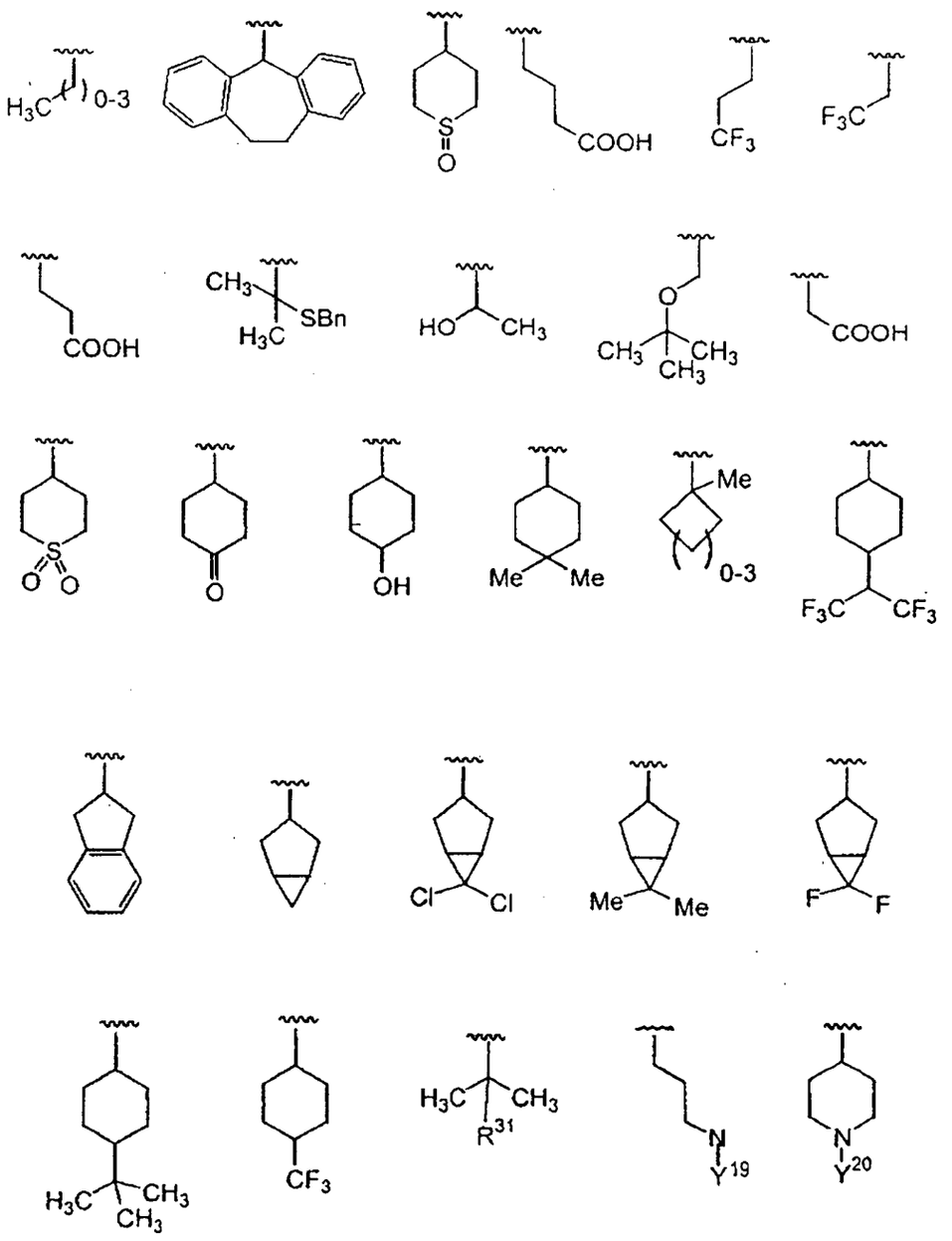
600298


O
CH3
O
CH3
S(O)0-2
CH3
S(O)0-2
CH3
CH3
CH3
CH3
CH3
CH3
n = 0-3
F
F
n = 0-3
F
F
O
S
F
F
F
F
F

Los grupos funcionales preferidos para R^3 son:



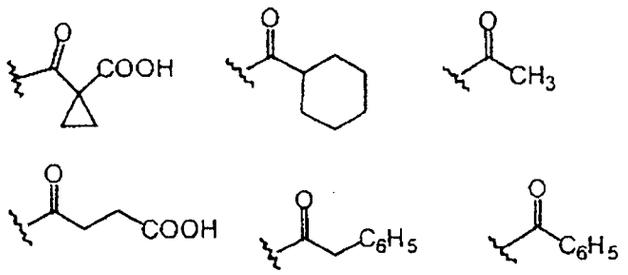
033300



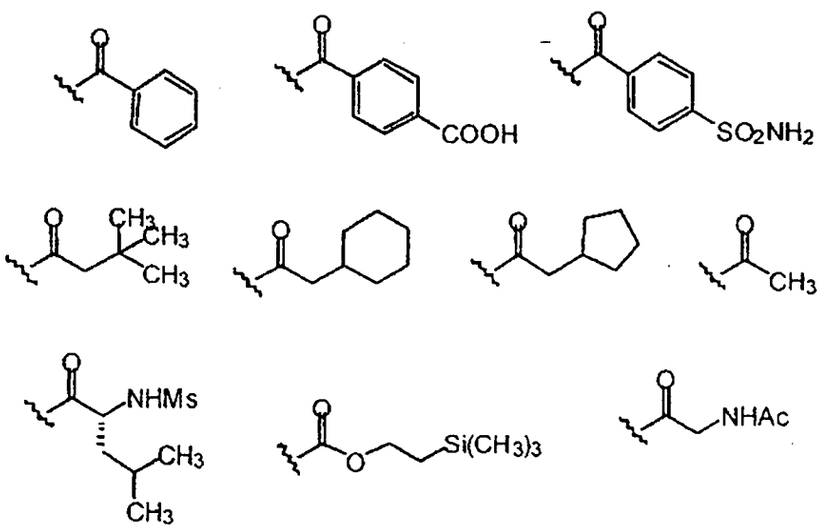
en los cuales R^{31}= OH u O-alquilo;

Y^{19} se selecciona de los siguientes grupos funcionales:

033301

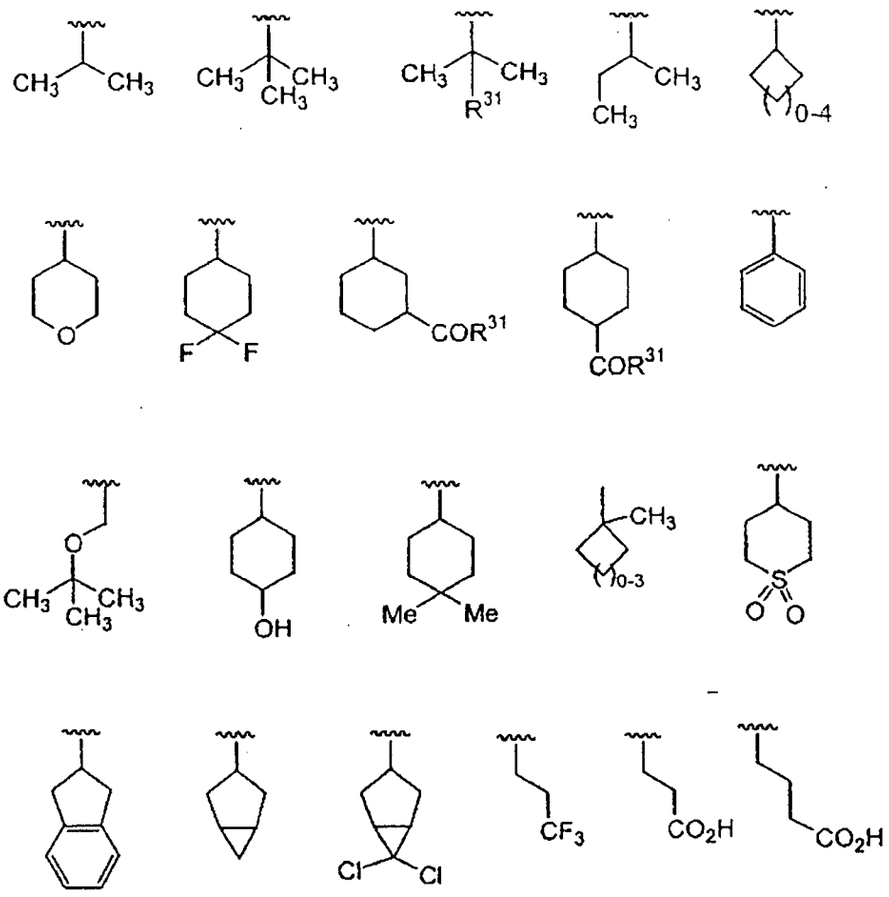


e Y^{20} se selecciona de los siguientes grupos funcionales:



Los grupos funcionales más preferidos para R^3 son:

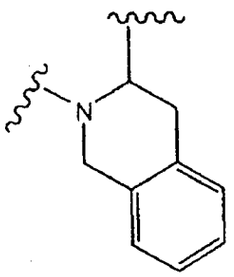
000302

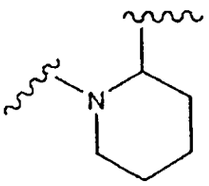


Algunos grupos funcionales preferidos adicionales son: para Z es N, para R^4 es H, y para W es C=O.

En forma adicional, el grupo funcional Z-C-R^3 en la Fórmula I, donde R^4 está ausente, puede representarse por las siguientes estructuras:

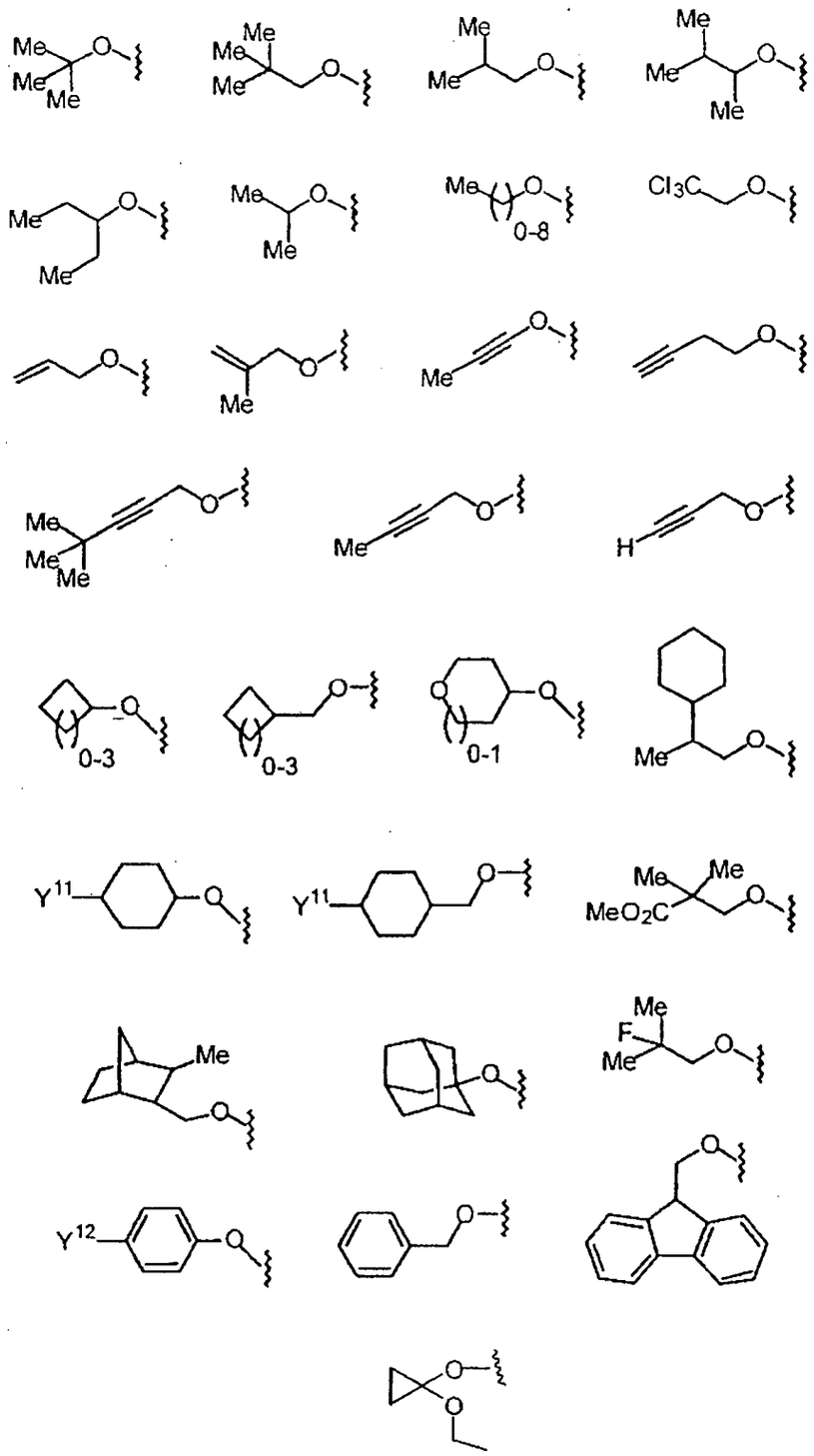
033303



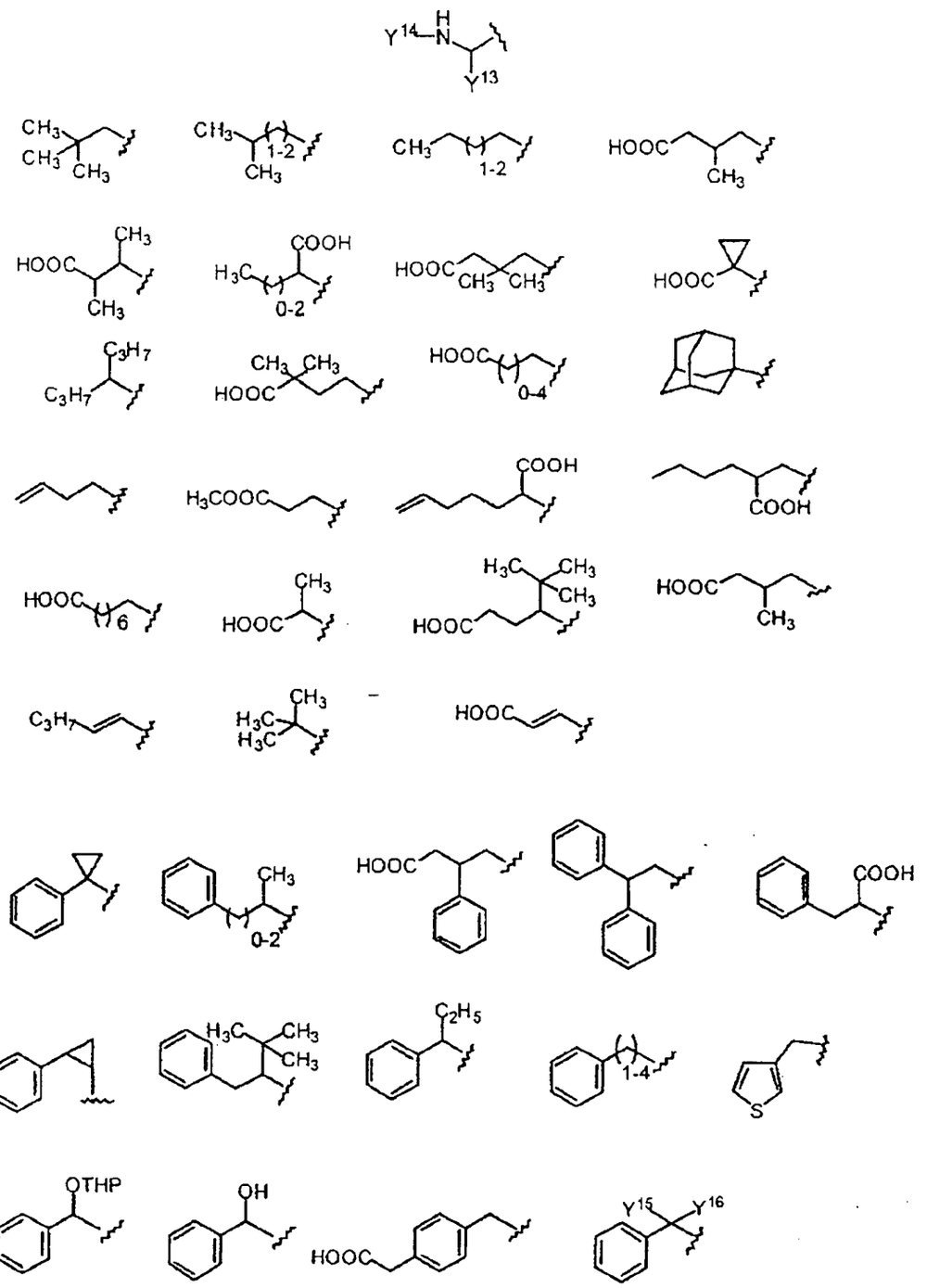


030304

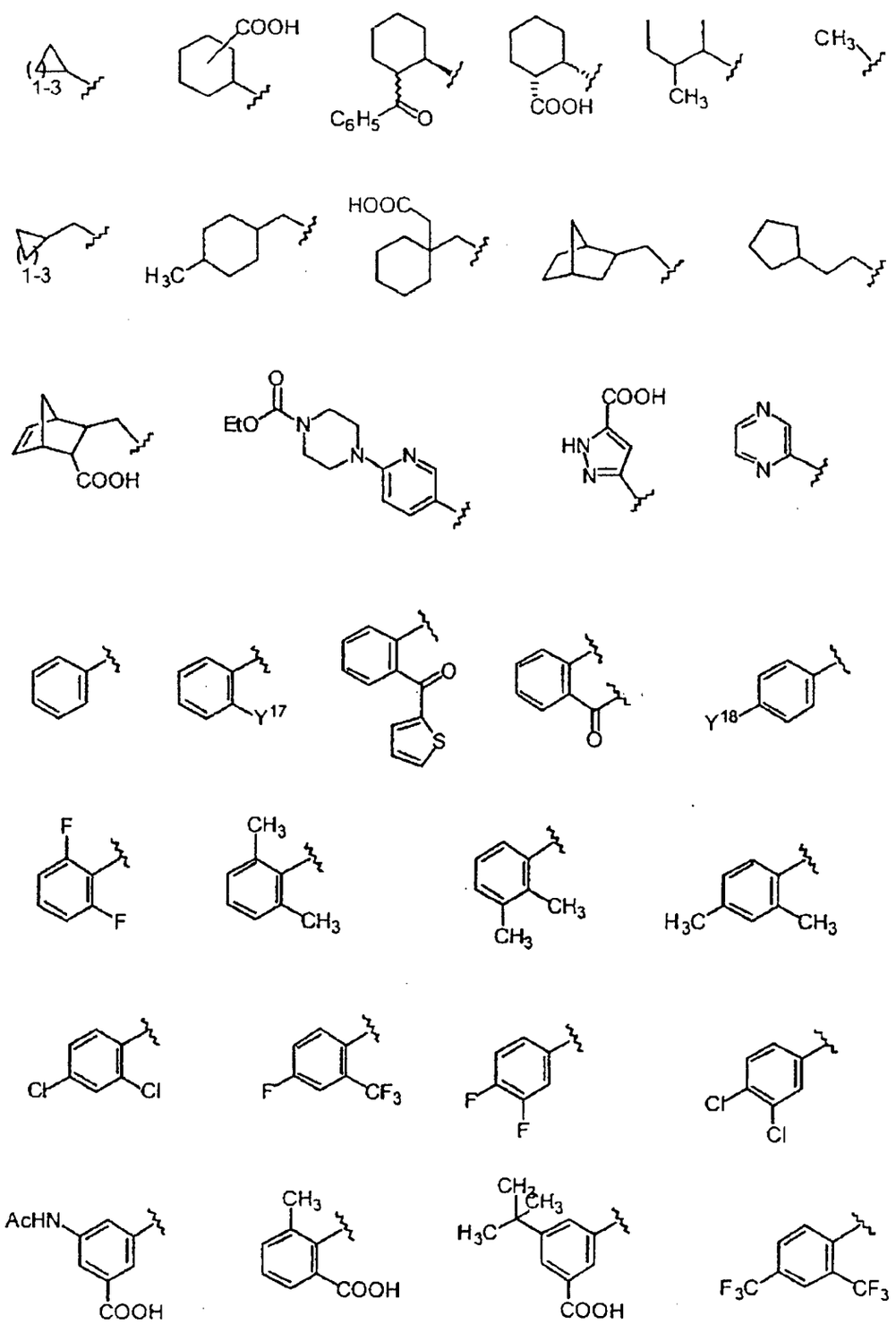
Los grupos funcionales preferidos para Y son:



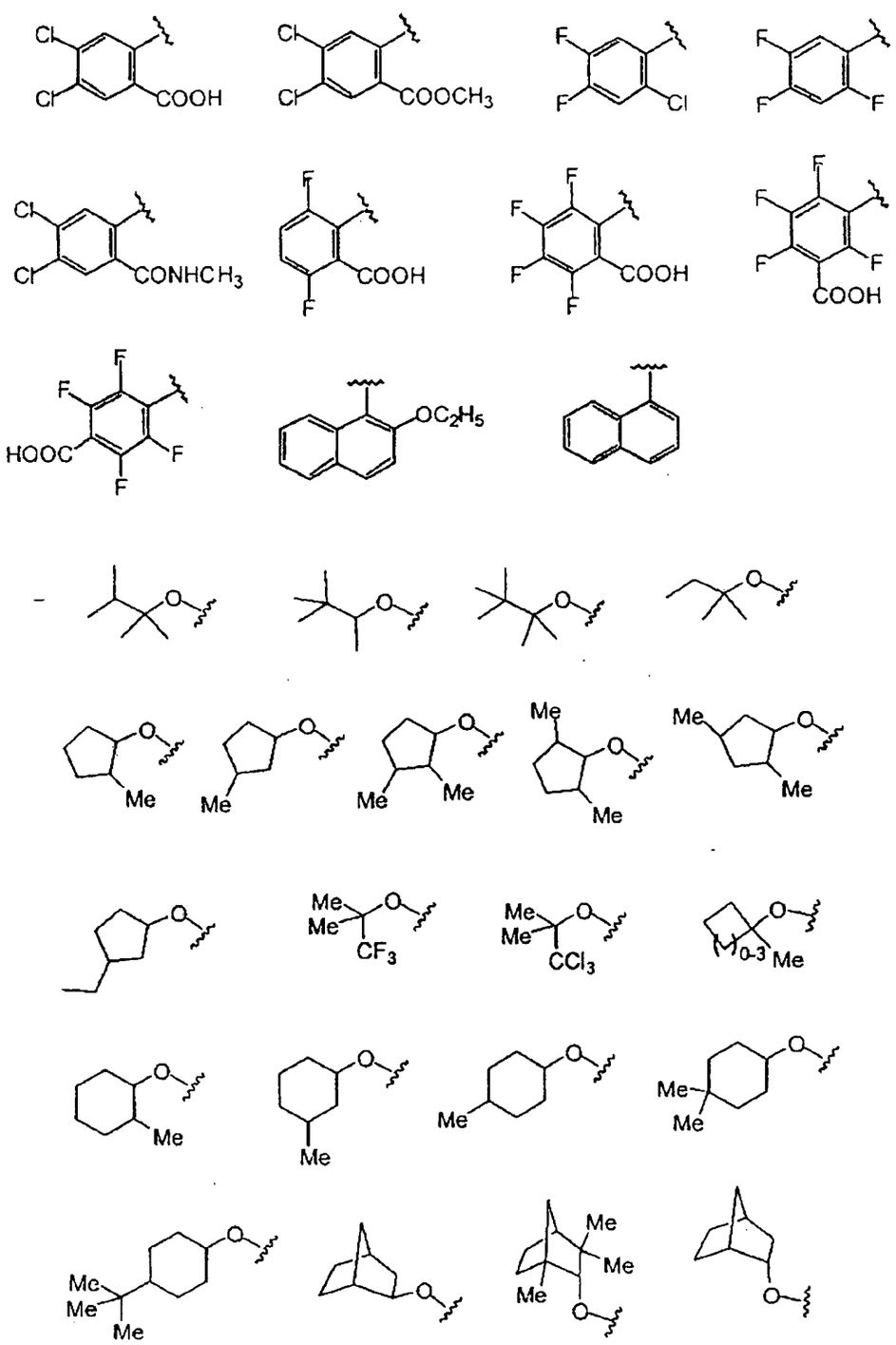
033335

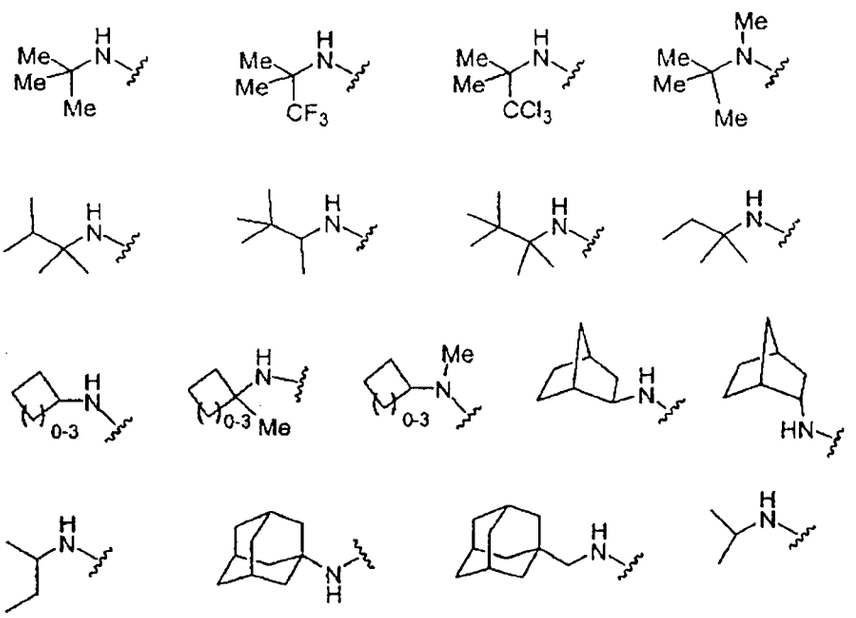

Y14
H
N
Y13
CH3
CH3
CH3
CH3
1-2
CH3
CH3
1-2
HOOC
CH3
HOOC
CH3
CH3
COOH
H3C
0-2
HOOC
CH3
CH3
HOOC
C3H7
C3H7
CH3
CH3
HOOC
HOOC
0-4
H3COOC
COOH
COOH
HOOC
6
HOOC
CH3
H3C
CH3
CH3
HOOC
HOOC
CH3
C3H7
CH3
H3C
H3C
HOOC
CH3
0-2
HOOC
COOH
OTHP
OH
HOOC
H3C
CH3
CH3
C2H5
1-4
S
Y15
Y16

000306


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

683367



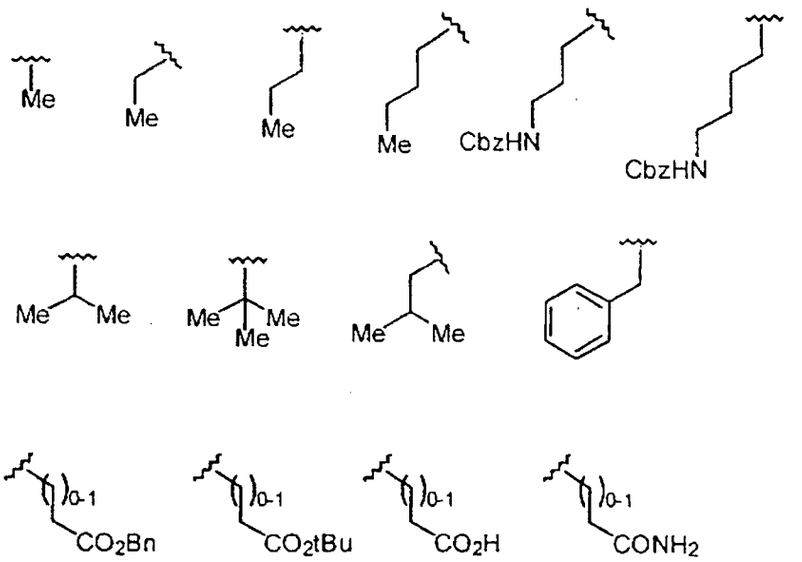


en los cuales:

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 grupos funcionales.



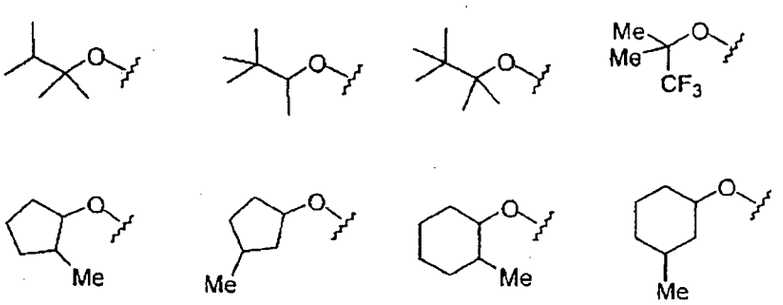
Y^{14} se selecciona de $MeSO_2$, Ac, Boc, iBoc, Cbz, o Alloc;

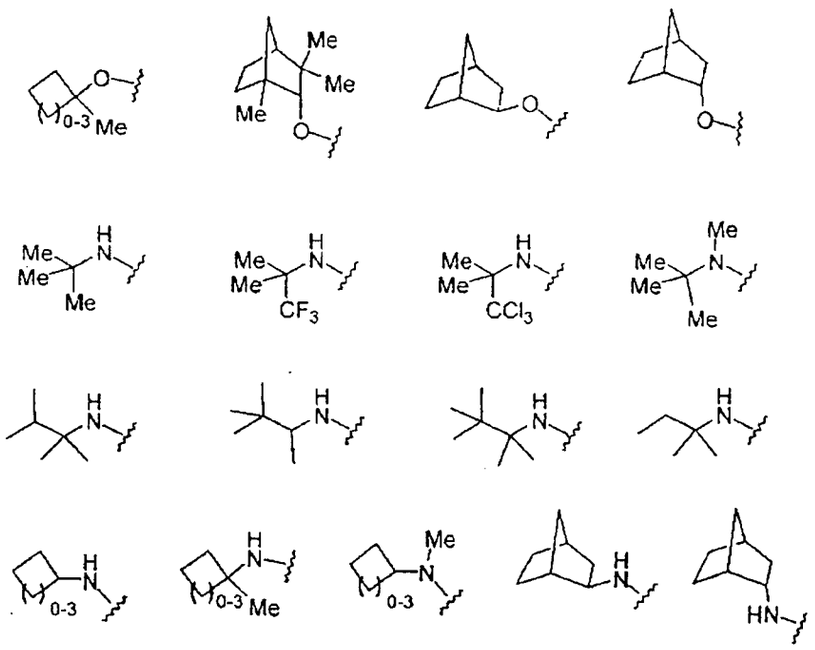
Y^{15} e Y^{16} se seleccionan en forma independiente de alquilo, arilo, heteroalquilo, y heteroarilo;

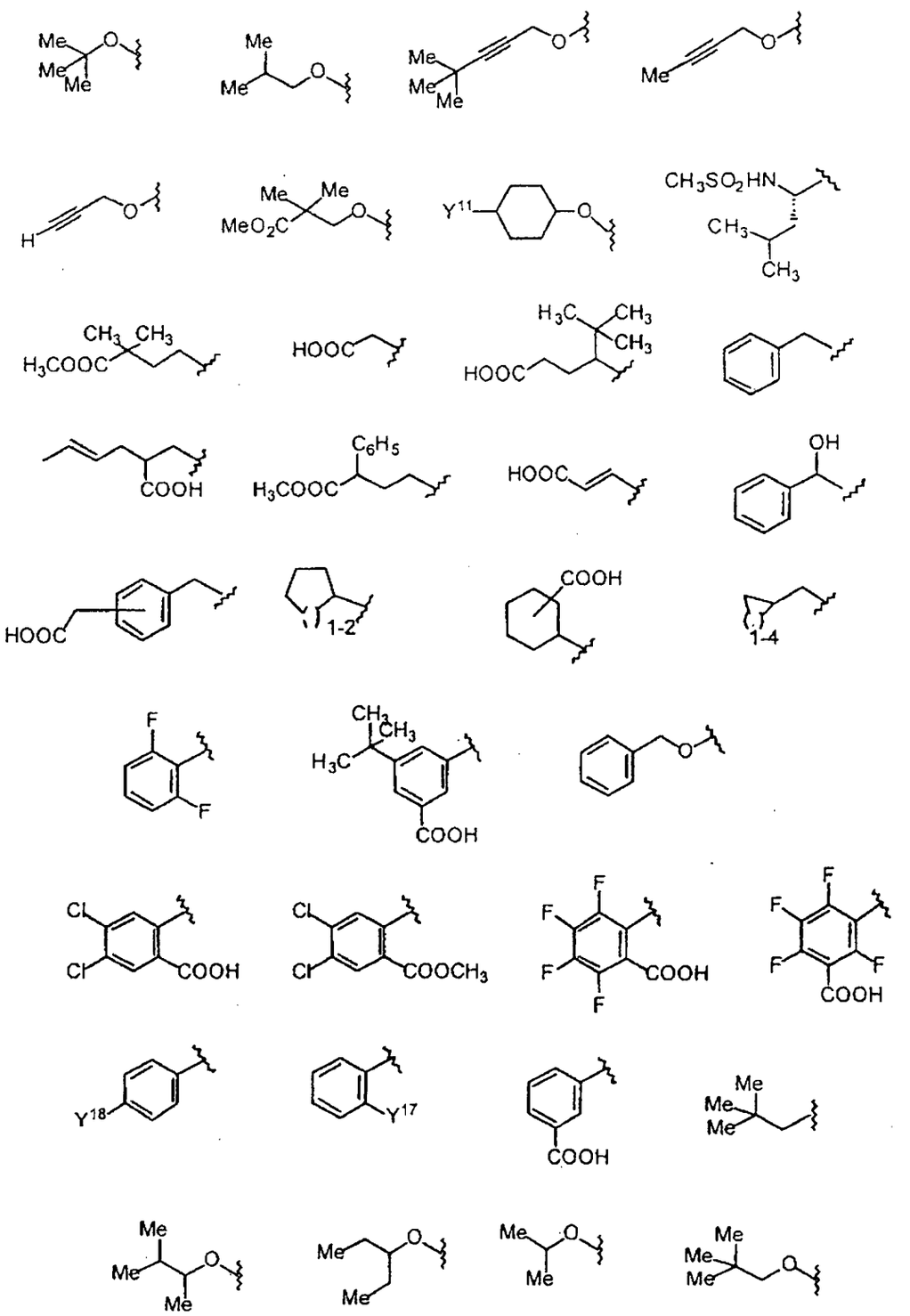
Y^{17} es CF_3, NO_2, $CONH_2$, OH, $COOCH_3$, OCH_3, OC_6H_5, C_6H_5, COC_6H_5, NH_2, o COOH; y

Y^{18} es $COOCH_3$, NO_2, $N(CH_3)_2$, F, OCH_3, CH_2COOH, COOH, SO_2NH_2, o $NHCOCH_3$.

Y puede representarse con mayor preferencia por:




Me
Me
Me
O
0-3
Me
O
O
H
N
Me
Me
Me
H
N
Me
Me
CF3
H
N
Me
Me
CCl3
Me
N
Me
Me
Me
H
N
H
N
H
N
H
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H
N
0-3
H
N
0-3
Me
Me
N
0-3
H
N
HN

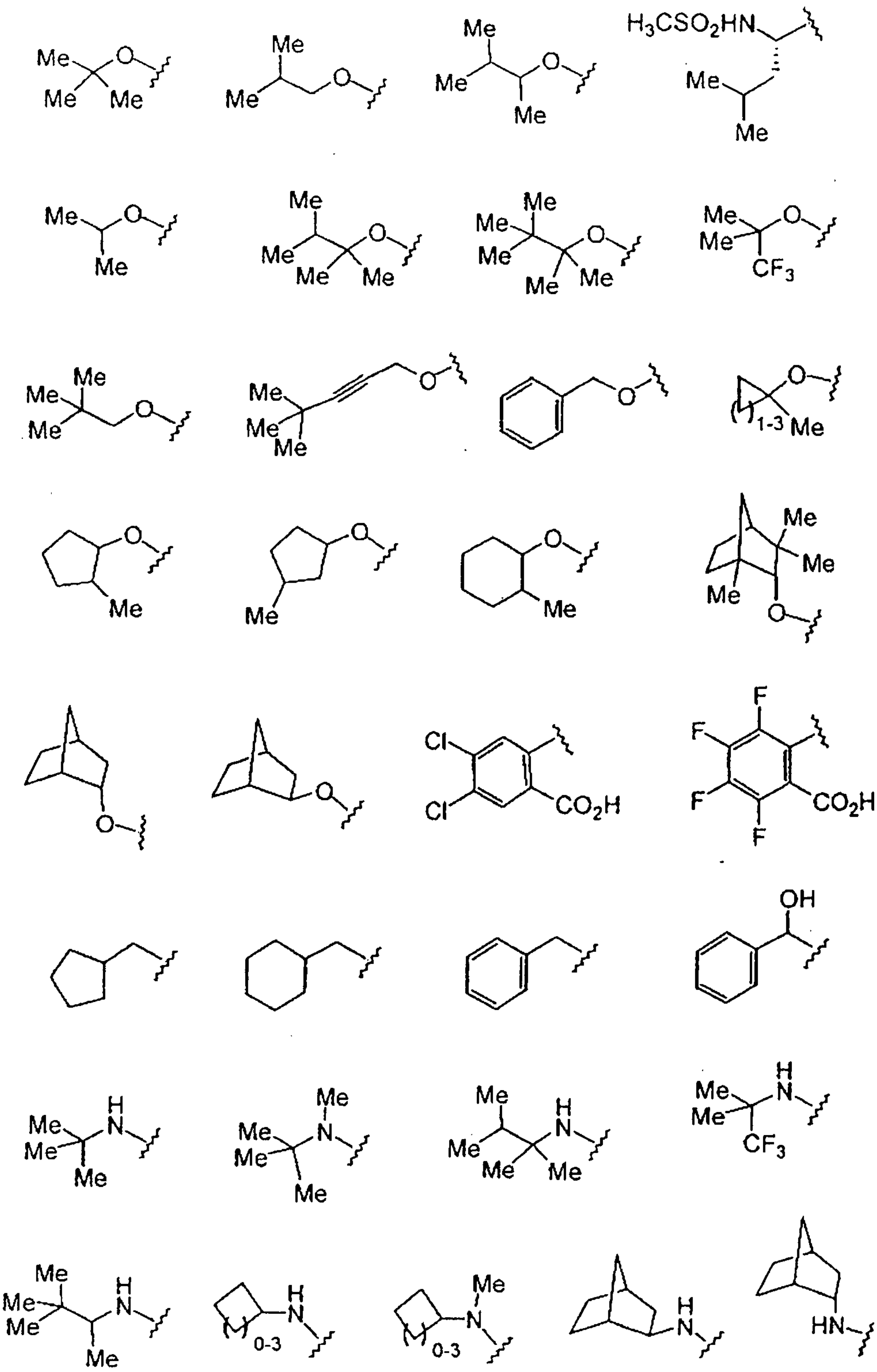


donde:

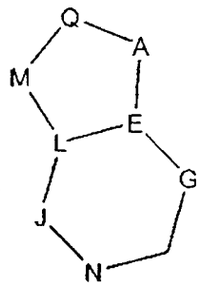
Y^{17} = CF_3, NO_2, $CONH_2$, OH, NH_2, o COOH;

Y^{18} = F, COOH,

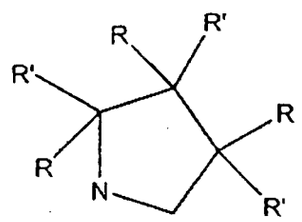
Los grupos funcionales aún más preferidos para Y son:



Como se muestra en la Fórmula I, la unidad:

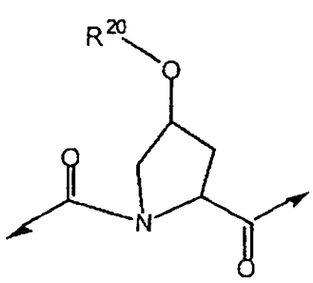


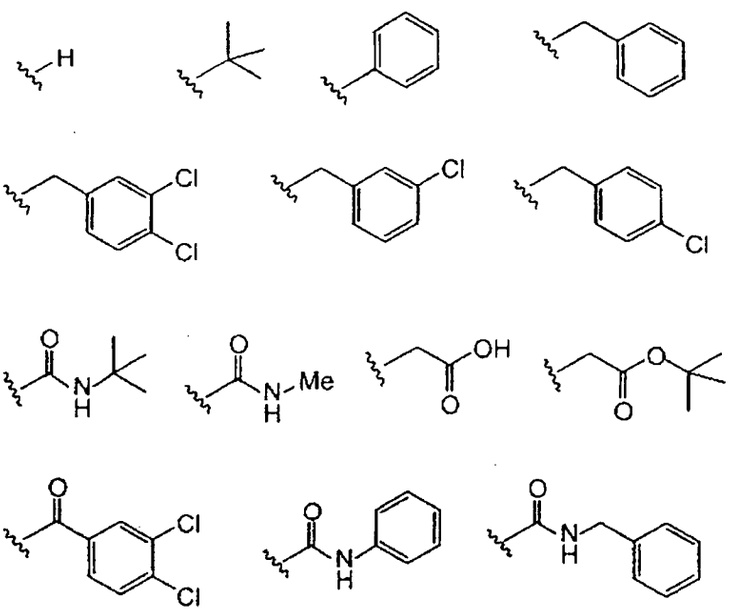
representa una estructura de anillo cíclico, que puede ser una estructura de anillo de cinco o seis elementos. Cuando ese anillo cíclico representa un anillo de cinco elementos, un requerimiento de esta invención es que el anillo cíclico de cinco elementos no contenga un grupo carboxilo como parte de la estructura cíclica. Con preferencia, ese anillo de cinco elementos tiene la estructura:



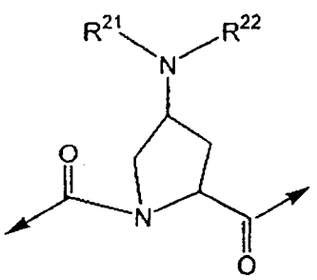
donde R y R' son como se los definió con anterioridad. Las representaciones preferidas para la estructura de anillo de cinco elementos es:

donde R^{20} se selecciona de los siguientes grupos funcionales:

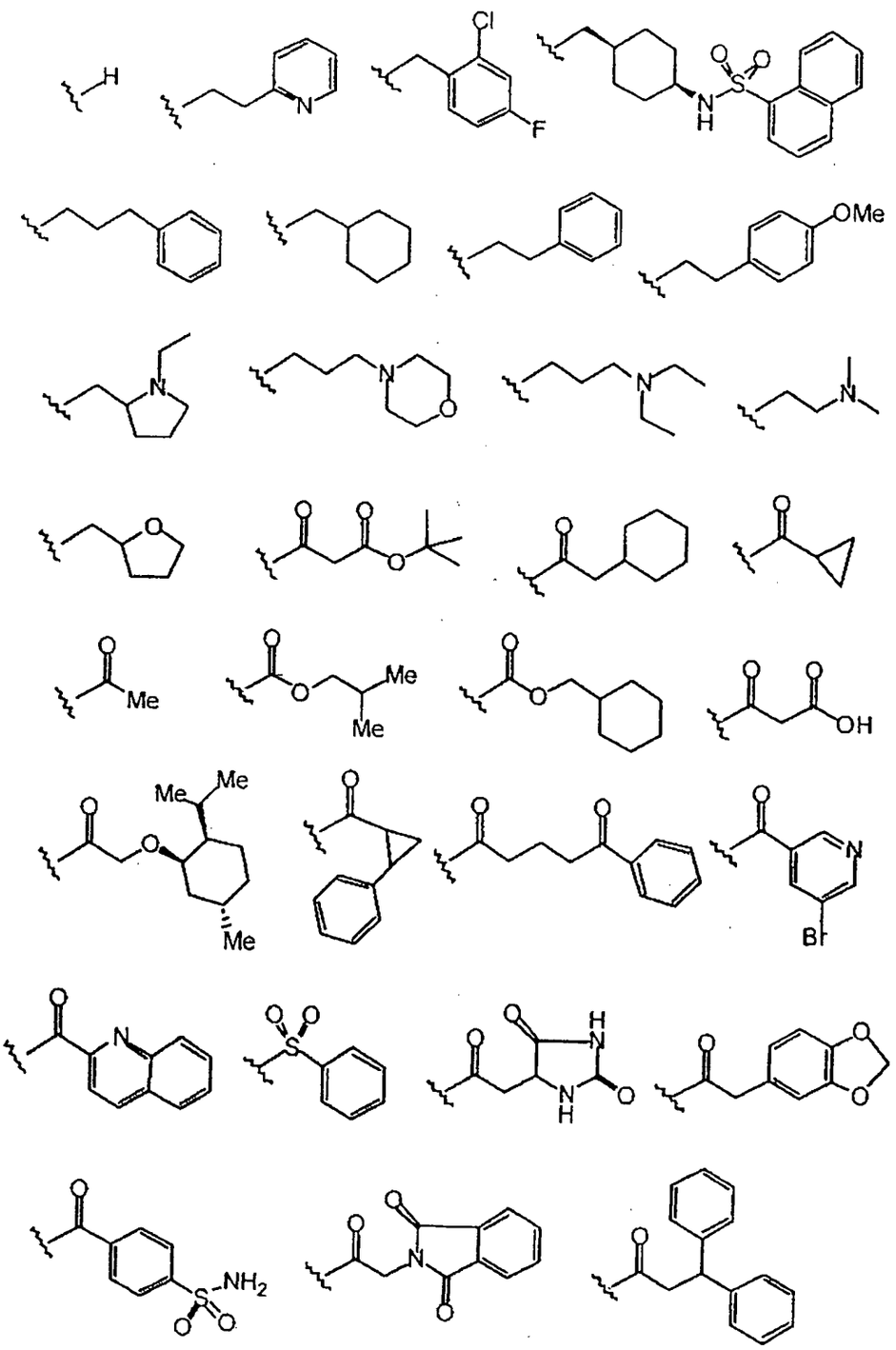




Además, ese anillo de cinco elementos, junto con sus dos carbonilos exocíclicos adyacentes, pueden representarse de la siguiente manera:

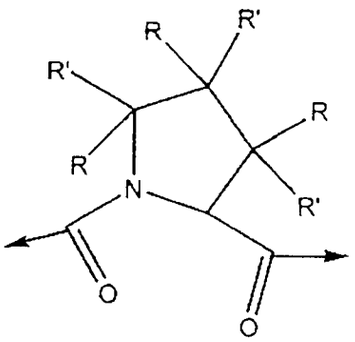


en cuyo caso, R^{21} y R^{22} pueden ser iguales o diferentes y se seleccionan en forma independiente de los siguientes grupos funcionales:



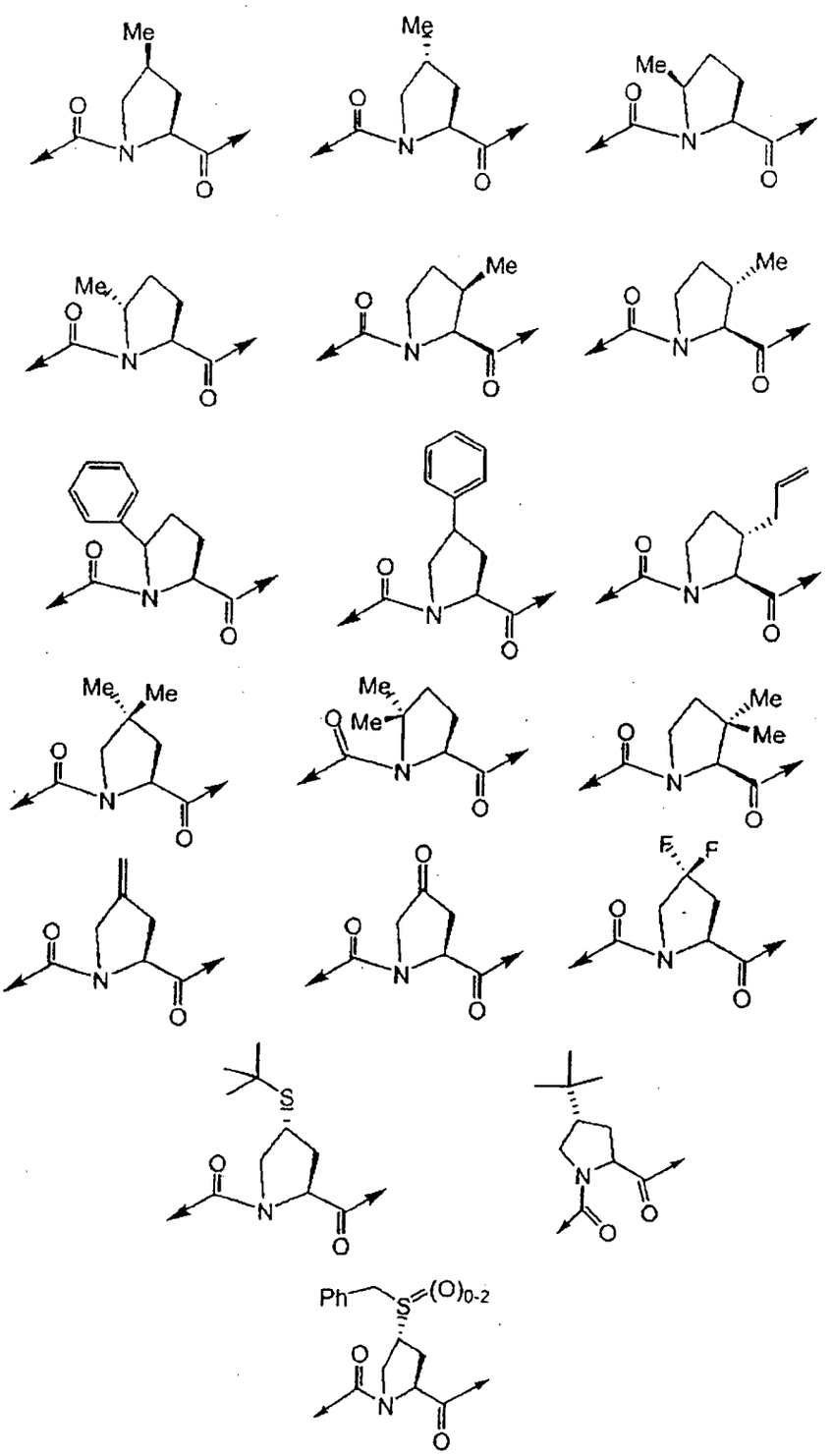
Algunas ilustraciones preferidas para la estructura de anillo de cinco elementos:

000316

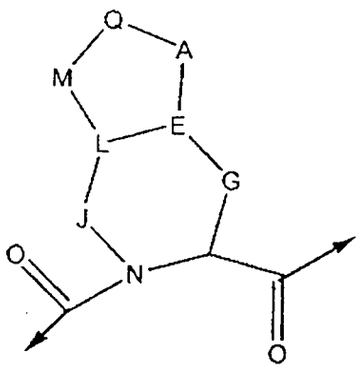


son de la siguiente manera:

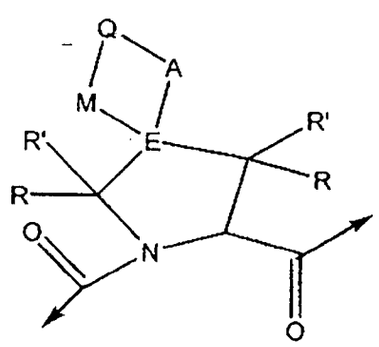
317



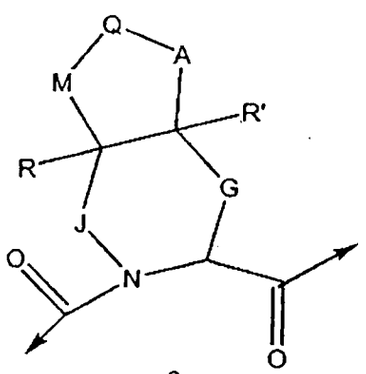
En forma adicional, la unidad:



en la Fórmula I puede representarse por las siguientes estructuras b y c:



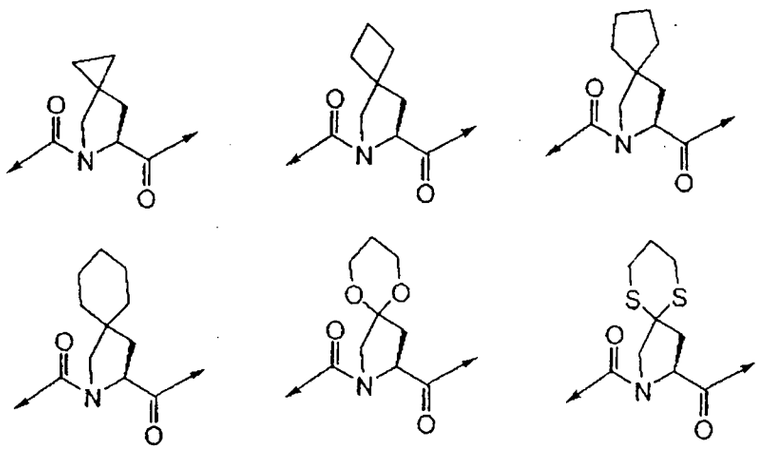
b

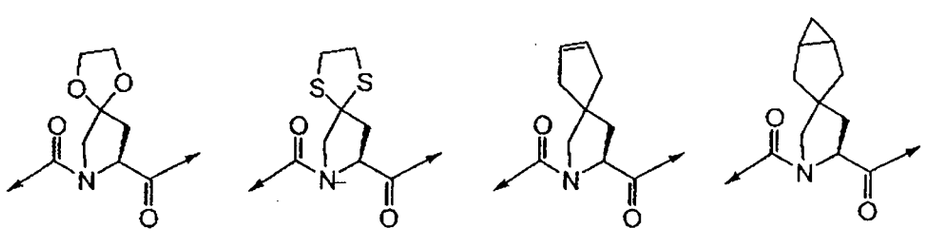


c

Las definiciones preferidas para b son:

-030319

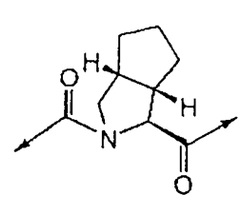
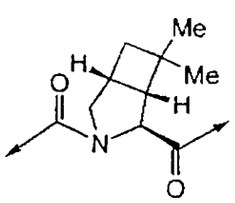
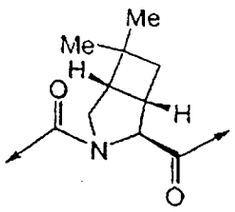
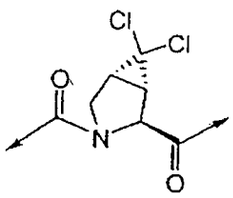
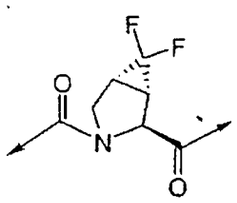
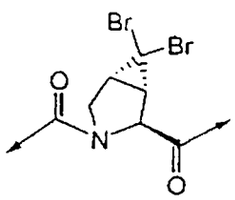
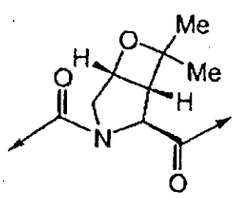
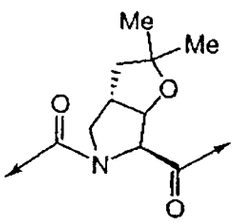
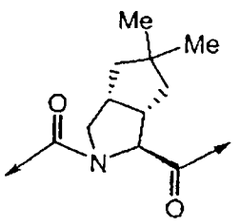
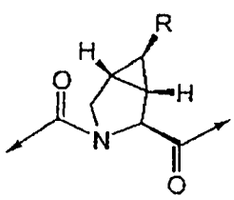
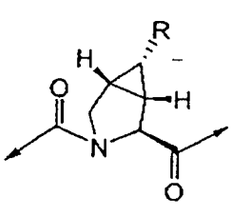
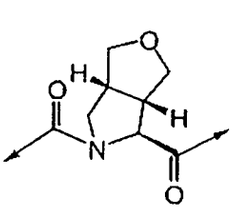




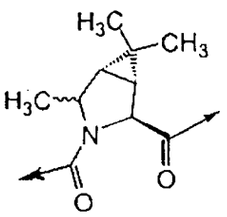
En c, G y J se seleccionan en forma independiente del grupo que consiste de $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ y $(CRR')_p$; A y M se seleccionan en forma independiente del grupo que consiste de O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ y $(CRR')_p$; y Q es CH_2, CHR, CRR', NH, NR, O, S, SO_2, NR; $(CH_2)_p$, $(CHR)_p$, y $(CRR')_p$.

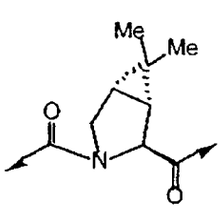
320

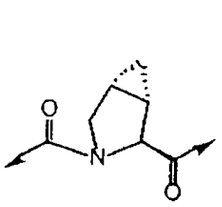
Las definiciones preferidas para c son:

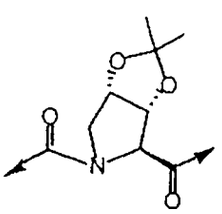













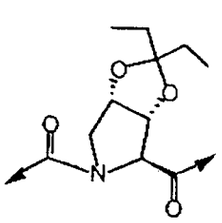
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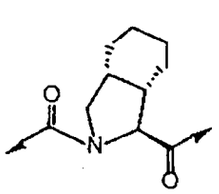


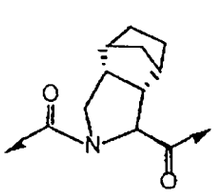


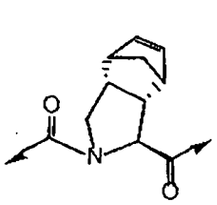


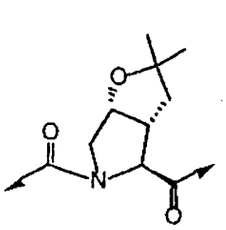


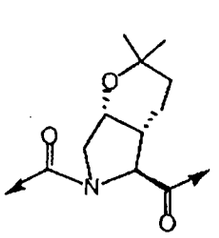


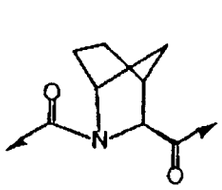


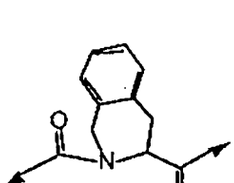


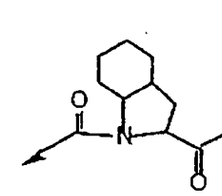


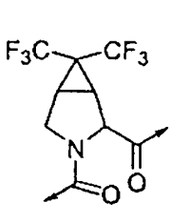






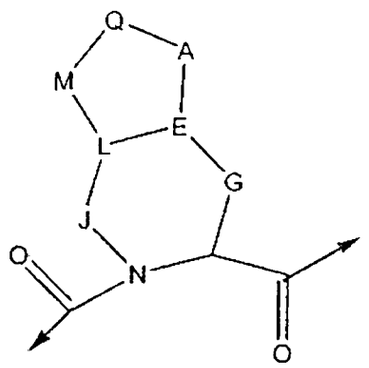






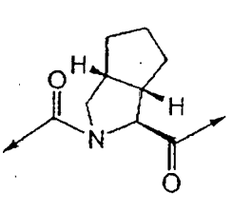
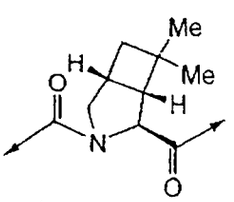
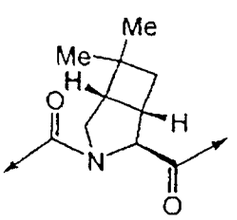
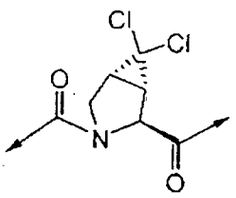
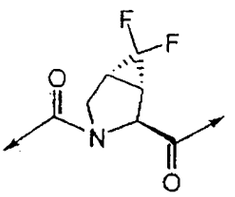
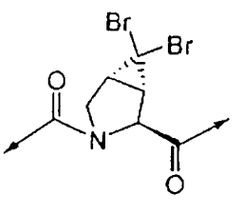
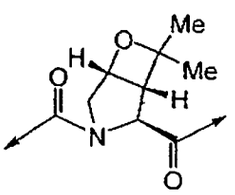
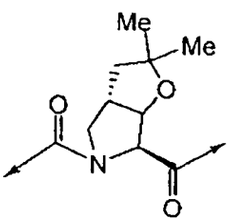
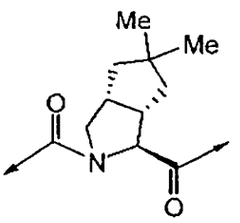
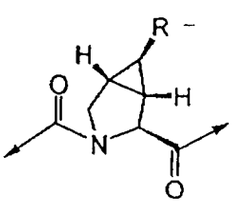
Cuando la estructura de anillo cíclico se muestra como:

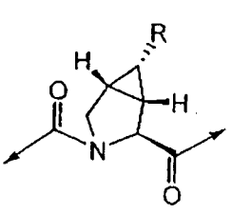
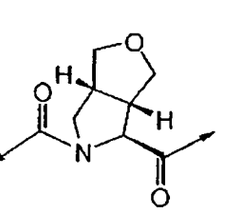
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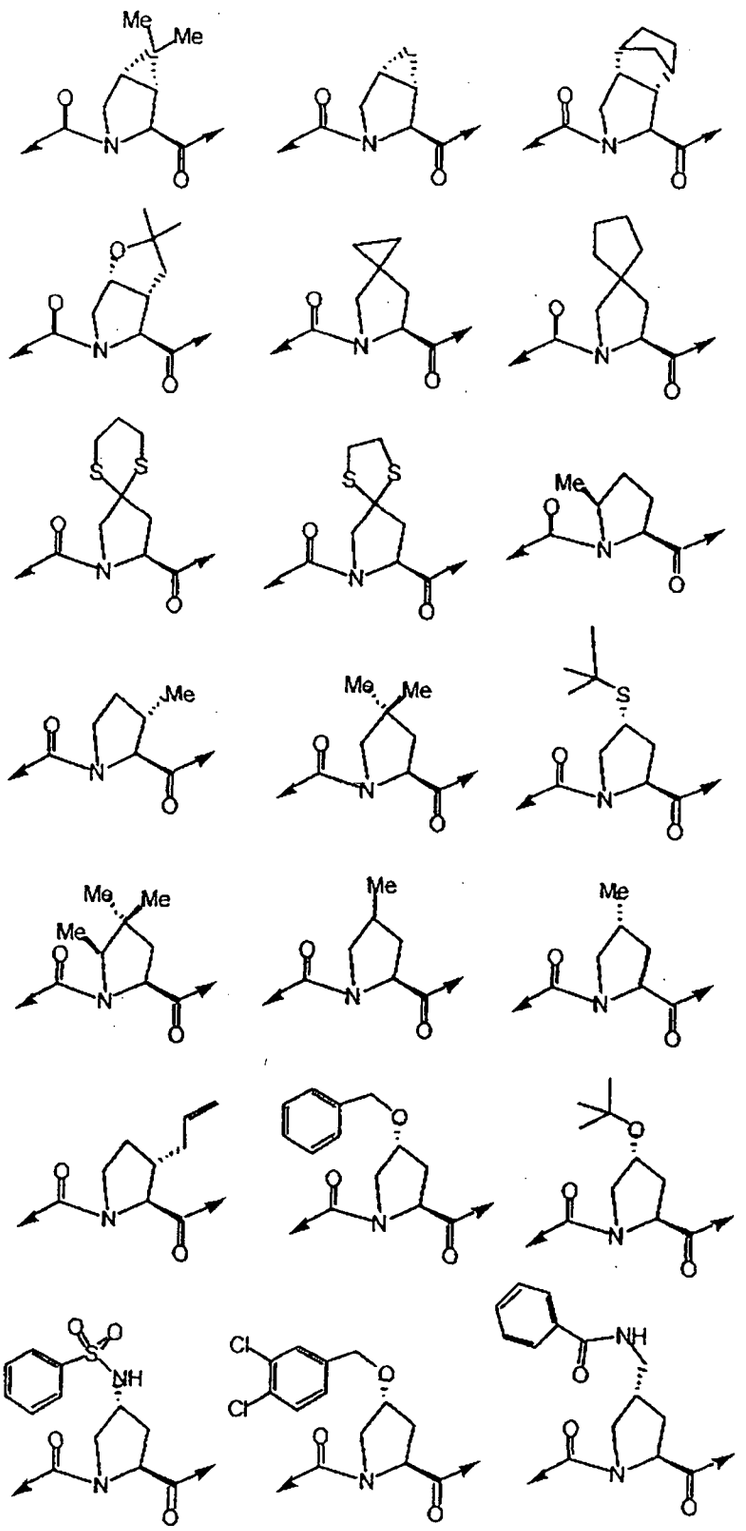
Las ilustraciones más preferidas son las siguientes:

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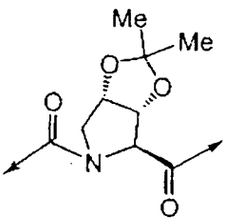











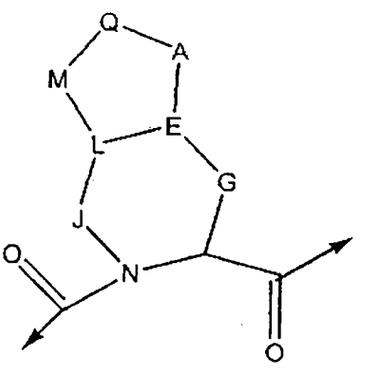
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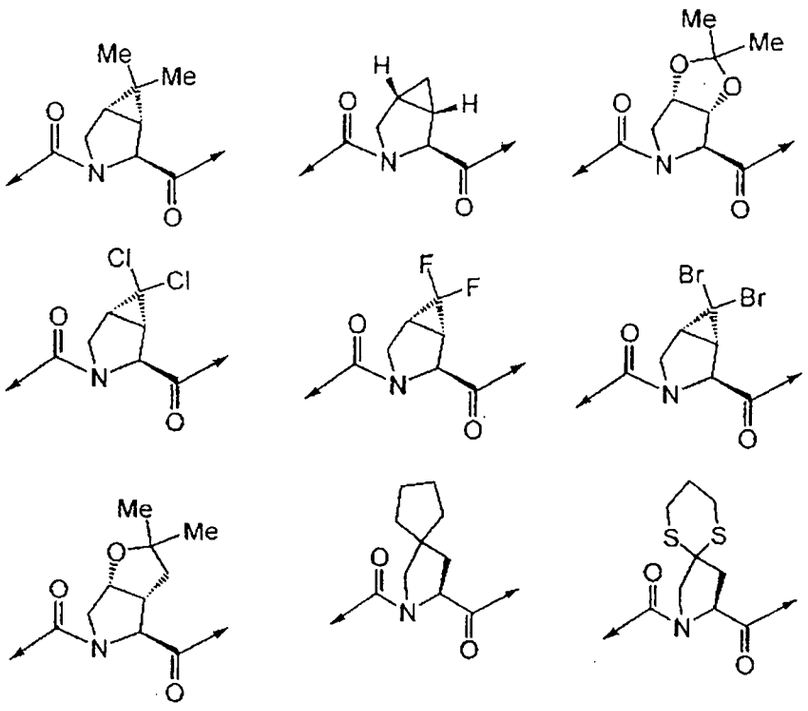


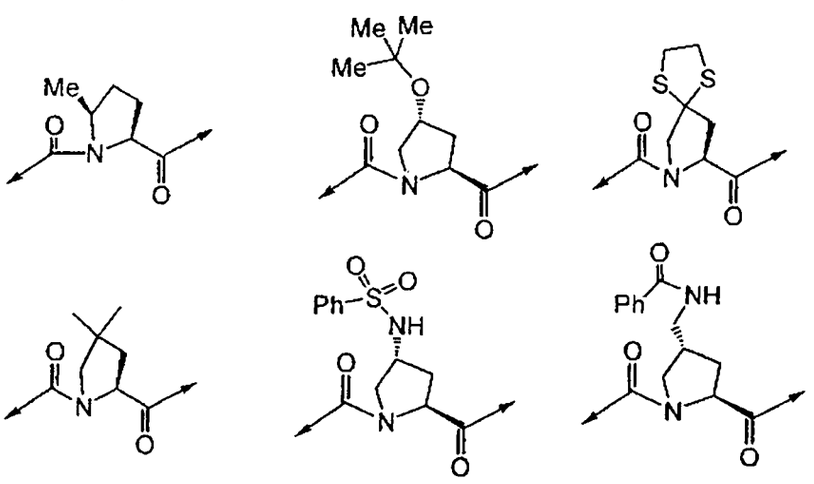
Algunos de los grupos funcionales aún preferidos para la unidad:



que se muestran anteriormente, son:

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A menos que se indique lo contrario, todos los términos técnicos y científicos utilizados aquí tienen el mismo significado comprendido normalmente

333327

por un experto en el arte al cual pertenece la invención. Así, por ejemplo, el término alquilo (incluyendo las porciones alquilo del alcoxi) se refiere a un grupo monovalente derivado de un hidrocarburo saturado de cadena recta o ramificada por medio de la eliminación de un solo átomo que tiene de 1 a 8 átomos de carbono, con preferencia 1 a 6;

arilo - representa un grupo carbocíclico que tiene 6 a 14 átomos de carbono y que tiene por lo menos un anillo bencenoide, donde todos los átomos de carbono aromático sustituibles que se encuentran disponibles del grupo carbocíclico son posibles puntos de unión. Los grupos arilo preferidos incluyen, fenilo, 1-naftilo, 2-naftilo e indanilo, y, en especial, fenilo y fenilo sustituido;

aralquilo - representa un grupo funcional que contiene un grupo arilo enlazado a través de un alquilo inferior;

aralquilo - representa un grupo funcional que contiene un alquilo inferior enlazado a través de un grupo alquilo;

cicloalquilo - representa un anillo carbocíclico saturado que tiene de 3 a 8 átomos de carbono, con preferencia 5 ó 6, sustituidos en forma opcional.

heterocíclico - representa, además de los grupos heteroarilo definidos anteriormente, grupos orgánicos saturados o insaturados que tienen por lo menos un átomo O, S y/o N interrumpiendo la estructura de anillo carbocíclico que consiste de un anillo o dos anillos fusionados, en los cuales cada anillo tiene 5, 6 ó 7 elementos y puede, o no, tener enlaces dobles que carecen de electrones pi no localizados, en los cuales la estructura tiene de 2 a 8, con preferencia de 3 a 6 átomos de carbono, por ejemplo, 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 O, S y/o N que interrumpe una estructura de anillo carbocíclico y que

333328

tiene un número suficiente de electrones pi no localizados para suministrar carácter aromático, donde el grupo heterociclilo aromático tiene de 2 a 14, con preferencia 4 ó 5 átomos de carbono, por ejemplo, 2-, 3- o 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, además, estar sustituidos en forma opcional. En forma adicional, a menos que se defina lo contrario, como se indicó anteriormente, el término "sustituido o insustituido", u "opcionalmente sustituido" se refiere al grupo funcional que se sustituye en forma opcional y químicamente estable con un grupo funcional que pertenece R^{12} o R^{13}. Según se lo utiliza aquí, el término "prodroga" se refiere a compuestos que son precursores de drogas, que, luego de la administración a un paciente, liberan la droga *in vivo* a través de algún proceso químico o fisiológico (por ejemplo, una prodroga llevada al pH fisiológico o a través de la acción enzimática se convierte en la forma de droga deseada).

También se incluyen en la invención los tautómeros, rotámeros, enantiómeros y otros isómeros ópticos, como también las prodrogas, de los compuestos de la Fórmula I, como también sales aceptables para uso farmacéutico, solvatos y sus derivados.

Una característica adicional de la invención son las composiciones farmacéuticas que contienen, como ingrediente activo, un compuesto de la Fórmula I (o su sal, solvato, o isómeros) junto con un vehículo o excipiente aceptable para uso farmacéutico.

La invención también suministra métodos para preparar compuestos de la Fórmula I, como también métodos para el tratamiento de enfermedades como, por ejemplo, HCV, SIDA (Síndrome de Inmunodeficiencia Adquirida), y trastornos relacionados. Los métodos para el tratamiento comprenden la administración a

030329

un paciente que sufre de dicha enfermedad o enfermedades de una cantidad efectiva terapéuticamente de un compuesto de la Fórmula I, o composiciones que comprenden un compuesto de la Fórmula I.

También se describe el uso de un compuesto de la Fórmula I para la fabricación de un medicamento para el tratamiento de HCV, SIDA y trastornos relacionados.

También se describe un método para el tratamiento 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.

También se describe un método para modular la actividad de la proteasa del virus de la hepatitis C (HCV), que comprende el contacto de la proteasa de HCV con uno o más de los compuestos de la invención.

También se describe un método de tratamiento, prevención o alivio de uno o más síntomas de la hepatitis C, que comprende la administración de una cantidad efectiva de uno o más compuestos de la invención. La proteasa de HCV es la proteasa NS3 o NS4a. Los compuestos de la invención inhiben dicha proteasa. 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 la Fórmula I como inhibidores de la proteasa HCV, en especial la proteasa serina NS3/NS4a de HCV, o uno de sus derivados aceptables para uso farmacéutico, de los cuales se suministraron las definiciones anteriormente.

Los compuestos representativos de la invención, que muestran excelente actividad de inhibición de la proteasa de HCV se describen a continuación en las **Tablas 1 a 5** junto con su actividad (rangos de valores Ki* en nanomolar, nM).

En las Reivindicaciones se describen en forma adicional varios compuestos, como también compuestos adicionales.

Tabla 1: Compuestos y resultados del ensayo continuo de la proteasa de 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

333331

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

8	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

033334

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

033335

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

330336

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
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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

833337

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

333338

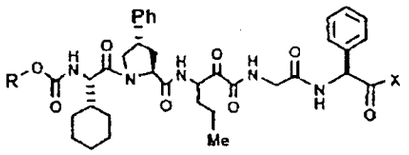
352	C
353	C
354	C
355	C
356	A
357	A
358	C
359	A
360	B
361	B
362	C

Rango Ki* del ensayo continuo de HCV:

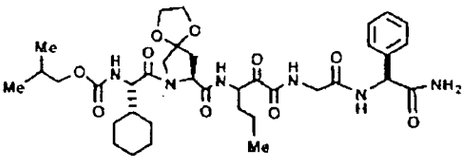
Categoría A= 1-100 nM; Categoría B= 101-1.000 nM; Categoría C >1.000 nM

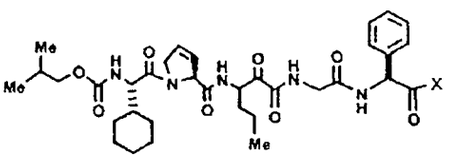
Algunos de los tipos de compuestos de la invención y los métodos de sintetizar varios tipos de los compuestos de la Fórmula I de la invención se describen a continuación, luego se describen en forma esquemática, seguidos de Ejemplos ilustrativos.

033339

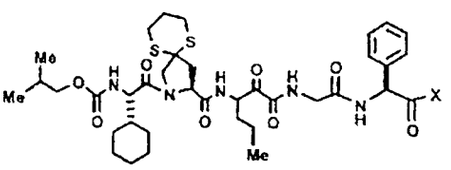


(R= t-butilo, X= NH_2)
(R=Isobutilo, X NH_2)
(R= t-butilo, X= OH)
(R= tricloroetilo, X= OH)

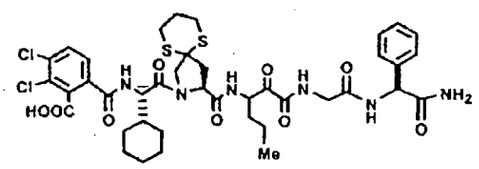


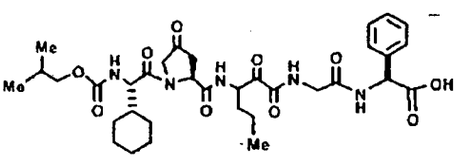


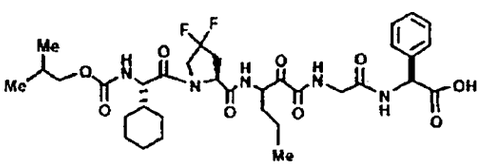
(X = O^{t}Bu)
(X = OH)

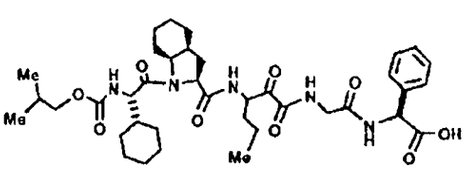


(X = OH)
(X = O^{t}Bu)
(X = NH_2)
(X = NHMe)
(X = NMe_2)

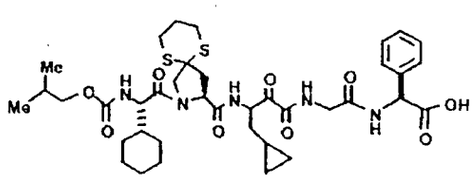


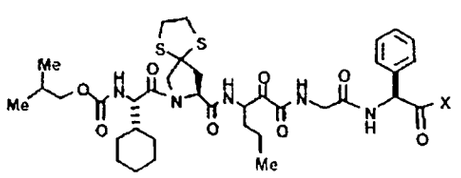




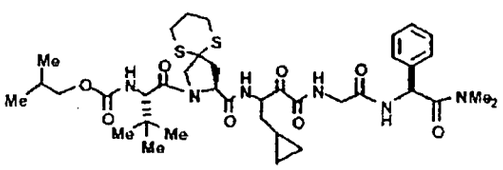


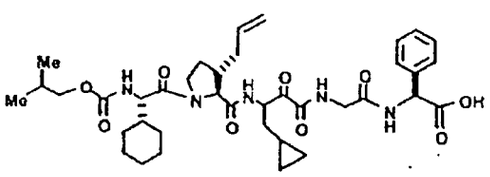
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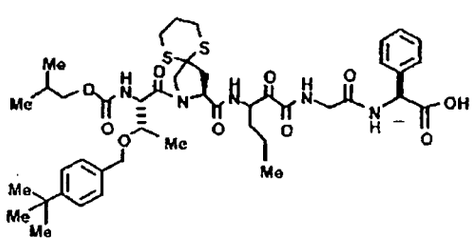


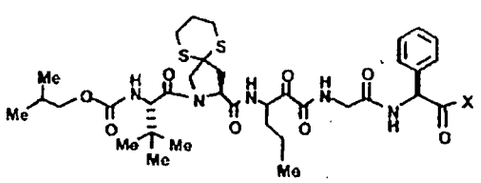


(X = NH_2)
(X = NMe_2)
(X = NHMe)
(X = OH)

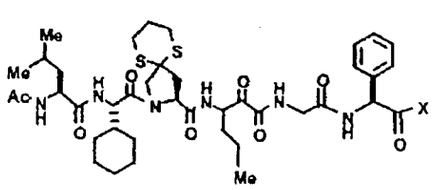




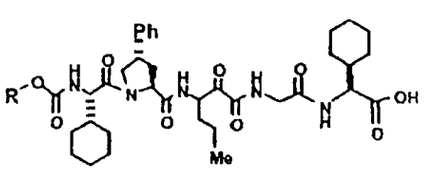




(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)

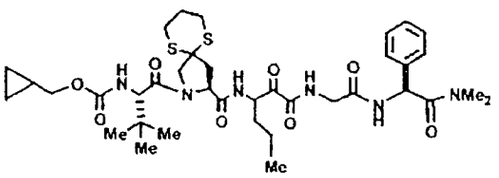


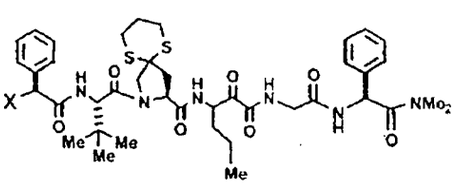
(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)
(X = NMeOMe)



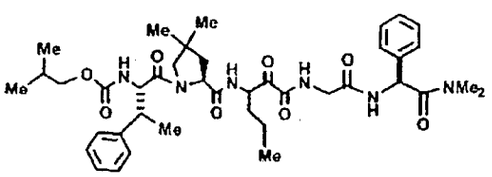
(R = t-butyl)
(R = Isobutyl)

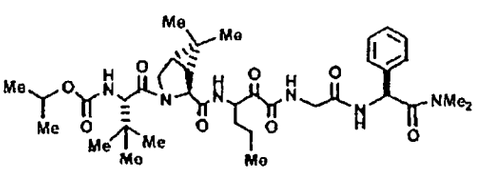
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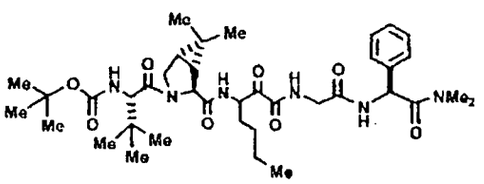


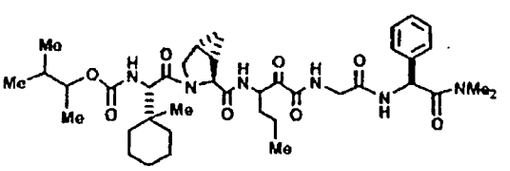


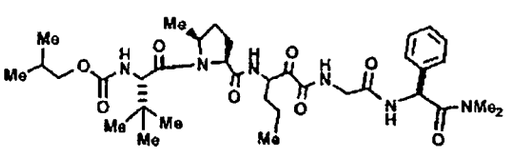
(X = Me, Y = CH_2Me)
(X = OAc, Y = Me)

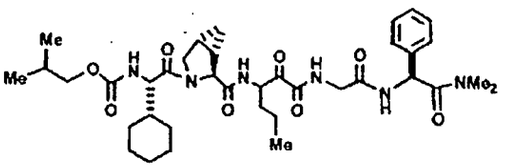


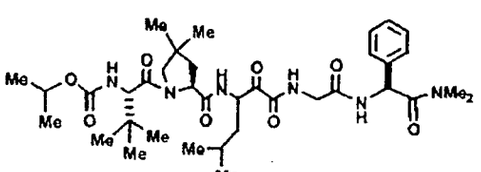


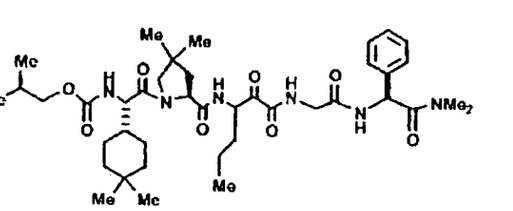




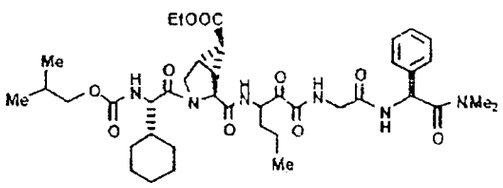


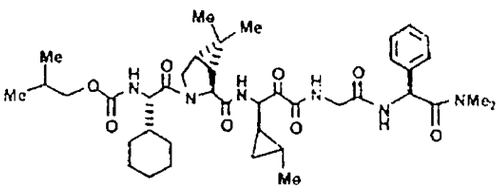


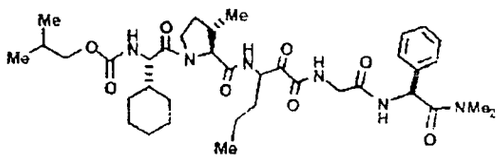


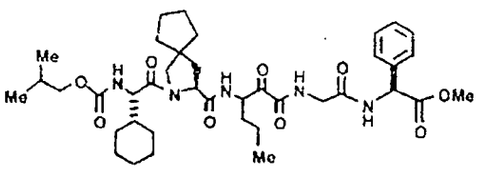


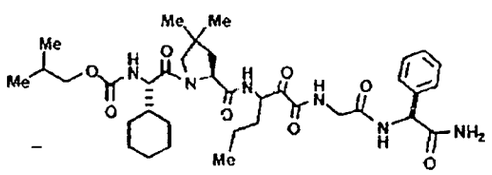
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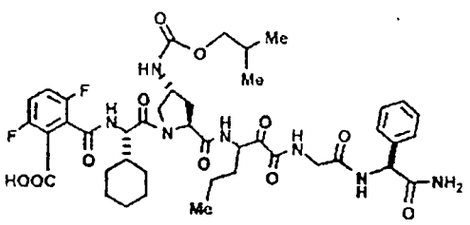


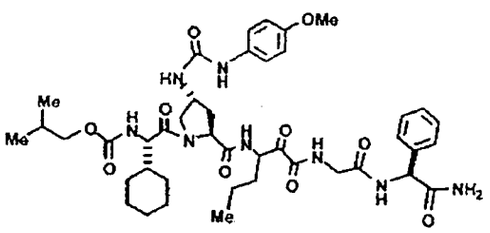


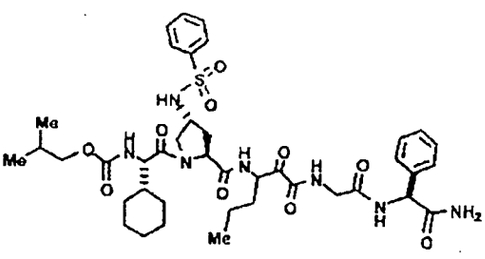


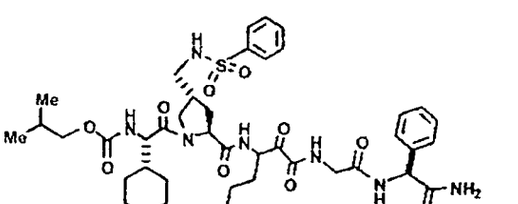


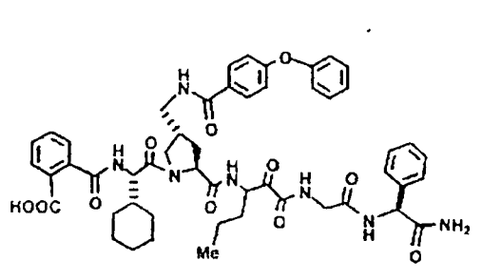








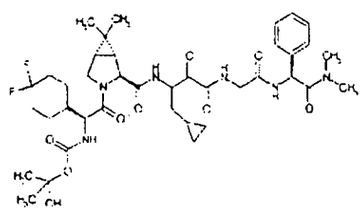


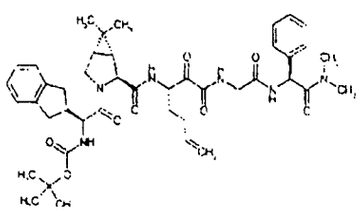


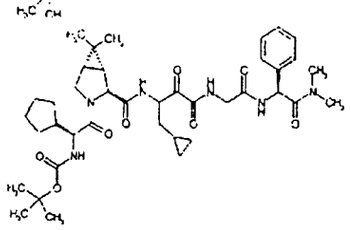


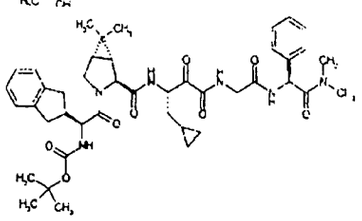


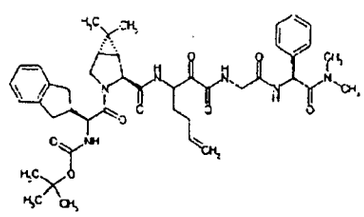
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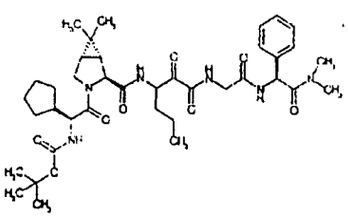


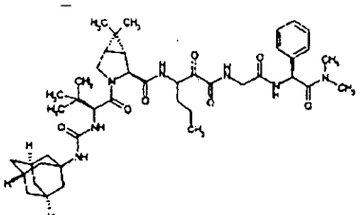


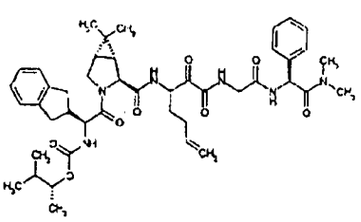


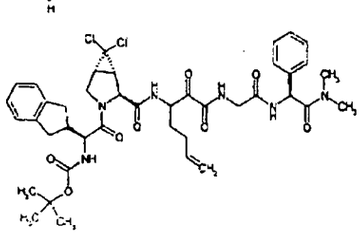


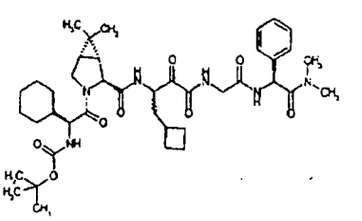


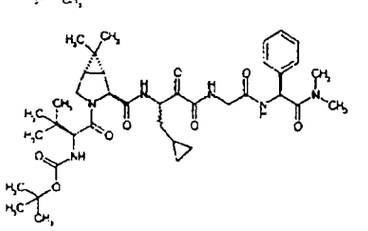


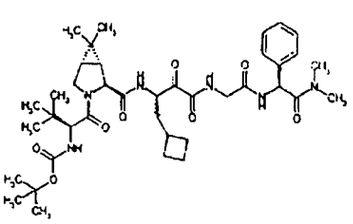




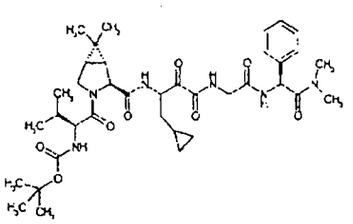


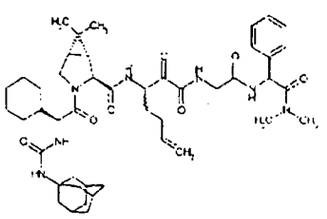


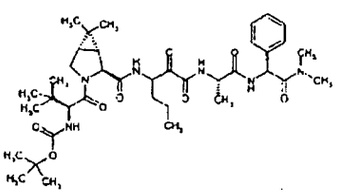


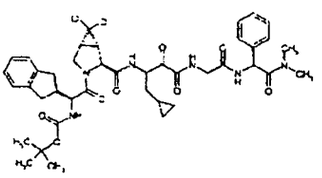


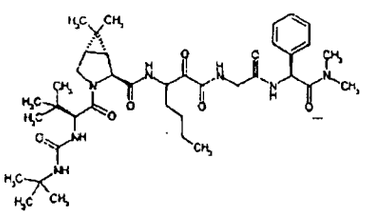
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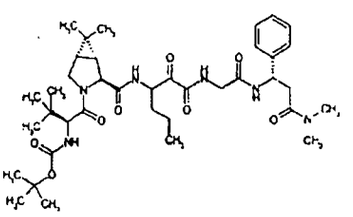


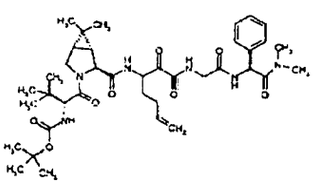


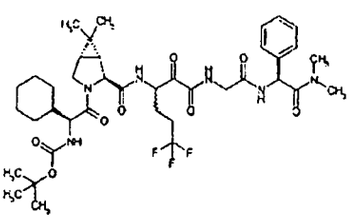


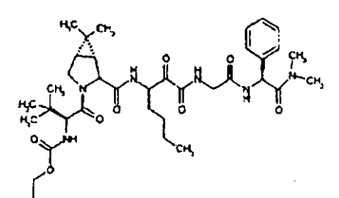


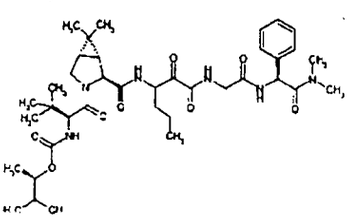




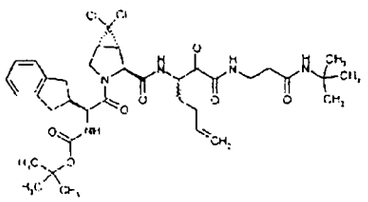


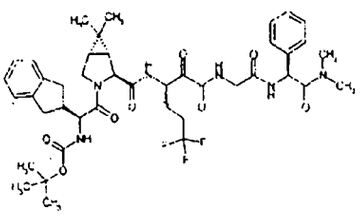


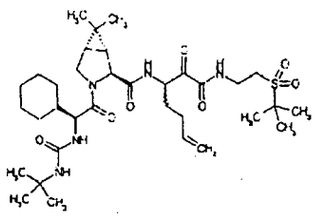


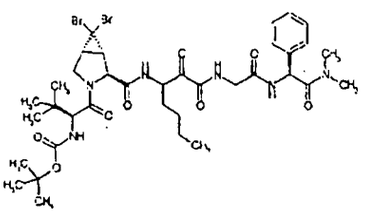


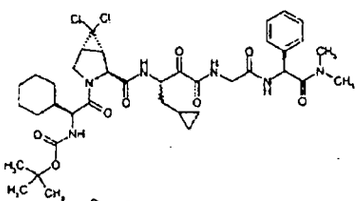
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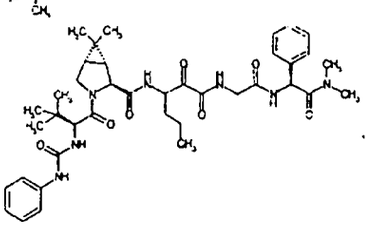


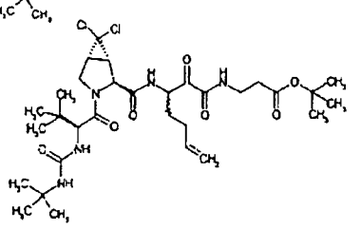


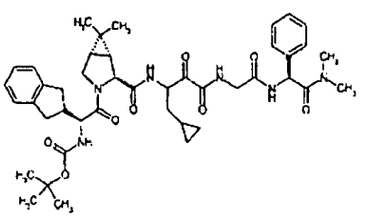


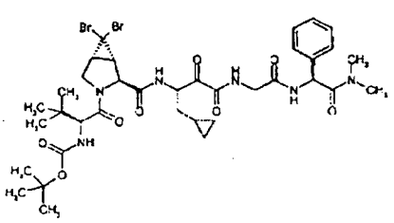


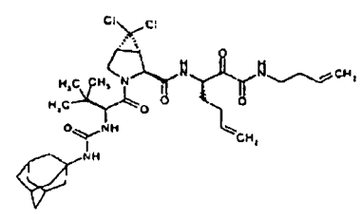


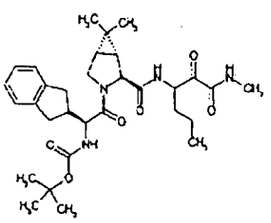


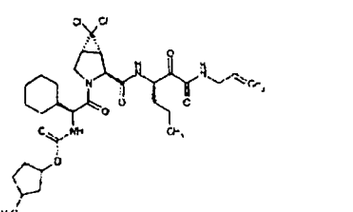


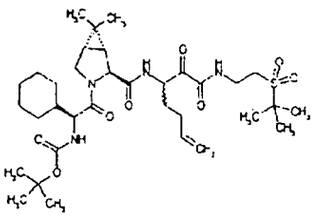


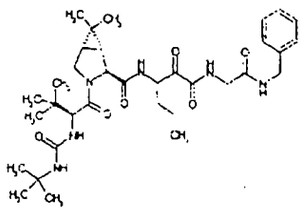


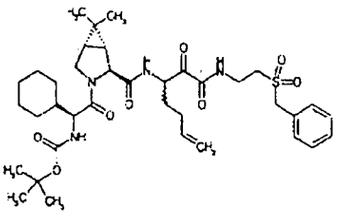


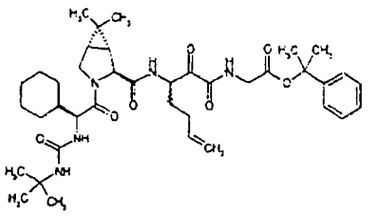


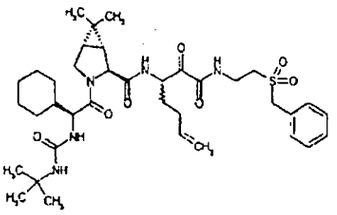


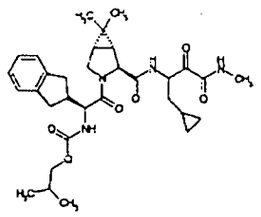


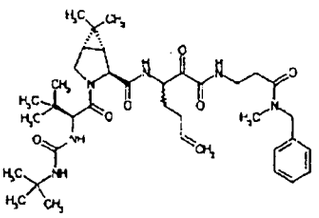


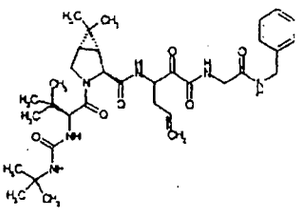


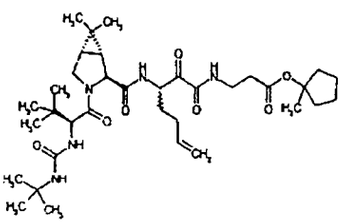


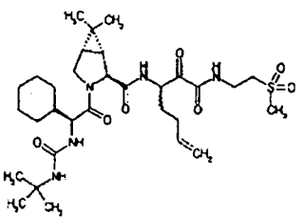


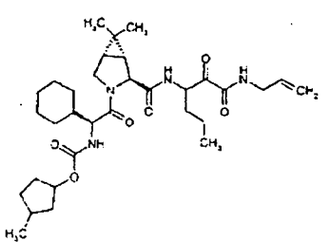


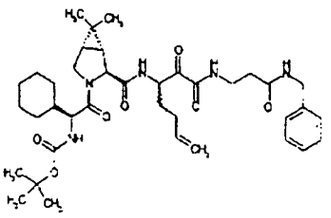




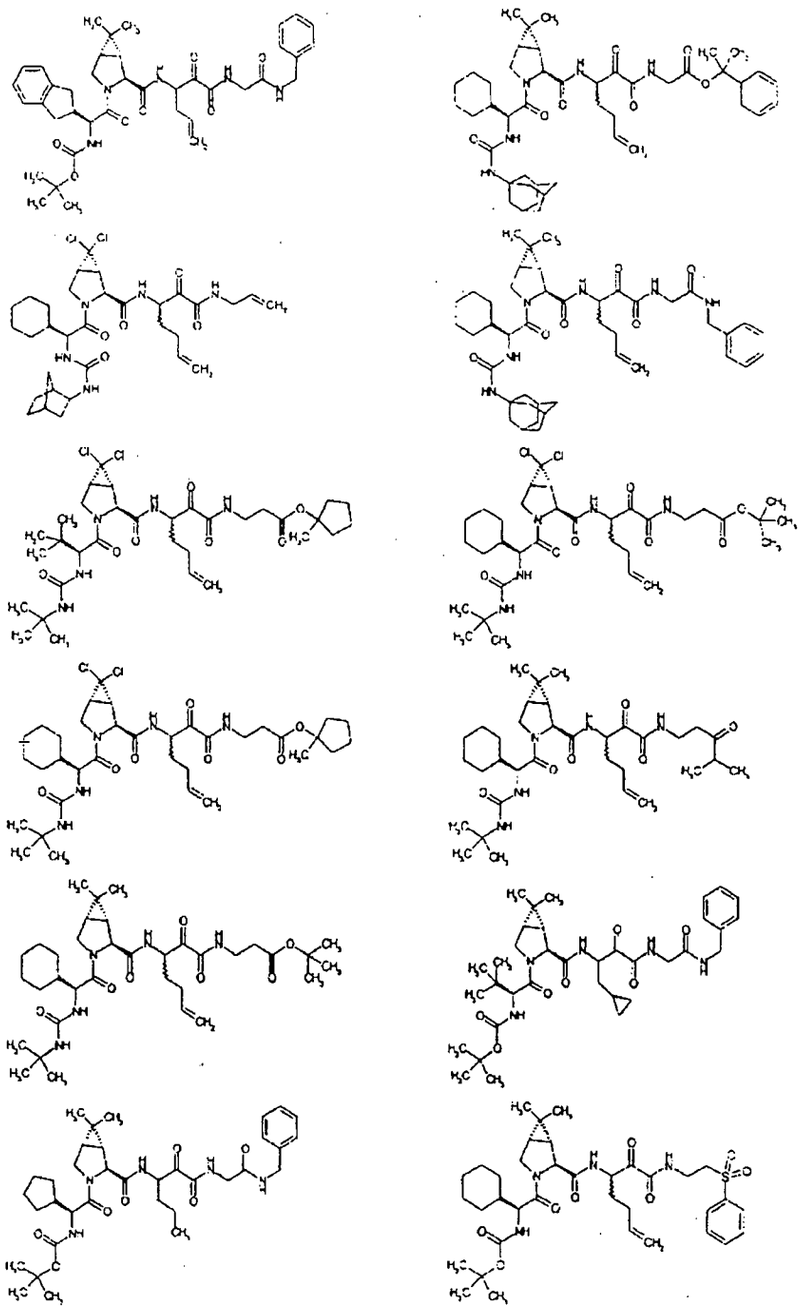




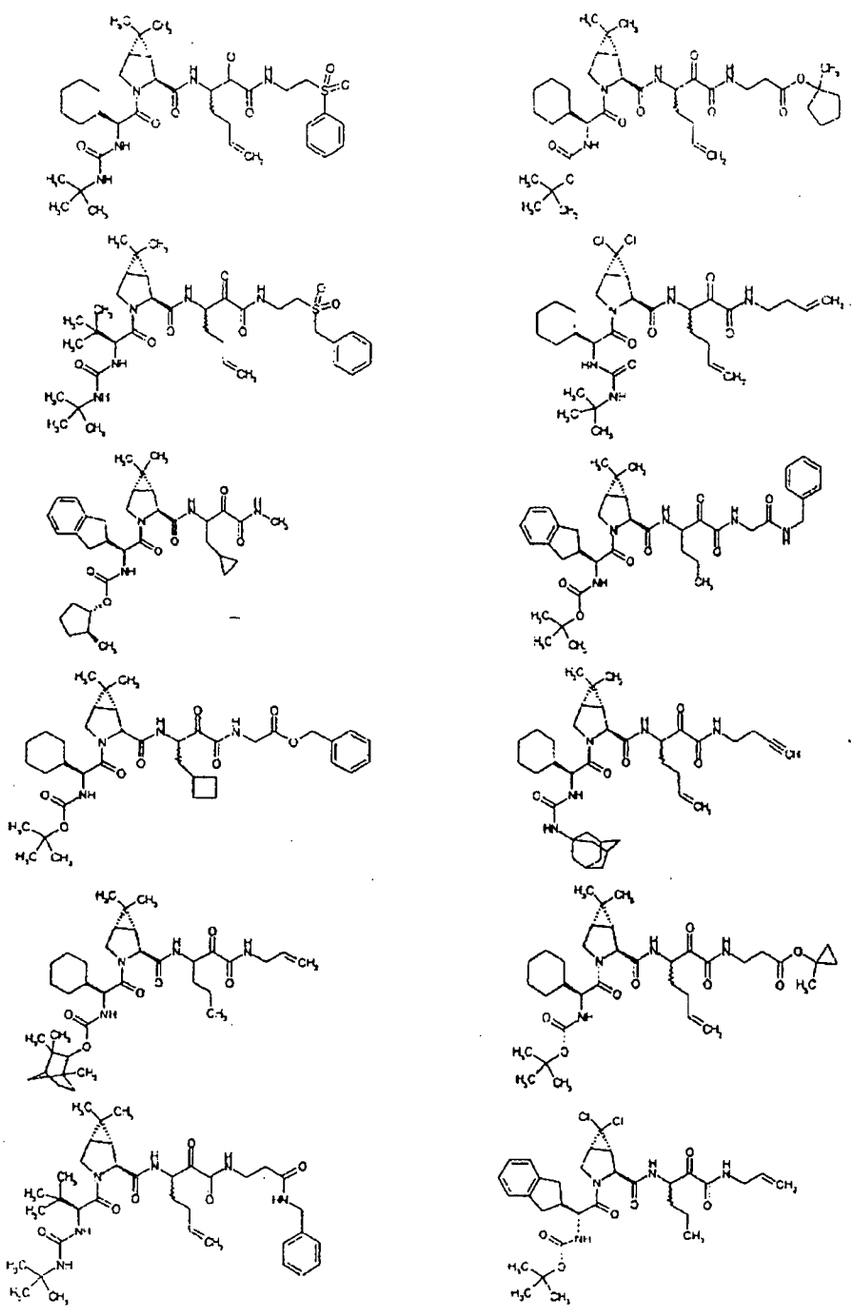




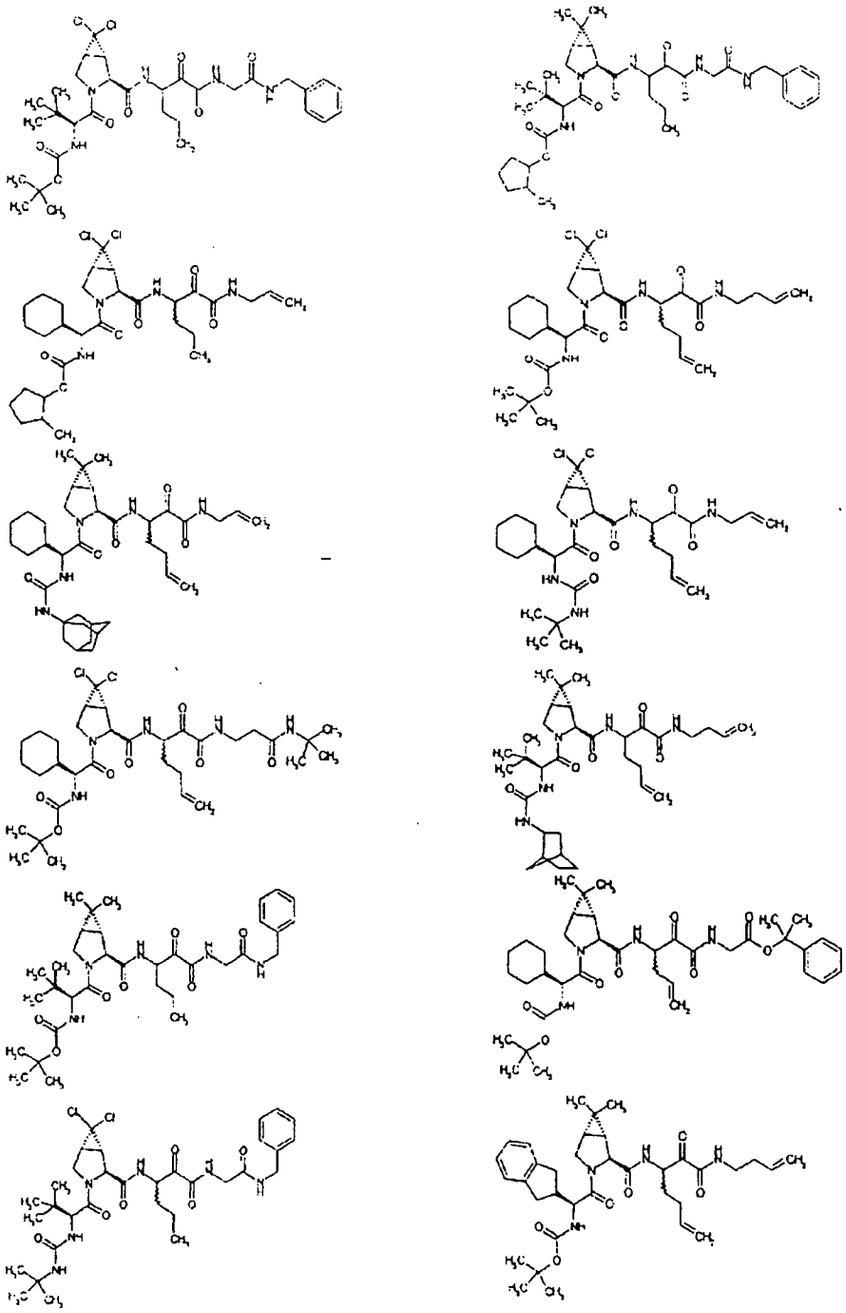
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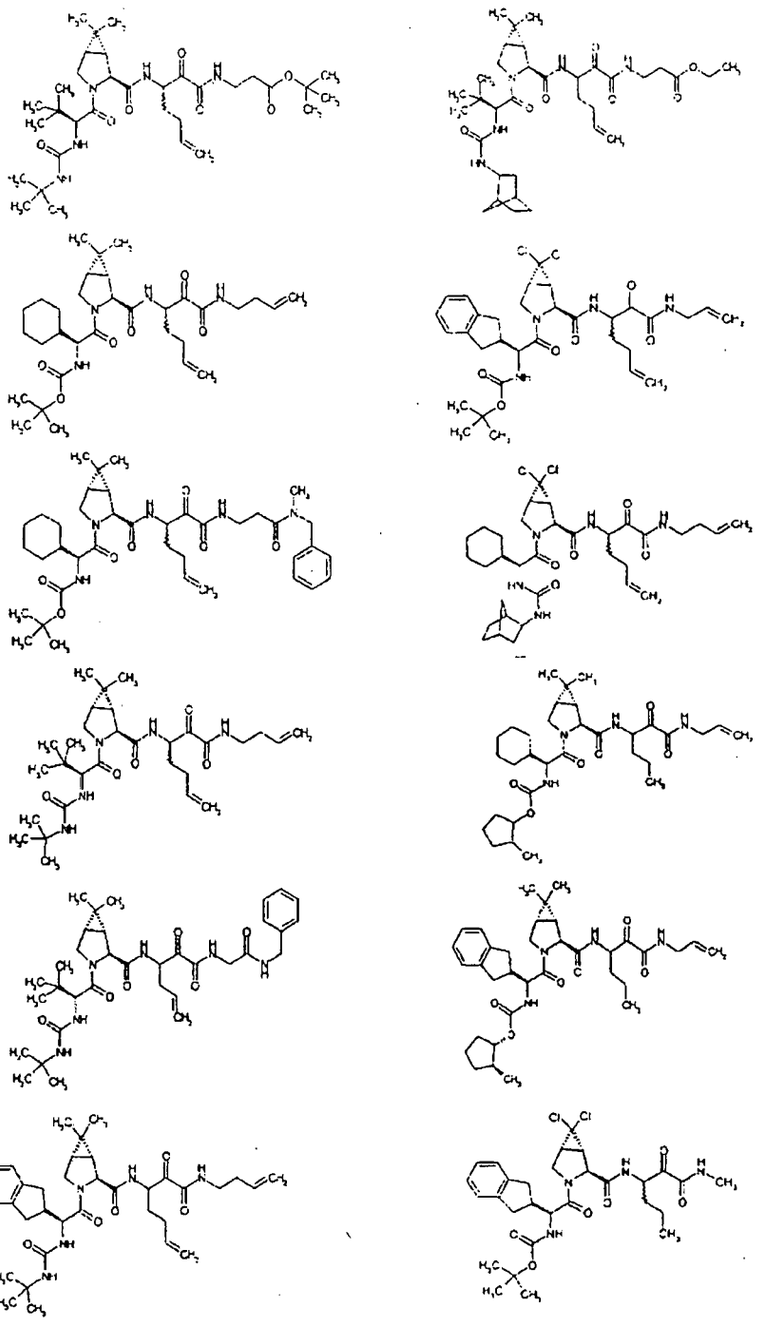
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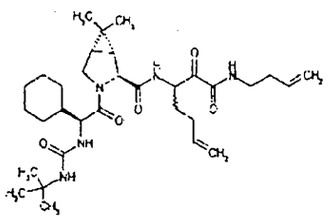
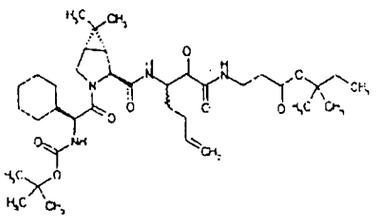
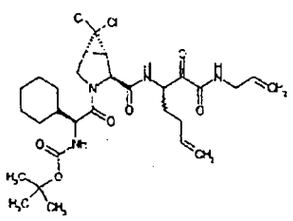
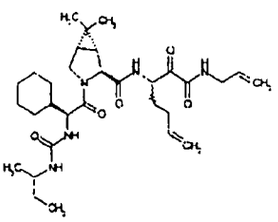
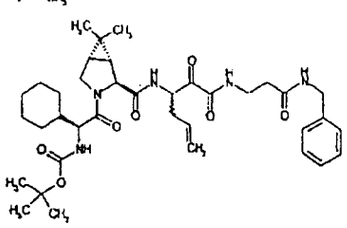
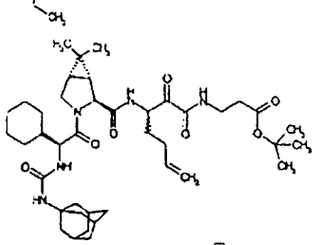
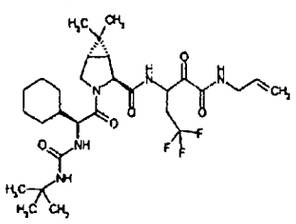
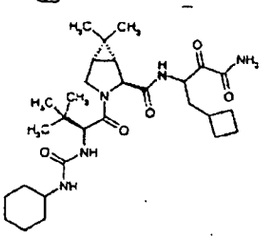
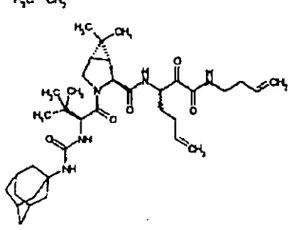
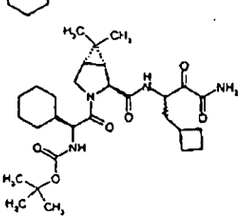
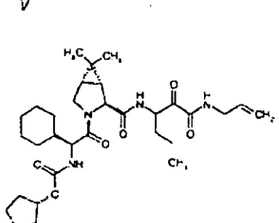
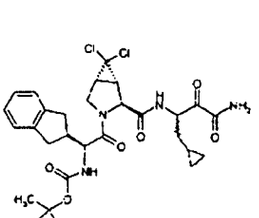
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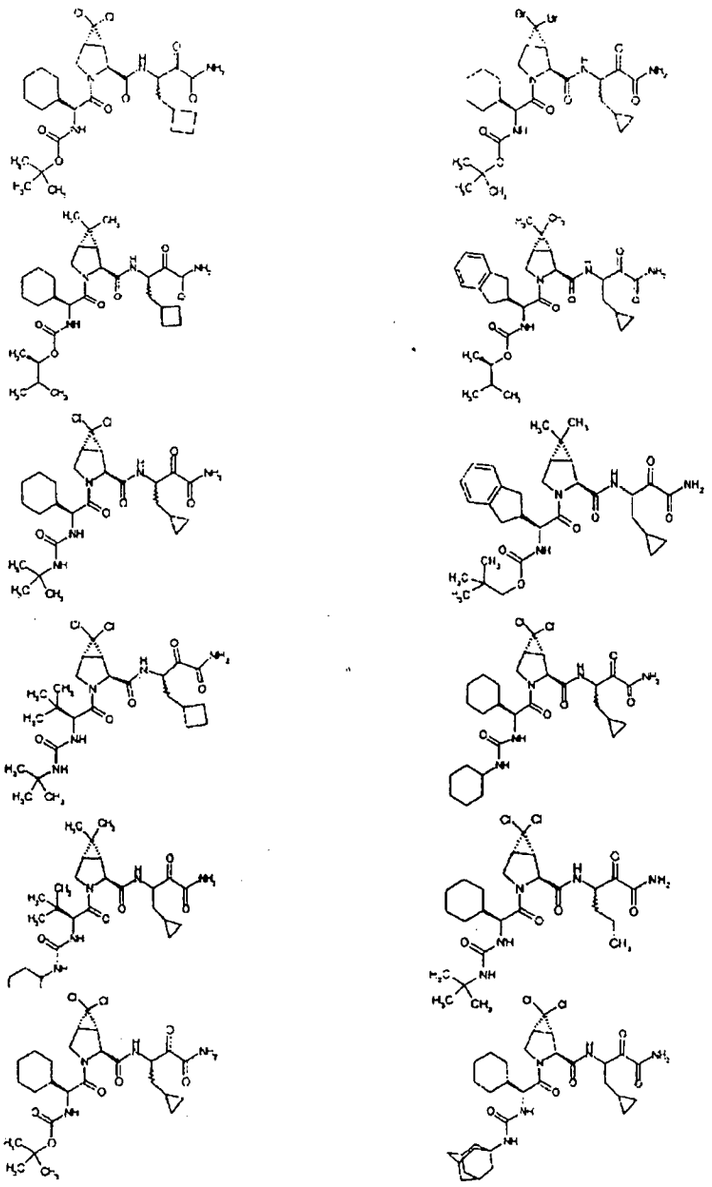


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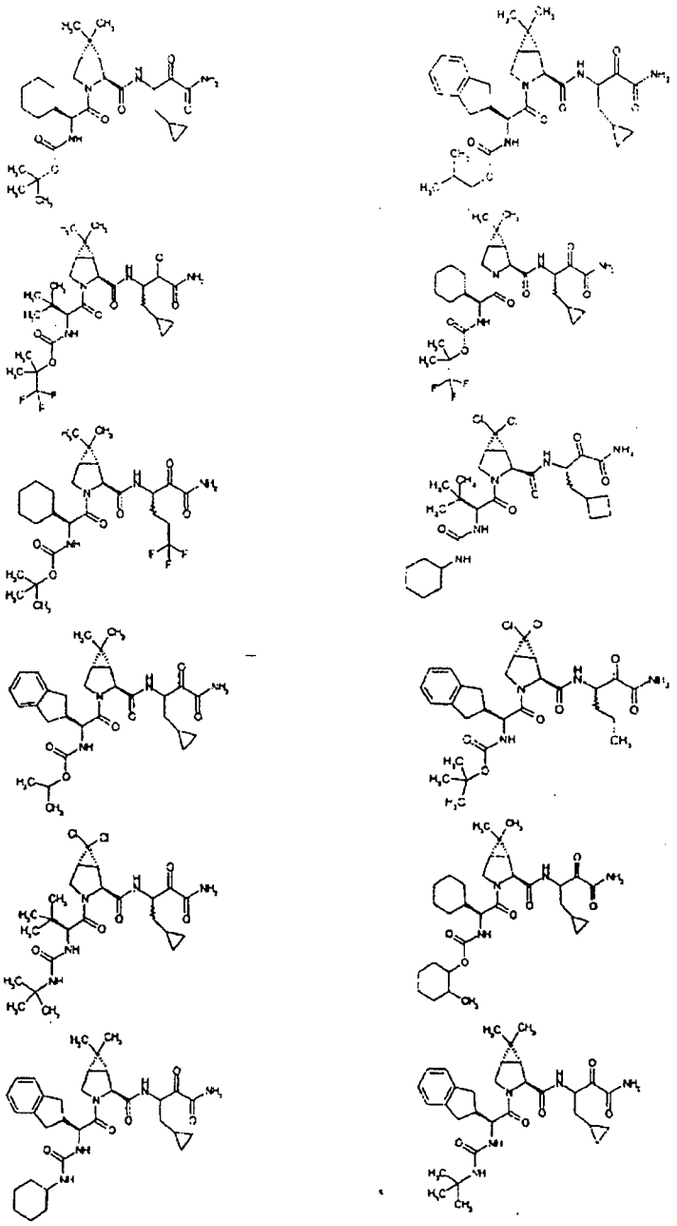


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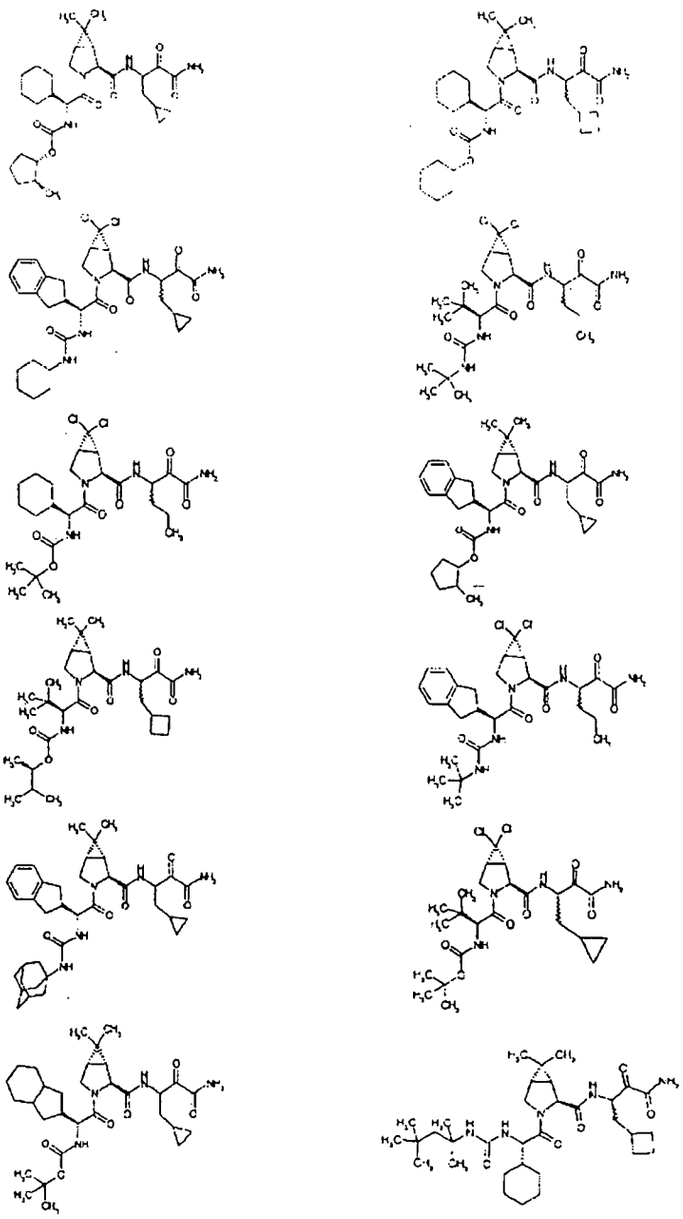















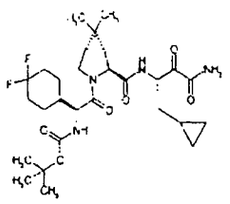
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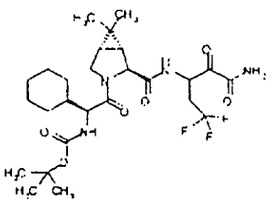


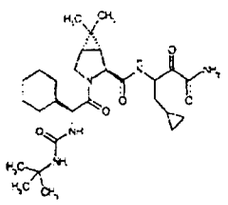
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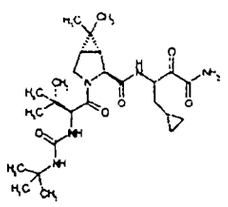


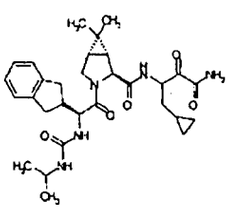
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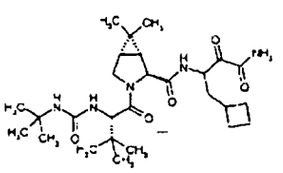


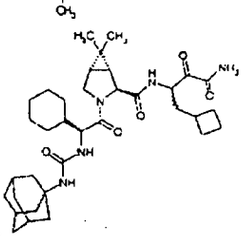


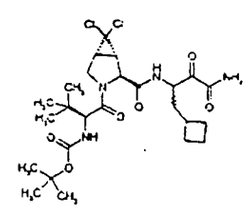


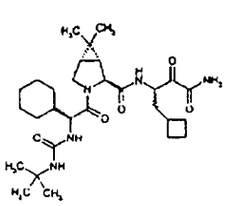


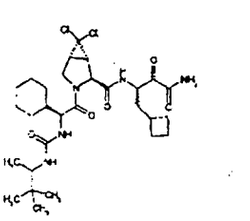




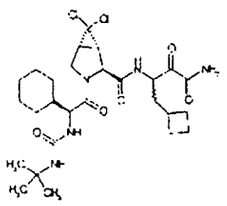


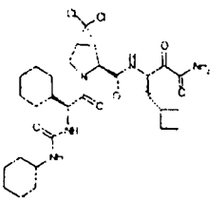


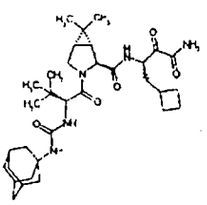


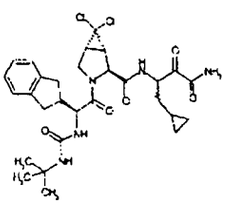


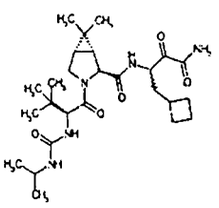
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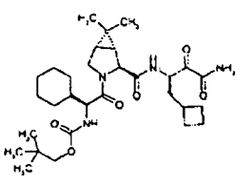


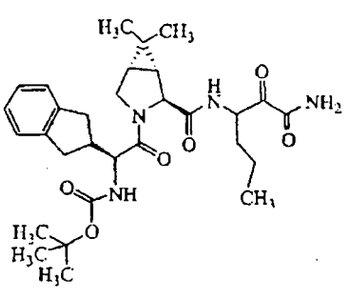




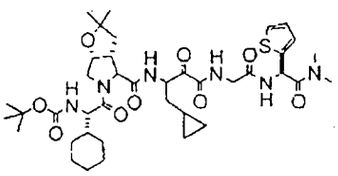


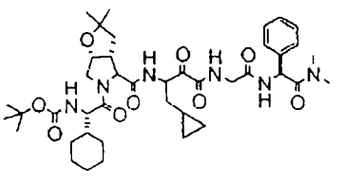


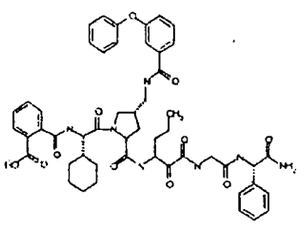


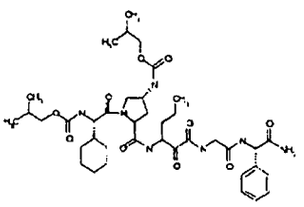


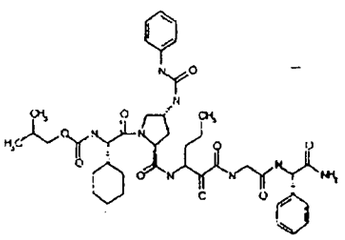
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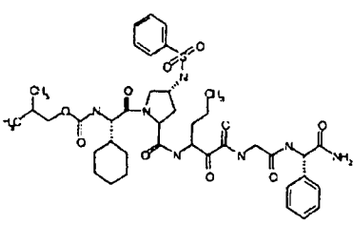


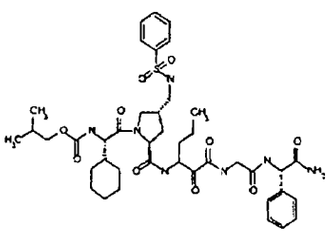


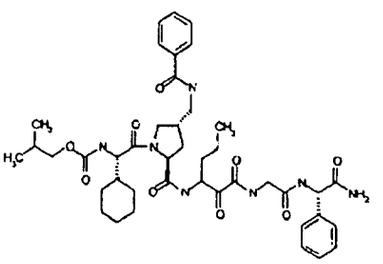




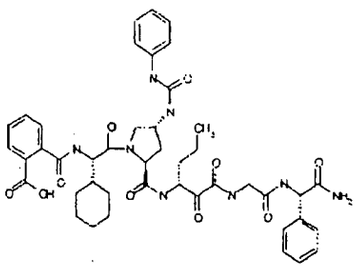


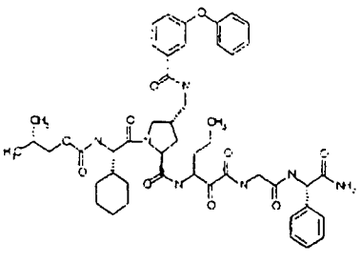


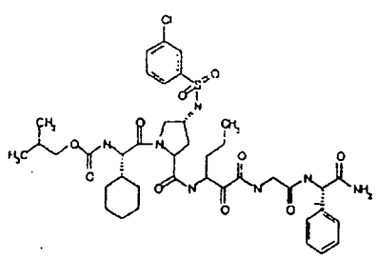


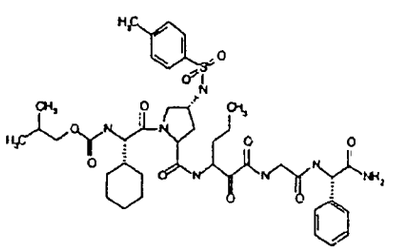


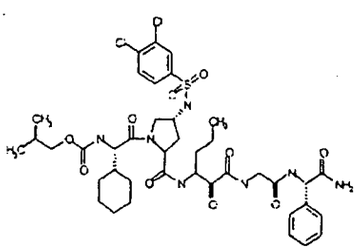
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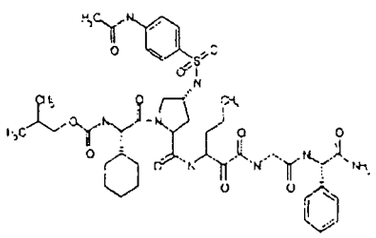


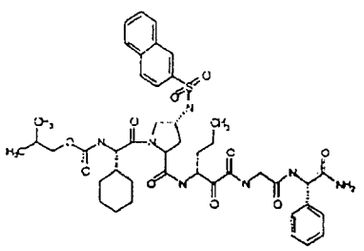


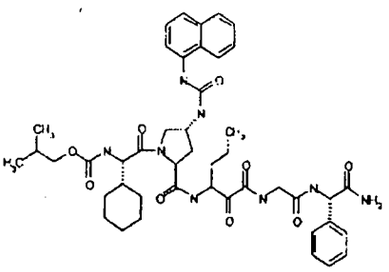


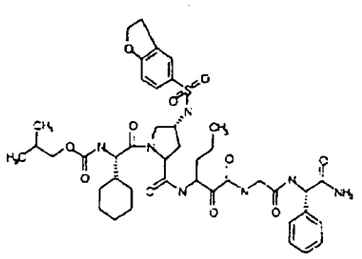


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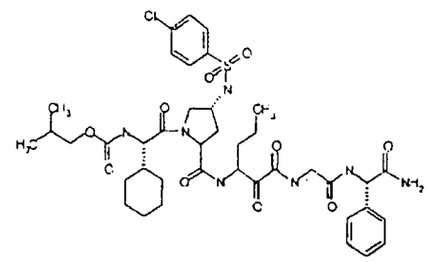


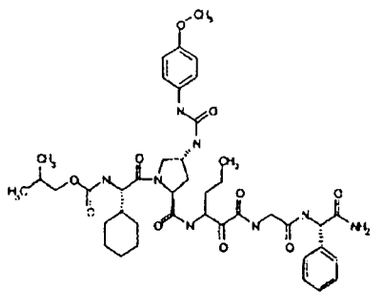


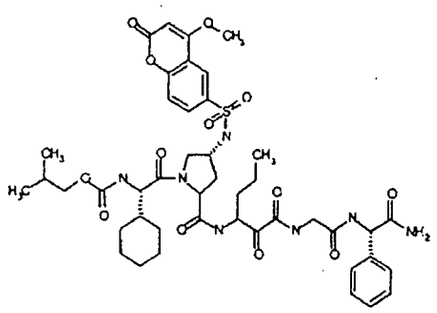




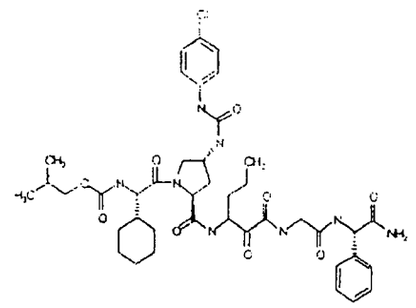
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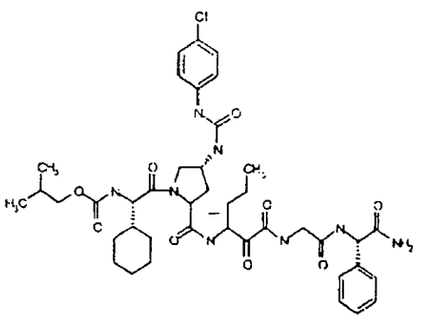


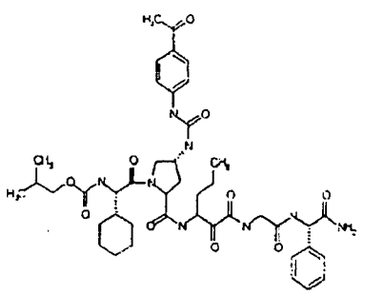




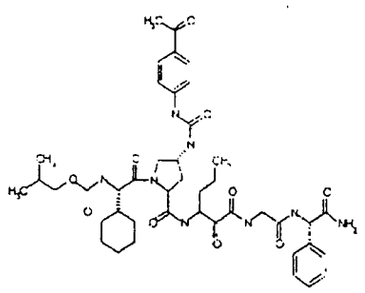
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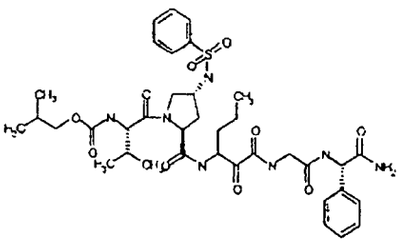


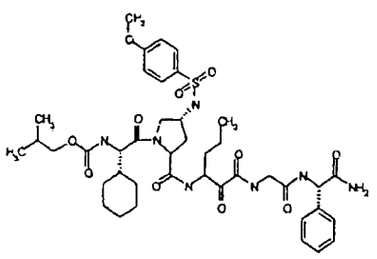


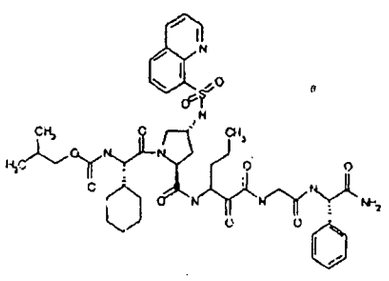


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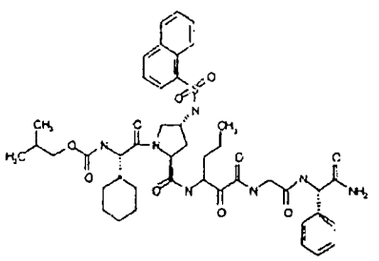


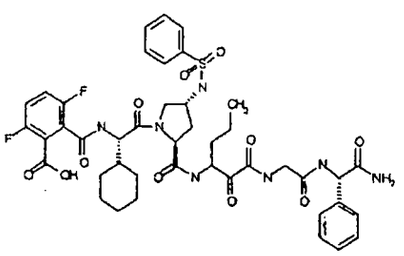


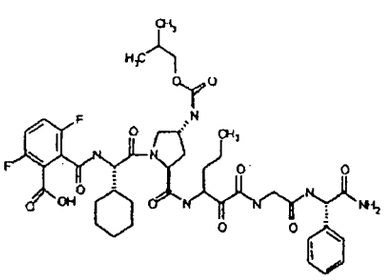




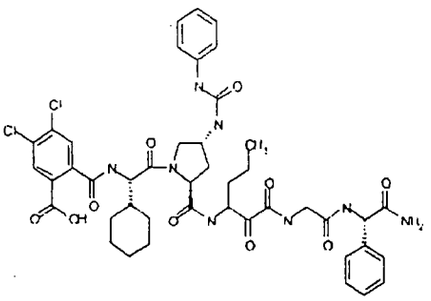
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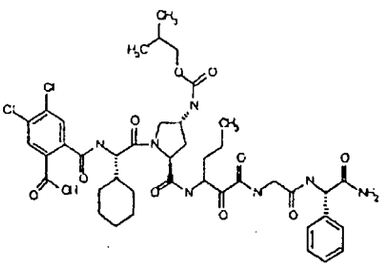


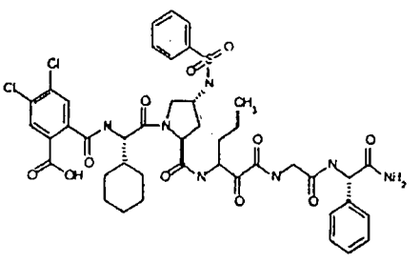


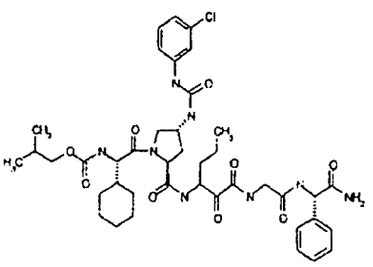


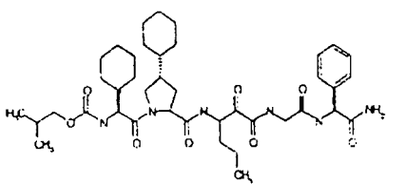
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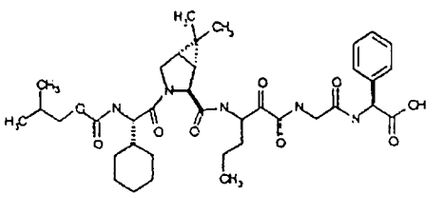


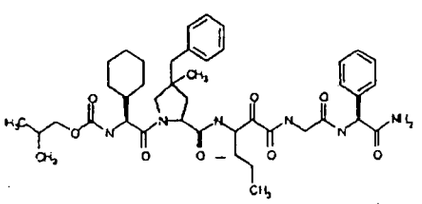


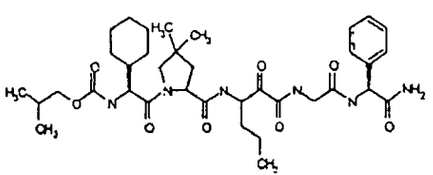


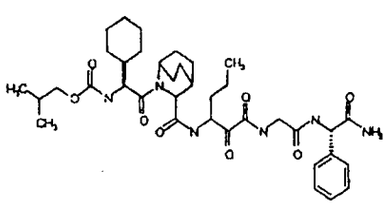


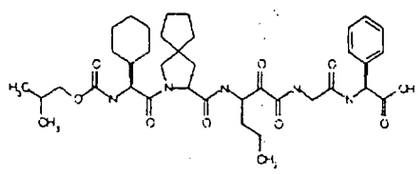


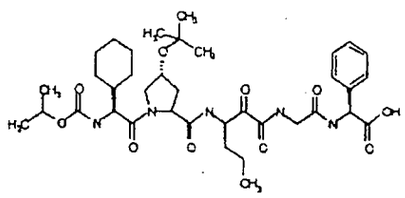


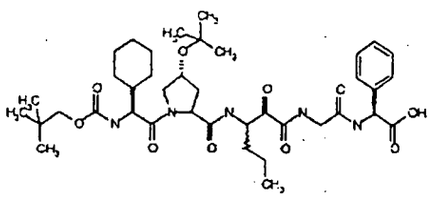


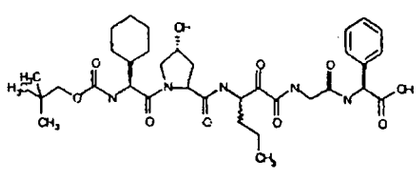


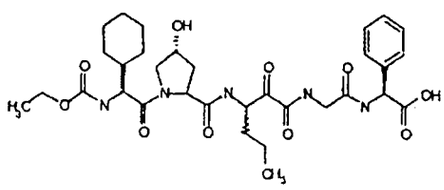


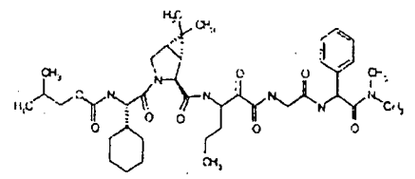


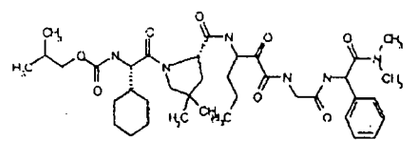


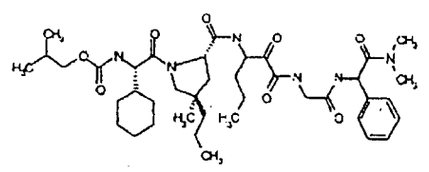


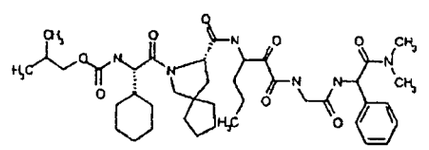


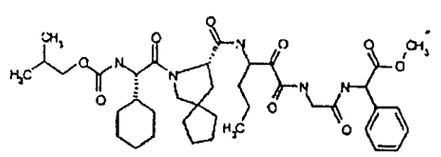


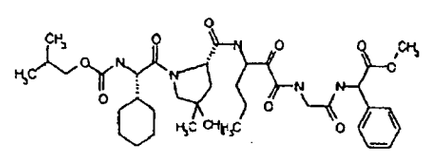




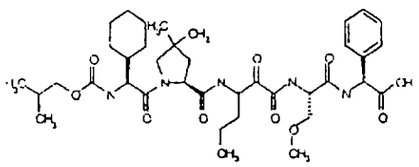


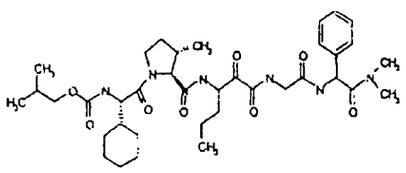


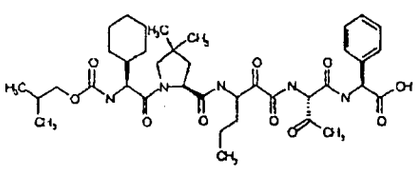


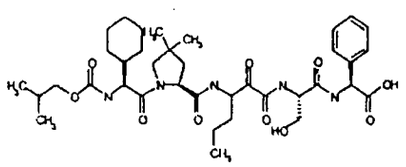


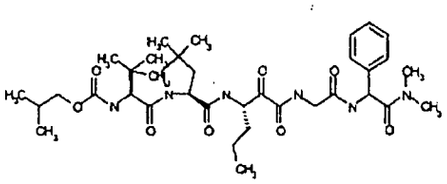
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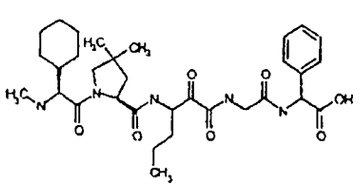


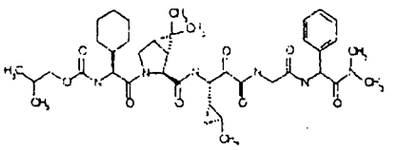


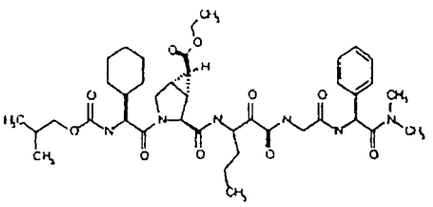


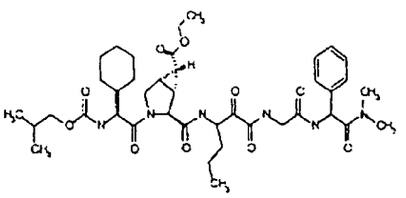


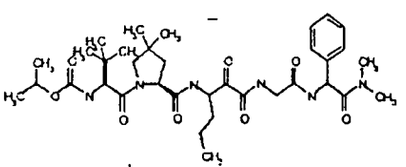
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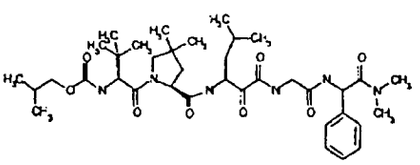


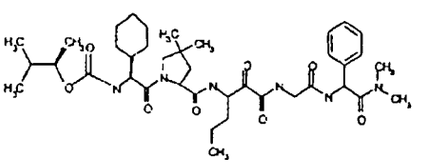




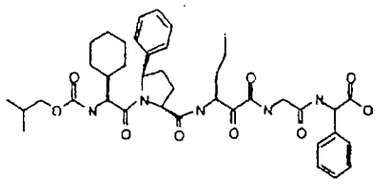


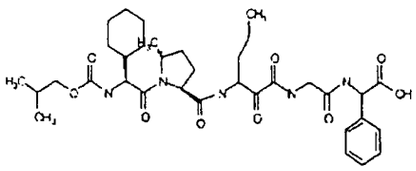


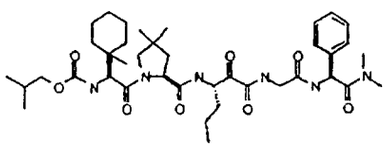


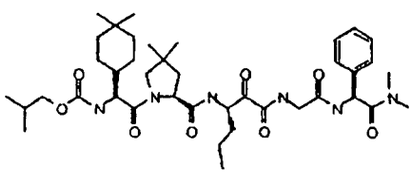


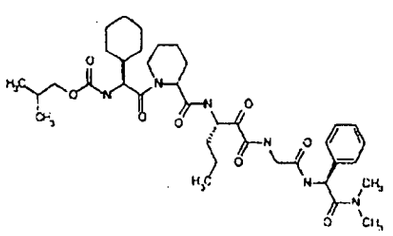
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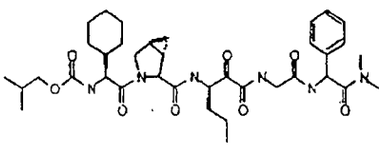


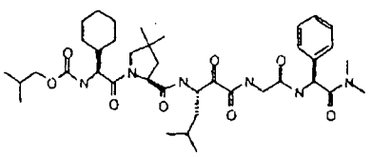


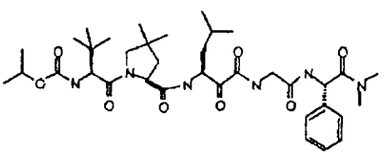


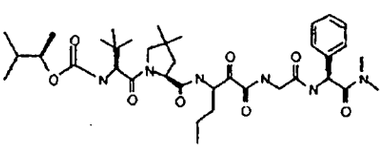


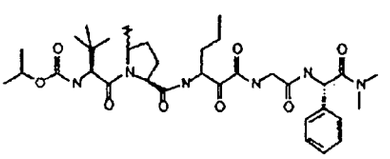


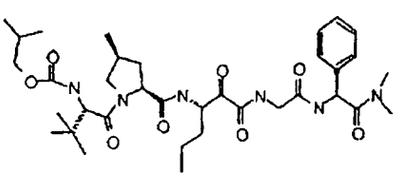


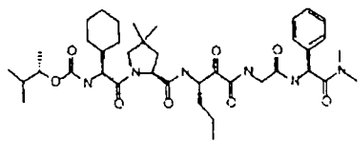


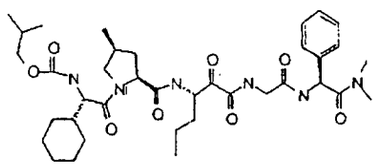


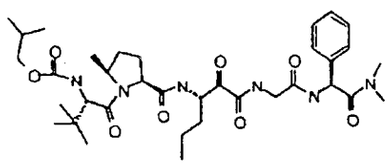


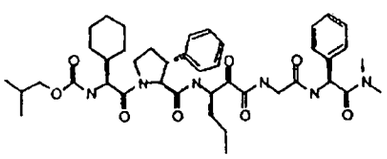


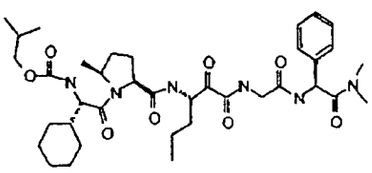


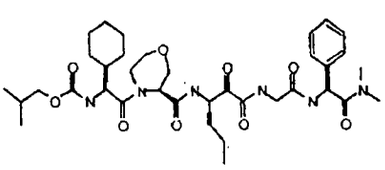


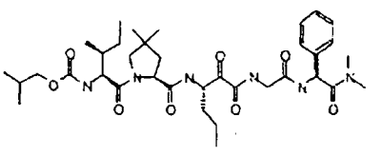


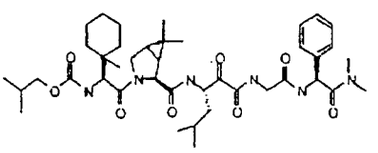


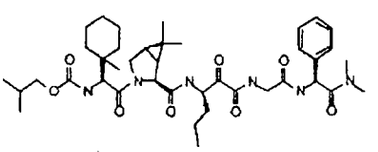


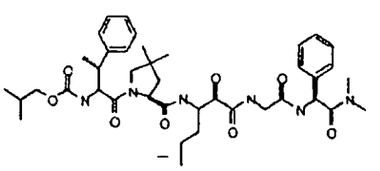


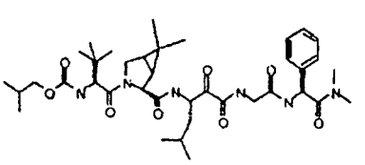


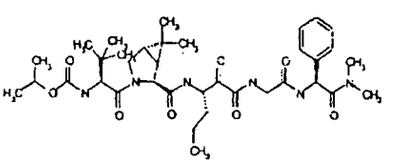


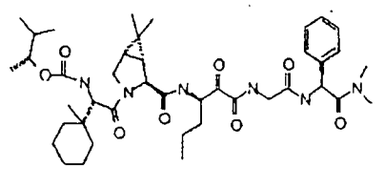


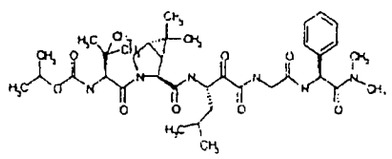


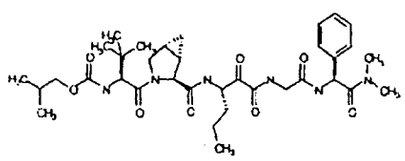


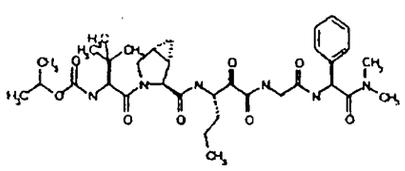


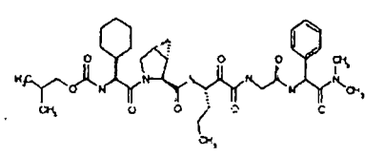


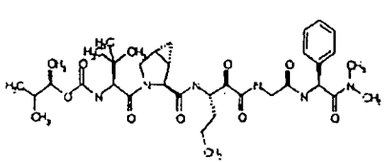


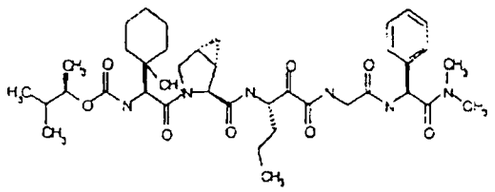












Dependiendo de su estructura, los compuestos de la invención pueden formar sales aceptables para uso farmacéutico con ácidos orgánicos o inorgánicos, o bases orgánicas o inorgánicas. Los ejemplos de ácidos apropiados para dicha formación de sales son el ácido clorhídrico, sulfúrico, fosfórico, acético, cítrico, malónico, salicílico, málico, fumárico, succínico, ascórbico, maleico, metansulfónico y otros ácidos minerales y carboxílicos, conocidos por aquellos 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 suministra composiciones farmacéuticas que comprenden los péptidos de la invención como ingrediente activo. Las composiciones farmacéuticas, comprenden, en general de un modo adicional, un diluyente vehículo, excipiente o vehículo aceptable para uso farmacéutico (denominado colectivamente aquí como materiales vehículo). Debido a su actividad inhibidora de 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, en una mezcla con materiales vehículos apropiados, seleccionados de modo apropiado con respecto a la forma de administración pretendida, es

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decir, comprimidos orales, cápsulas (ya sea con relleno sólido, con relleno semisólido o con relleno líquido), polvos para constitución, geles orales, elixires, gránulos dispersables, jarabes, suspensiones, y similares, y son consistentes con las prácticas farmacéuticas convencionales. Por ejemplo, para administración oral en la forma de comprimidos o cápsulas, el componente de droga activo puede combinarse con cualquier vehículo inerte no tóxico de administración oral 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 deseen o se necesiten, se pueden incorporar a la mezcla, además, agentes aglutinantes, lubricantes, desintegrantes y agentes colorantes. Los polvos y los comprimidos pueden estar formados de aproximadamente 5 a aproximadamente 95 por ciento de la composición de la invención. Los aglutinantes apropiados incluyen almidón, gelatina, azúcares naturales, edulcorantes de maíz, gomas naturales y sintéticas como acacia, alginato de sodio, carboximetilcelulosa, polietilenglicol y ceras. Entre los lubricantes se pueden mencionar, para utilizar en estas formas de aplicación de la dosis, ácido bórico, benzoato de sodio, acetato de sodio, cloruro de sodio, y similares. Los desintegrantes incluyen almidón, metilcelulosa, goma guar y similares.

Los agentes edulcorantes y saborizantes y los conservantes también pueden incorporarse cuando resulte apropiado. Algunos de los términos mencionados anteriormente, es decir, desintegrantes, diluyentes, lubricantes, aglutinantes y similares, se describen con más detalle a continuación.

En forma adicional, las composiciones de la presente invención pueden formularse en forma de liberación prolongada para suministrar la liberación controlada de cualquiera de los componentes, ya sea uno o más, o ingredientes activos, para optimizar los efectos terapéuticos, es decir, la actividad de

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inhibición de HCV y similares. Las formas apropiadas de aplicación de la dosis para la liberación prolongada incluyen los comprimidos en capas que contienen capas de tasas variables de desintegración o matrices poliméricas de liberación controlada impregnadas con los componentes activos y tienen la forma de comprimido o cápsulas que contienen dichas matrices poliméricas porosas impregnadas o encapsuladas.

Las preparaciones de forma líquida incluyen soluciones, suspensiones y emulsiones. Como ejemplo se pueden mencionar agua o soluciones de agua-propilenglicol para las inyecciones parenterales o el agregado de edulcorantes y suavizantes para las soluciones, suspensiones y emulsiones orales. 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 encontrarse combinados con un vehículo aceptable para uso farmacéutico como gas inerte comprimido, por ejemplo, nitrógeno.

Para preparar supositorios, primero se mezcla una cera de bajo punto de fusión, como una mezcla de glicéridos de ácido graso como manteca de cacao, y se dispersa el ingrediente activo en forma homogénea por agitación o un proceso de mezclado similar. La mezcla homogénea fundida luego se vierte en moldes de tamaño conveniente, se los deja enfriar y, por consiguiente, solidificar.

También se incluyen las preparaciones de forma sólida que tienen como finalidad convertirse, apenas antes de su uso, en preparaciones de forma líquida tanto para administración oral como parenteral. Dichas formas líquidas incluyen las soluciones, suspensiones y emulsiones.

Los compuestos de la invención también pueden aplicarse por vía transdérimica. Las composiciones de aplicación transdérmica pueden tomar la

forma de cremas, lociones, aerosoles y/o emulsiones y pueden incluirse parche transdérmico del tipo matriz o con reservorio como se conocen en para este fin.

Con preferencia, el compuesto se administra en forma oral, intraver subcutánea.

Con preferencia, la preparación farmacéutica es una forma de apli unitaria de la dosis. En dicha forma, la preparación se subdivide en unitarias de tamaño apropiado que contienen cantidades apropiadas componentes activos, por ejemplo, una cantidad efectiva para lograr el pro deseado.

La cantidad de composición activa de la invención en una dosis unit preparación puede variar, generalmente, o ajustarse, de aproximadamen miligramo a aproximadamente 1.000 miligramos, con preferenci aproximadamente 1,0 miligramos a aproximadamente 950 miligramos, con preferencia de aproximadamente 1,0 a aproximadamente 500 miligran típicamente de aproximadamente 1 a aproximadamente 250 miligramo acuerdo con la aplicación en particular. La dosificación real empleada variar dependiendo de la edad, el sexo, el peso del paciente y la severidad condición que debe tratarse. Dichas técnicas son conocidas para ac personas con experiencia en el arte.

En general, la forma de dosificación oral en humanos que contie ingredientes activos puede administrarse 1 ó 2 veces por día. La cantida frecuencia de administración se regularán de acuerdo con el criterio del mé cargo. Un régimen de dosificación diaria generalmente recomendado variar de aproximadamente 1,0 miligramo a aproximadamente 1.000 milig por día, en dosis únicas o divididas.

Algunos términos útiles se describen a continuación:

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Cápsula - Se refiere a un contenedor o recinto especial realizado de metilcelulosa, alcoholes polivinílicos, o gelatinas desnaturalizadas o almidón para sostener o contener las composiciones que comprenden los ingredientes activos. Las cápsulas de recubrimiento duro normalmente están realizadas con mezclas de gelatinas de piel de cerdo y hueso de resistencia de gel relativamente elevada. La cápsula en sí misma puede contener pequeñas cantidades de colorantes, agentes opacantes, plastificadores y conservantes.

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 las mezclas o granulaciones obtenidas por granulación húmeda, granulación seca o por compactación.

Gel oral - se refiere a los ingredientes activos dispersos o solubilizados en una matriz hidrofílica semisólida.

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 porción mayor de la composición o forma de dosificación. Los diluyentes apropiados incluyen azúcares, como latosa, 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 de aproximadamente 10 a aproximadamente 90% en peso del total de la composición, con preferencia de aproximadamente 25 a aproximadamente 75%, con mayor preferencia de aproximadamente 30 a aproximadamente 60% en peso, aún con mayor preferencia de aproximadamente 12 a aproximadamente 60%.

Desintegrante - se refiere a materiales agregados a la composición para ayudar a romperla (desintegrarla) y liberar los medicamentos. Los desintegrantes

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apropiados incluyen almidones: almidones modificados "solubles en agua fría" como almidón de carboximetilo sodio; gomas naturales y sintéticas como vaina de acacia, caraya, guar, tragacanto y agar; derivados de la celulosa, como metilcelulosa y carboximetilcelulosa sódica; celulosas microcristalinas y celulosas microcristalinas entrecruzadas como croscarmelosa de sodio; alginatos como ácido algínico y alginato de sodio; arcillas como bentonitas; y mezclas efervescentes. La cantidad de desintegrante en la composición puede variar de aproximadamente 2 a aproximadamente 15% en peso de la composición, con mayor preferencia de aproximadamente 4 a aproximadamente 10% en peso.

Aglutinante - Se refiere a sustancias que unen o "pegan" los polvos y los hacen cohesivos mediante la formación de gránulos, sirviendo así como el "adhesivo" en la formulación. Los aglutinantes agregan fuerza cohesiva ya disponible en el diluyente o el agente volumétrico. Los aglutinantes apropiados incluyen azúcares como sacarosa; almidones derivados del trigo, el maíz, el arroz y la papa; gomas naturales como acacia, gelatina y tragacanto; derivados de las algas marinas como ácido algínico, alginato de sodio y alginato de calcio y amonio; materiales a base de celulosa como metilcelulosa y carboximetilcelulosa sódica e hidroxipropilmetilcelulosa; polivinilpirrolidona; y agentes inorgánicos como silicato de magnesio y aluminio. La cantidad de aglutinante presente en la composición puede variar de aproximadamente 2 a aproximadamente 20% en peso de la composición, con mayor preferencia de aproximadamente 3 a aproximadamente 10% en peso, aún con mayor preferencia de aproximadamente 3 a aproximadamente 6% en peso.

Lubricante - se refiere a una sustancia incorporada a la forma de dosificación para permitir que el comprimido, los gránulos, etc., luego de comprimirlos, se liberen del molde o troquel mediante fricción o desgaste reductor. Los lubricantes apropiados incluyen estearatos metálicos como

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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-eucina. Los lubricantes se agregan, en general, en el último paso antes de la compresión, ya que deben estar presentes en la superficie de los gránulos y entre ellos y las partes de la prensa para comprimidos. La cantidad de lubricante presente en la composición puede variar de aproximadamente 0,2 a aproximadamente 5% en peso de la composición, con preferencia de aproximadamente 0,5 a aproximadamente 2%, con mayor preferencia de aproximadamente 0,3 a aproximadamente 1,5% en peso.

Deslizante - material que evita la formación de tortas y mejora las características de fluidez de las granulaciones, de modo tal que el flujo es suave y uniforme. Los deslizantes apropiados incluyen dióxido de silicona y talco. La cantidad de deslizante presente en la composición puede variar de aproximadamente 0,1% a aproximadamente 5% en peso de la composición total, con preferencia de aproximadamente 0,5 a aproximadamente 2% en peso.

Agentes colorantes - excipientes que suministran coloración a la composición o forma de aplicación de la dosis. Dichos excipientes pueden incluir colorantes de grado alimenticio y colorantes de grado alimenticio adsorbidos en un adsorbente apropiado como arcilla u óxido de aluminio. La cantidad de agente colorante puede variar de aproximadamente 0,1 a aproximadamente 5% en peso de la composición, con preferencia de aproximadamente 0,1 a aproximadamente 1%.

Biodisponibilidad - se refiere a la tasa y la extensión hasta la cual la droga activa o el grupo funcional terapéutico se absorbe en la circulación sistémica a partir de una forma de dosificación administrada, si se compara con un estándar o control.

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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 los métodos húmedos u otros procedimientos especiales. Los métodos convencionales para realizar otras formas para administración como, por ejemplo, cápsulas, supositorios y similares, son conocidos, también, en el arte.

Otra realización de la invención describe el uso de las composiciones farmacéuticas que se describieron anteriormente para el tratamiento de enfermedades como, por ejemplo, la hepatitis C y similares. El método comprende la administración de una cantidad efectiva de la composición farmacéutica de la invención a un paciente que sufre de dicha enfermedad o enfermedades y que necesite 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 modo de tratamiento combinado (por ejemplo, combinación dual, combinación mixta, etc.) como, por ejemplo, en combinación con agentes antivirales y/o agentes de modulación inmunológica. Algunos ejemplos de dichos agentes antivirales y/o moduladores inmunológicos incluyen Ribavirin (de Schering-Plough Corporation, Madison, New Jersey) y Levovirin™ (de ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (de Viropharma, Incorporated, Exton, Pennsylvania), ISIS 14803™ (de ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (de Ribozyme Pharmaceuticals, Boulder, Colorado) VX497™ (de Vertex Pharmaceuticals, Cambridge, Massachusetts), Thymosin™ (de SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), micofenolato mofetilo (de Hoffman-LaRoche, Nutley, New Jersey), interferon (como, por ejemplo, interferon-alfa, conjugados de interferon alfa-PEG) y similares. Los "conjugados de interferon alfa-PEG" son moléculas de

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interferon alfa adheridas en forma covalente a una molécula de PEG. Los conjugados de interferon alfa-PEG ilustrativos incluyen interferon alfa-2a (Roferon™, de Hoffman La-Roche, Nutley, New Jersey) en forma de interferon alfa-2a pegilado (por ejemplo, comercializado con la marca Pegasys™), interferon alfa-2b (Intron™, de Schering-Plough Corporation) en forma de interferón alfa-2b pegilado (por ejemplo, comercializado con la marca PEG-Intron™), interferon alfa-2c (Berofor Alpha™, de Boehringer Ingelheim, Ingelheim, Alemania) o interferon de consenso definido por la determinación de una secuencia de consenso de interferon alfa de formación natural (Infergen™; de Amgen, Thousand Oaks, California).

Como se indicó anteriormente, la invención incluye también tautómeros, rotámeros, enantiómeros y otros estereoisómeros de los compuestos de la invención. Así, como lo puede apreciar una persona con experiencia en el arte, algunos de los compuestos de la invención pueden existir en formas isoméricas apropiadas. Dichas variaciones se contemplan dentro del alcance de la invención.

Otra realización de la invención describe un método para realizar los compuestos que se describieron aquí. Los compuestos pueden prepararse mediante varias técnicas conocidas en el arte. Los procedimientos ilustrativos representativos se definen en los siguientes esquemas de reacción. Se comprenderá que mientras que los siguientes esquemas ilustrativos describen la preparación de algunos compuestos representativos de la invención, la sustitución apropiada de cualquiera de los amino ácidos, ya sea naturales o no naturales, producirá la formación de los compuestos deseados sobre la base de dicha sustitución. Dichas variaciones se contemplan dentro del alcance de la invención.

Las abreviaturas que se utilizan en las descripciones de los esquemas, las preparaciones y los ejemplos que siguen, son:

THF: Tetrahidrofurano:

Dioxane: Dioxano

DMF: *N,N*-Dimetilformamida

EtOAc: Acetato de etilo

AcOH: Ácido acético

HOOBt: 3-hidroxi-1,2,3-benzotriazin-4(3H)-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-diclohexilcarbodiimida

TEMPO: 2,2,6,6-Tetrametil-1-piperidiniloxi

Phg: Fenilglicina

Chg: Ciclohexilglicina

Bn: Bencilo

Bzl: Bencilo

Et: Etilo

Ph: Fenilo

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iBoc: isobutoxicarbonilo

iPr: isopropilo

^{t}Bu o Bu^{t}: *ter*butilo

Boc: terbutoxicarbonilo

Cbz: Benciloxicarbonilo

Cp: Ciclopentildienilo

Ts: p-toluensulfonilo

Me: Metilo

HATU: hexafluorofosfato de O-(7-azabenzotriazol-1-il)-1,1,3,3-tetrametiluronio

DMAP: 4-N,N-dimetilaminopiridina

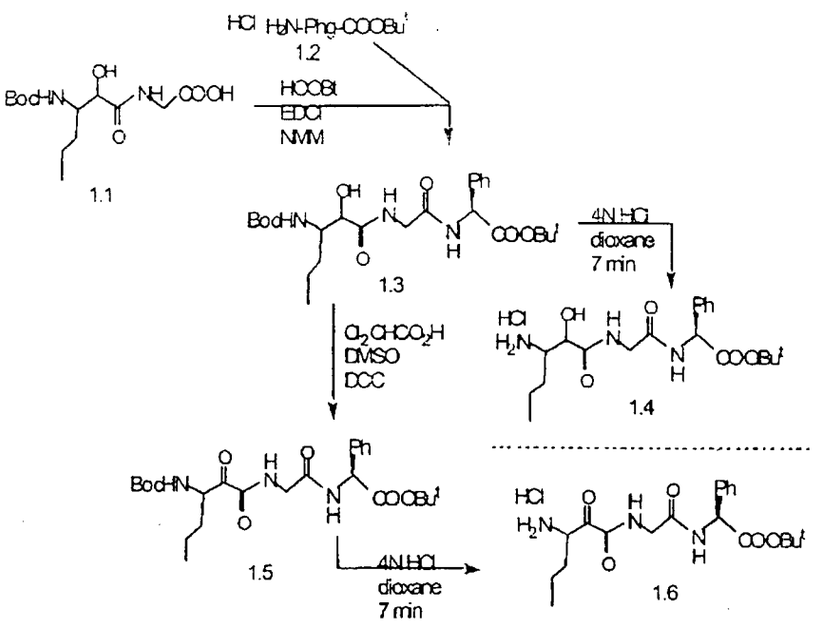
Bop: Benxotriazol-1-il-oxi-tris(dimetilamino)hexafluorofosfato

Esquemas de Preparación General:

Los siguientes esquemas describen los métodos de síntesis de bloques formadores de intermediarios:

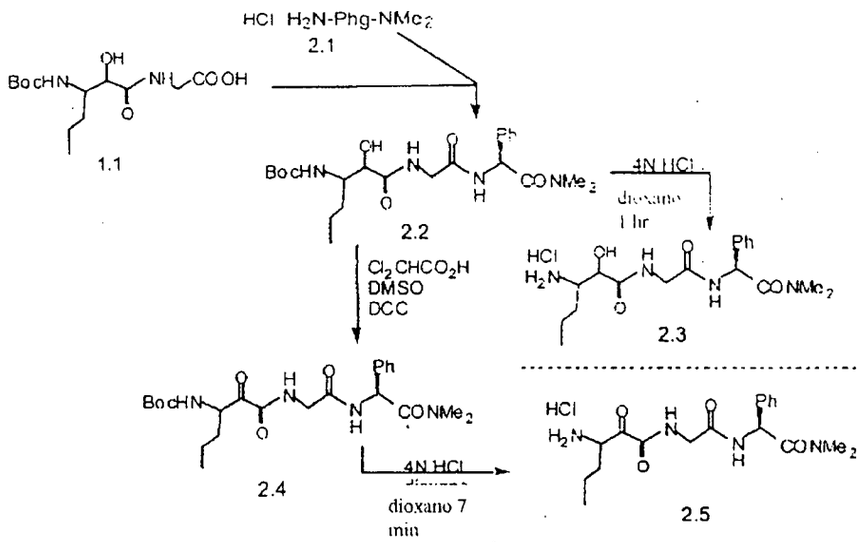
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Esquema 1

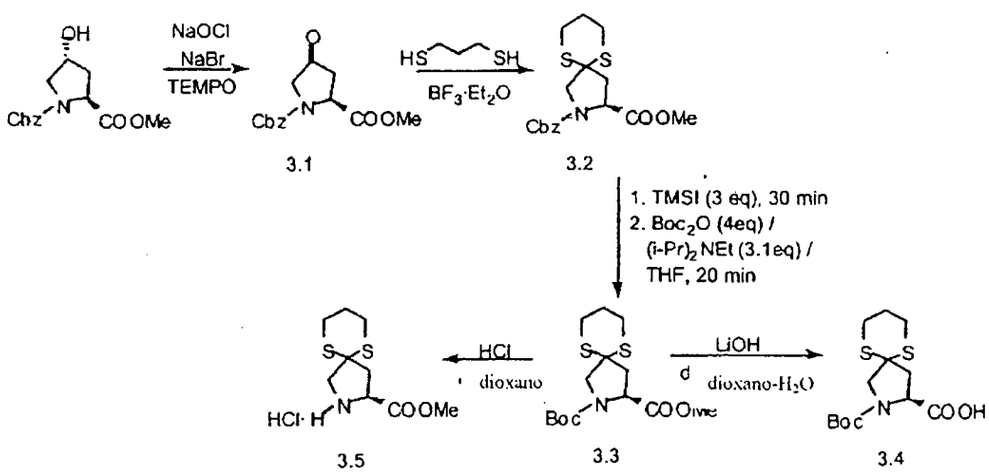


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Esquema 2

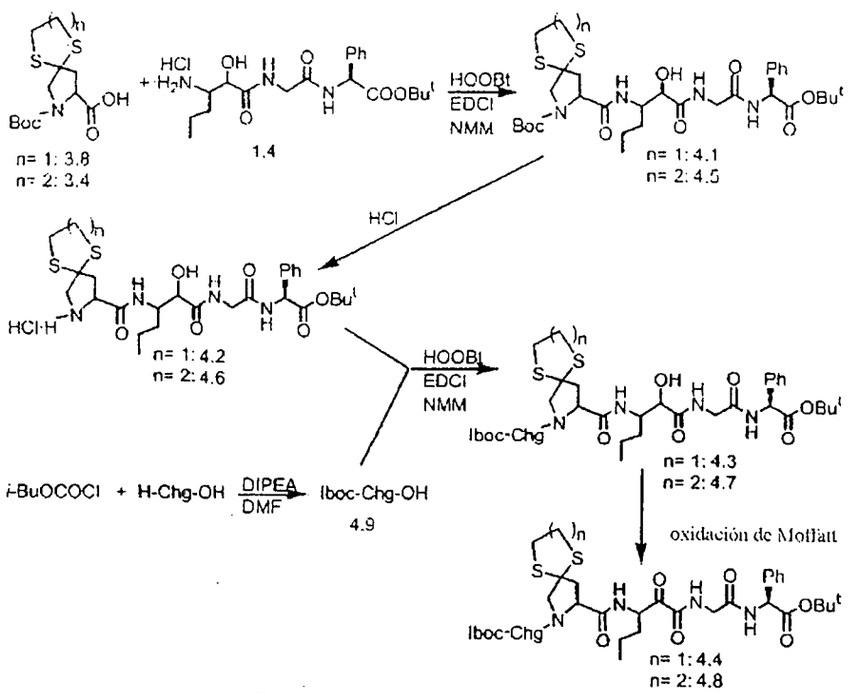


Esquema 3



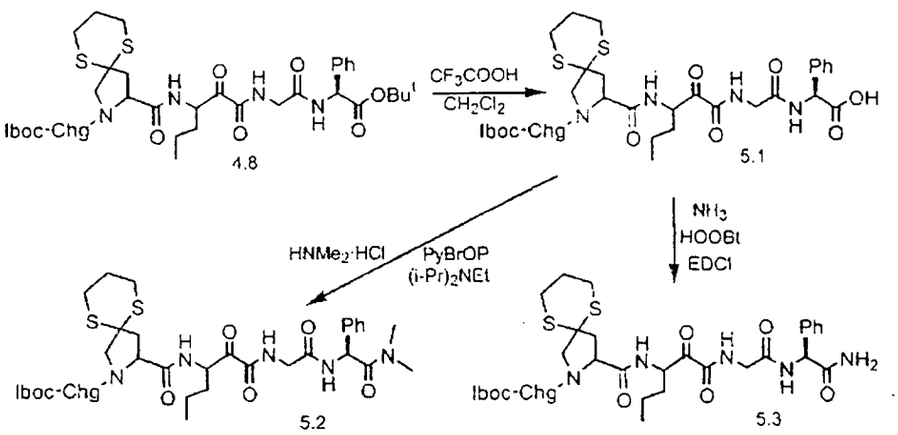
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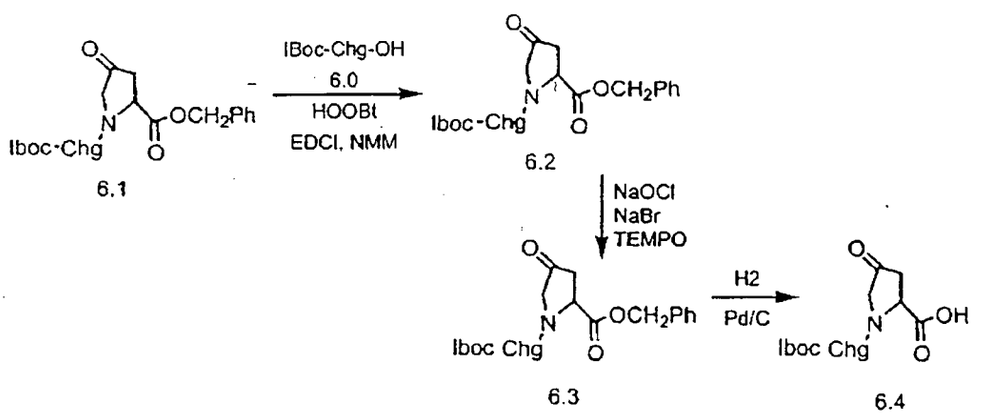


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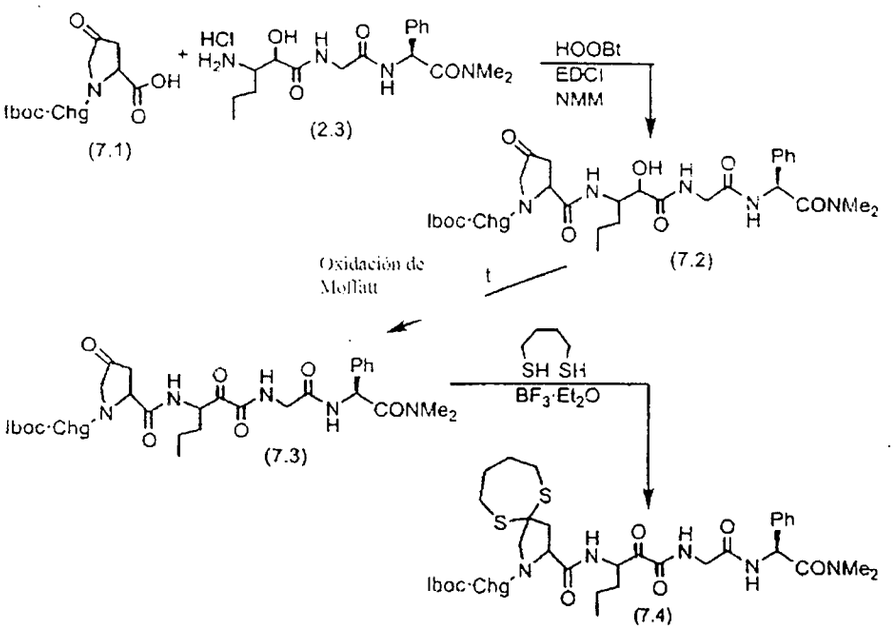


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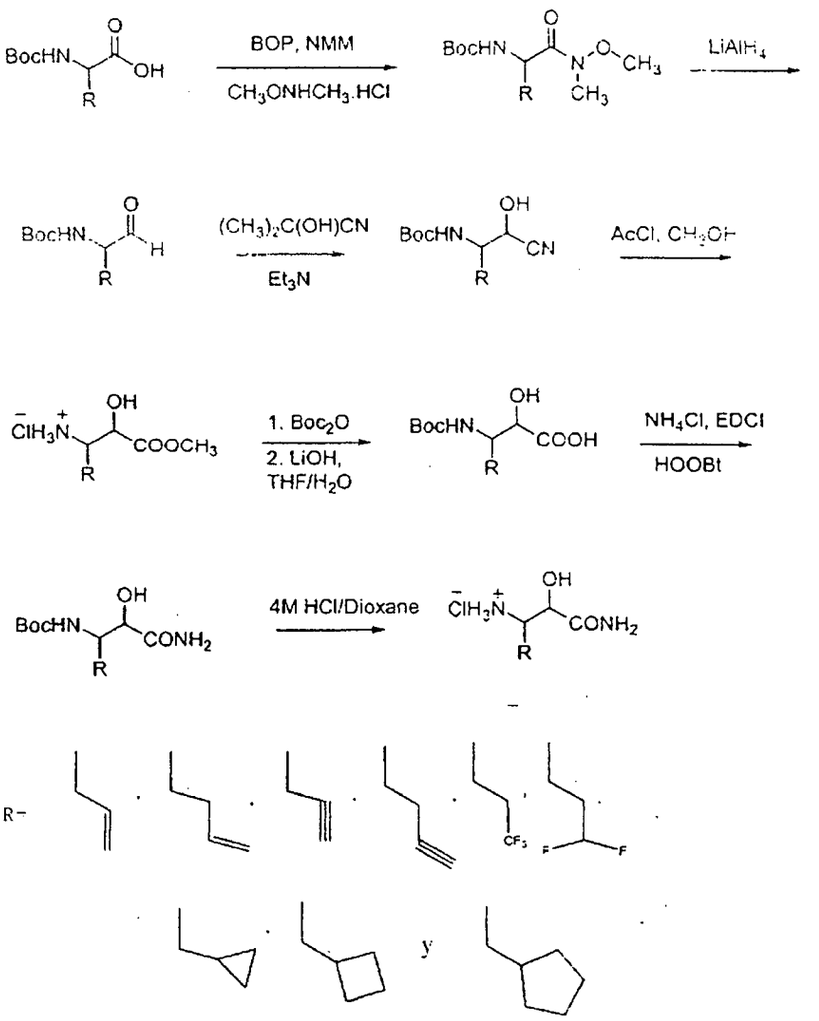


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Esquema 7



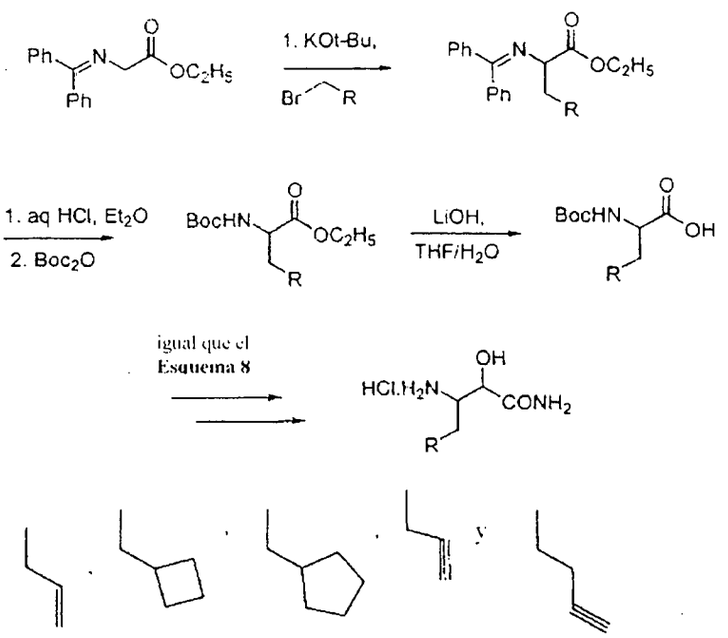
Esquema 8



donde R=

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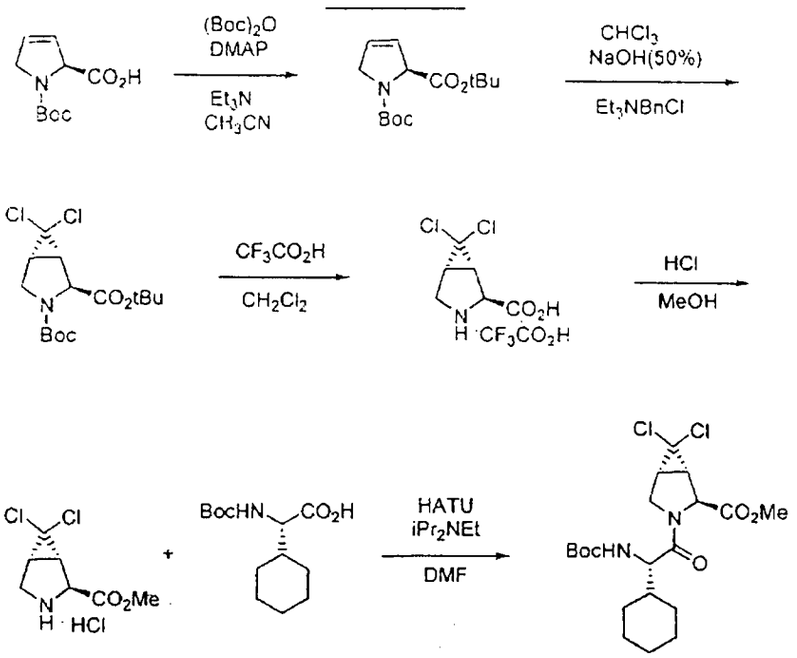
Esquema 9



donde R=

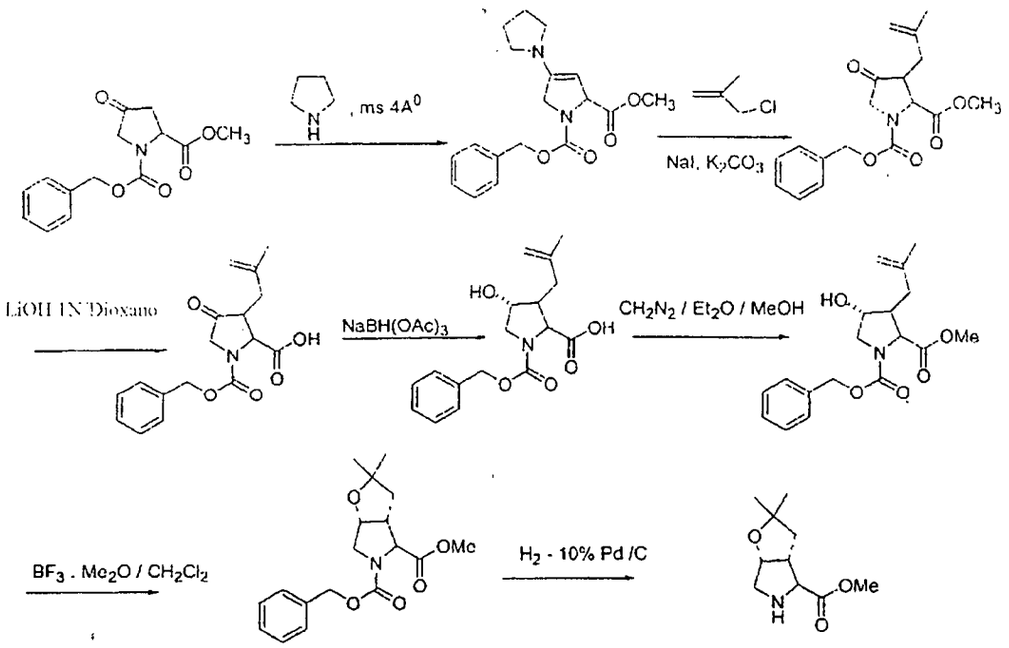
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Esquema 10



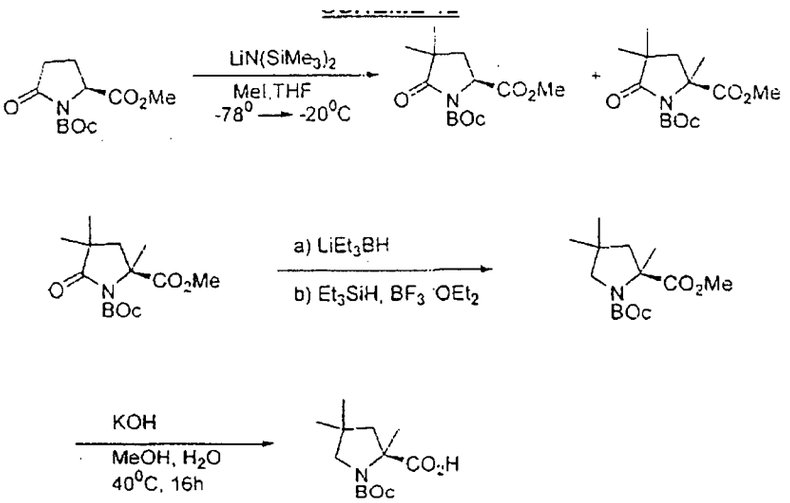
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Esquema 11

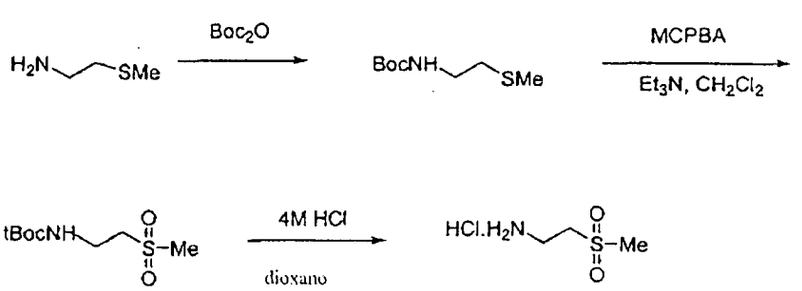


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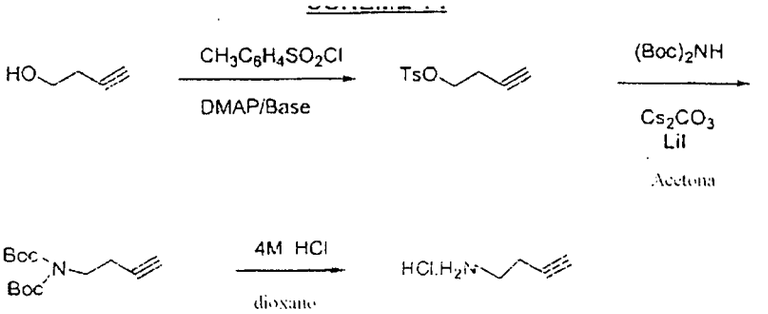
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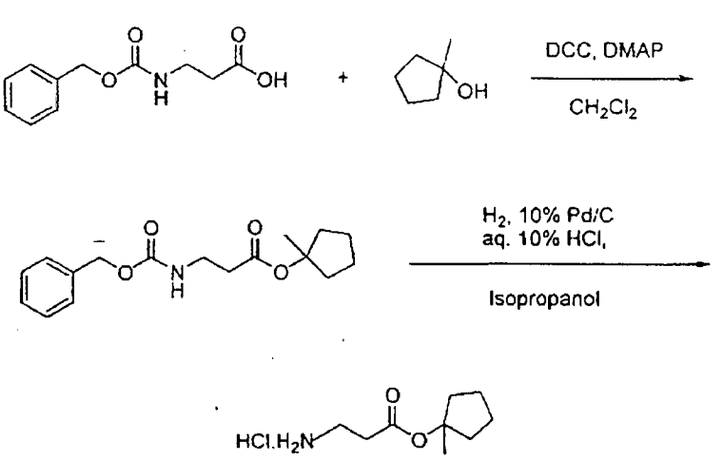
Esquema 13



Esquema 14

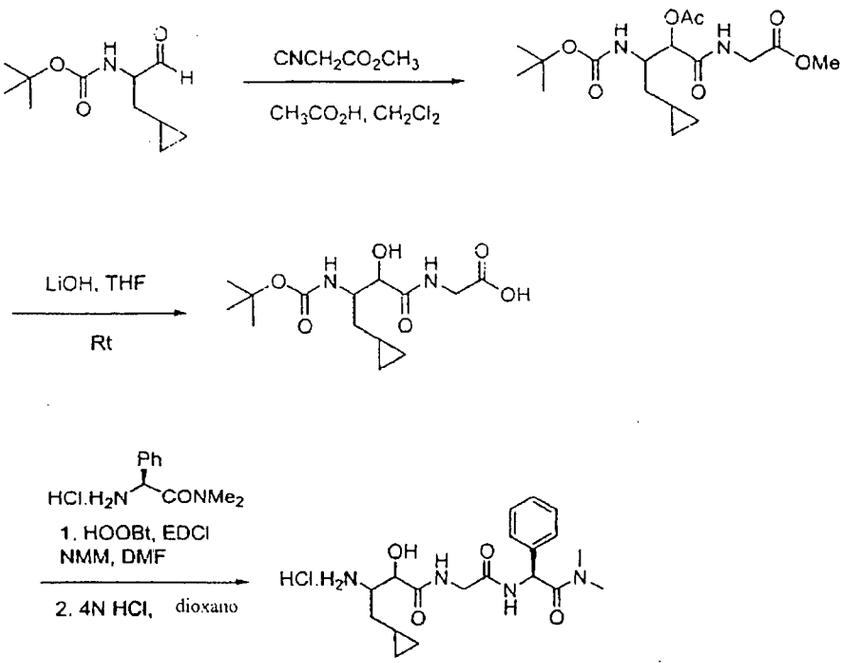


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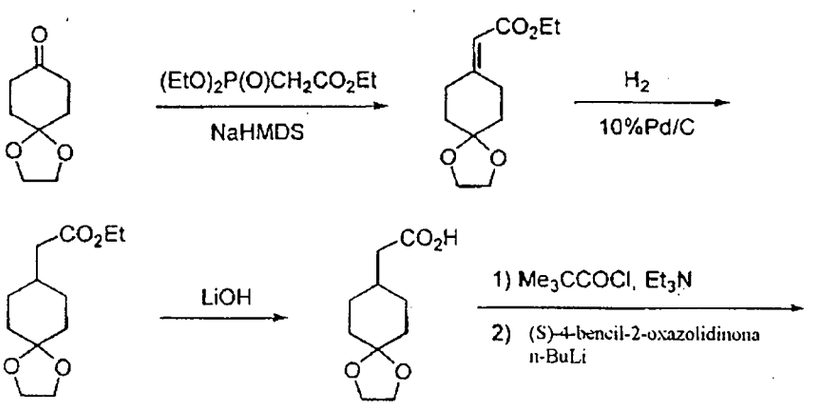


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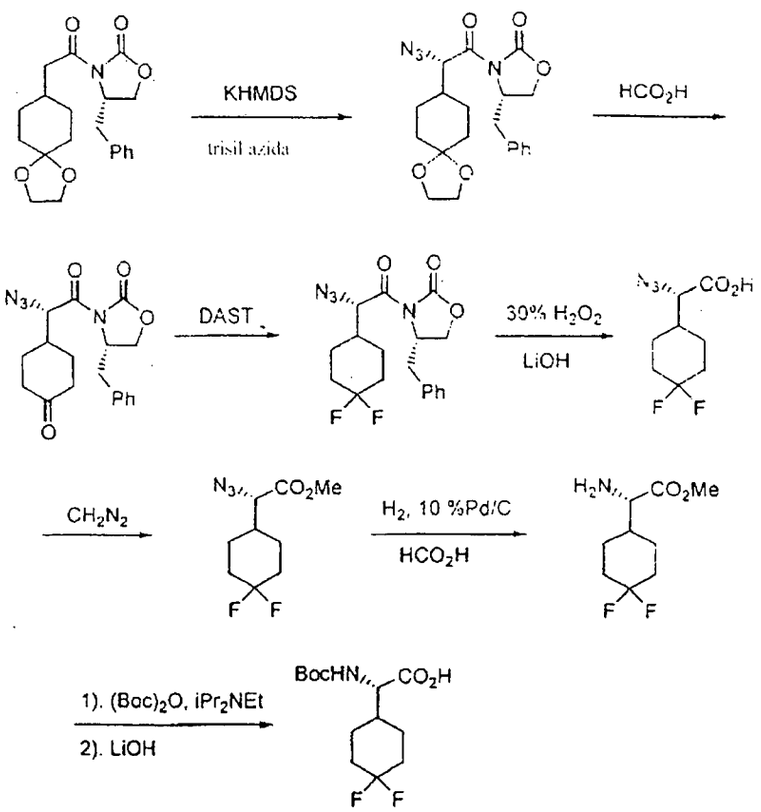
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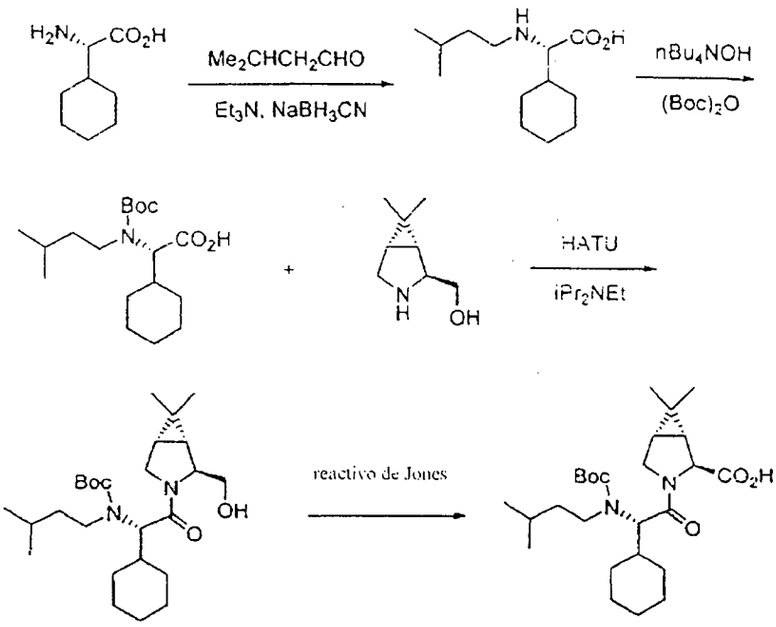
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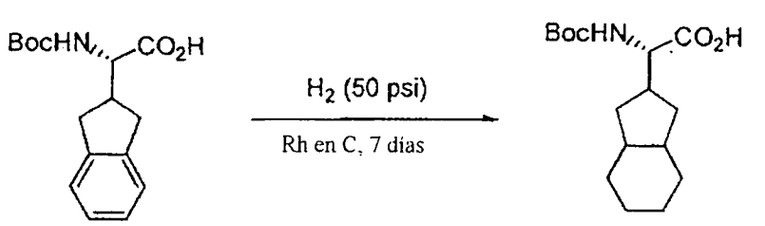
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KHMDS
trisil azida
HCO2H
DAST
30% H2O2
LiOH
CH2N2
H2, 10 %Pd/C
HCO2H
1). (Boc)2O, iPr2NEt
2). LiOH
Ph
N3
CO2H
CO2Me
BocHN
H2N
F
O
N

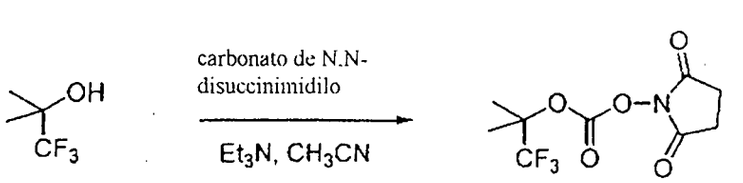
Esquema 18



Esquema 19



Esquema 20

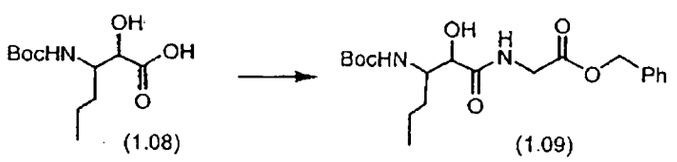


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Preparación de los Intermediarios:

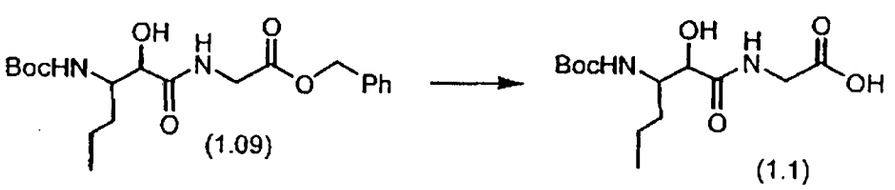
Ejemplo de Preparación 1

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.Cem.* 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-metilo morfolino (4,0 mL, 36,0 mmol) y EDCI (2,79 g, 14,5 mmol) y se agitó durante 10 minutos, seguido de el 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 la dilución con EtOAc (150 mL). La solución de EtOAc luego se lavó dos veces con $NaHCO_3$ saturado, H_2O, H_3PO_4 al 5%, salmuera, se secó en N_a2SO_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)

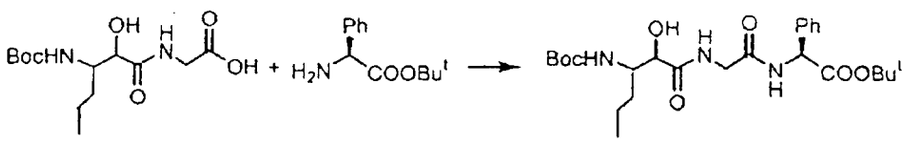


Una solución del compuesto (1.09) (7,00 g, 17,8 mmol) en etanol absoluto (300 mL) se agitó a temperatura ambiente en una atmósfera de hidrógeno en presencia de Pd-C (300 mg, 10%). El progreso de la reacción se siguió mediante TLC

Luego de 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.), Compuesto (1.2) (de Novabiochem, Catálogo No. 04-12-5147) (1.03 eq.), HOOBt (1.03 eq.), N-metilomorfoleno (2.2 eq.), y dimetiloformamida (70 mL/g) se agitó a -20°C. EDCI (1.04 eq.) se agregó y la reacción se agitó durante 48 hr. La mezcla de reacción se vertió en KH_2PO_4 acuoso al 5 % y se extrajo con acetato de etilo (2 x). Las fases orgánicas combinadas se lavaron con K_2CO_3 acuoso frío al 5%, luego KH_2PO_4 acuoso al 5%, luego salmuera, y la capa orgánica se secó en $MgSO_4$ anhidro. La mezcla se filtró, luego se evaporó y el filtrado se secó al vacío, el residuo se trituró con Et2O-hexano, y se filtró para dejar el compuesto del título (1.3) (86% de rendimiento), $C_{25}H_{39}N_3O_7$ (493,60), espec. de masa (FAB) M+1 = 494,3.

Paso B Compuesto (1.4)

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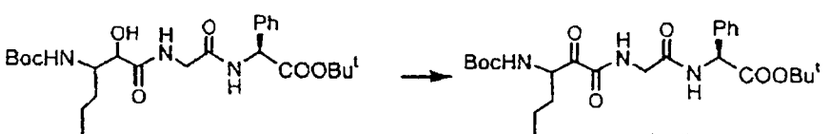


(1.3) (1.4)

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 lo dejó enfriar 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 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, oscurecido con D_2O), 1,7-1,1 (m, 4H), 1,35 (s, 9H), 0,83 (m, 3H).

Ejemplo de preparación 3

Compuesto (1.5)



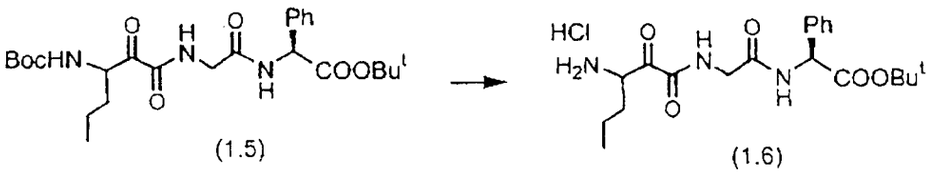
(1.3) (1.5)

El Compuesto (1.3) del Ejemplo de preparación 2, Paso A, se trató en esencia, de la misma manera que en el Ejemplo de preparación 7, Paso A que sigue para obtener el Compuesto (1.5).

Ejemplo de preparación 4

Compuesto (1.6)

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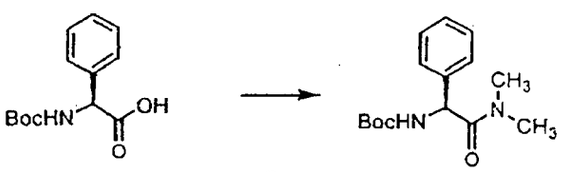


(1.5) (1.6)

El Compuesto (1.5) del Ejemplo de preparación 3, se trató en esencia, de la misma manera que en el Ejemplo de preparación 2, Paso B, para obtener 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, el 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 anhidro (200 mL) y CH_2Cl_2 (150 mL) a -20°C se agregó NMM (5,90 mL, 53,7 mmol). Luego de agitarse a esta temperatura durante 30 min., la mezcla de reacción se mantuvo en un congelador durante la noche (18 h). Luego se lo dejó entibiar hasta lograr la temperatura ambiente, y se agregaron EtOAc (450 mL), salmuera (100 mL) y H_3PO_4 al 5% (100 mL). Luego de separar las capas, la capa orgánica se lavó con H_3PO_4 al 5% (100 mL), solución de bicarbonato de sodio acuoso saturado (2 X 150 mL), agua (150 mL), y salmuera (150 mL), se secó ($MgSO_4$), se filtró y se concentró al vacío para obtener el Compuesto (2.09) (4,86 g) como sólido blanco, que se usó sin purificación adicional.

Paso B Compuesto (2.1)

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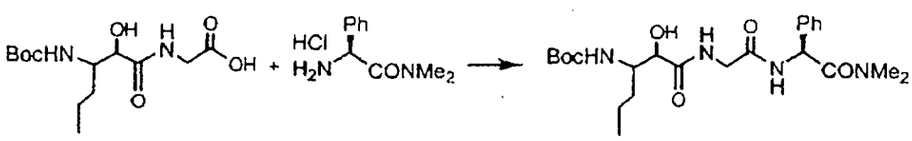


(2.09) (2.1)

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. Se monitoreó el progreso de la reacción por medio de TLC. Luego de 4 h, la solución se concentró al vacío para lograr el Compuesto (2.1) como un sólido blanco que se usó en la próxima reacción sin purificación adicional. LRMS m/z MH^+= 179,0.

Ejemplo de preparación 6

Paso A Compuesto (2.2)

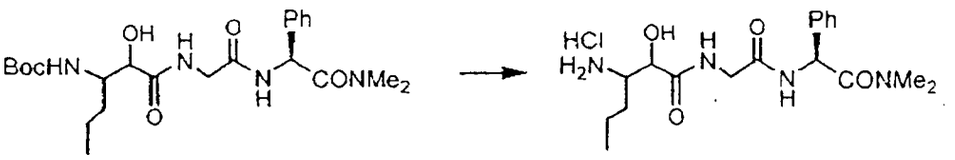


(1.1) (2.1) (2.2)

En esencia, de la misma manera que en ejemplo de preparación 2, Paso A. sustituyendo el clorhidrato de fenilglicina N,N-dimetilamida en lugar del clorhidrato del éster *t*-butílico de fenilglicina, se preparó el Compuesto (2.2) espec. de masa (FAB) M+1 = 465,3.

Paso B Compuesto (2.3)

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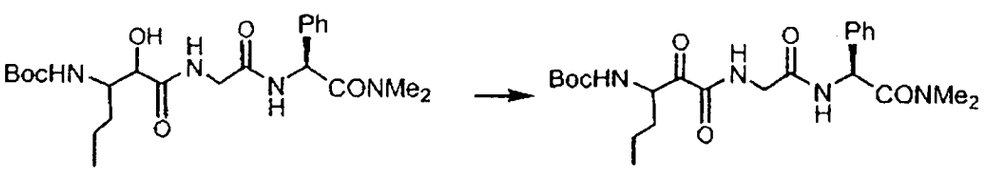


(2.2) (2.3)

El Compuesto (2.2) de Paso A (1.85 g) se sometió a reacción 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 en éter isopropílico, se filtró, y se secó para obtener el Compuesto (2.3) (1,57 g, 98% de rendimiento), $C_{18}H_{28}N_4O_4$.HCl, espec. de masa (FAB) M+1 = 365,3

Ejemplo de preparación 7

Paso A Compuesto (2.4)



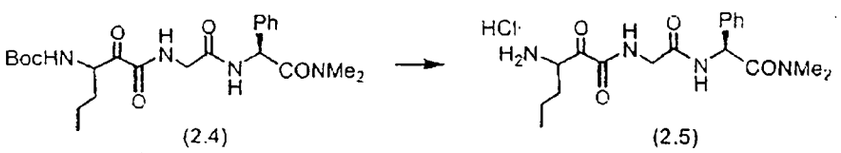
(2.2) (2.4)

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 de diciclohexilocarbodiimida 1 M / diclorometano (8,5 mL). El baño frío se removió y la mezcla se agitó durante 22 hr. Luego se agregó 2-propanol (0,5 mL), y se agitó durante 1 hr adicional. La mezcla se filtró, luego se lavó con NaOH 0,1 N frío en hielo (50 mL), luego HCl 0,1N frío en hielo (50 mL), luego KH_2PO_4 acuoso al 5%, luego salmuera saturada. La solución orgánica se secó en sulfato de magnesio anhidro, luego se filtró. El filtrado se evaporó, y se sometió a cromatografía en gel de sílice, eluyendo con acetato de etilo para

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obtener el Compuesto (2.3) (1,87 g, 94% de rendimiento), $C_{23}H_{34}N_4O_6$, espec. de masa (FAB) M+1 = 463,3.

Paso B Compuesto (2.5)



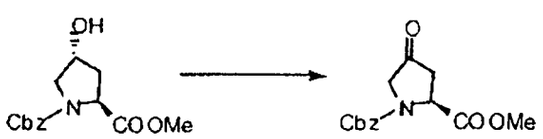
(2.4) (2.5)

En esencia, de la misma manera que en ejemplo de preparación 2, Paso B,

se preparó el Compuesto (2.5).

Ejemplo de preparación 8

Paso A Compuesto (3.1)



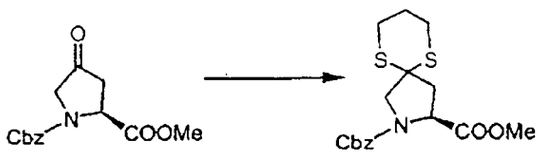
(3.01) (3.1)

En un frasco, se combinaron éster metílico de N-Cbz-hidroxiprolina (provisto por Bachem Biosciences, Incorporated, King of Prussia, Pennsylvania), el 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 de NaBr/agua (1,28 g /5 mL). A esto se agregó el radical libre 2,2,6,6-tetrametilo-1-piperidenilooxi (TEMPO, 17 mg, de Aldrich Chemicals, Milwaukee, Wisconsin). La mezcla agitada se enfrió a 5°C y luego se agregó a solución preparada de oxidante [blanqueador disponible en el mercado, Clorox® (18 mL), $NaHCO_3$ (2,75 g) y agua para formar 40 mL] por goteo durante 0,5 hr. A esto se agregó 2-propanol (0,2 mL). La fase orgánica se separó, y la fase acuosa

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se extrajo con acetato de etilo. Se combinaron los extractos orgánicos, se lavaron con tiosulfato de sodio al 2%, luego salmuera saturada. La solución orgánica se secó en $MgSO_4$ anhidro, se filtró, and se evaporó el filtrado al vacío para dejar a una goma de color amarillo pálido para posteriores reacciones (2,9 g, 97% de rendimiento), $C_{14}H_{15}NO_5$ (277,28), espec. 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 estearato de trifluoruro recientemente destilado (3,7 mL). La mezcla se agitó a temperatura ambiente durante 18 h. Mientras se agitaba vigorosamente, se agregó con cuidado una solución de K_2CO_3/agua (2 g/30 mL), seguido de $NaHCO_3$ saturado (10 mL). La fase orgánica se separó de la fase acuosa (pH -7,4), se lavó con agua (10 mL), luego con salmuera. La solución orgánica se secó en $MgSO_4$ anhidro, se filtró, y se evaporó. El residuo se sometió a cromatografía en gel de sílice, eluyendo con tolueno, luego con un gradiente de hexano-Et_2O (2:3 a 0:1) para obtener un aceite de color marrón (7,0 g, 68% de rendimiento), $C_{17}H_{21}NO_4S_2$ (367,48), espec. de masa (FAB) M+1 =368,1.

Paso C Compuesto (3.3)

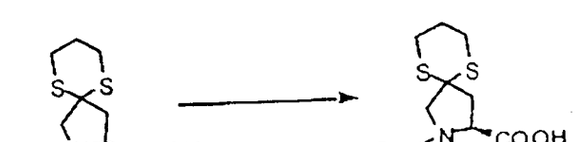
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(3.2) (3.3)

Una solución del compuesto (3.2) de Paso B anterior (45 g) en acetonitrilo (800 mL) a 20°C se trató con yodotrimetilsilano recientemente destilado (53 mL) de una vez. La reacción se agitó durante 30 min., luego se vertió sobre una solución de di-t-butildicarbonato preparada recientemente (107 g), éter etílico (150 mL), y diisopropiletiloamina (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 capa de acetonitrilo inferior, y luego la capa se lavó con KH_2PO_4 acuoso al 10% (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 0,1N, NaOH 0,1N, KH_2PO_4 acuoso al 10%, y salmuera. La solución orgánica se secó en $MgSO_4$ anhidro, se filtró, y se evaporó al vacío. El residuo (66 g) se sometió a cromatografía en gel de sílice (2 kg), eluyendo con hexano (2 L), luego Et_2O/hexano (55:45, 2 L), luego Et_2O (2 L) para obtener una goma de color naranja que se cristalizó lentamente en reposo (28 g, 69% de rendimiento), $C_{14}H_{23}NO_4S_2$ (333,46), espec. de masa (FAB) M+1 = 334,1.

Paso D Compuesto (3.4)

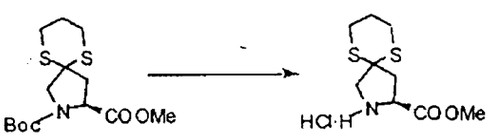


(3.3) (3.4)

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Una solución del compuesto (3.3) de 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 acuosa 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 en $MgSO_4$ 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), espec. de masa (FAB) M+1 = 320,1.

Paso E Compuesto (3.5)

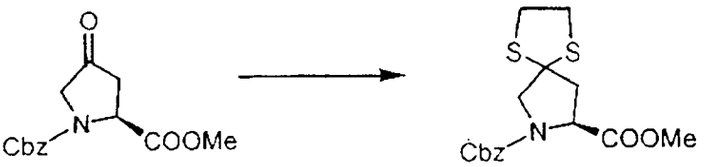


(3.3) (3.5)

A una solución del compuesto (3.3) del Paso C anterior (1 g) en dioxano (5 mL), se agregó solución de HCl 4N-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 Et2O, y se filtró para dejar el compuesto del título (0,76 g, 93% de rendimiento), $C_9H_{15}NO_2S_2$.HCl (269,81), espec. 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 que en el Ejemplo de preparación 8, Paso B, sustituyendo ditiol etano por ditiol propano, se obtuvo el compuesto (3.6).

Paso B Compuesto (3.7).



(3.6) (3.7)

Siguiendo Esencialmente el mismo procedimiento que en el Ejemplo de preparación 8, Paso C, sustituyendo el compuesto (3.6) por el compuesto (3.2), se obtuvo el compuesto producto (3.7).

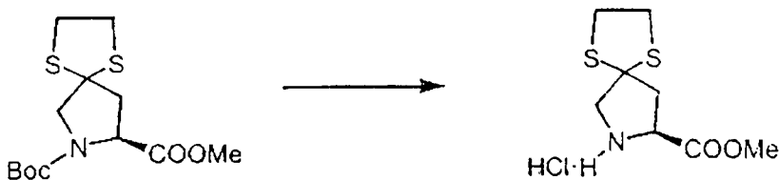
Paso C Compuesto (3.8)



(3.7) (3.8)

Siguiendo Esencialmente el mismo procedimiento que en el 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)

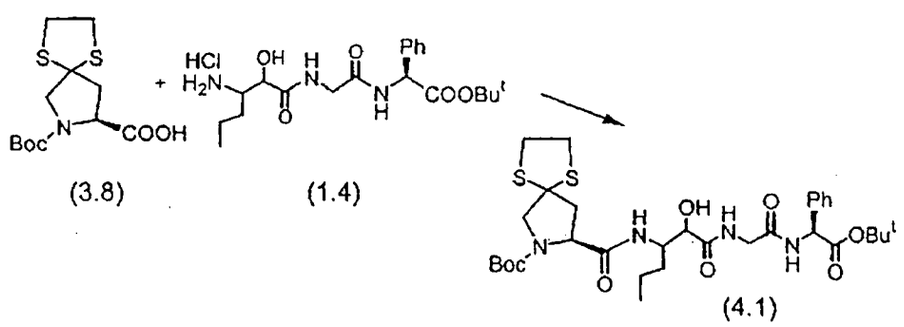


(3.7) (3.9)

Siguiendo Esencialmente el mismo procedimiento que en el 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)

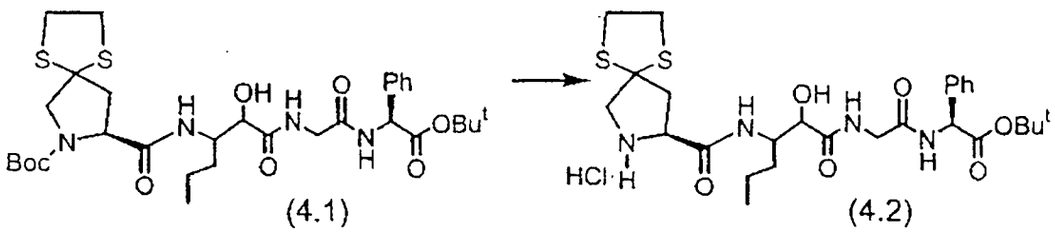


(3.8) (1.4) (4.1)

En esencia, de la misma manera 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)

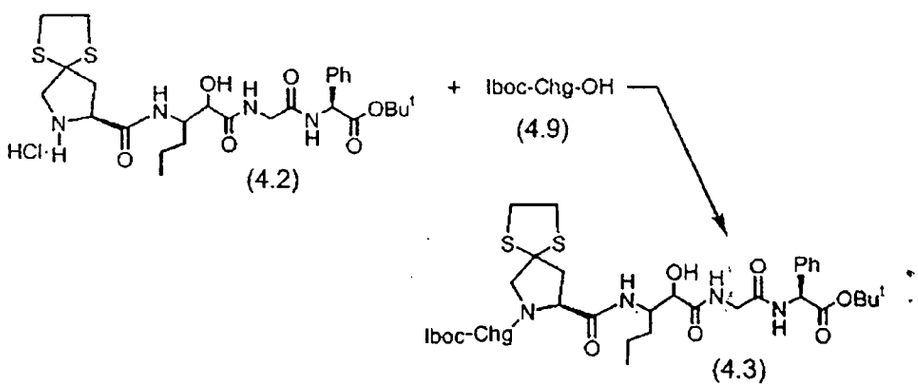
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(4.1) (4.2)

En esencia, de la misma manera que en ejemplo de preparación 2, Paso B, se preparó el Compuesto (4.2) espec. de masa (FAB) M+1 = 609,3.

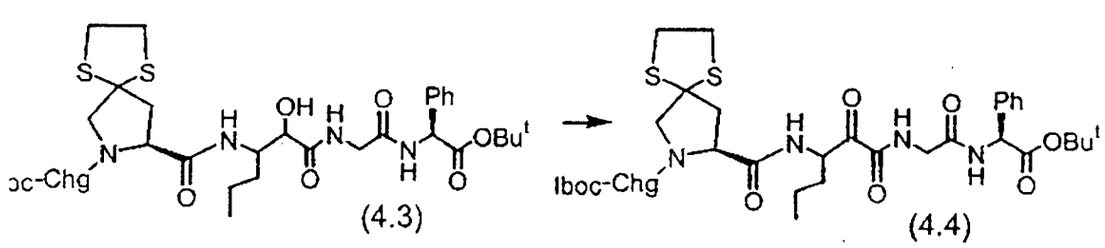
Paso C Compuesto (4.3)



(4.2) (4.9) (4.3)

En esencia, de la misma manera que en ejemplo de preparación 2, Paso A, se preparó el Compuesto (4.3), $C_{41}H_{61}N_5O_{10}S_2$ (708,89), espec. de masa (FAB) M+1 = 709,3.

Paso D Compuesto (4.4)

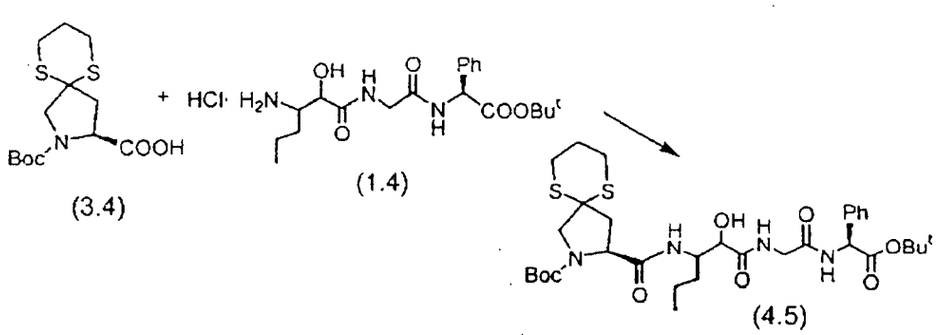


(4.3) (4.4)

En esencia, de la misma manera que en ejemplo de preparación 7, Paso A, se preparó el Compuesto (4.4).

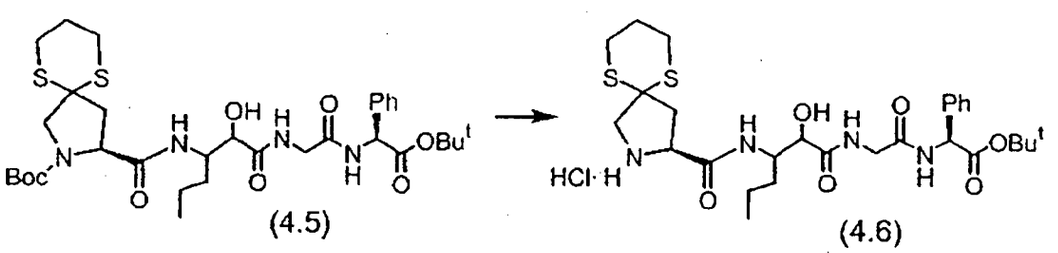
Ejemplo de preparación 11

Paso A Compuesto (4.5)



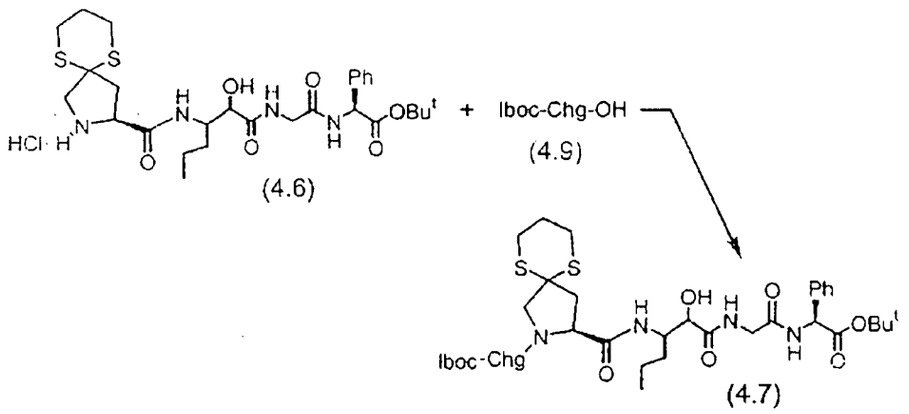
En esencia, de la misma manera que en ejemplo de preparación 2, Paso A, se preparó el Compuesto (4.5).

Paso B. Compuesto (4.6)



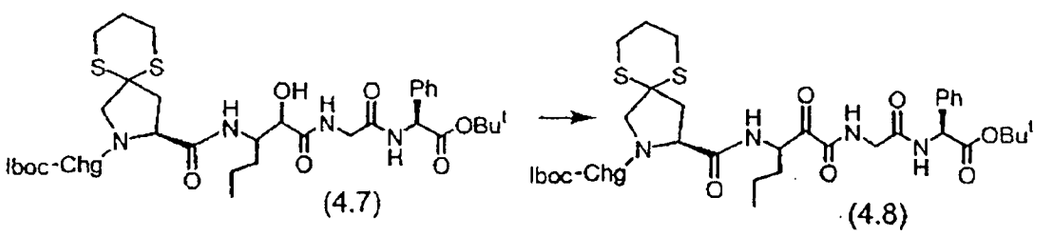
En esencia, de la misma manera que en el Ejemplo de preparación 2, Paso B, se preparó Compuesto (4.6).

Paso C. Compuesto (4.7)



El Compuesto (4.9) del Ejemplo de preparación 12, se sometió a reacción con el Compuesto (4.6) de Paso B anterior, en esencia, de la misma manera que en Ejemplo de preparación 2, Paso A, para obtener el Compuesto (4.7).

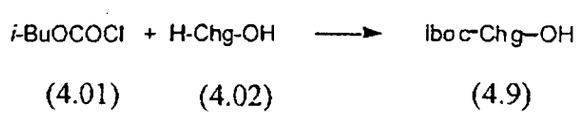
Paso D, Compuesto (4.8)



En esencia, de la misma manera que en Ejemplo de preparación 7, Paso A, se preparó el Compuesto (4.8).

Ejemplo de preparación 12

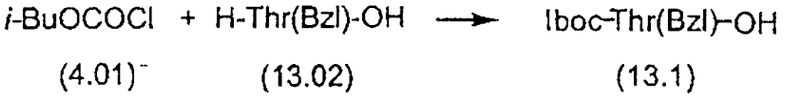
Compuesto (4.9)



Una solución de L-ciclohexilglicina (4.02) (1,0 eq.), dimetiloformamida (20 mL/g), y diisopropiletilamina (1.1 eq.) a 5°C se trata con cloroformiato de isobutilo (4.01) (1.1 eq.). Se remueve el baño frío y se agitó durante 6 hr. La mezcla de reacción se vierte sobre KH_2PO_4 acuoso al 5% y se extrajo con acetato de etilo (2 x). Las fases orgánicas combinadas se lavan con K_2CO_3 acuoso frío al 5%, luego KH_2PO_4 acuoso al 5%, luego salmuera, y se secan los orgánicos en $MgSO_4$ anhidro. La mezcla se filtró, el filtrado se evaporó al vacío, el residuo se sometió a cromatografía de ser necesario o se trituró el residuo con Et_2O-hexano, y se filtró para dejar el compuesto del título (4.9), $C_{13}H_{23}NO_4$ (257,33).

Ejemplo de preparación 13

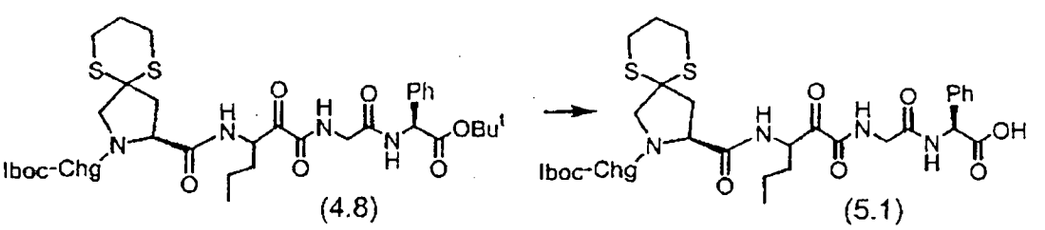
Compuesto (13.1)



(4.01) (13.02) (13.1)

En esencia, de la misma manera que en Ejemplo de preparación 12, sustituyendo la L-O-bencilotreonina (13.02) (Wang et al, J. Cem. Soc., *Perken Trans.* 1, (1997) No. 5, 621-624.) por L-ciclohexiloglicina (4.02) se prepara Compuesto (13.1) $C_{16}H_{23}NO_5$ (309,36), espec. de masa (FAB) M+1 = 310,2.

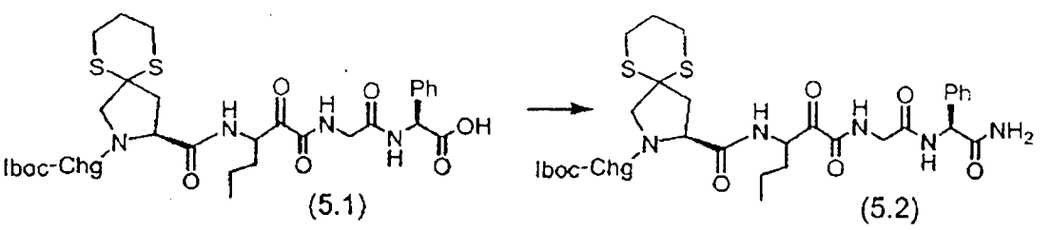
Ejemplo de preparación 14



El Compuesto (4.8) del Ejemplo de preparación 11, Paso D (1.0 g) se sometió a reacción con una solución de ácido trifluoroacético anhidro

-diclorometano (1:1, 50 mL) durante 2 hr. La solución se diluyó con xiloano (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), espec. de masa (FAB) M+1 =776,5.

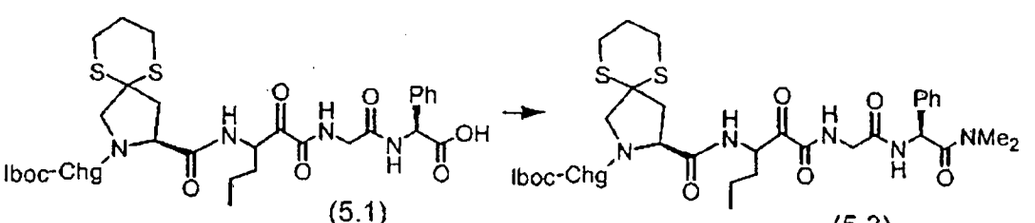
Paso B Compuesto (5.2)



(5.1) (5.2)

En esencia, de la misma manera que en Ejemplo de preparación 2, Paso A, Compuesto (5.1) se sometió a reacción con amonia (solución de 1,4-dioxano 0,5 M), para obtener el compuesto del título (5.2) $C_{37}H_{54}N_6O_8S_2$ (774,99), espec. de masa (FAB) M+1 = 775,4.

Ejemplo de preparación 15



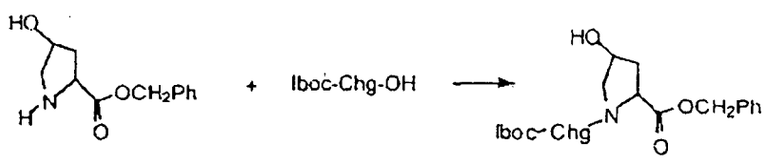
(5.1) (5.3)

Una mezcla del compuesto (5.1) del Ejemplo de preparación 14, Paso A (0.15 g), N,N-dimetilamina (0,12 mL de solución de THF 2M), dimetiloformamida (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 H_3PO_4 acuoso al 5% (50 mL) y se extrajo con acetato de

etilo (2 x). Las fases orgánicas combinadas se lavaron con cold K_2CO_3 acuoso al 5%, luego KH_2PO_4 acuoso al 5%, luego salmuera. La solución orgánica se secó en $MgSO_4$, se filtró, y se evaporó al vacío. El residuo se sometió a cromatografía en gel de sílice, eluyendo con MeOH-CH_2Cl_2 para obtener el compuesto del título (5.3), $C_{39}H_{58}N_6O_8S_2$ (803,05), espec. de masa (FAB) M+1 =803,5.

Ejemplo de preparación 16

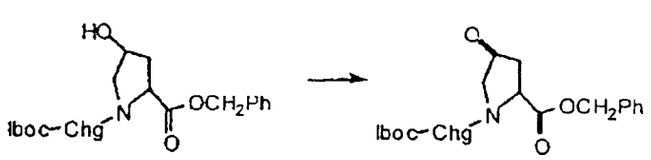
Paso A Compuesto (6.2)



(6.1) 4.9) (6.2)

En esencia, de la misma manera que en Ejemplo de preparación 2, Paso A, Compuesto (6.1) el clorhidrato de éster bencílico de hidroxiprolina se sometió a reacción 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), espec. de masa (FAB) M+1 = 461,2.

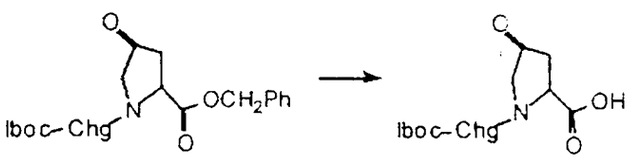
Paso B Compuesto (6.3)



(6.2) (6.3)

En esencia, de la misma manera que en Ejemplo de preparación 8, se preparó el Compuesto (6.3), $C_{25}H_{34}N_2O_6$ (458,55), espec. de masa (FAB) M+1 = 459,2.

Paso C Compuesto (6.4)

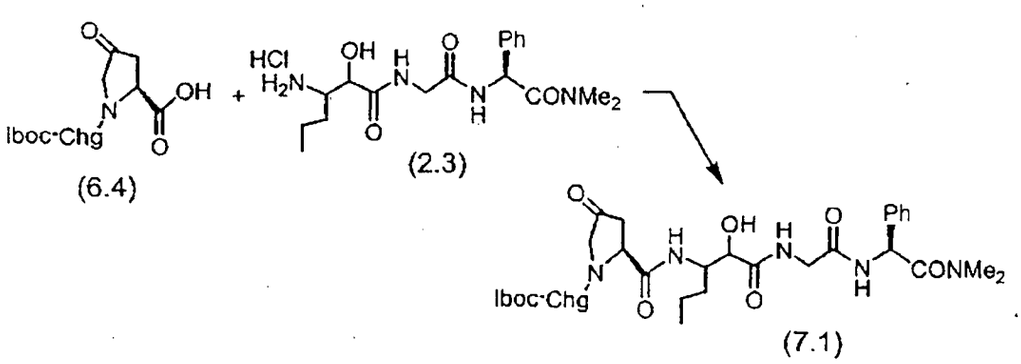


(6.3) (6.4)

Una mezcla del compuesto (6.3) de Paso B (1 g), Pd/C al 10% (0,05 g), y EtOH (100 mL) se agitó en 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) espec. de masa (FAB) M+1 = 369,2.

Ejemplo de preparación 17

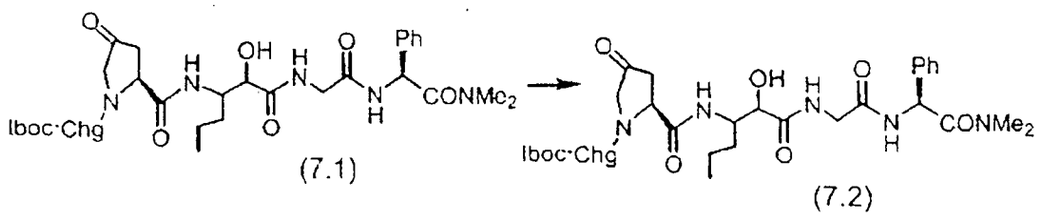
Paso A Compuesto (7.1)



(6.4) (2.3) (7.1)

El Compuesto (6.4) del Ejemplo de preparación 16, Paso C, se sometió a reacción con el Compuesto (2.3) del Ejemplo de preparación 6, Paso B, en, esencialmente, la misma manera que en Ejemplo de preparación 2, Paso A, para obtener el Compuesto (7.1), $C_{36}H_{54}N_6O_9$ (714,85), espec. de masa (FAB) M+1 = 715,9.

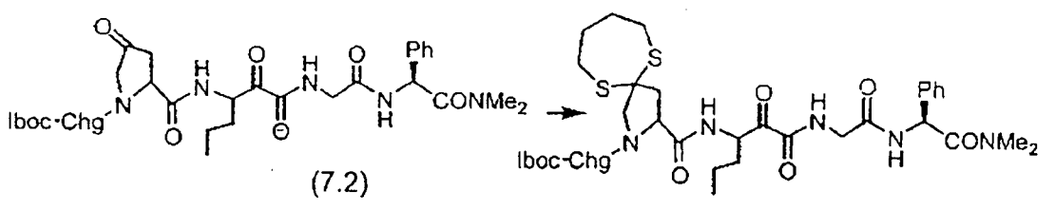
Paso B Compuesto (7.2)



(7.1) (7.2)

El Compuesto (7.1) se sometió a reacción en esencia, de la misma manera que en el Ejemplo de preparación 7, Paso A, para obtener el Compuesto (7.2), $C_{36}H_{52}N_6O_9$ (712,83), espec. de masa (FAB) M+1 = 713,5.

Paso C Compuesto (7.3)



(7.2) (7.3)

El Compuesto (7.2) de Paso B anterior, se sometió a reacción en esencia, de la misma manera que en Ejemplo de preparación 8, Paso B, con 1,4-butanditiol, para el compuesto del título (7.3), $C_{40}H_{60}N_6O_8S_2$ (817.07), espec. de masa (FAB) M+1 = 817,5.

Usando los procedimientos mencionados anteriormente, se prepararon los compuestos que se presentan en la **Tabla 2** anexa. Como nota general para todas las Tablas que se anexan a la presente, como también a los Ejemplos y Esquemas de esta memoria descriptiva, cualquier átomo de nitrógeno de extremo abierto con valencia no completa en las estructuras químicas en los Ejemplos y las Tablas se refiere a NH, o en el caso de un nitrógeno termina, $-NH_2$. De un modo similar, cualquier átomo de oxígeno de extremo abierto con valencia no

completa en las estructuras químicas en los Ejemplos y las Tablas, se refiere a -OH.

Síntesis de la Fase Sólida:

Procedimiento General para las reacciones de acoplamiento de la fase sólida

La síntesis se realizó en un recipiente para reacción que se construyó con un cartucho para jeringa de polipropileno adaptado con un frito de polipropileno en la parte inferior. Los aminoácidos protegidos por Fmol se acoplaron mediante técnicas estándar de fase sólida. Cada recipiente de reacción se cargó con 100 mg de resina inicial Fmoc-Sieber (aproximadamente 0,03 mmol). La resina se lavó con porciones de 2 mL de DMF (2 veces). El grupo protector Fmoc se removió mediante tratamiento con 2 mL de una solución al 20% v/v de piperidina en DMF durante 20 minutos. La resina se lavó con porciones de 2 mL de DMF (4 veces). El acoplamiento se realizó en DMF (2 mL), con el uso de 0,1 mmol de Fmoc-amino ácido, 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, se drenó el recipiente de la reacción y la resina se lavó con porciones de 2 mL de DMF (4 veces). El ciclo de acoplamiento se repitió con el siguiente Fmoc-amino ácido o grupo protector.

Procedimiento general para oxidación de Dess-Martin en fase sólida

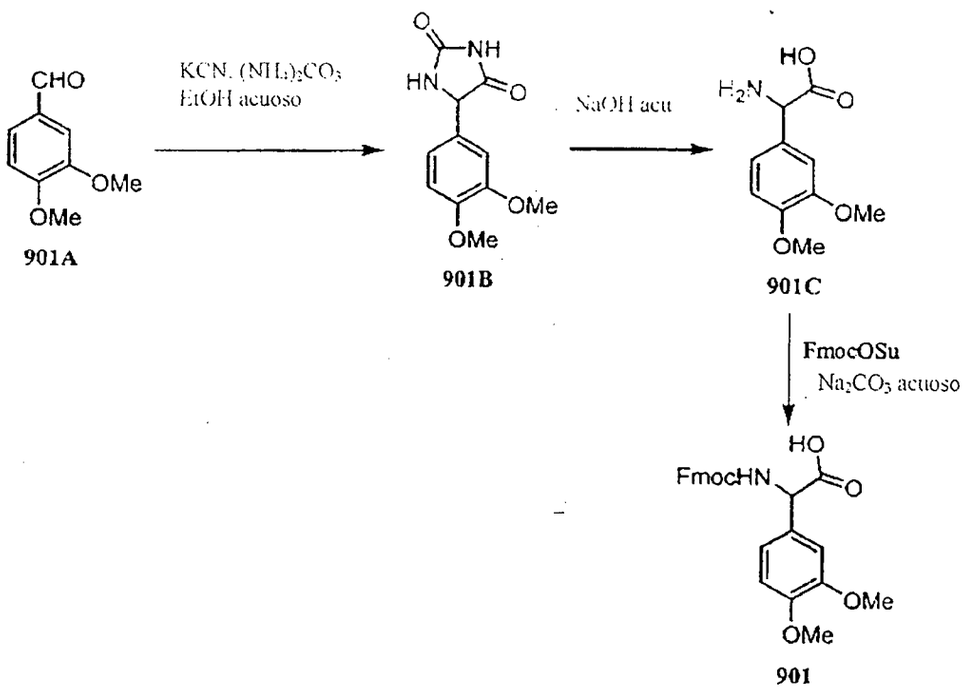
Esta síntesis se condujo en un recipiente para reacción que se construyó con un cartucho para jeringa de polipropileno adaptado con un frito de polipropileno en la parte inferior. Se trató el compuesto de hidroxi unido a la resina (aproximadamente 0,03 mmol) con una solución de 0,12 mmol de periodinona 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 al 20% v/v de iPrOH en

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DCM, THF, una solución al 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'-dimetoxifenilglicina 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 40ºC durante 24 horas. El volumen de la solución se redujo hasta 10 mL por evaporación con presión reducida. Se agregó ácido clorhídrico concentrado (15 mL) y el compuesto **901B** se obtuvo como un precipitado blanco. El compuesto **901B** se aisló por filtración (2,2 g, 9,3 mmol). El compuesto **901B** se disolvió en solución acuosa de hidróxido de sodio al 10% p/p (15 mL) y la solución resultante se calentó a reflujo durante 24 horas. Se agregó ácido clorhídrico y el pH se ajustó hasta neutro (pH 7). La solución resultante, que

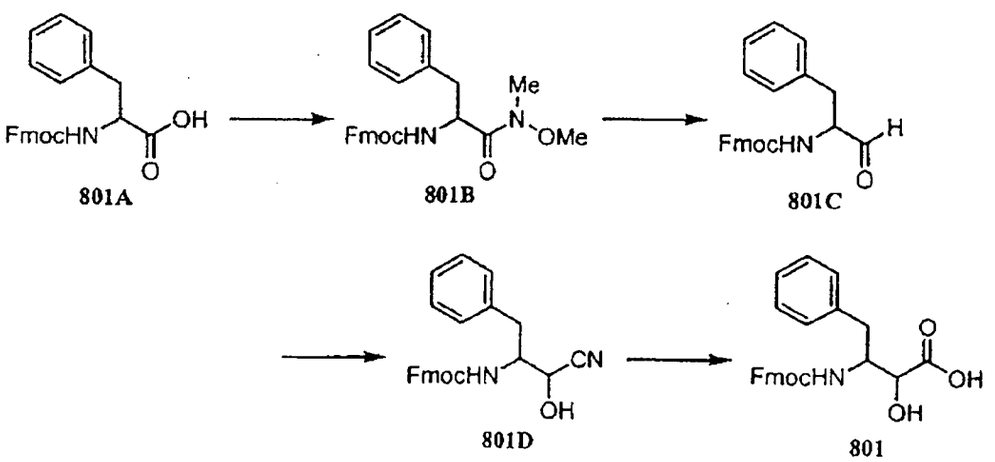
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contenía el compuesto **901C,** se evaporó con presión reducida. El residuo se disolvió en solución acuosa de bicarbonato de sodio al 5% p/p (150 mL).

La solución se enfrió hasta alcanzar los 0°C en un baño de hielo y se agregó 1,4-dioxano (30 mL) y una solución de carbonato de 9-fluorenilmetil succinimidilo (2,7 g, 8 mmol) en 1,4-dioxano (30 mL) a 0°C. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente y se agitó a temperatura ambiente durante 24 horas. El 1,4-dioxano se evaporó con presión reducida. La solución acuosa se lavó con éter dietílico. Se agregó ácido clorhídrico concentrado y se ajustó el pH hasta ser ácido (pH 1). Se agregó acetato de etilo y se lavó la fase orgánica con agua y salmuera. Se secó la fase orgánica en sulfato de sodio anhidro. Se evaporó el solvente bajo presión reducida para lograr el compuesto deseado **901** como un sólido espumoso de color blanco (3,44 g, 7,9 mmol). MS (LCMS-Electrospray) 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 a -30°C en un baño de acetona-hielo seco 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 se agregó una solución de 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). Se dejó entibiar la mezcla de reacción hasta la temperatura ambiente y se agitó a temperatura ambiente durante la noche, Se agregó tolueno y se lavó la fase orgánica con ácido clorhídrico diluido, solución acuosa de bicarbonato de sodio y salmuera. La fase orgánica se secó en sulfato de sodio anhidro. El solvente se evaporó con presión reducida para lograr el compuesto **801B** (4 g, 9,29 mmol).

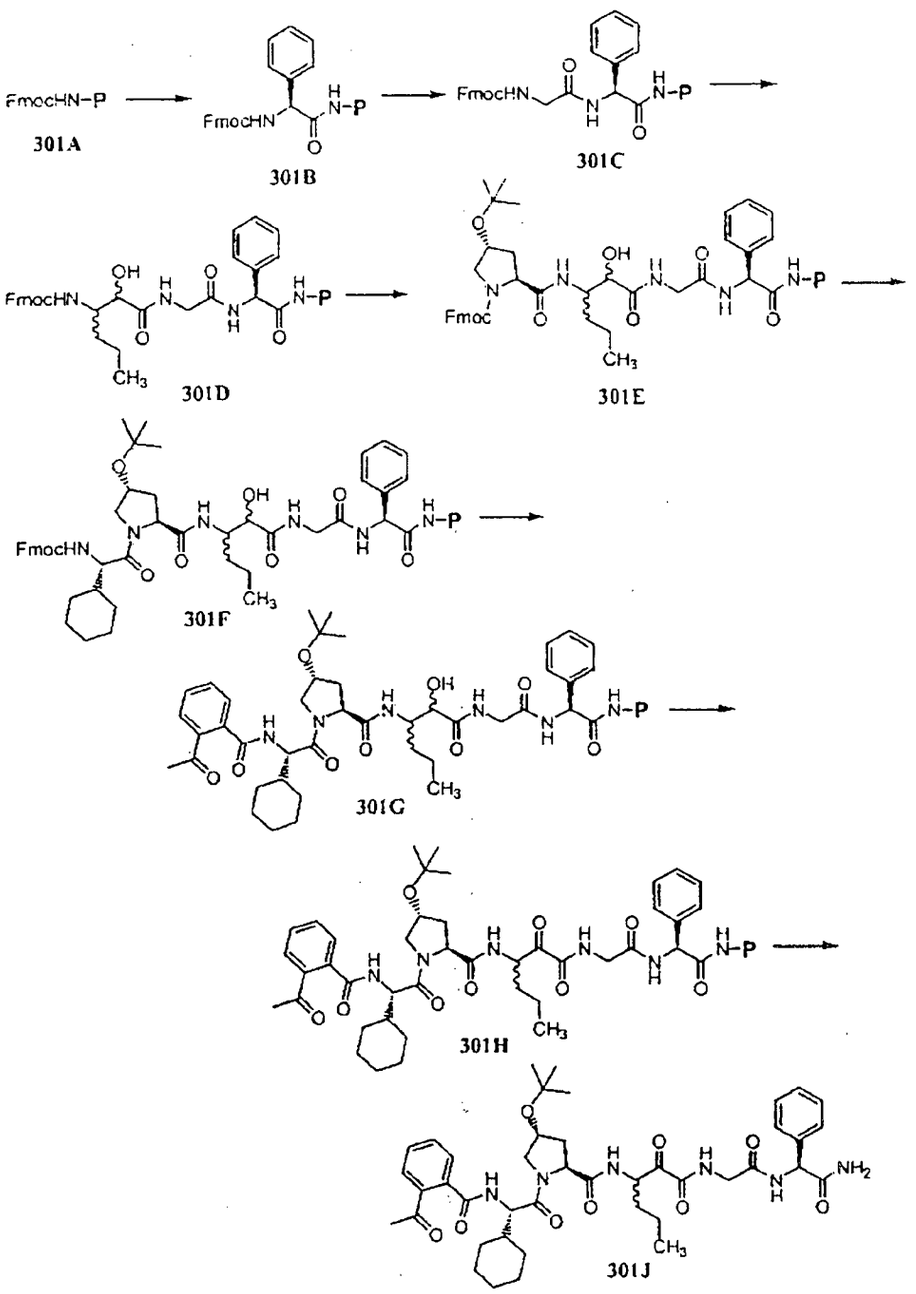
A una solución de Red-Al (6,28 mL, 21,4 mmol) en tolueno anhidro (8 mL) enfriada hasta -20°C en un baño de acetona-hielo seco se le agregó una solución del compuesto **801B** (4 g, 9,29 mmol) en tolueno anhidro (12 mL). La mezcla de reacción se agitó a -20°C durante 1,5 h. Se lavó la fase orgánica con ácido clorhídrico diluido, solución acuosa de bicarbonato de sodio y salmuera. La fase orgánica se secó en sulfato de sodio anhidro. Se evaporó el solvente con presión reducida y se usó el producto bruto **801C** en la siguiente reacción sin purificación adicional.

A una solución del compuesto **801C** (aproximadamente, 9,29 mmol) en hexano (15 mL) se agregó una solución de cianuro de potasio (24 mg, 0,37 mmol) y yoduro ditetrabutilamonio (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 se lavó la fase orgánica con agua y salmuera. La fase orgánica se secó en sulfato de sodio anhidro. El solvente se evaporó con presión reducida para obtener el compuesto **801D** (2,4 g, 6,03 mmol).

A una solución del compuesto **801D** (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. Se agregó acetato de etilo (25 mL) y agua (25 mL).

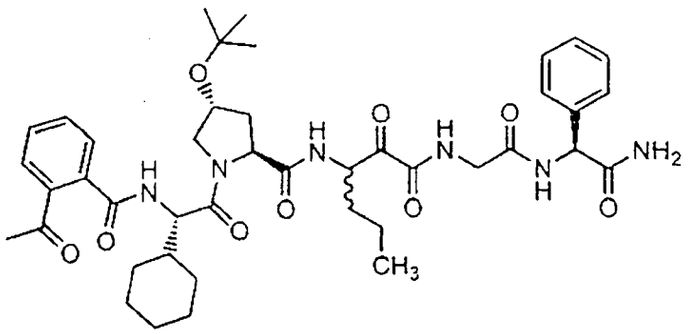
La fase orgánica se lavó con salmuera y se secó en sulfato de sodio anhidro. El solvente se evaporó con presión reducida para obtener el compuesto deseado **801** como un sólido espumoso de color blanco (2 g, 4,8 mmol). MS (LCMS-Electrospray) 418,1 MH^+.

Esquema 8



Ejemplo (301J):

Esquema 8 Compuesto (301J)

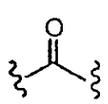


(301J)

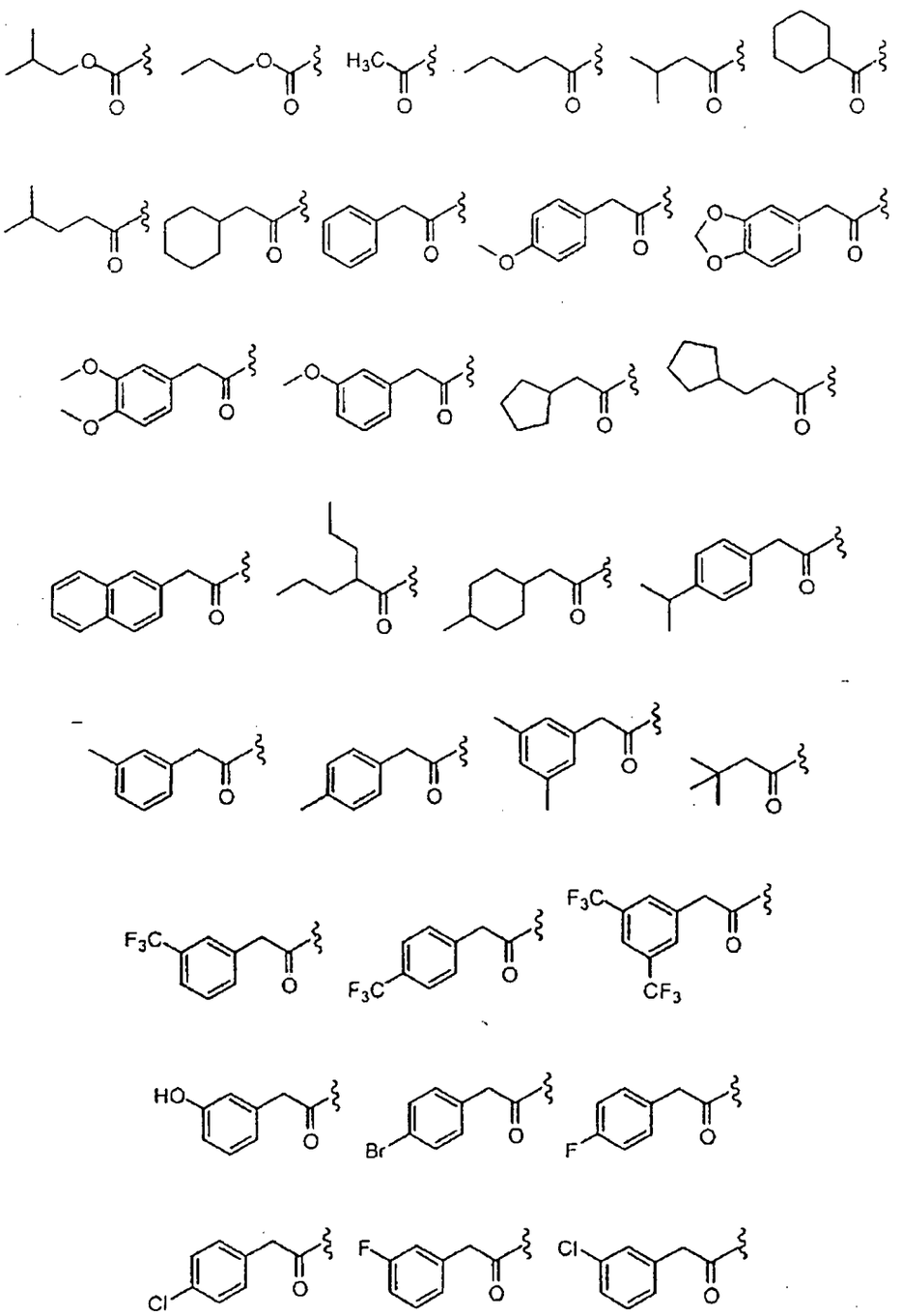
Los compuestos ligados con resina **301B, 301C, 301D, 301E, 301F** y **301G** se prepararon de acuerdo con el procedimiento general para las reacciones de acoplamiento de fase sólida comenzando con 100 mg de resina Fmoc-Sieber (0,03 mmol). El compuesto ligado con resina **301G** se oxidó al compuesto ligado con resina **301H** de acuerdo con el procedimiento general para oxidación de Dess-Martin de fase sólida. El compuesto ligado con resina **301H** se trató con 4 mL de una solución de TFA al 2% v/v en DCM durante 5 min. El filtrado se agregó a 1 mL de AcOH y la solución se concentró por centrifugado al vacío para suministrar el compuesto **301J** (0,0069 g, 29% de rendimiento). MS (LCMS-Electrospray) 771,2 MH^+.

Mediante el uso de las técnicas de síntesis en fase sólida detallados anteriormente, y los siguientes grupos funcionales para las diferentes funcionalidades en el compuesto de la Fórmula 1, se prepararon los compuestos de la **Tabla 3**:

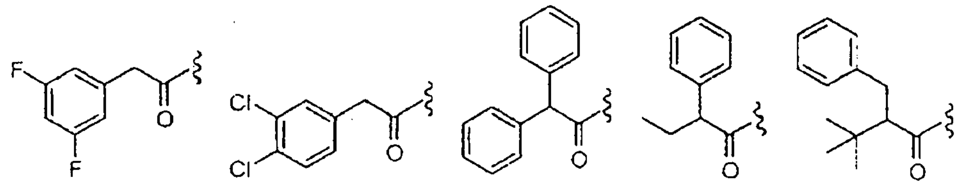
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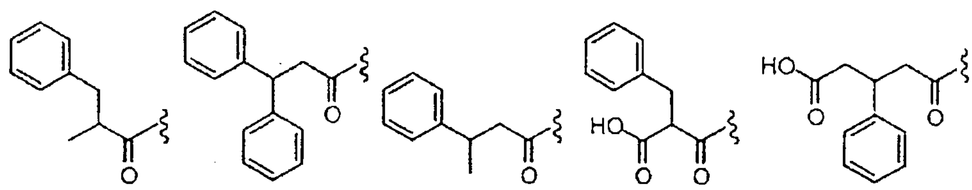


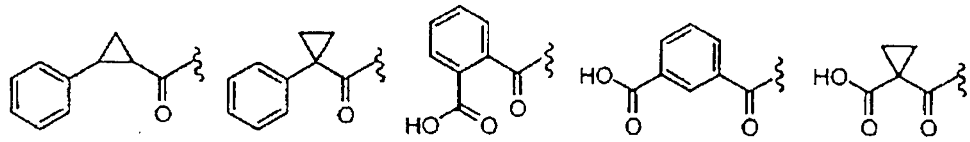
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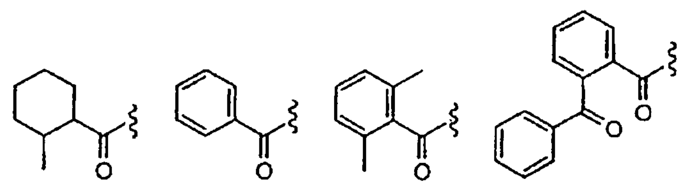

H3C
F3C
F3C
CF3
HO
Br
F
Cl
F
Cl

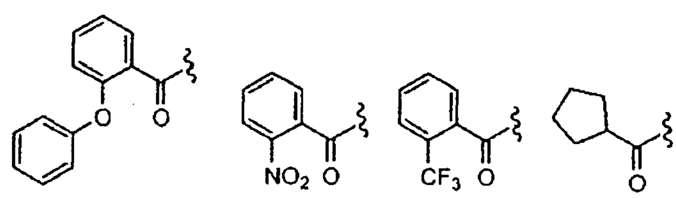
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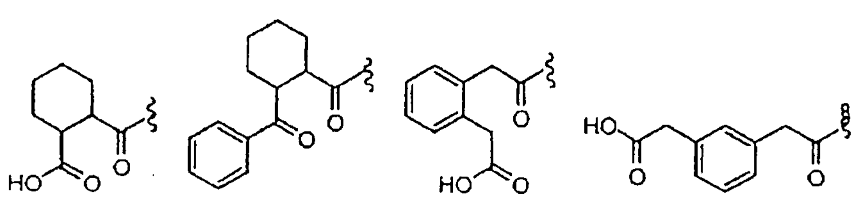


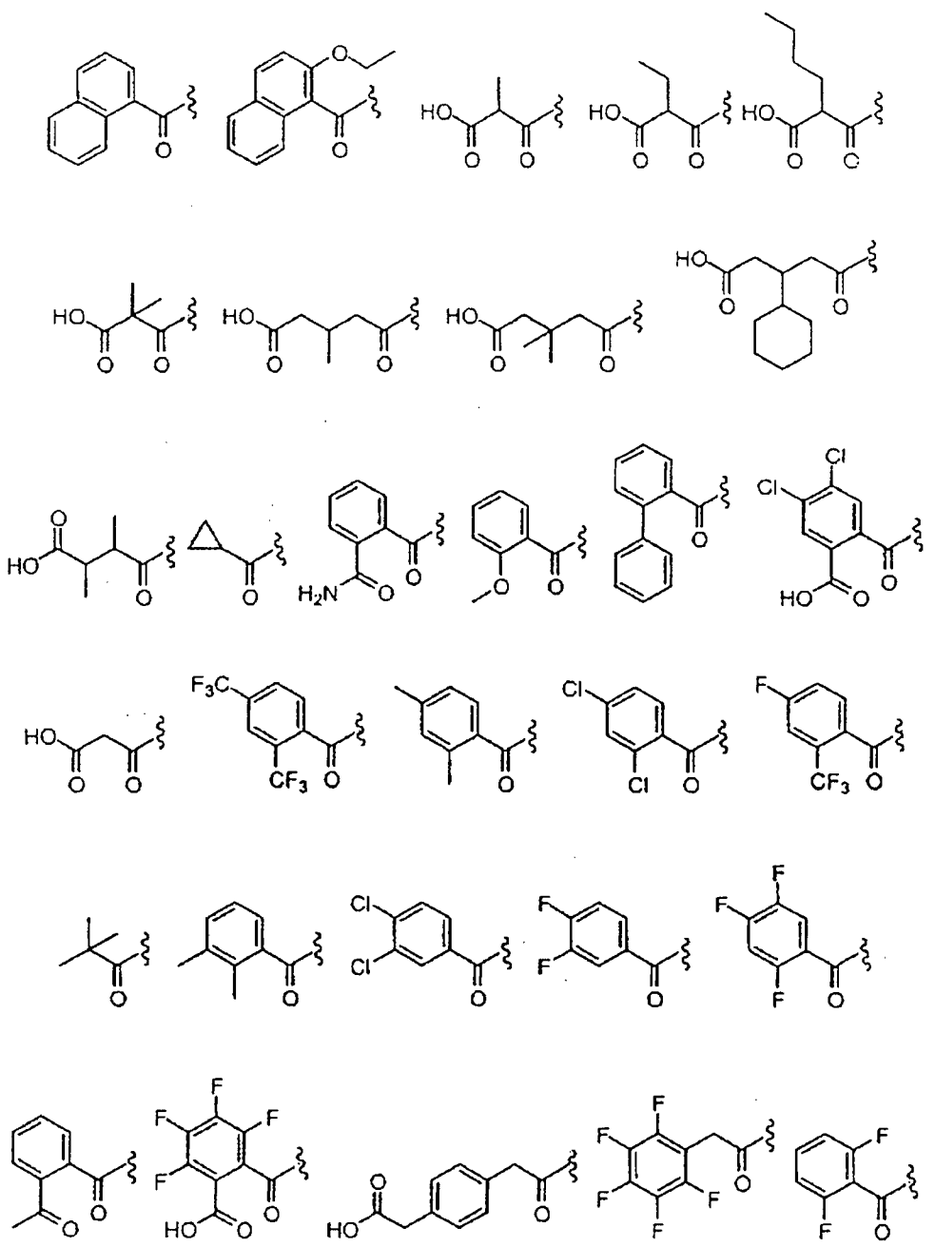


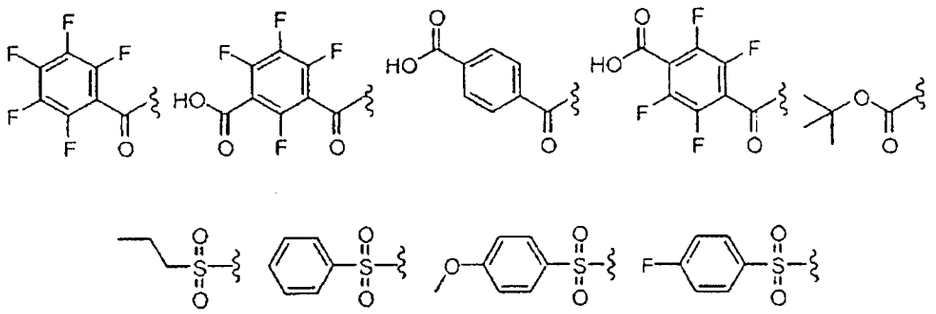












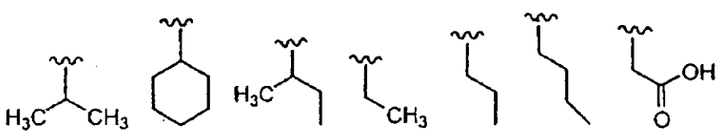
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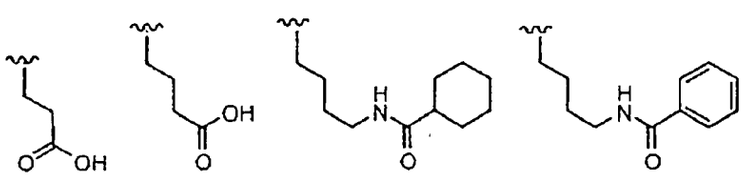


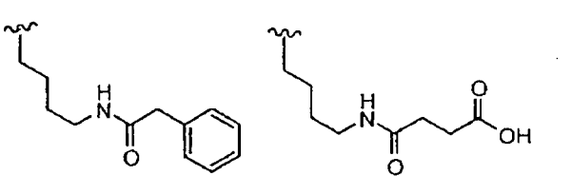
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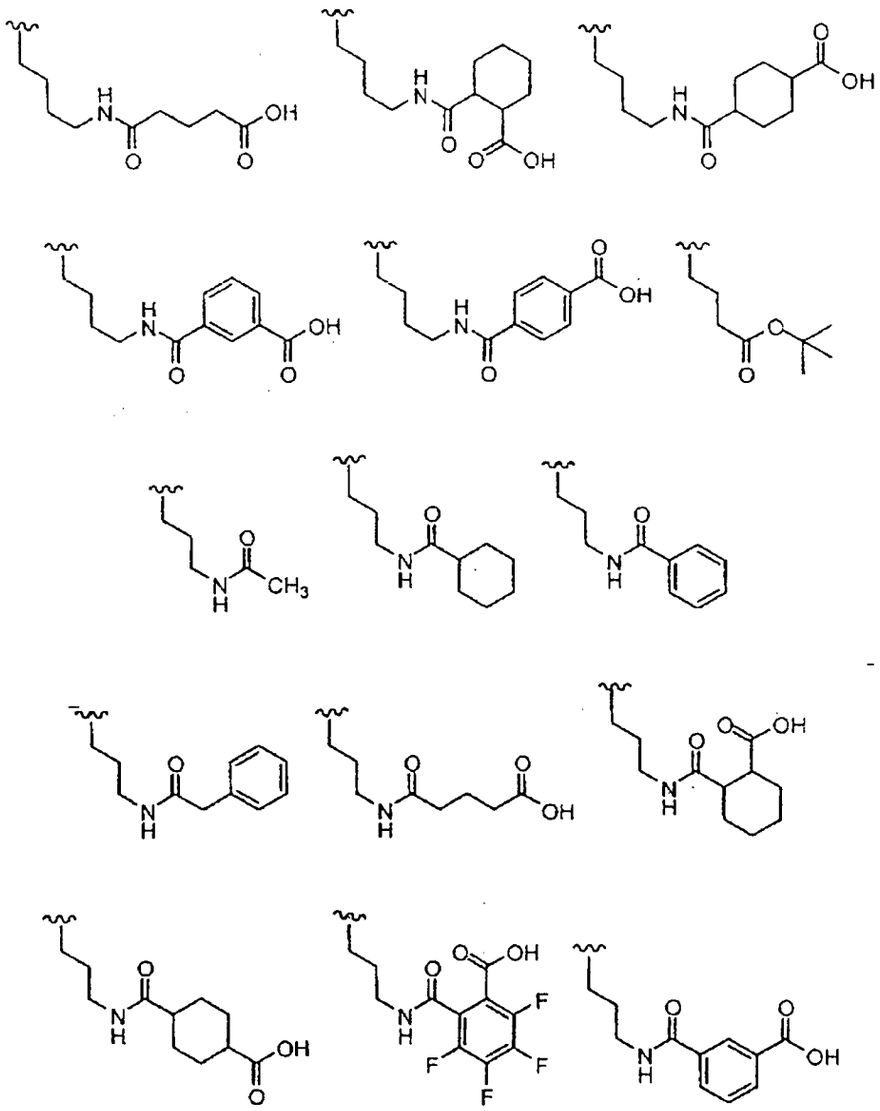


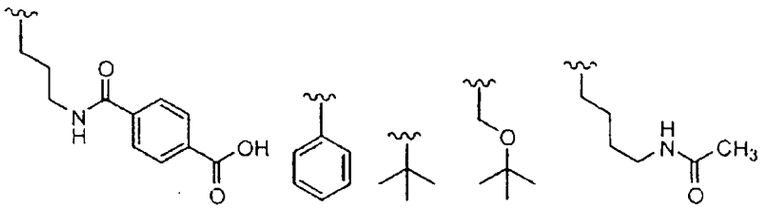
-R^3:



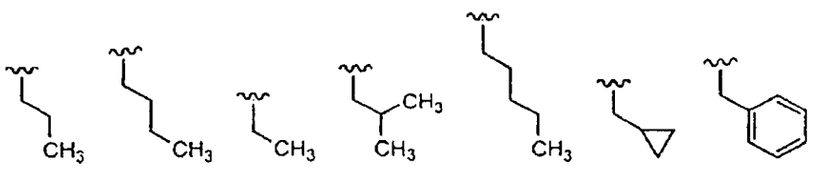








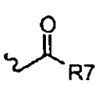
-R^2:



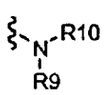
-R^1:



-R^5:



-R^7:

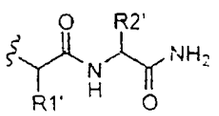


-R^9:

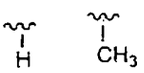


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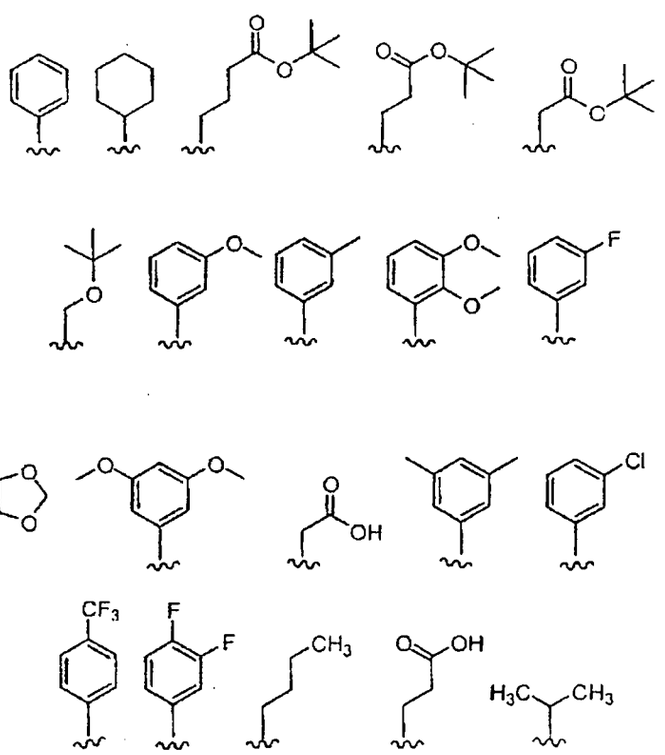
-R^{10}:



-$R^{1'}$:



-$R^{2'}$:



000434

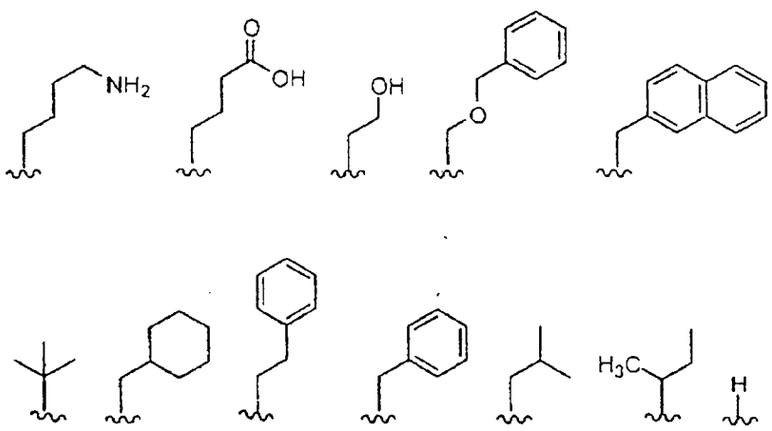
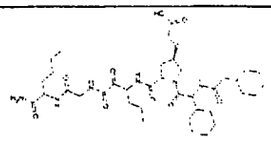
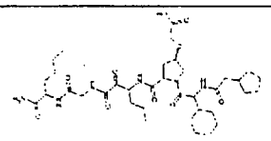
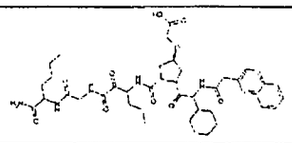
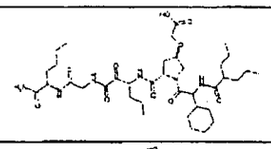
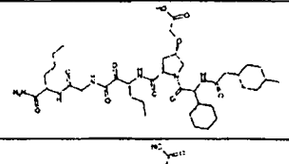
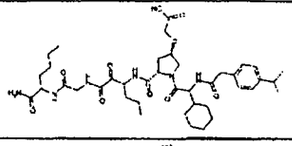
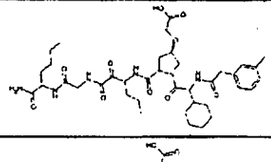
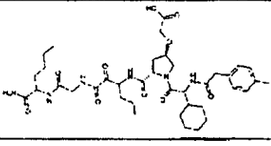
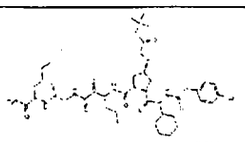
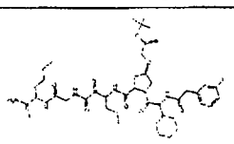
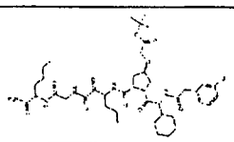
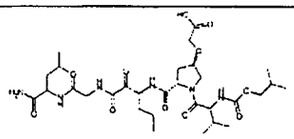
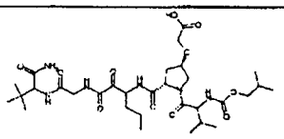
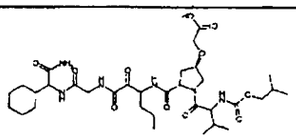
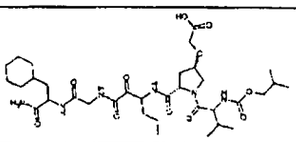
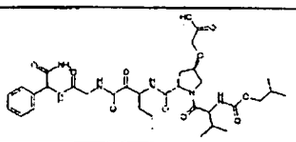


Tabla 3. Compuestos preparados mediante Síntesis de Fase Sólida

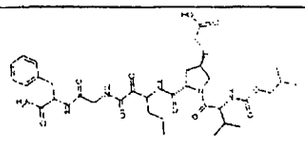
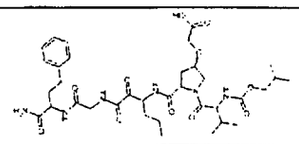
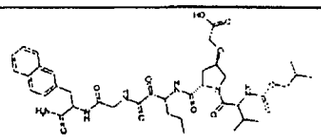
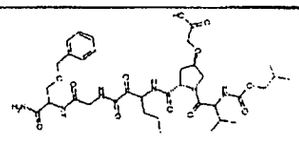
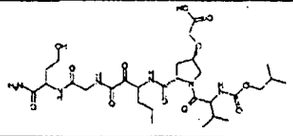
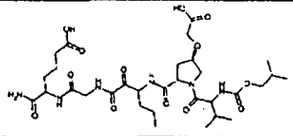
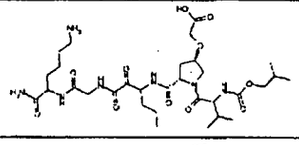
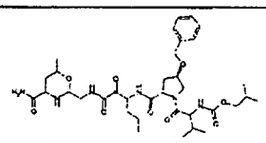
000435

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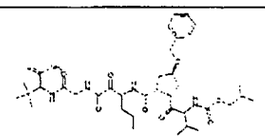
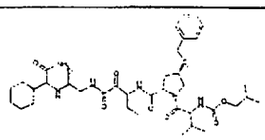
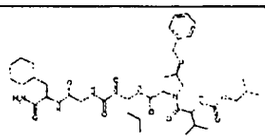
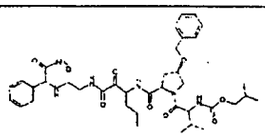
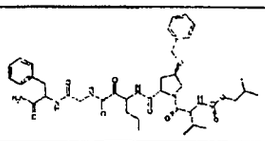
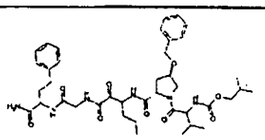
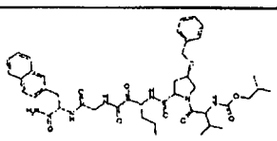
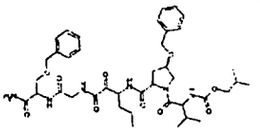
000436

Estructura	Clase Ki[a]
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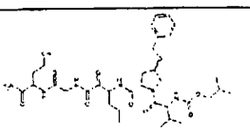
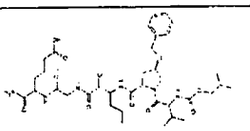
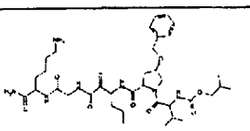
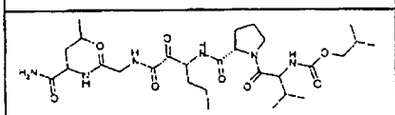
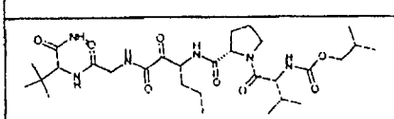
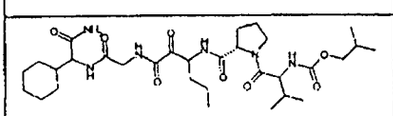
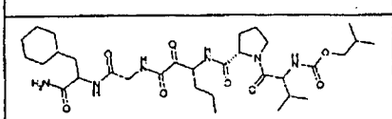
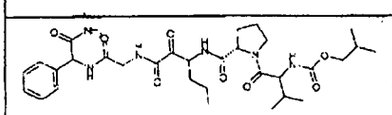
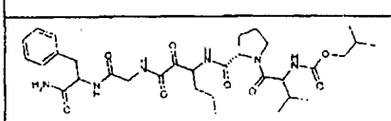
003437

ESTRUCTURA	Clase Kir
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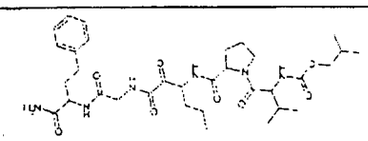
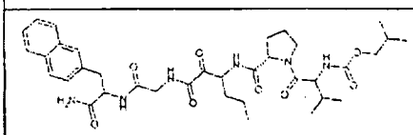
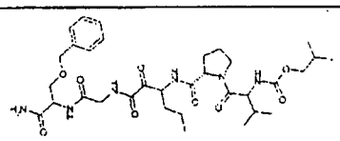
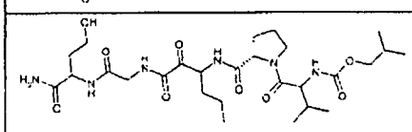
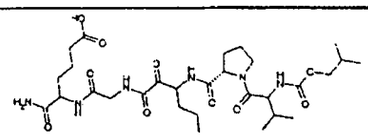
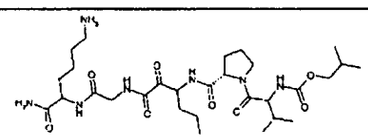
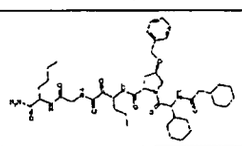
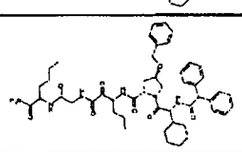
000438

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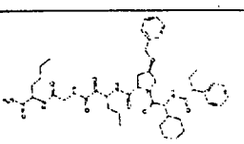
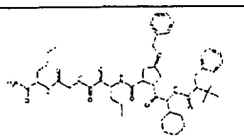
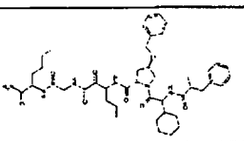
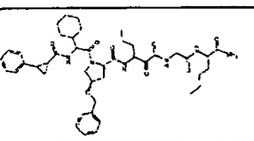
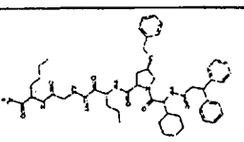
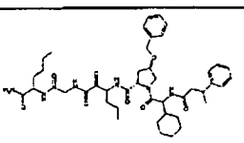
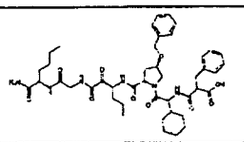
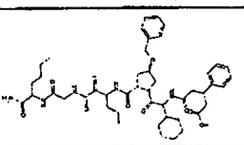
000439

ESTRUCTURA	Clase Ki*
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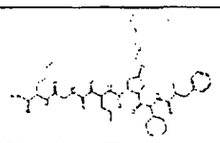
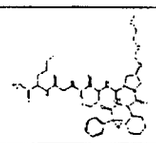
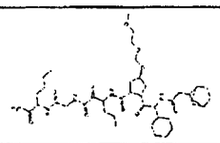
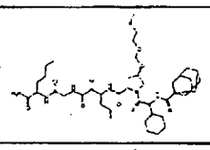
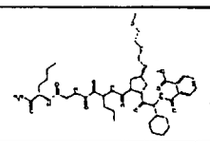
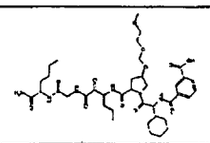
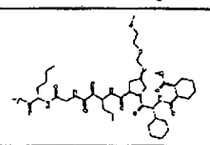
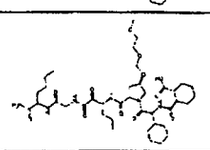
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ESTRUCTURA	Clase Kit*
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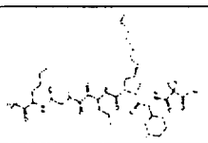
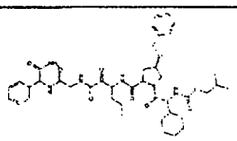
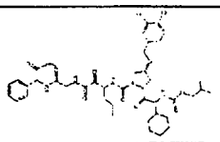
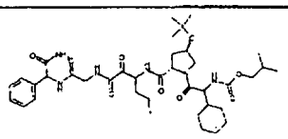
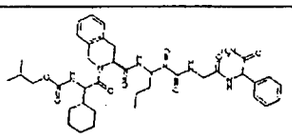
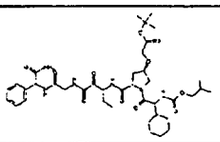
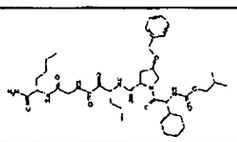
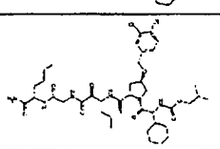
000441

ESTRUCTURA	Clase Kif
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	C
	C
	C

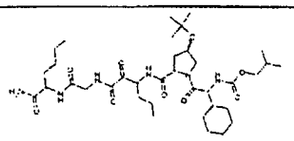
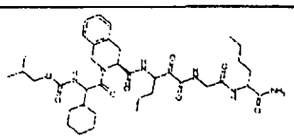
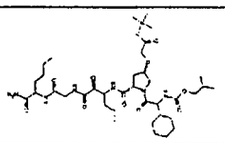
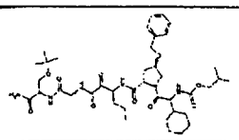
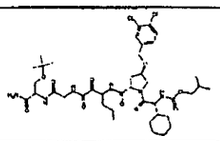
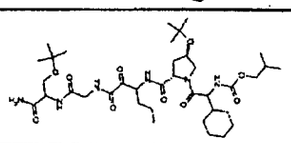
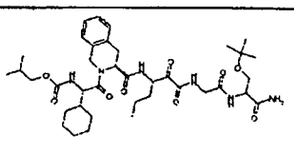
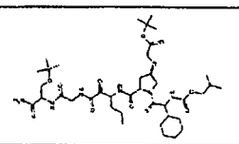
000442

ESTRUCTURA	Clase Ki*
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	B
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	C
	B
	B

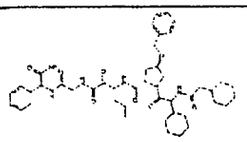
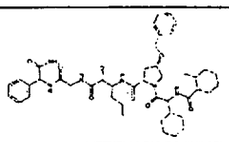
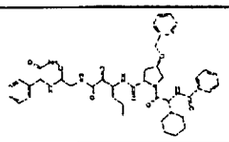
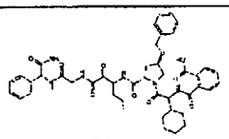
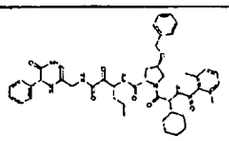
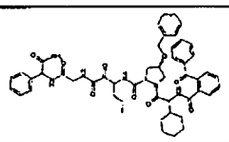
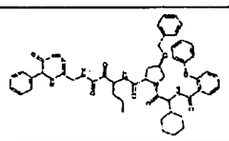
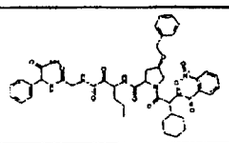
000443

ESTRUCTURA	Clase Ki*
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	A
	B
	B

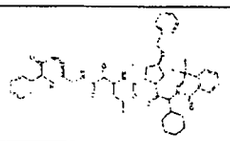
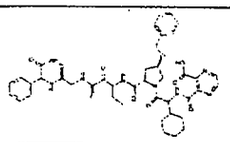
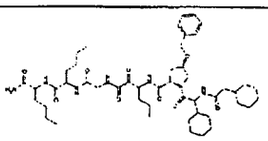
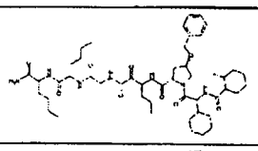
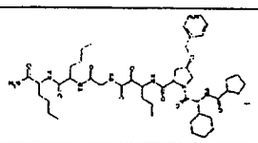
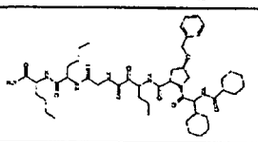
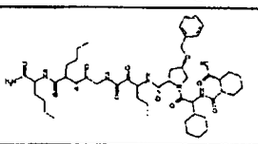
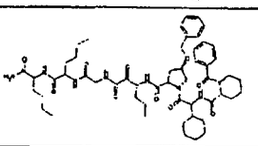
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ESTRUCTURA	Clase Kit*
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	C
	B

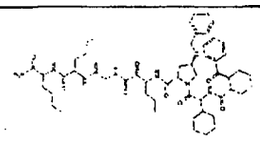
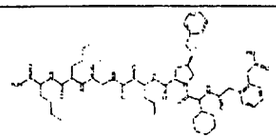
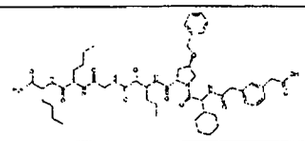
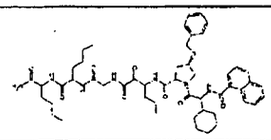
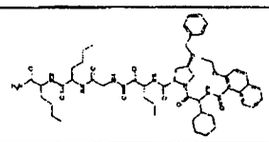
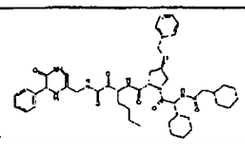
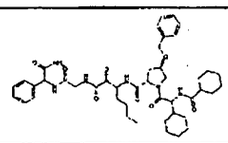
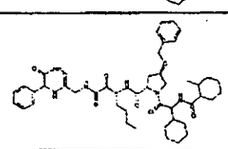
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ESTRUCTURA	Clase Kf*
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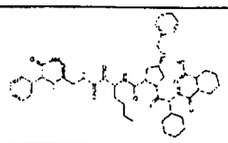
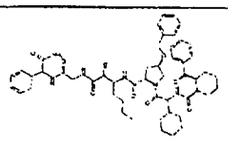
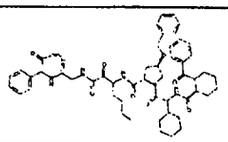
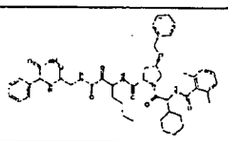
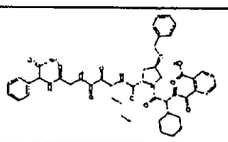
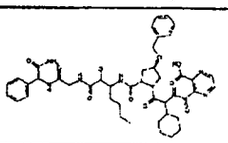
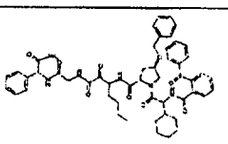
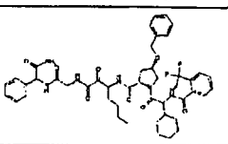
000446

ESTRUCTURA	Clase Ki*
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	B
	B
	B
	B
	B
	B
	C

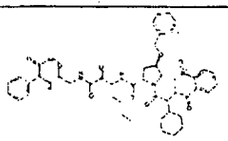
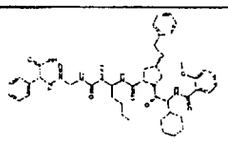
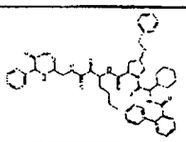
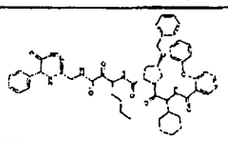
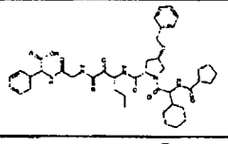
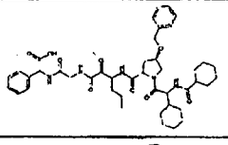
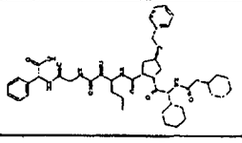
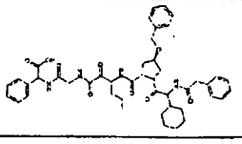
000447

ESTRUCTURA	Clase Kit
	B
	B
	B
	B
	B
	A
	B
	B

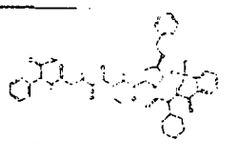
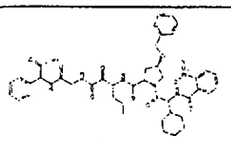
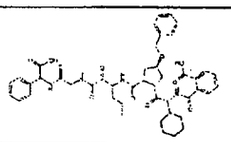
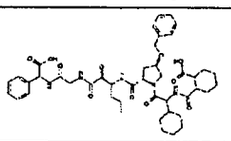
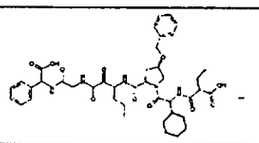
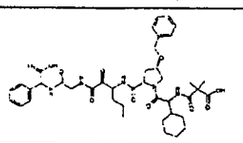
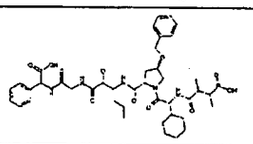
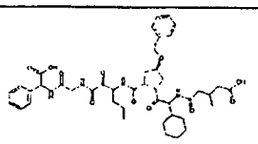
000448

ESTRUCTURA	Clase Ki*
	B
	B
	C
	B
	B
	B
	B
	B

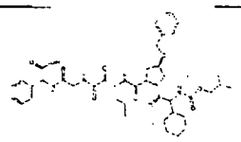
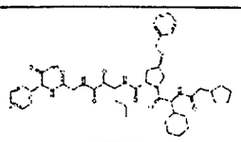
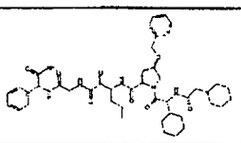
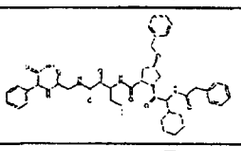
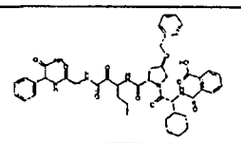
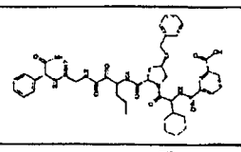
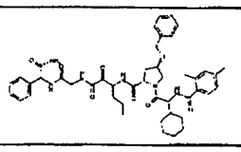
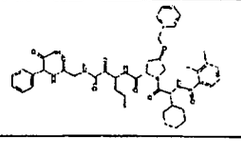
003449

ESTRUCTURA	Clase Ki*
	B
	C
	C
	C
	A
	B
	A
	A

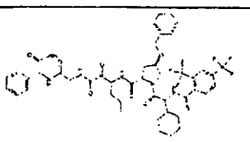
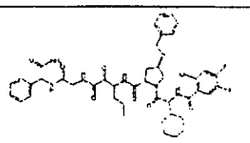
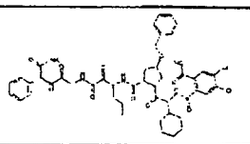
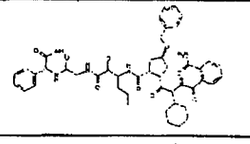
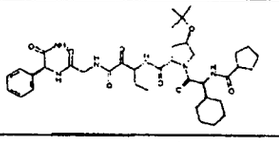
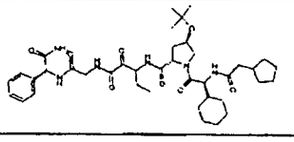
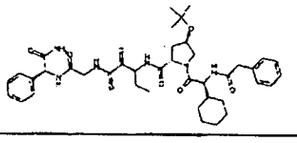
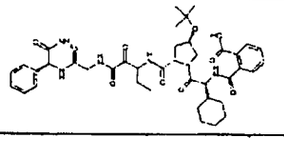
000450

ESTRUCTURA	Clase Ki*
	B
	A
	A
	A
	A
	B
	B
	A

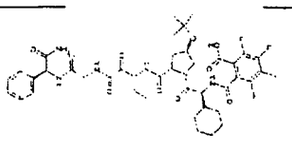
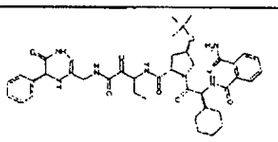
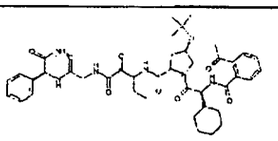
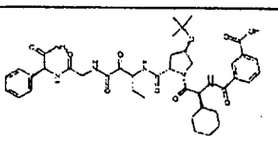
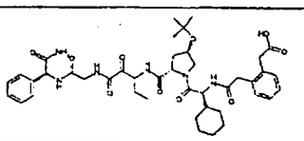
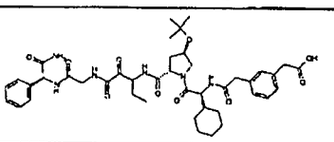
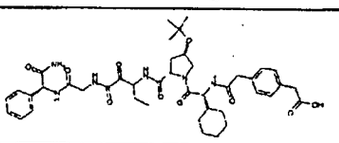
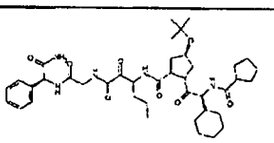
003451

ESTRUCTURA	Clase Kit*
	A
	B
	B
	C
	B
	B
	B
	B

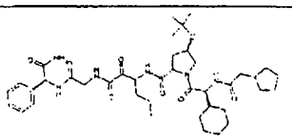
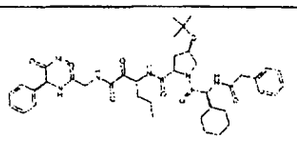
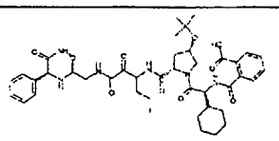
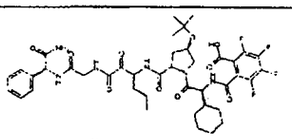
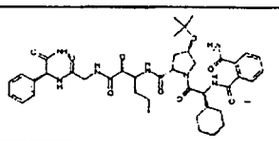
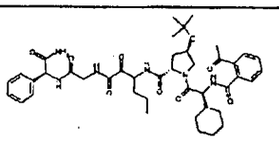
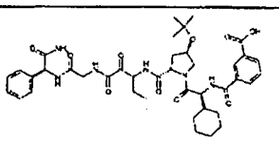
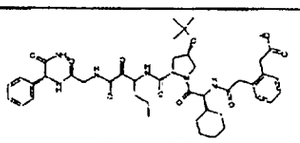
000452

ESTRUCTURA	Clase Ki*
	C
	C
	C
	C
	B
	B
	B
	B

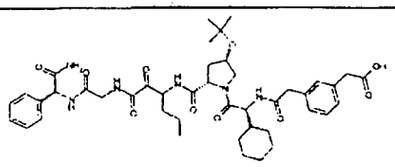
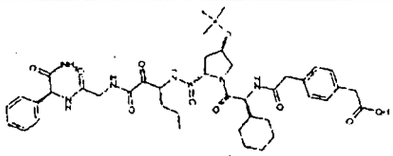
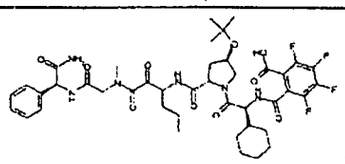
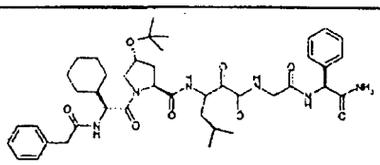
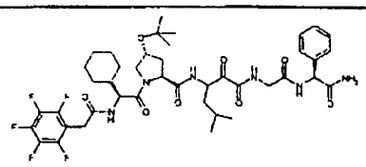
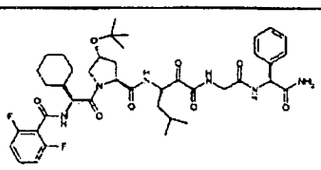
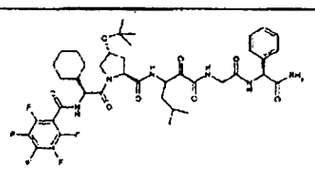
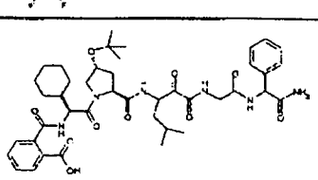
000453

ESTRUCTURA	Clase Ki*
	A
	B
	C
	C
	B
	B
	B
	B

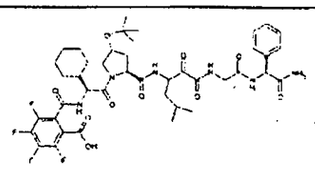
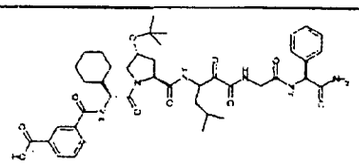
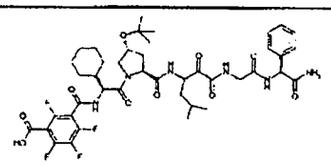
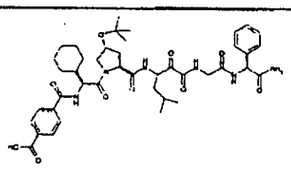
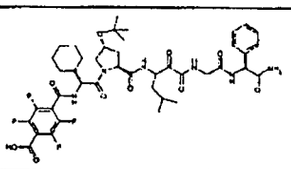
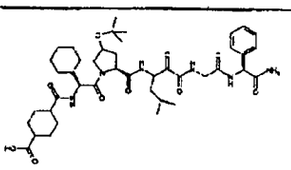
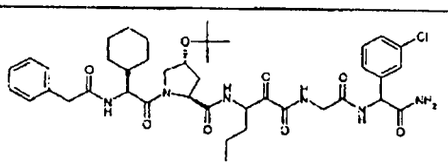
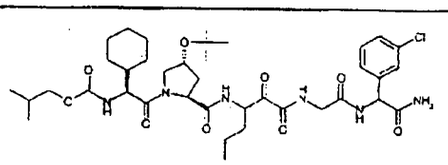
003454

ESTRUCTURA	Clase Ki*
	A
	A
	A
	A
	B
	C
	B
	A

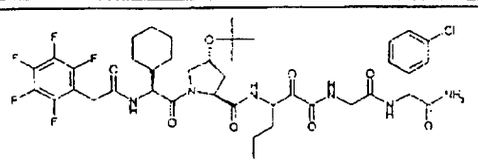
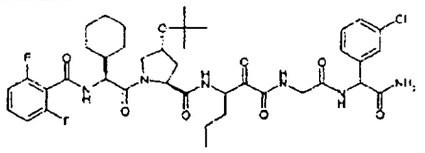
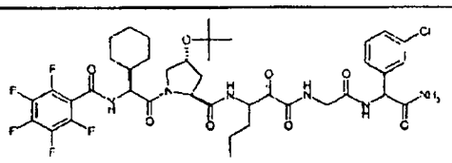
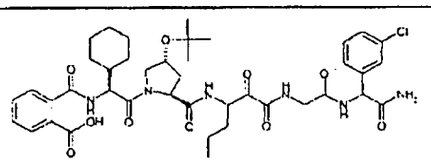
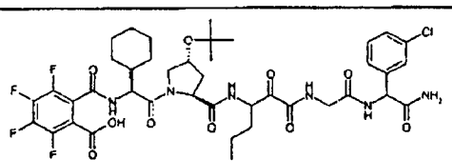
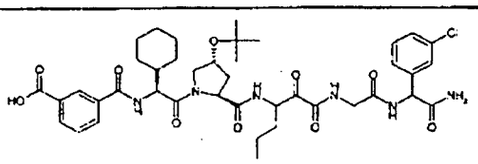
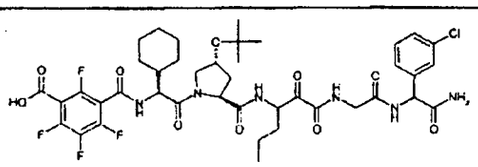
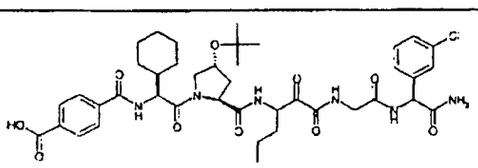
000455

ESTRUCTURA	Clase Ki*
	C
	A
	C
	C
	C
	C
	C
	C

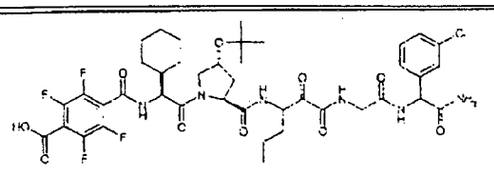
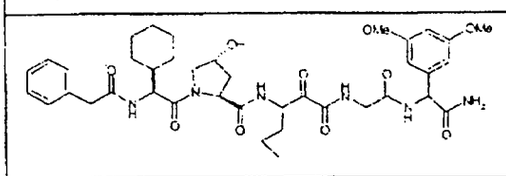
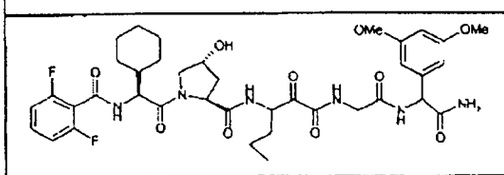
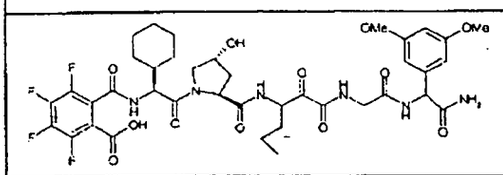
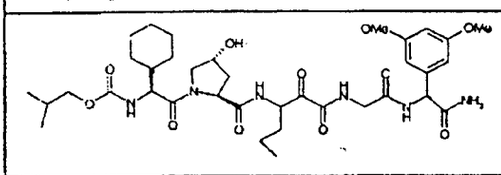
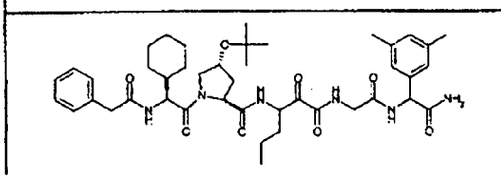
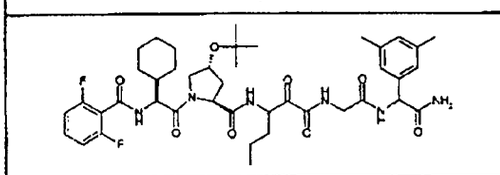
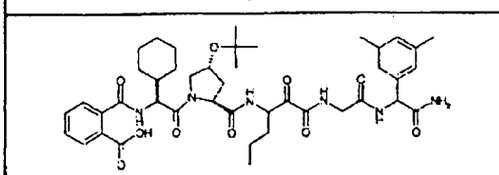
000456

ESTRUCTURA	Clase Ki*
	C
	C
	C
	C
	C
	C
	B
	B

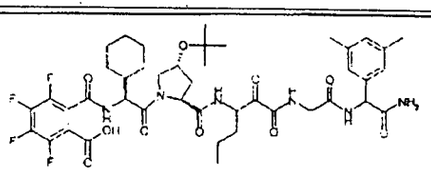
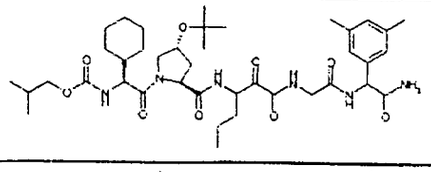
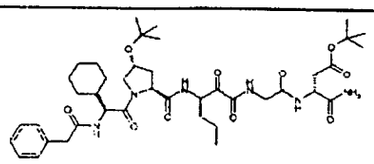
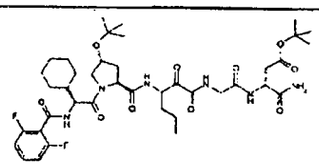
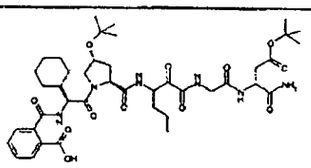
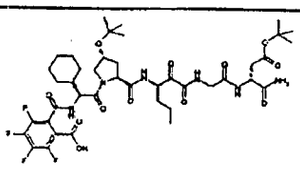
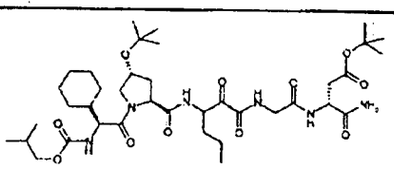
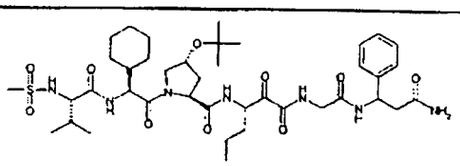
003457

ESTRUCTURA	Clase Ki*
	B
	B
	C
	B
	A
	B
	B
	B

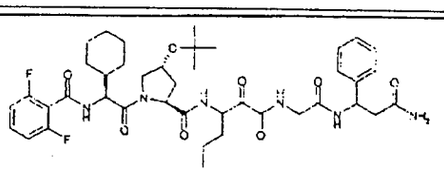
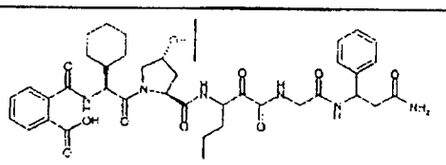
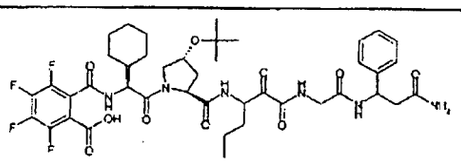
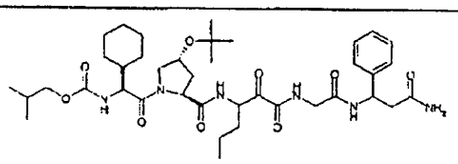
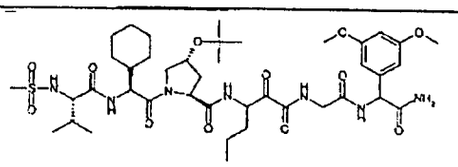
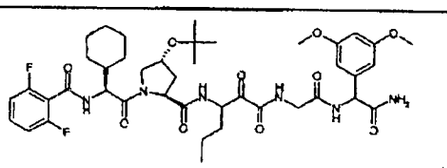
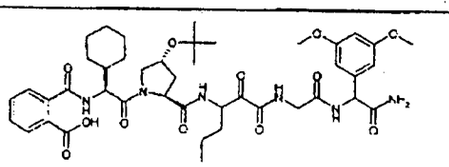
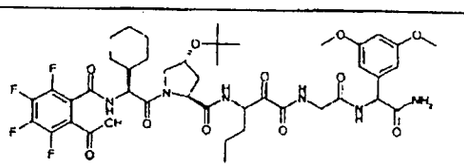
000458

ESTRUCTURA	Clase Ki*
	B
	B
	B
	B
	B
	B
	B
	B

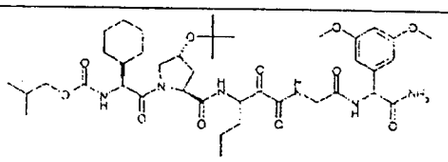
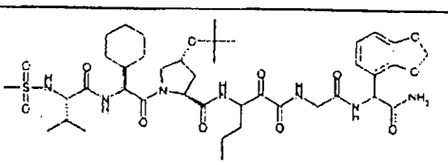
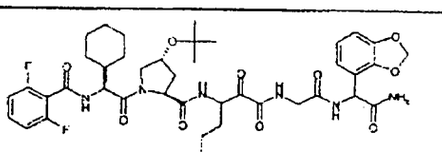
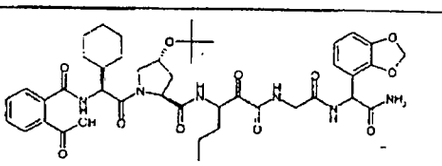
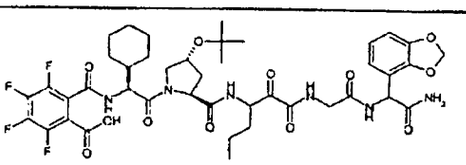
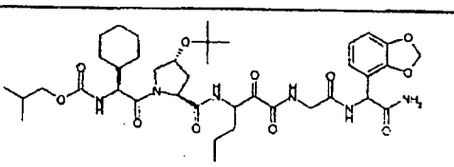
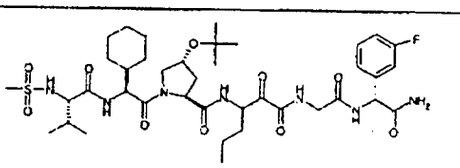
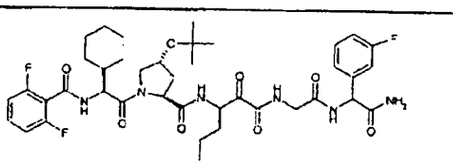
000459

ESTRUCTURA	Clase Ki*
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	B
	C
	C
	C
	C
	C
	B

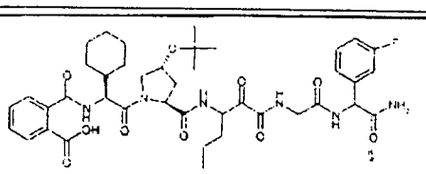
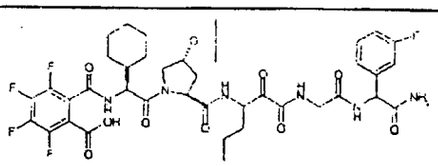
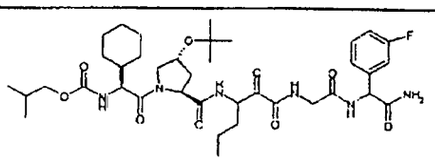
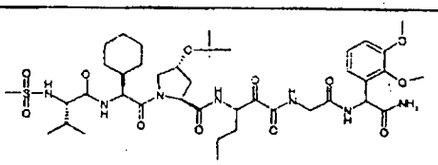
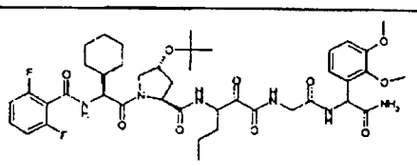
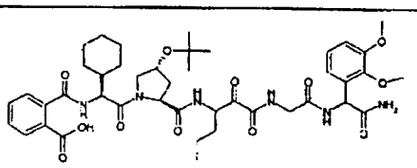
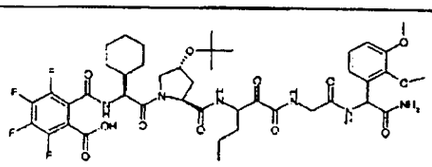
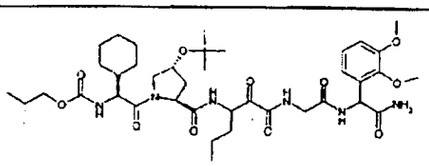
003460

ESTRUCTURA	Clase Ki*
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	B
	C
	B
	B
	B
	B

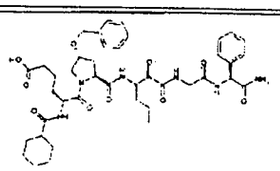
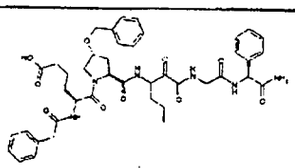
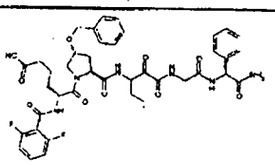
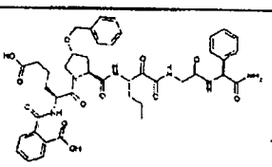
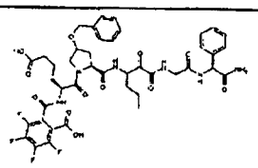
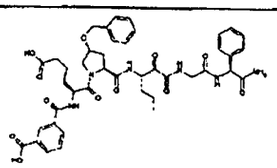
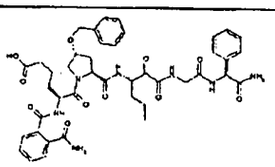
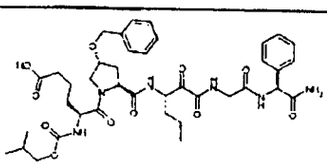
000461

ESTRUCTURA	Clase Ki*
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	B
	B
	B
	B
	B
	B
	B

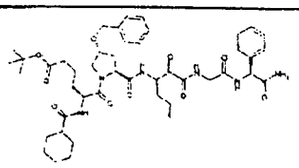
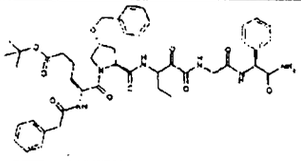
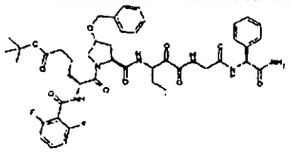
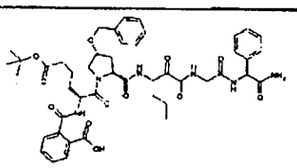
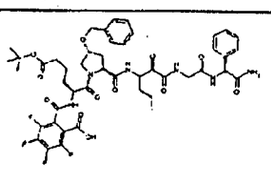
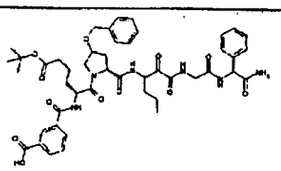
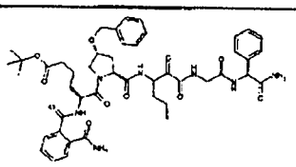
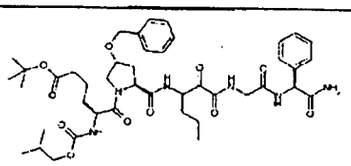
030462

ESTRUCTURA	Clase Ki*
	B
	B
	B
	B
	B
	B
	B
	B

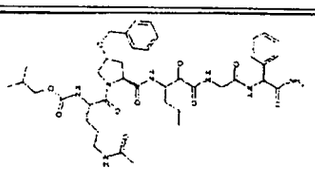
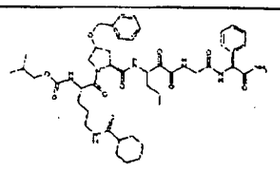
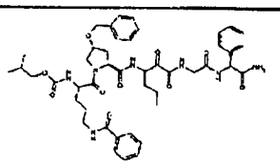
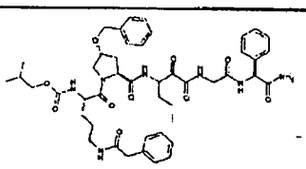
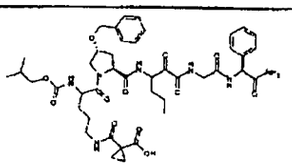
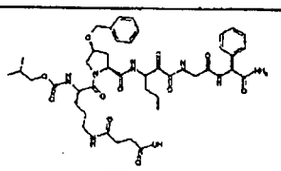
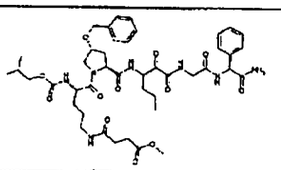
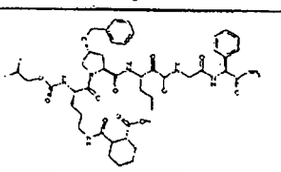
000463

ESTRUCTURA	Clase Ki*
	B
	B
	B
	B
	B
	C
	B
	B

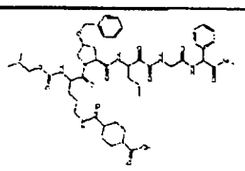
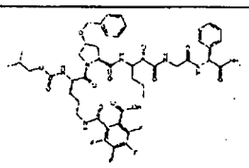
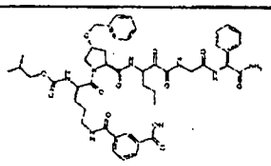
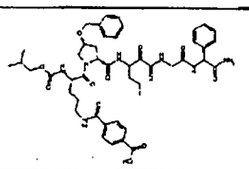
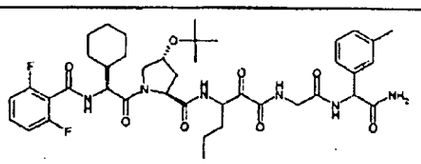
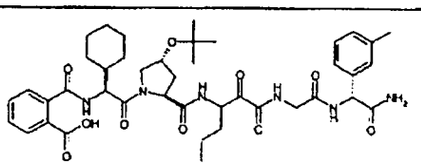
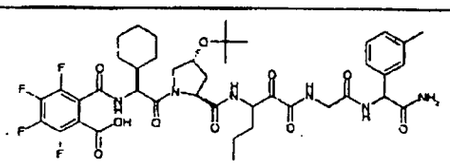
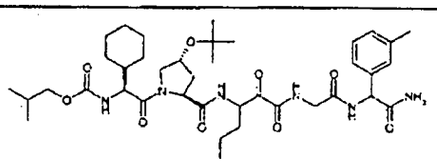
000464

ESTRUCTURA	Clase Ki*
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	C
	C
	C
	B
	C
	C
	C

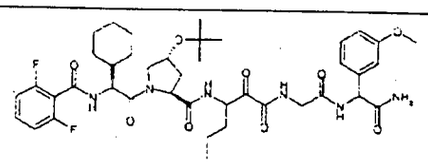
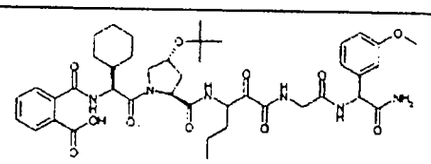
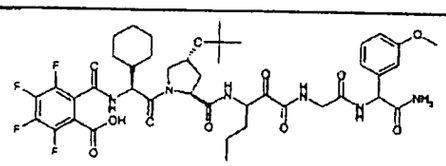
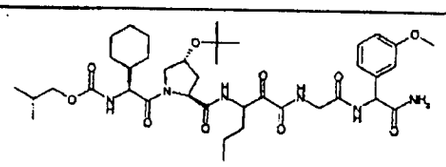
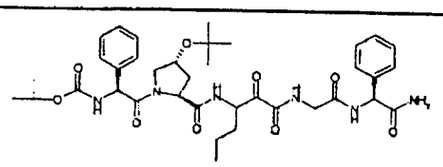
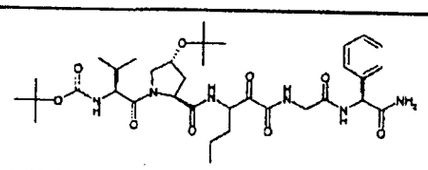
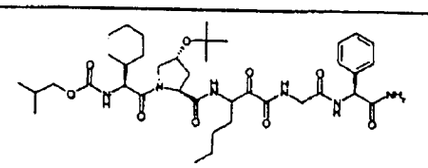
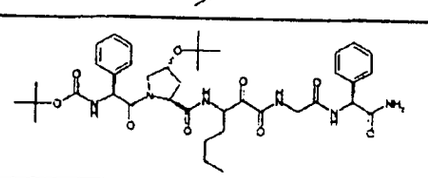
000435

ESTRUCTURA	Clase Ki*
	C
	C
	C
	C
	C
	C
	C
	C

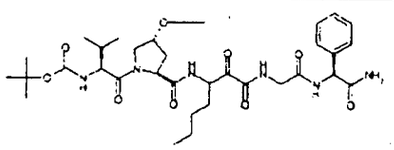
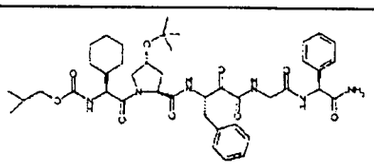
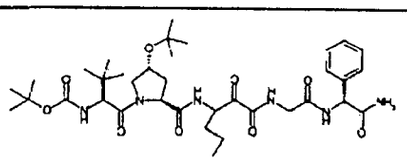
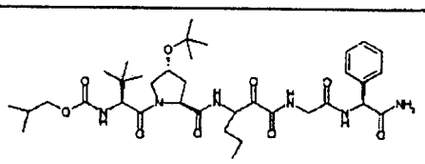
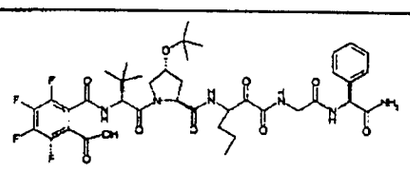
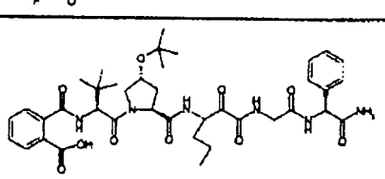
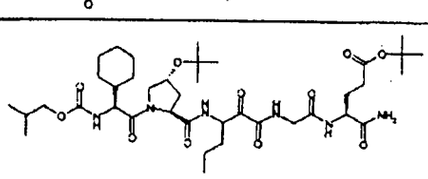
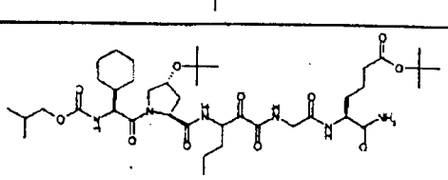
000466

ESTRUCTURA	Clase Ki*
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	C
	B
	B
	B
	B
	B
	B

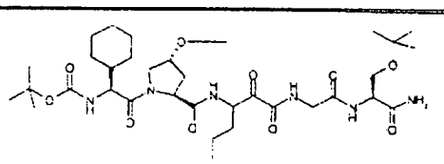
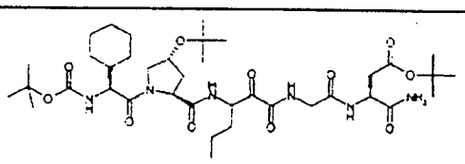
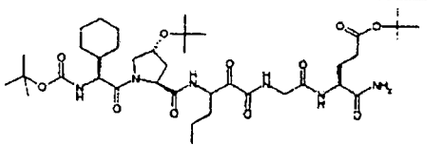
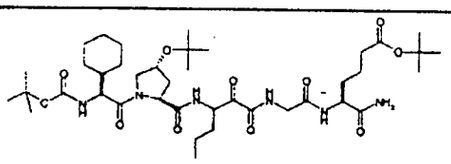
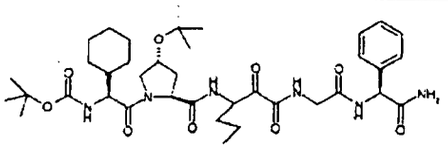
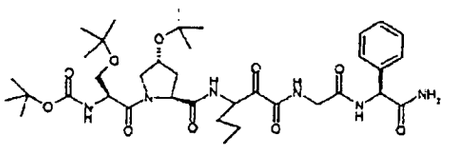
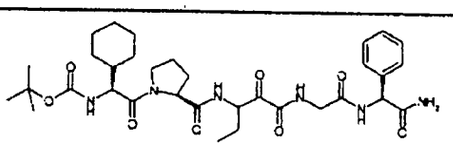
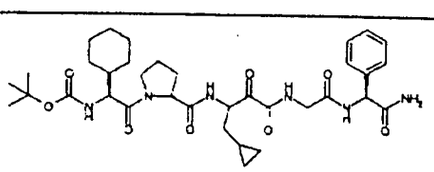
000437

ESTRUCTURA	Clase Ki*
	B
	B
	B
	B
	C
	B
	B
	C

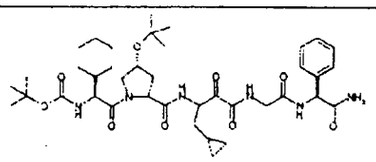
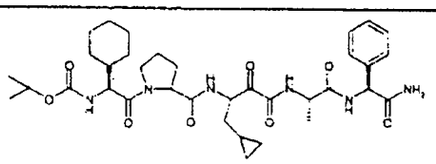
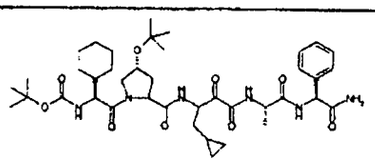
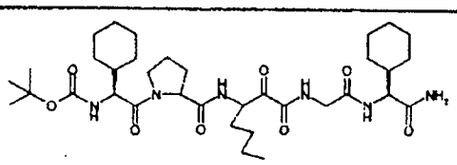
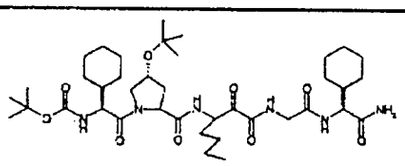
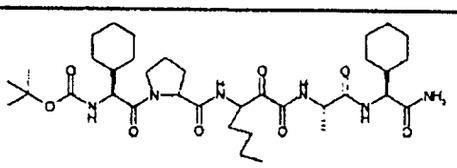
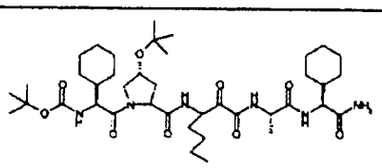
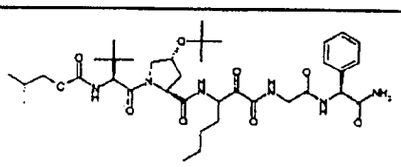
000438

ESTRUCTURA	Clase Ki*
	B
	C
	B
	B
	B
	B
	C
	C

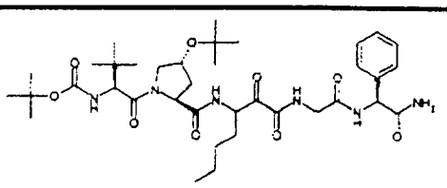
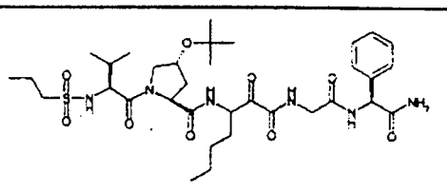
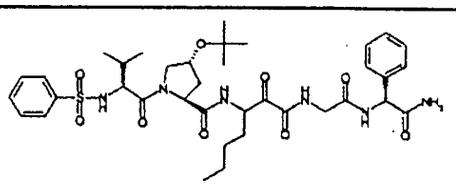
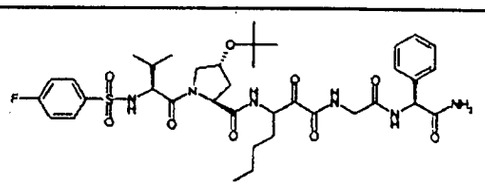
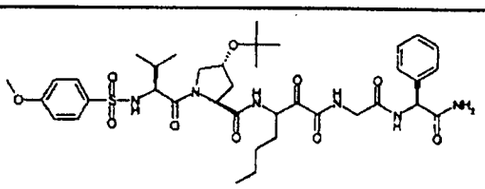
000469

ESTRUCTURA	Clase Ki*
	C
	C
	C
	C
	B
	C
	C
	C

033470

ESTRUCTURA	Clase Ki*
	B
	C
	B
	C
	C
	C
	C
	B

000471

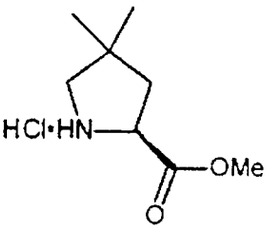
ESTRUCTURA	Clase Ki*
	B
	C
	C
	C
	C

Se prepararon compuestos adicionales y sus rangos de actividad (Ki*) se suministran en las **Tablas 4** y **5** que se anexan. El procedimiento utilizado para preparar los compuestos en las **Tablas 4** y **5** se define a continuación.

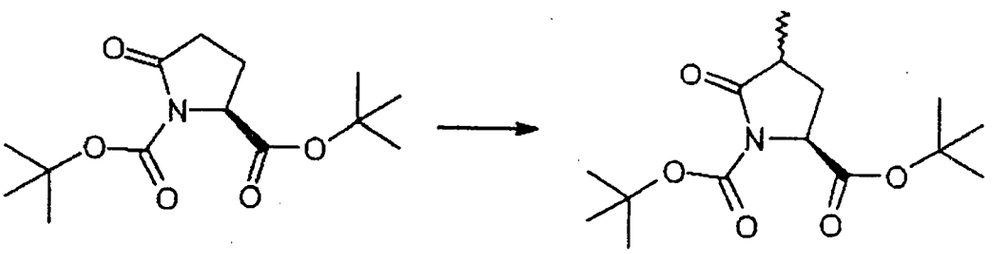
I) <u>Síntesis de los intermediarios para los compuestos de las Tablas 4 y 5:</u>

Ejemplo I. Síntesis de éster metílico de 4,4-dimetil prolina (H-Pro(4,4-diMe)-OMe)

000472



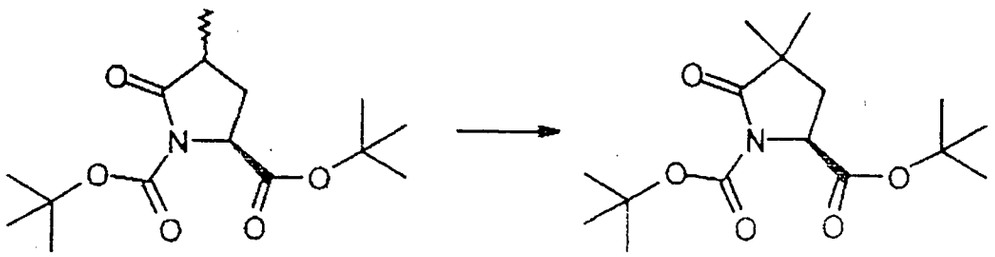
Paso 1. Síntesis de terbutil N-tert-butoxicarbonil-4-metil-L-piroglutamato (Boc-PiroGlu 4-metil)-OtBu):



A una solución de N-tert-butoxicarbonil-piroglutamato de terbutilo (11,5 g, 40 mmol) en THF (200 mL) bajo agitación a -78 °C, se agregó una solución 1M de hexametildisilazida de litio en THF (42 mL, 42 mmol) por goteo durante 5 minutos. Luego de 30 minutos, se agregó metilioduro (3,11 mL, 50 mmol). Luego de un adicional de 2 horas a -78 °C, el baño de frío se removió y se agregó cloruro de amonio acuoso saturado al 50% (200 mL). La solución se agitó durante 20 minutos, luego se extrajo con éter (3 x 200 mL). Las capas orgánicas combinadas se lavaron con salmuera (200 mL), se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se sometió a cromatografía con 1:1 acetato de etilo/hexanos para dar Boc-PiroGlu(4-metil)OtBu (10,6 gramos, 35,4 mmol, 88%) como una mezcla de isómeros (2:1 cis a trans).

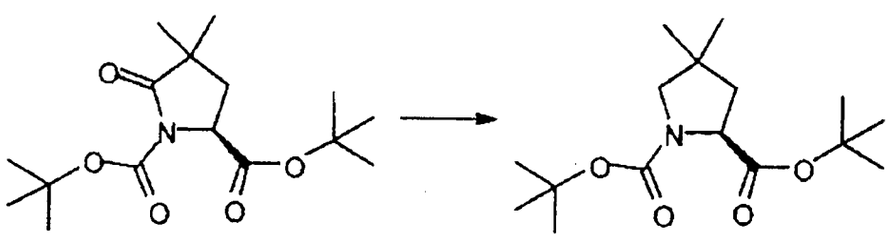
Paso 2. Síntesis de N-tert-butoxicarbonil-4,4-dimetil-L-piroglutamato de terbutilo (Boc-PirooGlu(4.4-dimetil)-OtBu):

000473



A una solución de N-tert-butoxicarbonil-4-metil-L-piroglutamato de terbutilo (12 g, 4,0 mmol) en tetrahidrofurano (20 mL) bajo agitación a -78 °C, se agregó una solución 1M de hexametildisilazida de litio en tetrahidrofurano (4,4 mL, 4,4 mmol) por goteo durante 5 minutos. Luego de 30 minutos, se agregó metilioduro (0,33 mL, 5,2 mmol). Luego de un adicional de 3 horas a -78 °C, el baño de frío se removió y se agregó cloruro de amonio acuoso saturado al 50% (40 mL). La solución se agitó durante 20 minutos, luego se extrajo con éter (2 x 50 mL). Las capas 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 BocPiroGlu(4,4-dimetil)-OtBu (0,673 g, 54%).

Paso 3 Síntesis de N-tert-butoxicarbonil-4.4-dimetilprolina de terbutilo (BocPro 4.4-dimetil -OtBu)

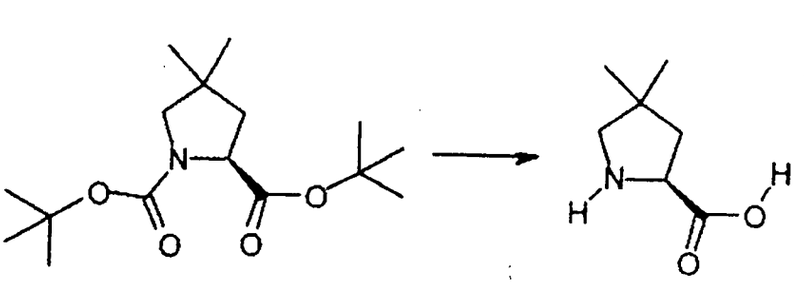


Modificación del procedimiento conocido: Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron Letters* **1994,** 35(13), 2053-2056).

000474

A una solución de N-tert-butoxicarbonil-4,4-dimetilpiroglutamato de terbutilo (2,0 mmol) en tetrahidrofurano (5 mL) bajo agitación a -78 °C, se agregó una solución 1M de trietilborohidruro de litio en tetrahidrofurano (2,4 mL, 2,4 mmol) por goteo durante 5 minutos. Luego de 30 minutos, el baño de frío se removió y se agregó bicarbonato de sodio acuoso saturado (5 mL). La mezcla de reacción se sumergió en un baño de hielo/agua y se agregó peróxido de hidrógeno acuoso al 30% (10 gotas). La solución se agitó durante 20 minutos a 0°C, luego la mezcla de reacción se concentró al vacío para remover el tetrahidrofurano. La solución acuosa se diluyó con agua (10 mL) y se extrajo con diclorometano (3 x 40 mL). Las capas 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 se agregó por goteo dietiletearato de trifluoruro de boro (270 µL, 2,13 mmol). Se continuó agitando durante 30 minutos, momento en el cual se agregaron trietilsilano adicional (310 µL, 2,0 mmol) y dietiletearato de trifluoruro de boro (270 µL, 2,13 mmol). Luego de bajo agitación a -78 °C durante un adicional de dos horas, el baño de frío se removió 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 capas orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron para dar Boc-Pro(4,4-dimetil)-OtBu.

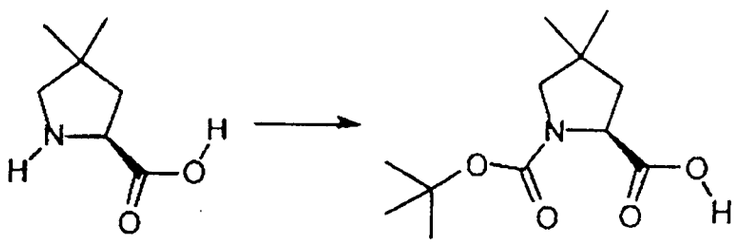
Paso 4. Síntesis de 4.4-dimetilprolina H-Pro 4.4-dimetil)-OH):



000475

Una solución de N-tert-butoxicarbonil-4,4-dimetilprolina de terbutilo en diclorometano (5 mL) y trifluoroacético (5 mL) se agitó a temperatura ambiente durante cinco horas. La solución se concentró, se secó en vacío extremo y se llevó hasta el paso siguiente sin purificación adicional.

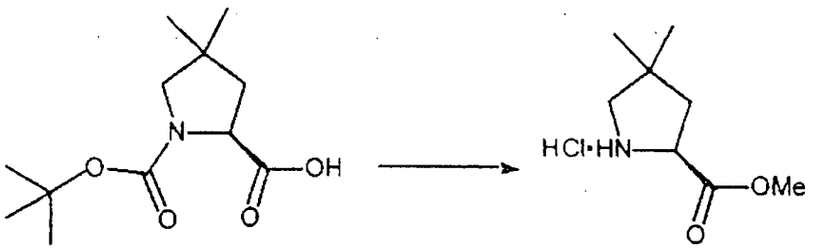
Paso 5. Síntesis de N-tert-butoxicarbonil 4.4-dimetilprolina (Boc-Pro(4.4-dimetil)-OH):



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-terbutil-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 capa acuosa se acidificó hasta pH=3 con ácido cítrico, luego se extrajo con diclorometano (3 x 40 mL). Las capas orgánicas combinadas se secaron en sulfato de sodio se filtraron y se concentraron.

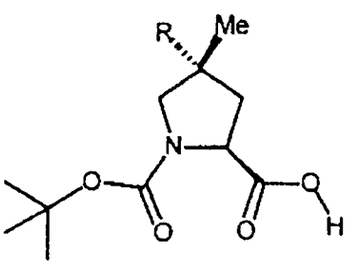
Paso 6. Síntesis de sal de clorhidrato del éster metílico de 4.4-dimetilprolina (HCl-HPro 4.4-dimetil)-OMe):

000476



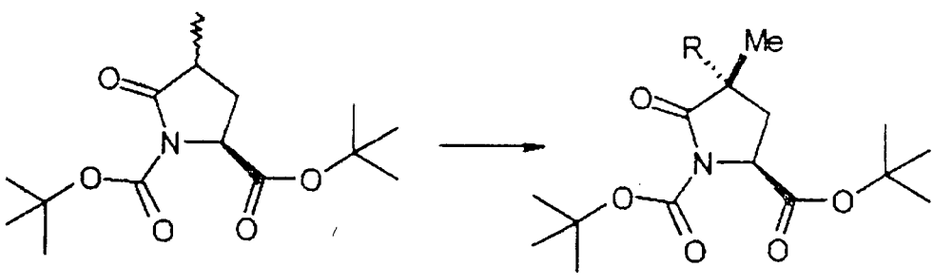
A una solución de Boc-Pro(4,4-diMe)-OH (0,5 g, 2,06 mmol) en metanol anhidro (8 ml) se agregó por goteo tionilcloruro (448 l, 6,18 mmol) y la reacción se agitó durante seis horas a temperatura ambiente. La mezcla de reacción se concentró hasta obtener un sólido amorfo (377 mg, 95%).

Ejemplo II. Procedimiento General para la síntesis de N-terbutoxicarbonil-4-alquil-4-metil-prolina:



En los siguientes pasos 1-4 se sintetizaron los compuestos en los cuales en grupo R es alilo y bencilo

Paso 1. Síntesis de N-tert-butoxicarbonil-4-alquil-4-metil-L-piroglutamato de terbutilo:

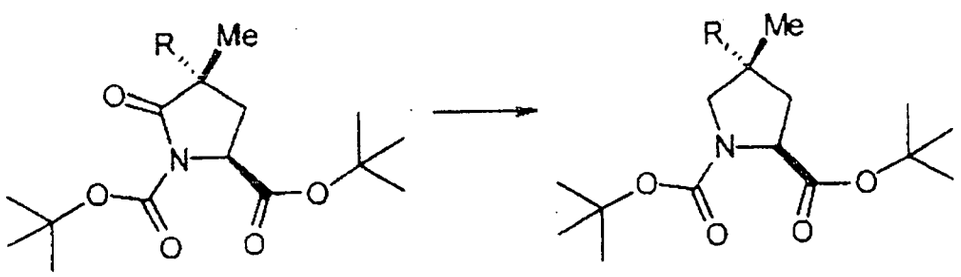


A una solución de N-tert-butoxicarbonil-4-metil-L-piroglutamato de terbutilo (10,2 g, mmol) (Ver el ejemplo I, paso 1) en tetrahidrofurano (170 mL) bajo agitación a -78 °C, se agregó una solución 1M de hexametildisilazida de litio en tetrahidrofurano (37,5 mL, 37,5 mmol) por goteo durante 5 minutos. Luego de 40 minutos, alquil haluro (61.4 mmol) se agregó. Luego de un adicional de 3 horas a -78 °C, el baño de frío se removió y cloruro de amonio acuoso saturado al 50% (200 mL) se agregó. La solución se agitó durante 20 minutos, luego se extrajo con éter (2 x 200 mL). Las capas orgánicas combinadas se diluyeron con hexanos (150 mL) y se lavó 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 con el uso de acetato de etilo en hexanos al 20% para dar el N-tert-butoxicarbonil-4-alquil-4-metil-L-piroglutamato de terbutilo puro.

Paso 2. Síntesis de N-tert-butoxicarbonil-4-alquil-4-metilprolina de terbutilo:

Modificación del procedimiento conocido: Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreno, M. C.; Garcia Ruano, J. L. *Tetrahedron Letters* (1994) 35(13), 2053-2056).

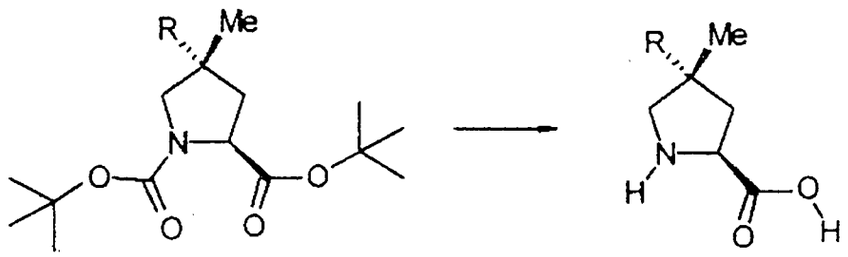
000478



A una solución de N-tert-butoxicarbonil-4-alquil-4metilpiroglutamato de terbutilo (16,6 mmol) en tetrahidrofurano (40 mL) bajo agitación a -78 °C, se agregó una solución 1M de trietilborohidruro de litio en tetrahidrofurano (20 mL, 20 mmol) por goteo durante 10 minutos. Luego de 120 minutos, el baño de frío se dejó entibiar hasta -25 °C cuando se agregó bicarbonato de sodio acuoso saturado (40 mL). La mezcla de reacción se sumergió en un baño de hielo/agua y se agregó peróxido de hidrógeno acuoso al 30% (4 mL). La solución se agitó durante 10 minutos a 0°C, luego la mezcla de reacción se concentró al vacío para remover el tetrahidrofurano. La solución acuosa se diluyó con agua (300 mL) y se extrajo con diclorometano (3 x 200 mL). Las capas 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 por goteo dietiletearato de trifluoruro de boro (2,2 mL, mmol). Se continuó la agitación durante 1 hora, cuando se agregaron trietilsilano adicional (2,6 mL, mmol) y dietiletearato de trifluoruro de boro (2,2 mL, mmol). Luego de bajo agitación a -78°C durante un adicional de 4 horas, el baño de frío se removió 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 capas orgánicas se secaron (Na_2SO_4), se filtraron y se concentraron.

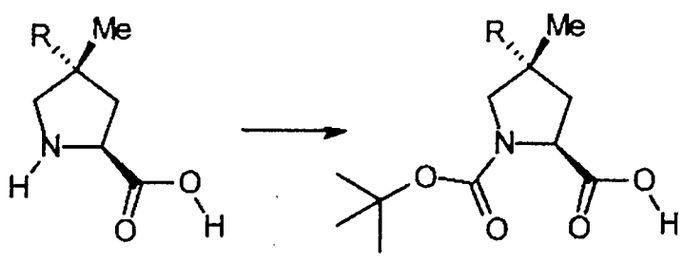
Paso 3. Síntesis de 4-alquil-4-metilprolina:

008479



Una solución de terbutil N-tert-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 en vacío extremo.

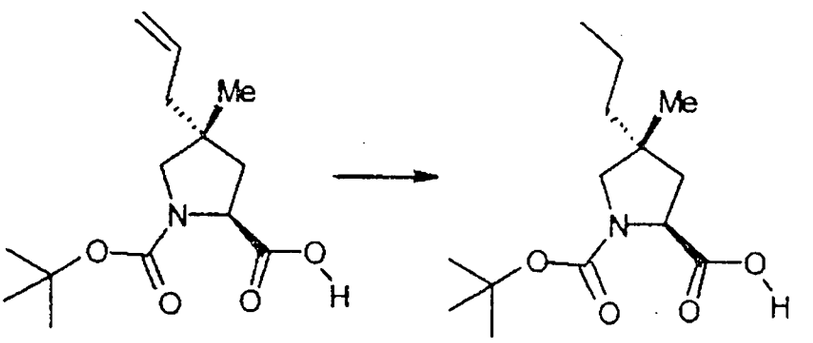
Paso 4. Síntesis de N-tert-butoxicarbonil 4-alquil-4-metilprolina:



A una solución de sal trifluoroacética de 4-alquil-4-metilprolina (1,5 mmol) en dioxano (7 mL), acetonitrilo (12 mL) y diisopropiletilamina (700 µL, 4 mmol) se agregó una solución de di-terbutil-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 capa acuosa se acidificó hasta pH=3 con ácido clorhídrico 1N, luego se extrajo con diclorometano (3 x 40 mL). Las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo se purificó por cromatografía flash mediante el uso de 1:1 acetato de etilo/hexanos con ácido acético al 1%.

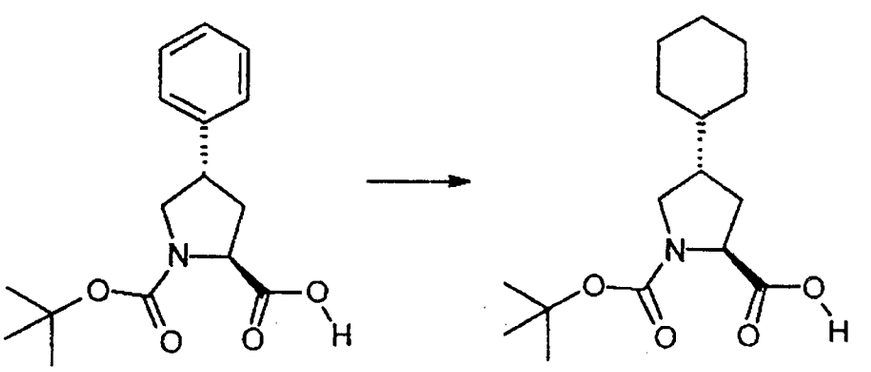
003480

Ejemplo III. Síntesis de N-tert-butoxicarbonil 4-propil-4-metilprolina:



Una solución de N-tertbutoxicarbonil-4-alil-4-metilprolina (400 mg, 1.48 mmol) (ver Ejemplo II Paso 4) y Pd al 10% en carbono (400 mg) en metanol (20 mL) se hidrogenó a 50 psi durante 4 horas. La mezcla se filtró y se concentró.

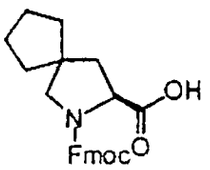
Ejemplo IV. Síntesis de Boc-4-ciclohexilprolina:



Una solución de la Boc-4-fenilprolina (750 mg) y Rh al 5% en carbono (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 de ácido Fluorenilmetoxicarbonil-Pro(4-espirociclo-pentano)carboxílico

000481



Paso 1. Síntesis de Boc-piroglutamic(4-alil)-tert-butiléster



A una solución fría (-78 °C) del N-Boc-tertbutil piroglutamato comercialmente disponible (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. Se agregó por goteo una solución de bromuro de alilo (6,1 ml, 70,2 mmol) en THF (39 mL) a la primera solución. Luego de dos horas a -78 °C, la reacción se inactivó por el agregado lento de solución de cloruro de amonio saturado (50 mL). La mezcla de reacción luego se diluyó con acetato de etilo y se separaron las capas. La capa orgánica se secó en sulfato de sodio y se concentró.

La cromatografía flash en columna realizada en 2:8 acetato de etilo: hexanos logró el producto (6 g, 53%). NMR δ ppm (CDCl3): 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).

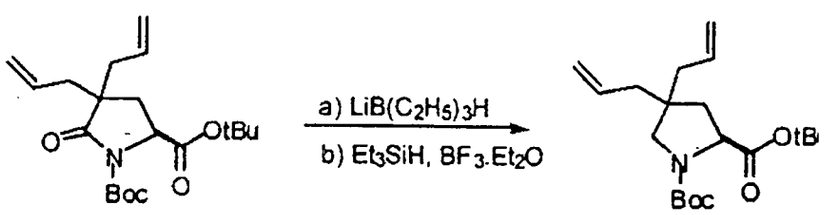
Paso 2. Síntesis de N-Boc-piroglutamic(4,4-dialil)-terbutiléster:

000482



El N-Boc-piroglutamic(4-alil)-terbutiléster 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 suministró 2,13 g de producto (71 %) como un aceite claro.

Paso 3. Síntesis de Boc-Pro(4.4-dialil)-terbutiléster:

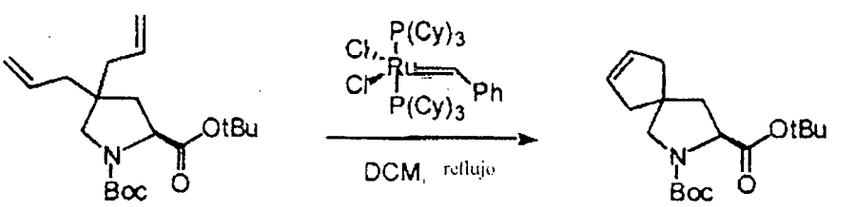


Parte a: A una solución fría (-78 °C) de Boc-PiroGlu(4,4-dialil)-tert-butiléster (2,13 g, 5,83 mmol) en tetrahidrofurano (14 ml) se agregó trietilborohidruro de litio (1M en tetrahidrofurano, 7,29 ml, 7,29 mmol) durante cinco minutos. Luego de dos horas a -78 °C, la reacción se entibió hasta 0 °C y se inactivó mediante el agregado lento de solución de bicarbonato de sodio saturado (20 ml) y peróxido de hidrógeno al 30% (20 gotas). Se continuó la agitación durante 20 minutos. El tetrahidrofurano se removió con presión reducida y el residuo blanco espeso restante se diluyó con agua (80 ml) y se extrajo tres veces con diclorometano. La capa orgánica se secó, se filtró y se concentró y se llevó hasta el paso siguiente sin purificación adicional.

Parte b): Al producto obtenido en la parte (a) en diclorometano (14 ml) se le agregó trietilsilano (931 µl, 5.83 mmol) seguido de estearato dietílico de

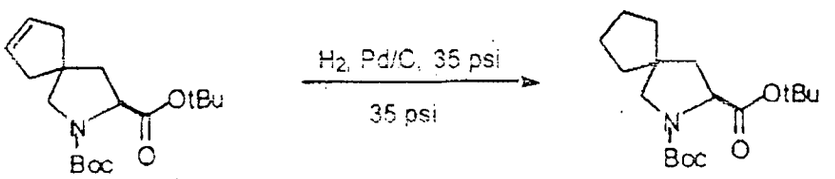
trifluoruro de boro (776 µ,l, 6,12 mmol). Luego de treinta minutos se agregaron más trietilsilano (931 µ1, 5,83 mmol) y estearato dietílico de trifluoruro de boro (776 µl, 6,12 mmol) y la reacción se agitó a -78 °C durante tres horas cuando la reacción se inactivó mediante la incorporación lenta de solución de bicarbonato de sodio saturado y agua . La mezcla de reacción se extrajo con diclorometano y la capa orgánica se secó, se filtró y se concentró. La cromatografía flash en columna en acetato de etilo en hexanos al 15% produjo 1,07 de aceite sin color (57%). NMR δ ppm (CDCI3): 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-espirocyciopenten)-terbutiléster:



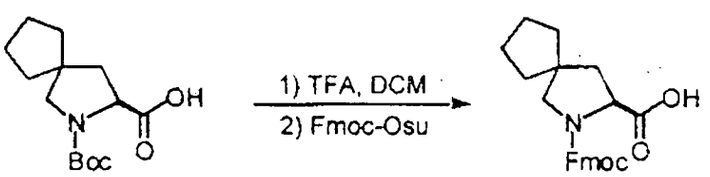
Al Boc-Pro(4,4-dialil)-terbutiléster (1,07 g, 3,31 mmol) en diclorometano (66 ml) se agregó dicloruro de Bis(triciclohexilfosfin)bencilideno rutenio IV al 5% (catalizador de Grubbs) y la mezcla se calentó a reflujo durante 1,5 horas. La mezcla de reacción se concentró y el residuo restante se purificó por cromatografía flash en columna en acetato de etilo en hexanos al 15%. Se obtuvo un aceite amarillo (0,57 g, 53%). NMR δ ppm (CDCI3): 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)-terbutiléster:



Una solución de Boc-Pro(4-espirociclopentan)-terbutiléster (1,12 g) en metanol (18 ml), agua (4 ml) y ácido acético (4 ml) se colocó en el agitador Parr y se hidrogenó durante tres horas a 35 psi en presencia de paladio al 10% en carbono (300 mg). El catalizador se filtró y el filtrado se concentró hasta lograr un aceite sin color (1,26 g). NMR δ ppm (CDCl3): 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).

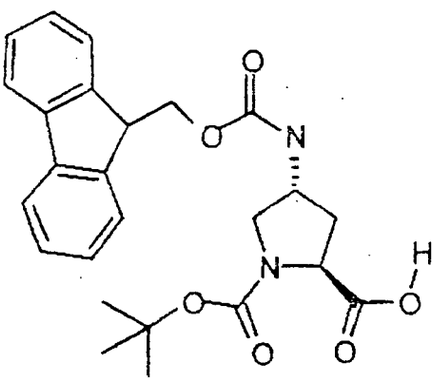
Paso 6. Síntesis de ácido Fmoc-Pro(4-espiroaclópentan)-carboxílico:



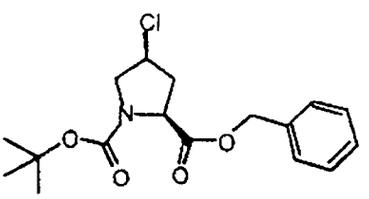
El Boc-Pro(4-espirocyciopentan)-terbutiléster (1,26, 3,9 mmol) se trató con diclorometano (10 ml) y ácido trifluoroacético (15 ml) durante tres horas. La mezcla de reacción se concentró y el aceite amarillo obtenido se disolvió en agua (6 ml). Se agregó por porciones carbonato de fluorenilmetil succinilo (1,45 g, 4,3 mmol) disuelto en dioxano (6 ml) 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 luna solución de bicarbonato de sodio saturado (10 mL) y se lavó con éter dietílico (3 x 10 ml). La capa acuosa luego se acidificó hasta un pH - 1 con una solución 1N de bisulfato de sodio y se extrajo con acetato de etilo. La capa orgánica se secó en sulfato de sodio, se filtró y se concentró hasta obtener una espuma beige (1,3 g, 100%).

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Ejemplo VI. Síntesis de Boc-Pro(4t-NH(Fmoc) -(OH:



Paso 1. Síntesis de éster bencílico de N$^{\alpha}$-tert-butoxicarbonil-cis-4-cloro-L-prolina:

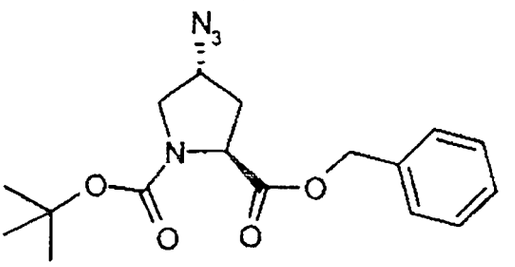


Una mezcla de la N-tert-butoxicarbonil-trans-4-hidroxi-prolina disponible en el mercado (8,79 g, 38 mmol), carbonato de potasio (13,0 g, 94 mmol), bromuro de bencilo (4,5 ml, 38 mmol) y dimetilformamida (150 mL) se agitó durante 18 h. Al agregado de acetato de etilo (100 mL) le siguió la filtración. El filtrado blanco turbio se clarificó mediante el agregado de HCl 1M (100 mL). Se separaron las capas y la capa acuosa se extrajo con acetato de etilo adicional (2 x 100 mL). Las capas 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 bencílico bruto, y la solución se filtró y se concentró. Se agregaron 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 h más. La solución se concentró

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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 por cromatografía flash mediante el uso de éter/hexano/diclorometano 2:2:1 para dar el compuesto del título (9,13 g, 26,9 mmol, 71 %) como un sólido blanco.

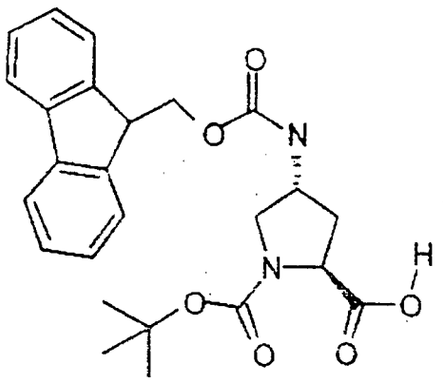
Paso 2 Síntesis de éster bencílico de N^{α}-tert-butoxicarbonil-trans-4-azido-L-prolina



Una solución de éster bencílico de N^{α}-tert-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 capas orgánicas combinadas se lavaron con agua (3 x 50 mL), se secaron (sulfato de sodio), se filtraron y se concentraron. El aceite se purificó por cromatografía flash mediante el uso de acetato de etilo/hexanos 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:

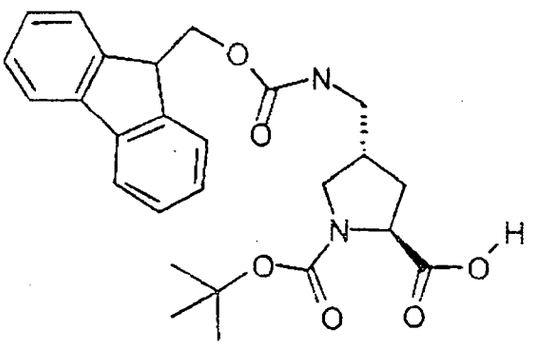
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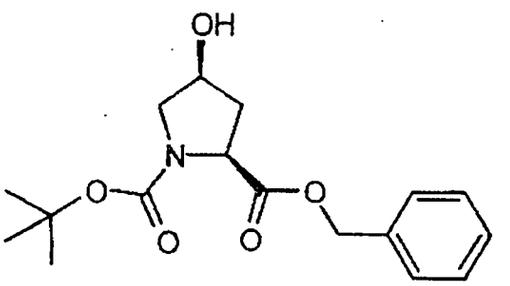
Una mezcla de éster bencílico de N-α-t-butoxicarbonil-trans-4-azido-L-prolina (8,59 g, 24,8 mmol) y paladio al 10% en carbono (900 mg) en etanol (500 mL) se hidrogenó a 50 psi durante 14 h mediante el uso de un aparato de hidrogenación Parr. La mezcla se filtró, se concentró, se disolvió en metanol (60 mL), se filtró y se concentró para dar un aceite sin color. El aceite se disolvió en agua (53 mL) que contenía carbonato de sodio (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 concentraron para remover 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 hasta 2 por el 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 capas 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)OH):

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Paso 1 Síntesis de éster bencílico de tert-butoxicarbonil cis-4-hidroxi-L-prolina (Boc Pro(4-cis-OH)-Obn):

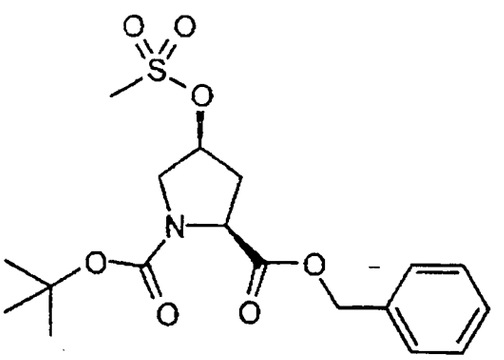


A una mezcla de cis-hidroxi-L-prolina (5 g, 38,1 mmol) en benceno (45 mL) y alcohol bencílico (45 mL) se agregó ácido p-toluenosulfónico monohidrato (7,6 g, 40,0 mmol). La mezcla de reacción se calentó a 125°C durante 20 h mientras el agua (2ml) se removió mediante el uso de una trampa de Dean-Stark. La solución se filtró mientras 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. Se recolectó el sólido resultante, se lavó con éter (100 mL) y se secaron 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-terbutil-dicarbonato (10 g, 45,8 mmol) durante 5 min. mientras se utilizaba un baño de hielo para mantener constante la temperatura de reacción. Luego de 10

000489

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 capas 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 bruto se purificó por cromatografía flash mediante el uso de 40-60% acetato de etilo en hexanos para dar el compuesto del título (10,04 g, 31,24 mmol, 82%).

Paso 2. Síntesis de éster bencílico de N-t-butoxicarbonil-cis-4-mesiloxi-L-prolina (Boc-Pro(4-cis-OMs)-OBn):

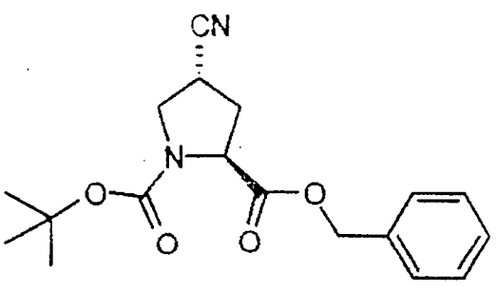


A un solución de Boc-Pro(4-cis-OH)-OBn (8,45 g, 26,3 mmol) en piridina (65 mL) a 0°C, se agregó cloruro de metansulfonilo (3,4 mL, 44 mmol) por goteo durante 7 min. La mezcla de reacción se dejó entibiar hasta alcanzar la temperatura ambiente durante 2 h, luego se agitó durante la noche. Una solución de agua al 10% 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 capas orgánicas combinadas se lavaron con agua (2 x 50 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 concentraron para remover traces of piridina. El residuo se secó al vacío durante 30 min. para

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obtener el compuesto del título (10,7 g, 102%), luego se usó en el paso siguiente sin purificación.

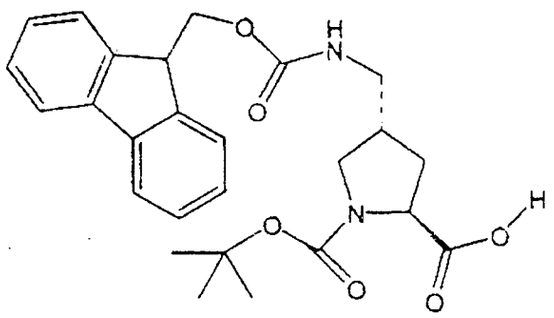
Paso 3: éster bencílico de N-t-butoxicarbonil-trans-4R-ciano-L-prolina (Boc-Pro(4-trans-CN -) OBn):



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 capas 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 por 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)

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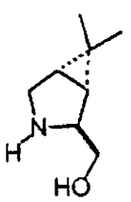


Una mezcla del compuesto del Paso 3 anterior (2,31 g, 7 mmol), agua (10 mL), metanol (85 mL) y paladio al 10% en carbono (700 mg) se hidrogenó a 50 psi durante 11 h mediante el uso de un aparato de hidrogenación Parr. La mezcla se filtró y se concentraron. Agua (15 mL) y carbonato de sodio (1,5 g, 14,2 mmol) se agregó al el 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 hasta 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 hasta 2 mediante el 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 capas orgánicas combinadas se secaron (sulfato de sodio), se filtraron y se concentraron. El producto bruto contenía una impureza mayor que necesitaba una purificación de tres pasos. El producto 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 4-(N-fluorenylmetiloxicarbonil-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-terbutildicarbonato (1,1 g, 5 mmol) en dioxano (5 mL). Luego de agitar durante 18 h, el pH de La

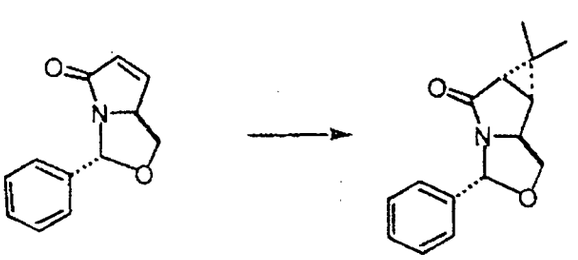
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solución se ajustó hasta 2 mediante el agregado de ácido cítrico (precaución: formación de espuma!) y agua (100 mL). La mezcla se extrajo con acetato de etilo (3 x 150 mL) y Las capas orgánicas combinadas se lavaron con cloruro de sodio acuoso saturado (100 mL), se secaron (sulfato de sodio), se filtraron y se concentraron. El producto bruto se disolvió en bicarbonato de sodio acuoso saturado(100 mL) y se lavó con éter (3 x 75 mL). La capa acuosa se ajustó hasta pH = 3 mediante el agregado de ácido cítrico, luego se extrajo con diclorometano (4 x 100 mL). Las capas orgánicas combinadas se secaron (sulfato de sodio), se filtraron y se concentraron hasta obtener el compuesto del título (1,373 g, 2,94 mmol, 42%).

Ejemplo VIII. Síntesis de 3.4-isopropilidenprolinol:



Paso I Reacción de ciclopropanación *(Tetrahedron Lett.* 1993. 34(16). 2691 y 2695):

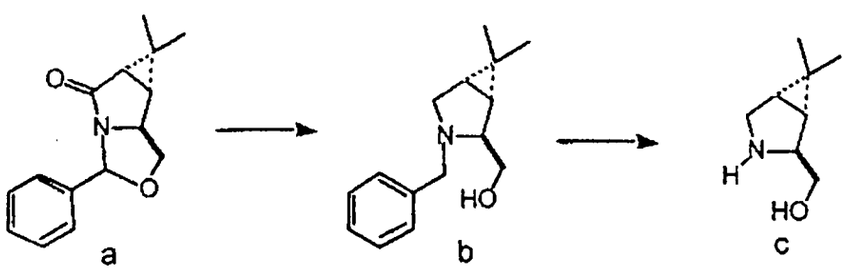


A una solución agitada de ioduro de isopropiltrifenil- fosfonio (4,14 g, 9,58 mmol) en tetrahidrofurano (60 mL) a 0°C, se agregó n-butillitio (1,6 M en hexanos,

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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-oxapirrolicin-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 removió 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 bruto deseado. El residuo se purificó por 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):

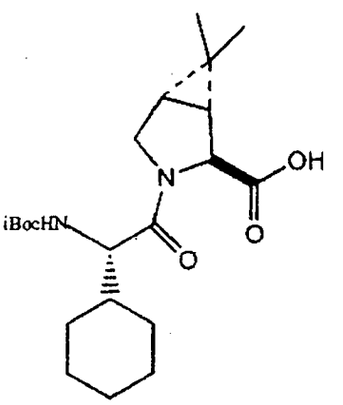


Una mezcla del producto obtenido en el paso 1 anterior (1,23 gramos, 5,06 mmol) y hidruro doble de litio y aluminio (1.0 M en THF, 15 mL, 15 mmol) se calentó a reflujo durante 5 horas. Luego de enfriar hasta 0°C, el hidruro de aluminio restante se inactivó cuidadosamente mediante el agregado por goteo 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 N-bencil aminoalcohol bruto (1,25 gramos), que se llevó al paso siguiente sin purificación adicional. Una solución de N-bencil aminoalcohol bruto (1,25 gramos, 5,06 mmol) en 1:1 ácido

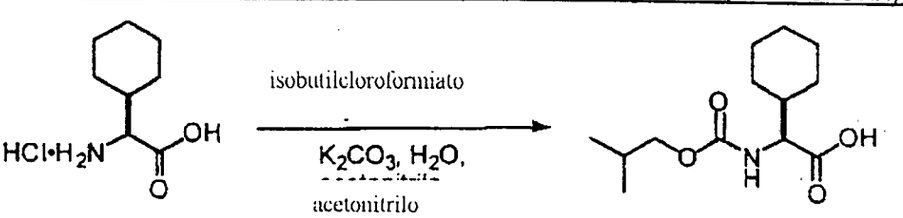
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acético/acetato de etilo (30 mL) con Pd al 10%/C (1 gramo) se hidrogenó a 50 psi durante 16 horas mediante el uso de un aparato para hidrogenación Parr. La mezcla de reacción se filtró para remover el catalizador con base de carbono y el filtrado se concentró. El residuo se disolvió en agua (30 mL) y el pH se ajustó hasta 13 con NaOH al 50%. La mezcla se extrajo con éter (3 x 60 mL). El extracto combinado se secó con sulfato de sodio, se filtró y se concentró para dar aminoalcohol bruto (485 mg, 3,43 mmol). Se llevó este material hasta el paso siguiente sin purificación adicional.

Ejemplo IX. Síntesis de ácido iBoc-G(Chx)Pro(3,4-isopropiliden)- carboxílico



Paso 1 Síntesis de isobutiloxicarbonil- ciclohexilglicina (iBoc-G Chx)-OH):

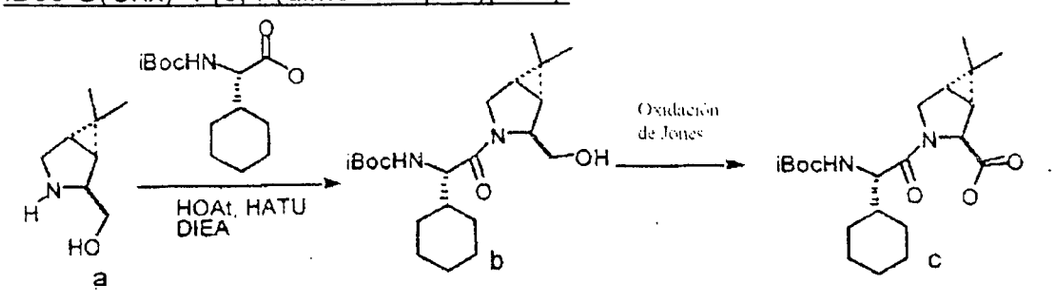


A una solución de disponible en el mercado clorhidrato de ciclohexilglicina (15 g, 77,4 mmol) en acetonitrilo (320 ml) y agua (320 ml) se agregó carbonato de potasio. Se agregó isobutilcloroformiato (11,1 ml, 85,1 mmol) a la solución clara durante 15 minutos y la reacción se agitó durante 17 horas. El acetonitrilo se removió con presión reducida y la fase acuosa restante se extrajo dos veces con éter (100 ml). Luego, la fase acuosa se acidificó hasta un pH 1 con ácido

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clorhídrico 6N y se extrajo con diclorometano (3 X 300 ml). La capa orgánica se secó en sulfato de sodio, se filtró y se concentró para producir 18,64 g (94%) como un sólido blanco.

Paso 2. Síntesis de isobutiloxicarbonil-ciclohexilalicil-3,4-isopropilidenprolina iBoc-G(Chx)- P[3,4-(diMe-cicloprol)]-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), HOA (476 mg, 3,5 gramos) y luego diisopropiletilamina (2,5 mL, 14 mmol). Luego de 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 capas orgánicas combinadas se secaron, se filtraron y se concentraron. El residuo se purificó por cromatografía flash eluyendo con 1:1 acetato de etilo/hexanos para dar el alcohol dipéptido puro iBoc-G(Chx)-3,4-isopropilidenprolinol (870 mg, 2,3 mmol, 67%)

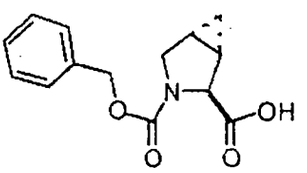
b) Paso de Oxidación de Jones

A una solución de alcohol dipéptido iBoc-G(Chx)-3,4-isopropilidenprolinol (100 mg, 0,26 mmol) en acetona (2 mL) bajo agitación a 0°C se agregó reactivo de Jones (300 µL) por goteo 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 hasta un volumen total de 50 mL.] Luego de agitar a 0°C

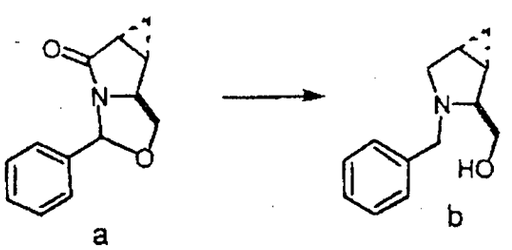
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durante 3 horas, se agregó isopropanol (500 µL) y se continuó la agitación durante un adicional de 10 minutos. La mezcla de reacción se diluyó con agua (20 mL) y se extrajo con acetato de etilo (3 x 70 mL). Las capas orgánicas combinadas se secaron, se filtraron y se concentraron para dar el dipéptido iBoc-G(Chx)-3,4-isopropilidenprolina (100 mg, 0,25 mmol, 96%).

Ejemplo X. Síntesis de N-Cbz-3.4-metanoprolina:



Paso 1. Síntesis de N-bencil-3,4-metanoprolinol:

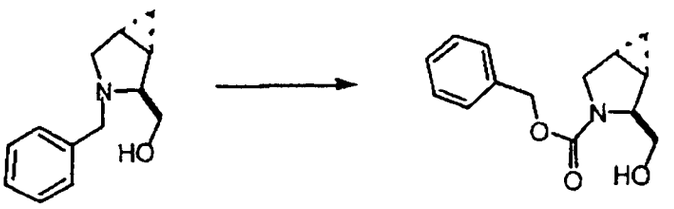


a b

Una mezcla del material inicial de bencilideno (J. Org. Chem. 1999, 64(2), 547) (4,6 gramos, 21,4 mmol) y hidruro doble de aluminio y litio (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 con cuidado mediante el agregado por goteo 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 N-bencil aminoalcohol bruto (3,45 gramos), que se llevó al paso siguiente sin purificación adicional.

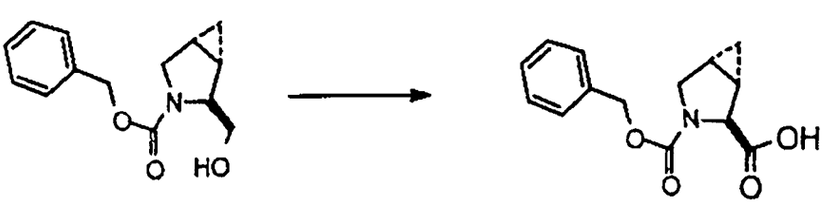
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Paso 2. Síntesis de N-benciloxicarbonil-3,4-metanprolinol (CBz-P(3.4-CH2)-ol:



Una solución de N-bencil aminoalcohol bruto (3 gramos, 14,76 mmol) en metanol (120 mL) y HCl concentrado (1.5 mL) con Pd al 10%/C (300 mg) se hidrogenó a 50 psi durante 16 horas. La mezcla de reacción se filtró para remover 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 capas orgánicas combinadas se secaron con sulfato de magnesio , se filtraron y se concentraron. El residuo se purificó por cromatografía flash mediante el uso de 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-methanoprolina (CBz-P(3.4-CH2)-OHM

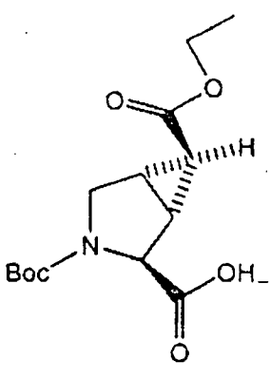


A una solución de N-Cbz-3,4-metanoprolinol (2,2 g, 8,90 mmol) en acetona (68 mL) bajo agitación a 0°C, se agregó reactivo de Jones (6,6 mL) por goteo durante 5 min. [Reactivo de Jones: Preparado a partir de trióxido de cromio (13.4

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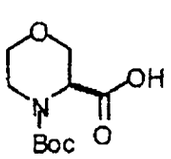
g) y ácido sulfúrico concentrado (11,5 mL) diluido con agua hasta un volumen total de 50 mL.] Luego de bajo agitación a 0°C durante 3 horas, se agregó isopropanol (11 mL) y se continuó la agitación durante un adicional de 10 minutos. La mezcla de reacción se diluyó con agua (400 mL) y se extrajo con acetato de etilo (3 x 500 mL). Las capas orgánicas combinadas se secaron en magnesio sulfate, se filtraron y se concentraron para dar N-Cbz-3,4-metanoprolina (2,25 g, 96%)

Ejemplo XI. Síntesis de Boc-(6S-carboetoximetano) prolina:



La síntesis del compuesto del título se realizó de acuerdo con el procedimiento publicado: Marinozzi, M.; Nataini, B.; Ni, M.H.; Costantino, G.; Pellicciari R. IL Farmaco (1995) 50 (5), 327-331.

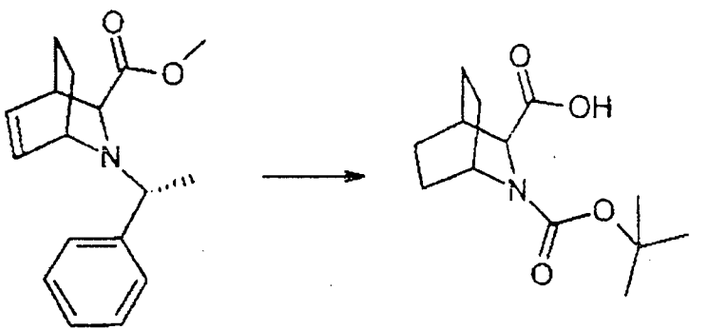
Ejemplo XII. Síntesis del Ácido Boc-3-morfolino carboxílico



La síntesis del compuesto del título se realizó de acuerdo con el procedimiento publicado: Kogami Y., Okawa, K. Bull. Chem. Soc. Jpn. (1987) 60, 2963-2965.

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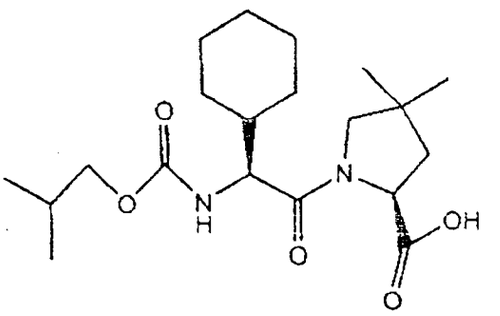
Ejemplo XIII. Síntesis de N-tert-butoxicarbonil 2-aza-3S-hidroxicarbonil-[2.2.2]-biciclooctano:



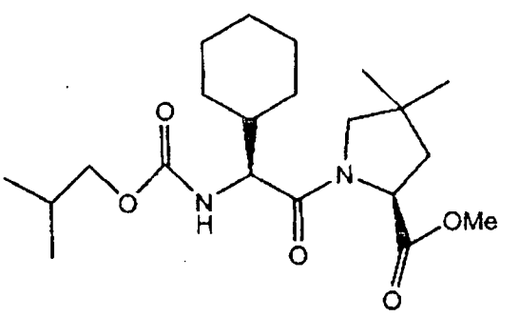
Una solución de 2-aza-2-(1-feniletil)-3S-metoxicarbonil-[2,2,2]biciclooct-5-eno bruto (10 mmol) (Tetrahedron (1992) 48(44) 9707-9718) y Pd al 10% en carbono (1 g) en metanol (30 mL) se acidificó con HCl 12N luego hidrogenar a 50 psi durante 16 horas mediante el uso de un aparato para hidrogenación Parr. La mezcla de reacción se filtró para remover 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 en acetonitrilo (50 mL). Se agregaron diisopropiletilamina (3,5 mL) y di-terbutildicarbonato (1 g). La mezcla de reacción se agitó durante 24 horas y luego se concentró. El residuo se disolvió en CH_2Cl_2 y ácido sulfúrico acuoso al 5%. La mezcla de reacción se extrajo con CH_2Cl_2 y las capas orgánicas combinadas se concentraron. El residuo se disolvió en bicarbonato de sodio saturado al 10%, se lavó con éter dietílico (2x) y se acidificó con ácido sulfúrico acuoso al 5%. La capa acuosa se extrajo con acetato de etilo (2x). Las capas combinadas de acetato de etilo se secaron se filtraron y se concentraron para dar N-tert-butoxicarbonil 2-aza-3S-hidroxicarbonil-. [2,2,2]-biciclooctano (650 mg).

Ejemplo XIV. Síntesis de isobutiloxicarbonil-ciclohexilglicil-4,4-dimetilprolina (iBoc-G(Chx)-P(4,4-dimetil)-OH):

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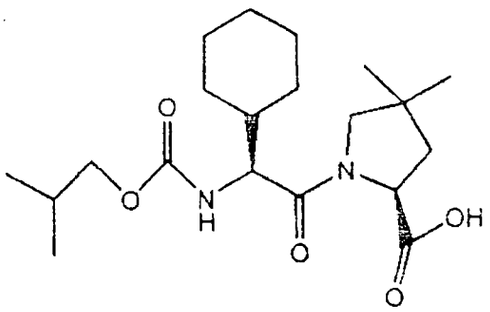
Paso I: Síntesis de iBoc-G(Chx)-P(4 4-dimetil)-OMe:



A una solución de iBoc-G(Chx)-OH (Ejemplo IX, Paso 1.) (377 mg, 1,95 mmol) en acetonitrilo (7 mL) se agregó en forma sucesiva 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 capa orgánica se lavó dos veces con porciones de 10 ml solución de bicarbonato de sodio saturado, solución clorhídrica 1N, y salmuera. La capa orgánica se secó en sulfato de sodio, se filtró y se concentró para obtener un sólido blanco (612 mg, 79%).

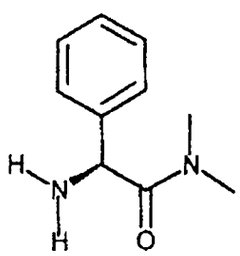
Paso 2 Síntesis de iBoc-G(Chx)-P(4,4-dimetil)-OH:

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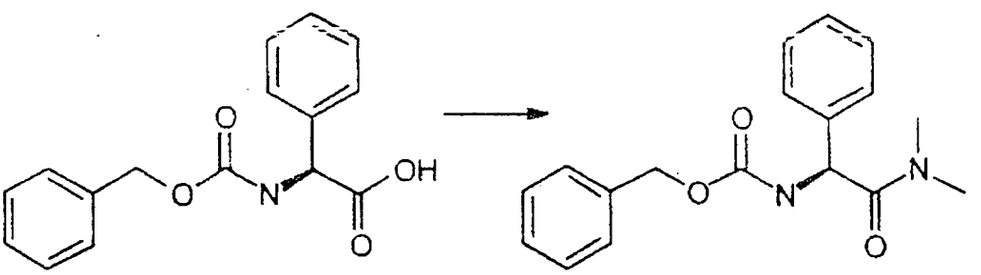
El éster metílico obtenido en Paso 1 anterior (612 mg, 1,54 mmol) en metanol (6 ml) se saponificó en presencia de hidróxido de litio 2M (1,16 ml) durante tres horas. El metanol se removió con presión reducida y el residuo restante se diluyó con acetato de etilo y se acidificó hasta un pH=2 con ácido clorhídrico 1N. Las capas se separaron y la capa orgánica se lavó con agua y salmuera, se secó en sulfato de sodio, se filtró y se concentró.

Ejemplo XV. Síntesis de L-fenilglicin dimetilamida

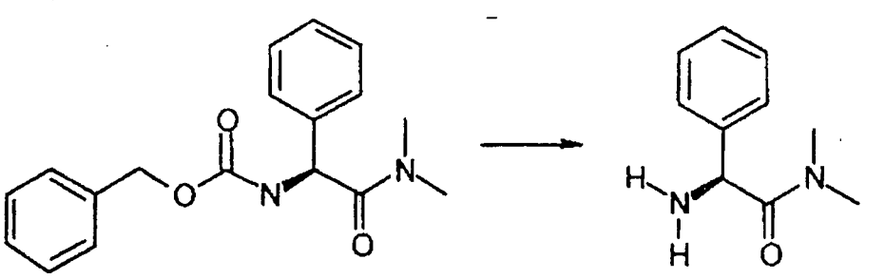


Paso 1. Síntesis de N-benciloxicabonil-L-fenilglicina dimetilamida (CBz-Pha-NMe2):

030502



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) e isobutilcloroformiato (11,4 mL, 88,0 mmols) y la mezcla se dejó en agitación durante 1 minuto. Se agregó dimetilamina (100 mL, 2M en THF) y la reacción se dejó entibiar hasta temperatura ambiente. La mezcla se filtró y el filtrado se concentró al vacío para obtener N-benciloxicabonil-L-fenilglicina dimetilamida (32,5 g) como un aceite amarillo.



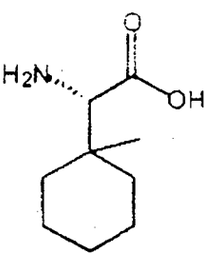
Paso 2. Síntesis de L-fenilglicina dimetilamida (H-Phg-NMe2):

La N-benciloxicarbonil-L-fenilglicina dimetilamida (32,5 g) obtenida en el paso anterior se disolvió en metanol (750 ml) y se agregó paladio al 10% en carbono activado (3,3 g). Esta mezcla se hidrogenó en un aparato Parr a 35 psi hidrógeno durante 2 Horas. La mezcla de reacción se filtró y el solvente se removió al vacío y el residuo se recristalizó a partir de metanol-hexanos para obtener dimetilamida de fenilglicina (26 g) como un sólido blanco grisáceo. El ee

000503

de este material se determinó en >99% por medio del análisis de HPLC del derivado de 2,3,4,6-tetra-O-acetlglucopiranosiltioisocianato.

Ejemplo XVI. Síntesis de (1-metilciclohexil) alucina:



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 enfriamiento se removió y la mezcla de reacción se agitó a temperatura ambiente durante dos días. El borano restante se inactivó mediante la lenta incorporación de bisulfato de sodio saturado (10 mL) durante 90 min. con frío. El bisulfato de sodio saturado adicional (200 mL) se agregó y luego de 20 min. de agitar la capa acuosa se removió. La capa orgánica se lavó con agua y cloruro de sodio saturado, se secó, se filtró y se concentró. El residuo se purificó por cromatografía flash mediante el uso de éter dietílico al 20% en hexanos para dar 1-metil-1-hidroximetilciclohexano (6,17 g, 48 mmol, 69%).

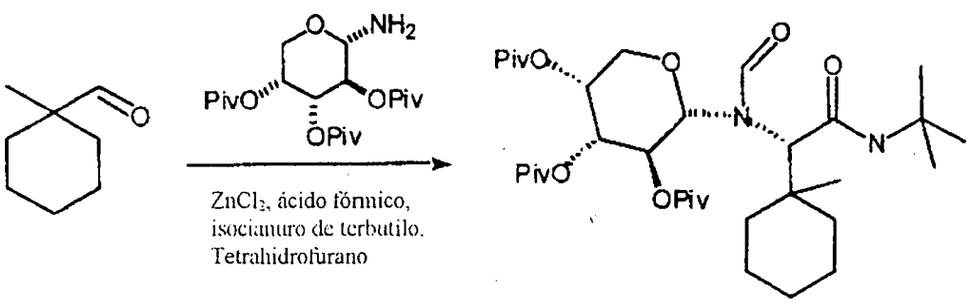
Paso 2. 1-metilciclohexilcarboxaldehído:

000504



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 sulfuro y piridina (22,9 g, 144 mmol) en dimetilsulfóxido (150 mL) durante 15 min. El baño de enfriamiento se dejó entibiar hasta temperatura ambiente durante dos horas, momento en cual la mezcla de reacción se vertió en salmuera con hielo (400 mL). Se separaron las capas y la capa acuosa se extrajo con diclorometano (200 mL). Las capas orgánicas combinadas se diluyeron con hexanos (600 mL) y se lavó con HCl 1M (2 x 150 mL), cloruro de sodio saturado (2 x 100 mL), se secó, se filtró y se concentró. El residuo se purificó por 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



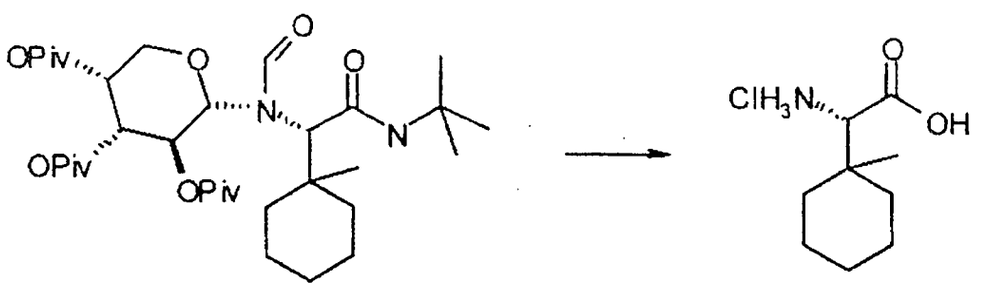
La síntesis de la 2,3,4-tri-O-pivaloil- -D-arabinosilamina se realizó de acuerdo con el procedimiento publicado (Kunz. H.; Pfrengle, W.; Ruck, K.; Wilfried, S. *Synthesis (1991)* 1039-1042).

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,

000505

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 capa orgánica se secó, filtró y concentró para dar un aceite claro. La cromatografía flash (acetato de etilo en hexanos al 20%) suministró el producto puro (4,3 g, 6,6 mmol, 33%)

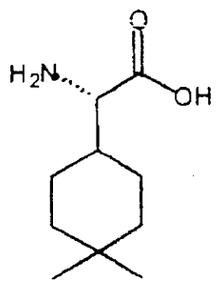
Paso 4. Síntesis de (1-metilciclohexil)glicina:



Una solución del producto obtenido en el paso 3 anterior (4.3 g, 6.6 mmol) en diclorometano (30 mL) y HCl metanólico 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 capa acuosa 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-metilcilohexil)glicina (790 mg, 3,82 mmol, 58%).

Ejemplo XVII. Síntesis de (4,4-dimetilciclohexil)glicina:

000536

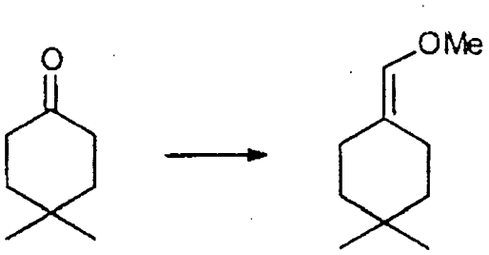


Paso 1. Síntesis de 4,4-dimetilciclohexanona:



Una mezcla de 4,4-dimetilciclohex-2-en-1-ona (12 mL, 91,2 mmol) y 10% Pd tipo Degussa en carbono (2 g) se hidrogenó a 40 psi durante 18 horas. La mezcla se filtró y se concentró (^{1}H NMR mostró una mezcla de cetona y alcohol en una relación de 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 enfriamiento se removió. Luego de 2 días el exceso de acetona se evaporó y el residuo resultante se disolvió en agua y éter dietílico. La capa de éter se lavó con agua hasta que no tuvo color, se secó, filtró y concentró para dar 4,4-dimetilciclohexanona (7,4 g, 58,6 mmol, 64%).

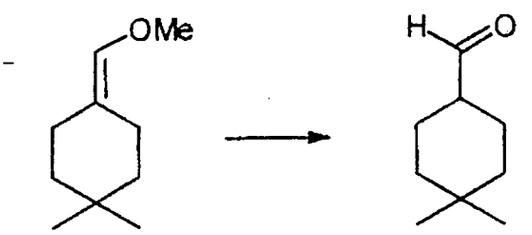
Paso 2. Síntesis del éter enol metílico de 4,4dimetilciclohexilcarboxaldehído:



000607

A una solución de cloruro de metoximetil trifenilfosfonio (8,6 g) en tetrahidrofurano (125 mL) a 0°C se agregó n-butillitio (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 enfriamiento se removió 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 capa orgánica se lavó con agua y salmuera, se secó, filtró y concentró. El residuo se agitó con hexanos (70 mL) durante 10 min. y se filtró. El filtrado se concentró y se sometió a cromatografía con el uso de acetato de etilo al 25% en hexanos para dar el compuesto del título (1,925 g, 12,5 mmol, 65%).

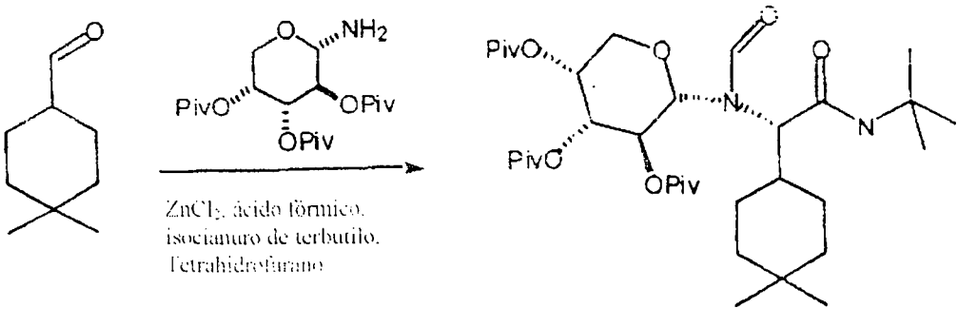
Paso 3: 4 4-dimetilciclohexilcarboxaldehido:



Una solución de el metil enol éter de 4,4dimetilciclohexilcarboxaldehído (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 capa orgánica se secó, filtró y concentró para dar 4,4-dimetilciclohexilcarboxaldehído (1,0 g, 7,1 mmol, 57%).

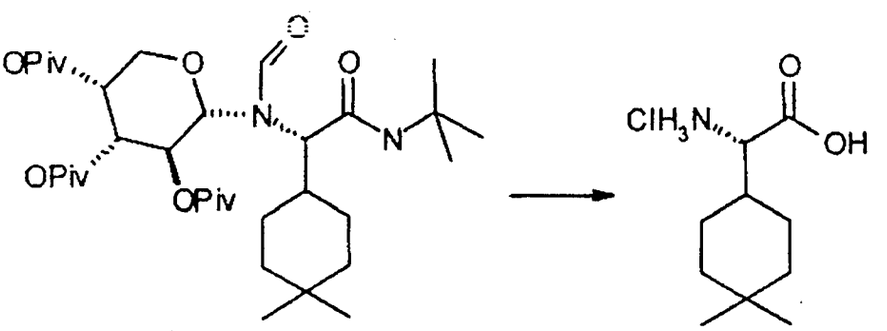
Paso 4. Síntesis de N-formil-N-glicosil- 4.4-dimetilciclohexil- ter-butilamida

000608



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 capa orgánica se secó, filtró y concentró para dar un aceite claro. La cromatografía flash (acetato de etilo al 20% en hexanos) suministró el producto puro (2,1 g, 3,3 mmol, 39%)

Paso 5. Síntesis de (4,4-dimetilcxclohexil)glicina:

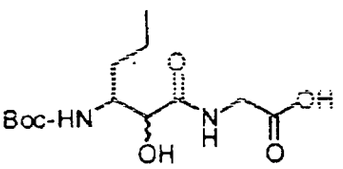


Una solución del producto Ugi obtenido en el paso 4 anterior (2,1 g, 3,3 mmol) en diclorometano (20 mL) y HCl metanólico anhidro saturado (20 mL) se agitó durante la noche. La solución se concentró y el residuo se disolvió en agua

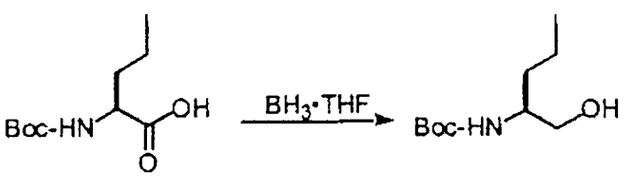
000599

(100 mL) y se lavó con pentano (2 x 100 mL). La capa acuosa 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 bruto (300 mg, 1,36 mmol, 41 %).

Ejemplo XVIII Síntesis de Boc-nVal-(CHOH)-Gli-OH:

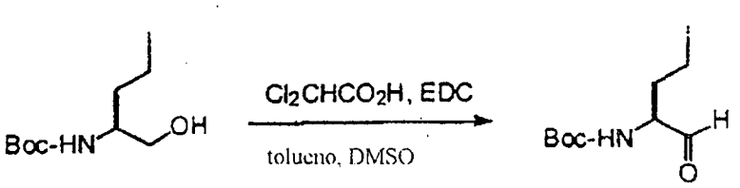


Paso 1. Preparación de Boc-norvalinol:



A una solución de Boc-norvalina (25,0 g, 0,115 mol) en tetrahidrofurano (461 mL), se enfrió hasta 0°C, se agregó el complejo borano/tetrahidrofurano (461 mL de una solución 1,0 M en tetrahidrofurano) por goteo. Luego de 1 hr a 0°C, la solución se entibió hasta temperatura ambiente durante un periodo de 1,5h. TLC indicó que la reacción estaba completa. Se agregó metanol para inactivar la reacción. La solución se concentró para producir el compuesto del título (22,56 g, 96%) como un jarabe espumoso. La TLC de los productos indicó pureza satisfactoria. R_f = 0,34 (40% acetato de etilo/hexanos).

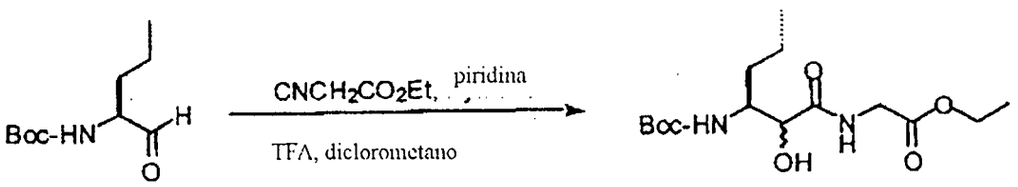
Paso 2. Preparación de Boc-norvalinal:



000510

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) por goteo. Luego de completar la adición, la reacción se agitó durante 15 min. La solución se dejó entibiar hasta temperatura ambiente durante un período de 2h. La mezcla de reacción se concentró para remover el tolueno, luego se disolvió en acetato de etilo. La solución se lavó en forma sucesiva con bisulfato de sodio 1N, bicarbonato de sodio saturado y salmuera, se secó sobre sulfato de sodio, se filtró y se concentró para obtener Boc-norvalinal bruto que se usó directamente en el paso siguiente. TLC R_f = 0,84 (acetato de etilo al 40%/hexanos).

Paso 3. Síntesis de Boc-nVal-(CHOH)- Gli-OEt:.

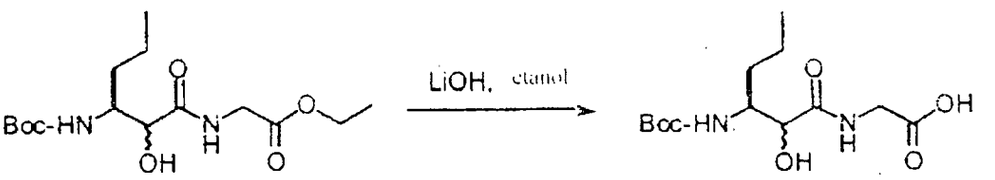


A una solución del Boc-norvalinal bruto (4,18 g, 20,77 mmol) en diclorometano (83 mL) se agregó etilisocianoacetato (2,72 ml, 24,93 mmol) y piridina (6,72 ml, 83,09 mmol). Luego de que la solución se enfrió hasta 0°C, ácido trifluoroacético (4,15 ml, 41,54 mmol) se agregó por goteo. Luego de agitar durante 1 hr, la solución se agitó a temperatura ambiente durante 18 horas mientras se permitió que el solvente de la mezcla de reacción en un recipiente no cubierto se evapore en condiciones ambientales. La mezcla de reacción se concentró, luego se disolvió en acetato de etilo. La solución se lavó en forma sucesiva 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 por cromatografía flash eluyendo con acetato de etilo al 20% a 40%/hexanos para obtener 2.8 g del compuesto del título como un jarabe amarillo. La

000511

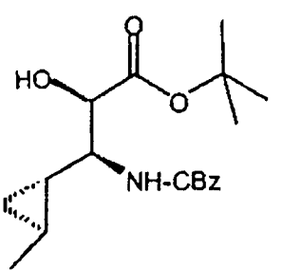
espectrometría de masa de baja resolución confirmó la presencia del producto deseado (MH+ 333).

Paso 4. Síntesis de Boc-nVal-(C HOFI)-Gli-OR



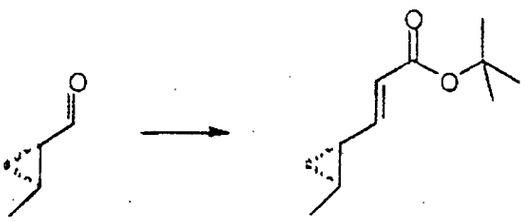
El producto obtenido (Boc-nVal-(CHOH)-Gli-OEt) (1,52 g, 4,70 mmol) disuelto en etanol (23 ml) se saponificó con hidróxido de litio 1N (18,81 ml) durante dos horas a temperatura ambiente. La mezcla de reacción se ácidoificó hasta un pH de aprox. 2 con resina de intercambio iónico Dowex® 50 WX8, se agitó 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 (2R,3S,4S,5S)-ter-Butil N-CBz-3-amino-2-hidroxi-4,5-metilen-hexanoato:



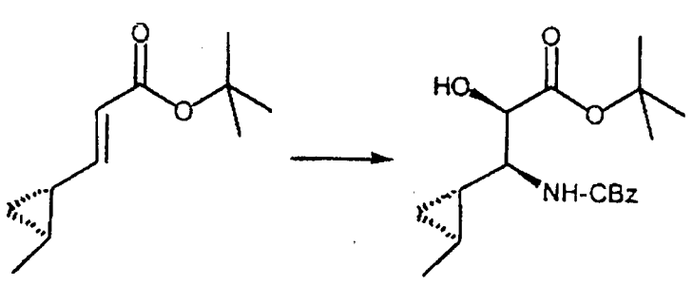
Paso 1:

000512



A una solución de ter-Butil dietilfosfonoacetato (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.; Doubleday, 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 hasta 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 capa orgánica se separó, se lavó con 50 mL salmuera y se secó sobre sulfato de sodio, se filtró y se concentró para obtener 3,5 g de un aceite claro. La cromatografía flash (acetato de etilo al 20% en hexanos) produjo el ter-butiléster insaturado puro (1,4 g).

Paso 2:

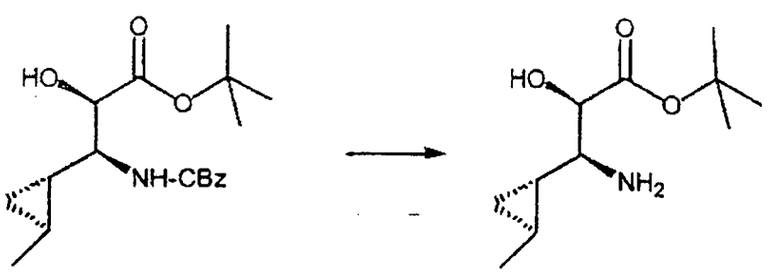


A una solución de carbamato de bencilo (3,55g, 23,5 mmols) en n-propanol (24 mL) se agregó una solución de hidróxido de sodio (900 mg, 22,7 mmol) en agua (48 mL), seguido de ter-butilhipoclorito (2,57 mL, 22,7 mmol). Luego de 15 minutos la reacción se enfrió hasta 0°C y se agregó $(DHQ)_2PHAL$ (350 mg, 0,45 mmol) en n-propanol (24 mL), seguido de insaturado ter-butil éster (1.4 g) de

000513

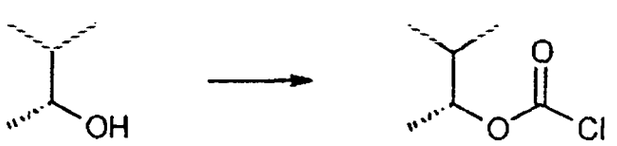
anterior en n-propanol (48 mL). Finalmente, se agregó osmato de potasio (110 mg, 0,30 mmol) en agua (2 mL) y la solución desarrolló muy rápido un color verde oscuro que persistió durante 4 horas. Luego de 6 horas sulfato de sodio saturado (50 mL) se agregó y la mezcla se extrajo con acetato de etilo (2 x 50 mL). Las capas orgánicas combinadas se lavaron con salmuera (30 mL), se secó sobre sulfato de sodio, se filtraron y se concentraron. La cromatografía flash con acetato de etilo al 20% en hexanos produjo el amino ter-butiléster protegido con cBz como un sólido blanco (316 mg).

Paso 3:



Una mezcla de amino ter-butiléster protegido con cBz (316 mg, 0,9 mmol) y 32 mg de paladio al 10% en carbono en 9 mL metanol se hidrogenó durante 8 horas. La mezcla se filtró y se concentró para obtener la amina libre como un aceite claro (195 mg).

Ejemplo XX. Síntesis de cloroformiato de 1R,2-dimetilPropilo:



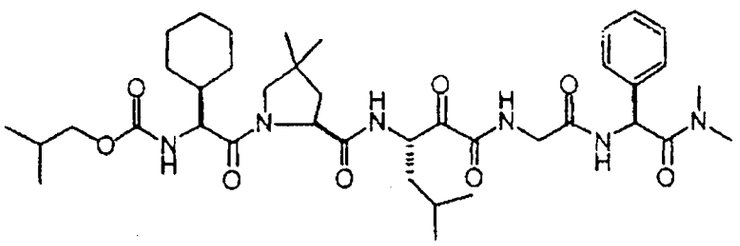
Al 2R-hidroxi-3-metilbutano disponible en el mercado (410 mg, 4,65 mmol) se agregó una solución de fosgeno al 20% en tolueno (1 mL, 2 mmol). La solución se agitó durante 6 horas para generar el cloroformiato (2 mmol) que se

030514

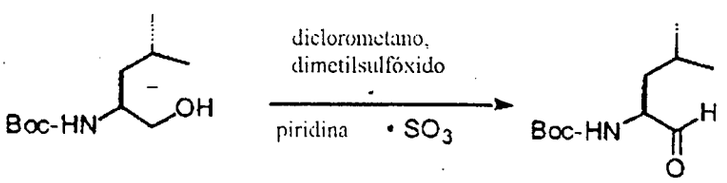
sometió a reacción directa en inmediatamente con la amina deseada. El S-isómero se sintetizó mediante el mismo procedimiento.

II) Síntesis de la fase de solución representativa de los inhibidores de HCV

Ejemplo XXI. Síntesis de la fase de solución de iBoc-G(Chx)-Pro(4,4-dimetil)-Leu-(CO)-Gli-Phg-dimetilamida:

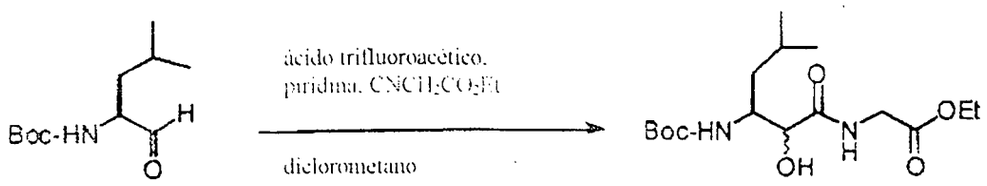


Paso 1. Síntesis de ter-butxloxicarbonil-leucinal (Boc-Leu-CHO):



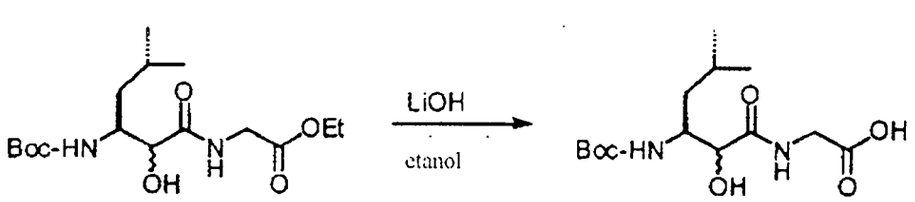
A una solución de Boc-L-leucinol disponible en el mercado (Advanced Chem Tech) (0,78 g, 3,6 mmol) en diclorometano anhidro (17,5 ml) se agregó trietil amina (2 ml, 14,36 mmol) y la mezcla se enfrió hasta 0°C. Se agregó sulfóxido de dimetilo (17,5 ml) seguido de complejo de piridina trióxido de sulfuro (2,3 g, 14,36 mmol) y la reacción se agitó durante dos horas. TLC en 1:1 acetato de etilo: hexanos confirmó la finalización de la reacción. La mezcla de reacción se concentró y el residuo restante se diluyó con acetato de etilo. La capa de acetato de etilo se lavó con ácido clorhídrico 1M (2 x 75 ml) seguido de solución de bicarbonato de sodio saturado (2 x 75 ml) y salmuera (75 ml). La capa orgánica se secó (sulfato de sodio), se filtró y se concentró para producir 775 mg de producto.

Paso 2. Síntesis de éster etílico de Boc-2-hidroxi-3-amino-5-metil hexanoil-alucina (Boc-Leu-(CHOH)-Gli-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) y etilisocianoacetato (0,4 ml, 4,66 mmol). La mezcla de reacción se enfrió hasta 0°C y ácido trifluoroacético (0,55 ml, 7/18 mmol) se agregó 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 capa orgánica se secó, se filtró y se concentró. El residuo obtenido se sometió a cromatografía flash en una columna de 2" x 6" de gel de sílice con el uso de acetato de etilo al 10% en hexanos (800 ml) seguido de 1:1 acetato de etilo en hexanos (800 ml). Las fracciones correspondientes al producto se reunieron y se concentraron para producir 980 mg (79%) de producto.

Paso 3. Síntesis de Boc-Leu(CHOH)-Gli-OH:

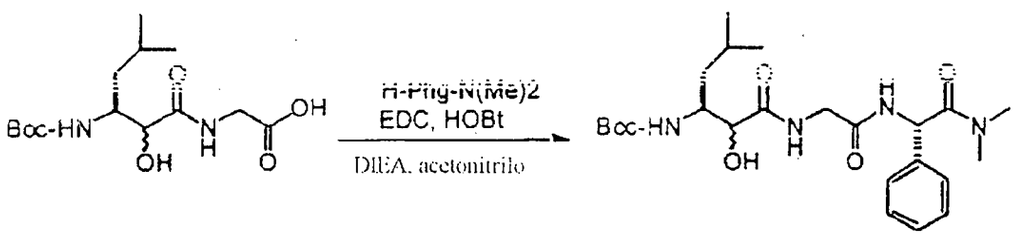


A una solución de Boc-Leu-(CHOH)-Gli-Oet (0,98 g, 2,83 mmol) en etanol (11,3 ml) se agregó hidróxido de litio 2M (4,25 ml) y la reacción se agitó durante

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cinco horas a temperatura ambiente. El etanol se removió con presión reducida y la capa acuosa se diluyó con acetato de etilo. La capa orgánica se lavó con ácido clorhídrico 1M seguido de salmuera, se secó, se filtró y se concentró para producir 775 mg (86%) de producto como un sólido blanco.

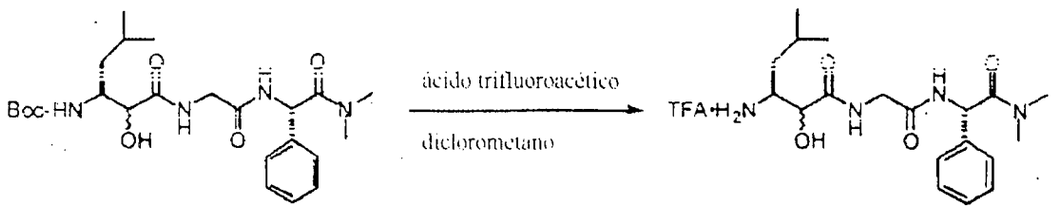
Paso 4. Síntesis de Boc-Leu-(CHOH)-Gli-Phg-dimetilamida:



A una solución de Boc-Leu-(CHOH)-Gli-OH (0,37 g, 1,18 mmol) en acetonitrilo (23 ml) se agregó en forma sucesiva dimetilamida de 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 en forma sucesiva con dos porciones de 75 ml ácido clorhídrico 1M, bicarbonato de sodio saturado y salmuera. La capa orgánica luego se secó, se filtró y se concentró. El producto bruto se sometió a cromatografía flash en una columna de 2" x 6" de gel de sílice con el uso de 4:1 acetato de etilo: hexanos (700 ml) seguido de acetato de etilo (1000 ml) y metanol al 10% en diclorometano (600 ml). Las fracciones correspondientes al producto se reunieron y concentraron para producir 445 mg (80%) de un sólido blanco.

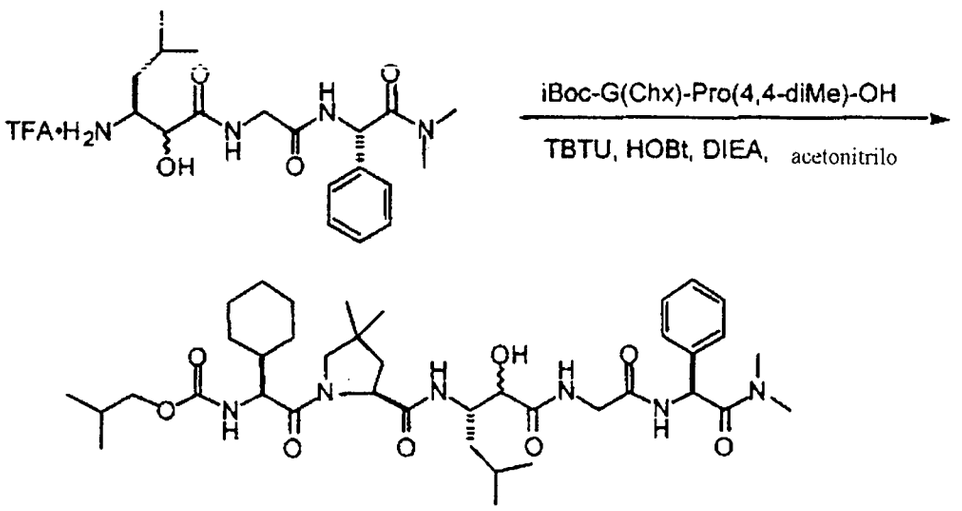
Paso 5 Síntesis de Sal de trifluoroacetato de H-Leu-(CHOH)-Gli-Phg-dimetilamida

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A una solución de Boc-Leu-(CHOH)-Gli-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 iBoc-G(Chx)-Pro(4,4-dimetil)-Leu-(CHOH)-Gli-Phg-dimetilamida:

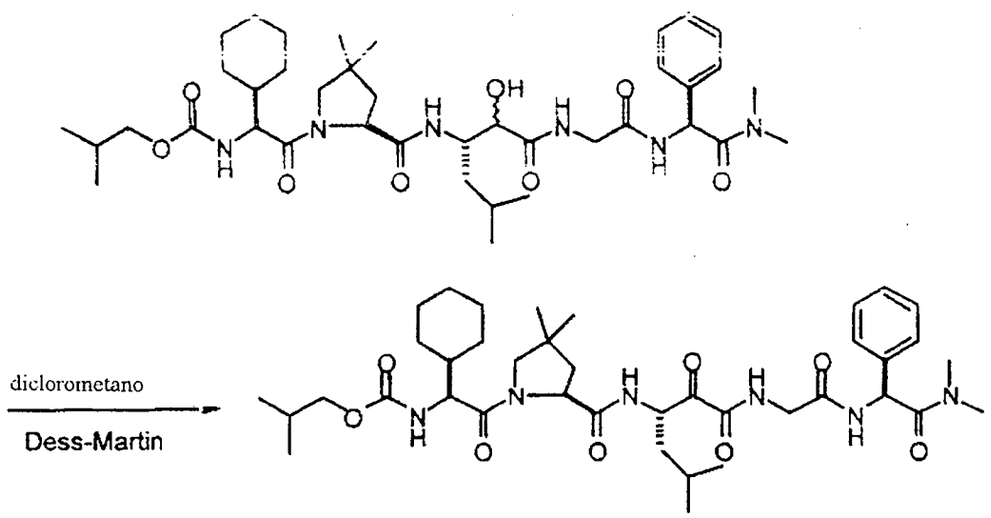


A una solución de iBoc-G(Chx)-P(4,4-diMe)-OH (Ejemplo XIV, paso 2) (53 mg, 0,148 mmol) en acetonitrilo (3 ml) se agregó en forma sucesiva TFA.2HN-Leu(CHOH)Gli-Phg-NMe2 (61 mg, 0,148 mmol), N-Hidroxibenzotriazol (HOBt) (23 mg, 0,148 mmol), TBTU (71,5 mg, 0,222 mmol y diisopropiletilamina (103 l, 0,593 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 de bicarbonato de sodio saturado (2

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x 5 ml), y salmuera (2 x 5 ml). La capa orgánica se secó, filtró y 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)-Gli-Phg-dimetilamida:



A una solución de iBoc-G(Chx)-Pro(4,4-dimetil)-Leu-(CHOH)-Gli-Phg-dimetilamida (30 mg, 0,04 mmol) en diclorometano (1 ml) se agregó el reactivo de Dess-Martin disponible en el mercado (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 tiosulfato de sodio al 5%. Luego se diluyó con diclorometano y las capas se separaron. La capa orgánica se lavó con tiosulfato de sodio (4 x 3 ml), seguido de agua y salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró. El producto bruto se disolvió en hexanos y alcohol isopropílico y se sometió a purificación por HPLC con el uso de una columna Kromasil 5 de fase normal de sílice (Fenomenex, 250 x 21.20 mm, tamaño de poros de 100 angstrom, partículas de gel de 5 µm) eluyendo con un gradiente a 30 minutos que consistía de 0 a 25% de alcohol isopropílico en hexanos (25 ml/minutos). Las fracciones correspondientes al producto se reunieron y concentraron. La

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liofilización del produjo 6,7 mg de polvo blanco. El especto de masa de baja resolución confirmó la masa deseada (MH+ = 741,4).

III) Síntesis de fase sólida: La síntesis de fase sólida es útil para la producción de pequeñas cantidades de ciertos compuestos de la presente invención. Como con la síntesis convencional de fase sólida de los péptidos, los reactores para la síntesis de fase sólida de peptidil cetoamidas están formados por un recipiente reactor con por lo menos una superficie permeable al solvente y reactivos disueltos, aunque no permeable a la resina de síntesis del tamaño seleccionado de malla. Dichos reactores incluyen recipientes de reacción de fase sólida de vidrio con un vidrio fritado sinterizado, tubos de polipropileno o columnas con frituras, o el reactor Kans™ fabricado por Irori Inc., San Diego CA. El tipo de reactor elegido depende del volumen de resina para fase sólida necesaria, y se pueden utilizar diferentes tipos de reactor en diferentes etapas de una síntesis. En los ejemplos posteriores se hará referencia a los siguientes procedimientos:

Procedimiento A: *Reacción por acoplamiento*: A la resina suspendida en N-metilpirrolidina (NMP) (10-15 mL/ gramo de resina) se agregó Fmoc-amino ácido (2 eq), HOAt (2 eq), HATU (2 eq) y diisopropiletilamina (4 eq). Se dejó que la mezcla reacciones durante 4-48 horas. Los reactivos se drenaron y la resina se lavó en forma sucesiva con dimetilformamida, diclorometano, metanol, diclorometano y éter dietílico (usar 10-15 mL de solvente/ gramo de resina). Luego la resina se secó al vacío.

Procedimiento B: *Desprotección de Fmoc*: La resina con Fmoc-desprotegido se trató con piperidina al 20% en dimetilformamida (10 mL de reactivo/ g de resina) durante 30 minutos. Los reactivos se drenaron y la resina se lavó en forma sucesiva con dimetilformamida, diclorometano, metanol, diclorometano y éter dietílico (usar 10 mL de solvente/ gramo de resina).

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Procedimiento C: *Desprotección de Boc*: La resina con Boc desprotegido se trató con una mezcla de 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 en forma sucesiva con diclorometano, dimetilformamida, diisopropiletilamina al 5% en dimetilformamida, dimetilformamida, diclorometano, y dimetilformamida (10 mL de solvente/ gramo de resina).

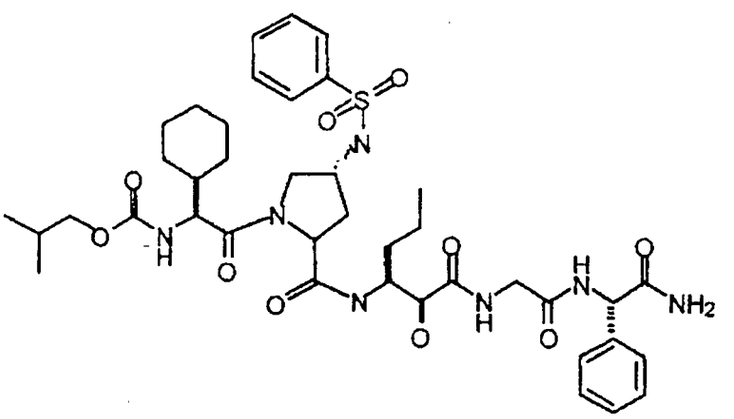
Procedimiento D: *Hidrólisis de semicarbazona*: Se suspendió la resina en un cocktail de disociación (10 mL/ g de resina) que consistía de ácido trifluoroacético: ácido pirúvico: diclorometano: agua 9:2:2:1 durante 2 Horas. Los reactivos se drenaron y se repitió el procedimiento tres veces más. La resina se lavó en forma sucesiva con diclorometano, agua y diclorometano y se secó al vacío.

Procedimiento E: *Disociación de HF*: La resina de péptido-nVal(CO)-G-O-PAM seca (50 mg) se colocó en un recipiente de HF que contenía una pequeña vara de agitación. Se agregó anisol (10% del volumen total) como depurador. En presencia de ácido glutámico y amino ácidos de cisteína, también se agregaron tioanisol (10%) y 1,2-etanditiol (0,2%). El recipiente de HF luego se colgó en un aparato para HF (Immuno Dynamics) y el sistema se lavó con nitrógeno durante cinco minutos. Luego se enfrió hasta -70°C con un baño de hielo seco/ isopropanol. Luego de 20 minutos, se destiló HF hasta el volumen deseado (10 mL de HF/ g de resina). Se dejó proceder la reacción durante una hora y media a 0°C. El trabajo consistió en remover todo el HF con el uso de nitrógeno. Luego se agregó diclorometano a la resina y se agitó la mezcla durante cinco minutos. A esto le siguió el agregado de ácido acético al 20% en agua (4 mL). Luego de agitar durante 20 minutos, se filtró la resina con el uso de un embudo fritado se removió el diclorometano con presión reducida. El residuo restante y la mezcla se lavaron con hexanos (2x) para remover los depuradores. Mientras tanto, se

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enjuagó la resina en 1 mL de metanol. La capa acuosa (HOAc al 20%) se agregó nuevamente a la resina y la mezcla se agitó durante cinco minutos y luego se filtró. Se removió el metanol con presión reducida y se liofilizó la fase acuosa. Luego se disolvió el péptido en metanol al 10-25% (que contenía ácido trifluoroacético al 0,1%) y se purificó por HPLC de fase inversa.

Ejemplo XXII Síntesis representativa en fase sólida de inhibidores de Hep C: (iBocG(Chx)-P(4t-NHSO2Ph)-nV-(CO)-G-G(Ph)-NH2)



Paso 1 Síntesis de Fmoc-nV-(dpsc)-Gli-OH:

A) Síntesis de isocianoacetato de alilo (pasos a-b a continuación):

a) Síntesis de sal de potasio del ácido osicianoacético:

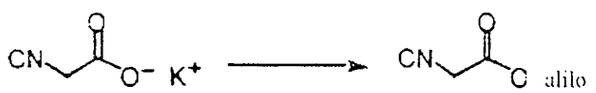


Se agregó etil isocianoacetato (96,6 ml, 0,88 mol) por goteo a una solución congelada de etanol (1,5 L) y hidróxido de potasio (59,52 g, 1,0 mol). La reacción se entibió lentamente hasta la temperatura ambiente. Luego de dos horas el producto precipitado se filtró en un embudo de vidrio y se lavó con varias porciones de etanol congelado. La sal de potasio del ácido isocianoacético

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obtenida de este modo se secó al vacío hasta obtener un sólido marrón dorado (99,92 g, 91,8%).

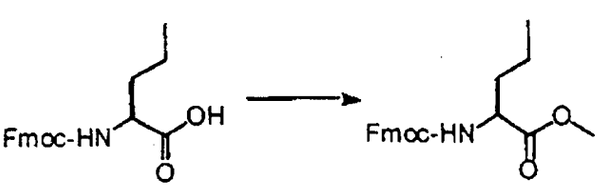
b) Síntesis de isocianoacetato de alilo:



Al el 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 de color 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 capa orgánica se secó, filtró y concentró para obtener un jarabe marrón oscuro. El producto bruto se purificó por destilación al vacío a 7 mm Hg (98 C) hasta obtener un aceite claro (78,92 g, 78%). NMR δ ppm (CDCl3): 5,9 (m, 1H), 5,3 (m, 2H), 4,7 (d, 2H), 4,25 (s, 2H).

<u>B) Síntesis de 9-fluorenilmetoxicarbonil-norvalinal (pasos a-c a continuación):</u>

a) Síntesis de éster metílico de 9-fluorenilmetoxicarbonil-L-norvalina (Fmoc-nVal-OMe):

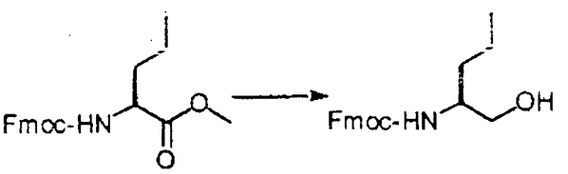


A una solución congelada de la Fmoc-norvalina disponible en el mercado (25 g, 73,75 mmol) en metanol anhidro (469 ml) se agregó cloruro de tionilo (53,76 ml, 737,5 mmol) durante una hora. El TLC en acetato de etilo tomado una hora después confirmó la finalización de la reacción (Rf = 0,85). La mezcla de reacción se concentró y el residuo restante se disolvió en acetato de etilo. La capa orgánica se lavó con varias porciones de 200 ml de bicarbonato de sodio saturado seguido de salmuera. La capa orgánica se secó, filtró y concentró para

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obtener FmocnorVal-OMe) como un sólido blanco (26,03 g) en rendimiento cuantitativo. NMR δ ppm (CD3Od): 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).

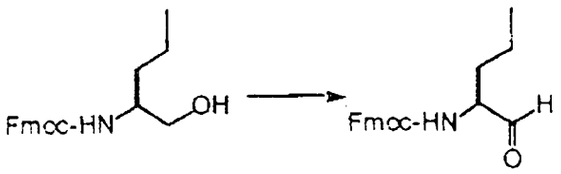
b) Síntesis de 9-fluorenilmetoxicarbonil-norvalinol (Fmoc-nValinol):



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 bajo agitación a temperatura ambiente durante 90 minutos. El TLC en 2:3 acetato de etilo: hexanos confirmó la finalización de la reacción (Rf = 0,25). La reacción se inactivó con la incorporación lenta de agua (100 ml) a 0°C., El metanol se removió con presión reducida y la fase acuosa restante se diluyó con acetato de etilo. La capa orgánica se lavó con agua (3 x 500 ml), bicarbonato de sodio saturado (3 x 500 ml) y salmuera (500 ml). La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró hasta obtener un sólido blanco (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) Síntesis de 9-fluorenilmetoxicarbonil-norvalinal (Fmoc-nVal-CHO):

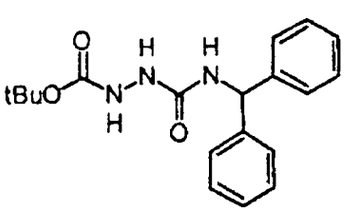
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A una solución de Fmoc-norValinol (21,70 g, 66,77 mmol) en diclorometano (668 ml) se agregó trietilamina (37,23 mi, 267 mmol) y la solución se enfrió hasta 0°C. Una suspensión de complejo de sulfuro de piridina trióxido (42,51 g, 267 mmol) en dimetilsulfóxido (96 ml) se agregó a la solución congelada. Luego de una hora, el TLC en 2:3 acetato de etilo: hexanos confirmó la finalización de la reacción. El diclorometano se removió con 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 capa orgánica se concentró para producir un sólido blanco. Se asumió el rendimiento teórico (21,57 g) y la reacción se llevó al paso siguiente sin purificación adicional.

c) Síntesis de sal de trifluoroacetato de difenilmetil semicarbazida (dpsc) (pasos a-b a continuación):

a) Síntesis de Boc-semicarbazid-4-il difenilmetano

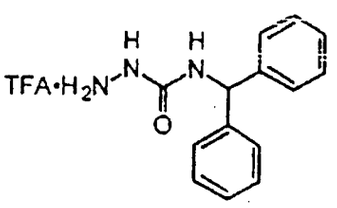


A una solución de carbonildiimidazol (16,2 g, 0,10 mole) en dimetilformamida (225 ml) se agregó una solución de carbazato de t-butilo (13,2 g, 0,100 mol) en dimetilformamida (225 ml) por goteo durante 30 minutos. Luego se agregó difenilmetilamina (18,3 g, 0,10 mol) durante 30 minutos. La reacción se

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dejó agitar a temperatura ambiente durante una hora. Se agregó agua (10 mL) y la mezcla se concentró hasta aproximadamente 150 mL con 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 de bicarbonato de sodio saturado 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 podría purificarse mediante recristalización de acetato de etilo/hexano, pero fue lo suficientemente puro como para usarlo en el paso siguiente: p.f. 142-143°C. ^{1}H NMR (CDCI3) δ 1,45 (s, 9H), 6,10 (cid, 2H), 6,42 (s, 1H), 6,67 (bs, 1H), 7,21-7,31 (m, 10H). Cálculo analítico 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.

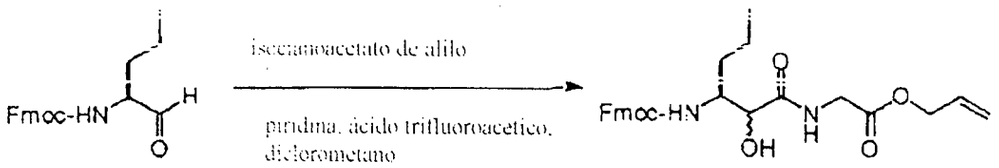
b) Síntesis de sal de trifluoroacetato de difenilmetil semicarbazida (dpsc)



Una solución de Boc-semicarbazid-4-il 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 por goteo a 75 mL de éter y el sólido resultante (2,7 g, 80%) se recolectó por filtración. p.f. 182-184°C. ^{1}H NMR (CD_3OD) δ 6,05 (s, 1H), 7,21-7,35 (m, 10H), ^{13}C NMR (CD_3OD) δ 57,6, 118,3 (q, CF3), 126,7, 127,9, 141,6, 156,9, 160,9 (q, $CF_3\underline{C}O_2H$).

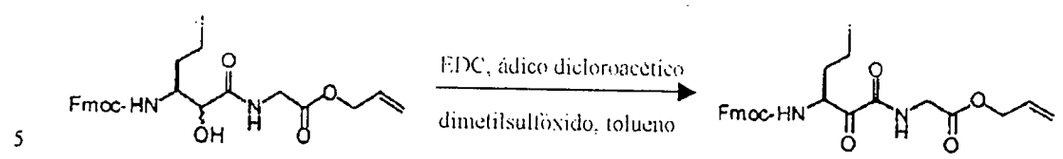
D) Síntesis de Fmoc-nVal-(CHOH)-Gli-Oalil:

000525



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 mrnol) 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) por goteo. La reacción se agitó a 0°C durante 1 hr, y luego a temperatura ambiente durante 48 horas. El TLC absorbido en acetato de etilo confirmó la finalización de la reacción. La mezcla de reacción se concentró y se sometió a cromatografía flash con el uso de 20% a 70% de acetato de etilo en hexanos. Las fracciones que contenían el producto deseado se reunieron y concentraron hasta obtener una espuma blanca (6,88 g, 87,3%). El TLC en 50:50 de acetato de etilo muestra una mancha (Rf = 0,37). NMR δ ppm (CD3OD): 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) Síntesis de Fmoc-nVal-(CO)-Gli-Oalilo:

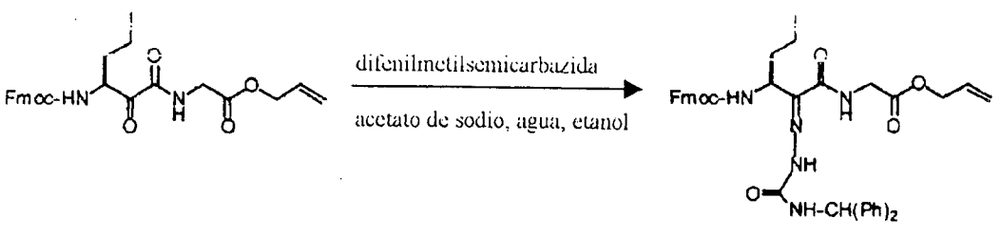


A una solución de Fmoc-nVal-(CHOH)-Gli-Oalil (Paso D) (5,01 g, 10,77 mmol) en dimetilsulfóxido (100 ml) y tolueno (100 ml) se agregó EDC (20,6 g, 107,7 mmol). La mezcla de reacción se enfrió hasta 0 °C y se agregó ácido dicloroacético (4,44 ml, 53,83 mmol) por goteo. La reacción se agitó durante 15

080526

minutos a 0°C y 1 hr a temperatura ambiente. Luego de enfriar nuevamente hasta 0°C , se agregó agua (70 ml) y el tolueno se removió con presión reducida. El residuo restante se diluyó con acetato de etilo y se lavó varias veces con una solución de bicarbonato de sodio saturado seguido de bisulfato de sodio 1N y salmuera. La capa orgánica se secó sobre sulfato de sodio, se filtró y se concentró. Se asumió el rendimiento teórico de 4,99 g y la reacción se llevó al paso siguiente sin purificación adicional. El TLC en 50:50 de acetato de etilo muestra una mancha (Rf = 0,73).

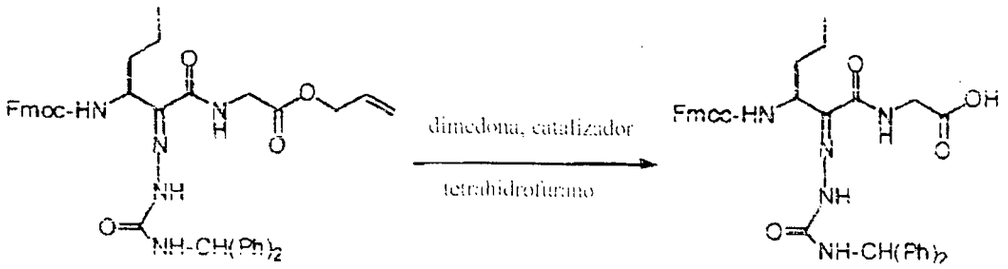
F) Síntesis de Fmoc-nVal-(dpsc)-Gli-Oalilo:



A una solución de Fmoc-nVal-(CO)-Gli-Oalil (Paso E) (4,99 g, 10,75 mmol) en etanol (130 ml) y agua (42 ml) se agregó sal de trifluoroacetato de difenilmetil semicarbazida (dpsc) (Paso IC) (7,6 g, 21,5 mmol) y acetato de sodio .$3H_2O$ (1,76 g, 12,9 mmol), en forma sucesiva. La mezcla de reacción se calentó a reflujo durante 90 minutos. La finalización de la reacción se confirmó por TLC tomado en 1:1 de acetato de etilo: hexano. El etanol se removió con 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 capa orgánica se secó, filtró y concentró. El residuo resultante se purificó por cromatografía flash en acetato de etilo al 20% a 50% en hexanos para dar un sólido blanco (5,76 g, 78%). El TLC en 50:50 de acetato de etilo: hexanos mostró dos manchas (cis y trans isómeros) con Rf = 0,42 y 0,5.

000527

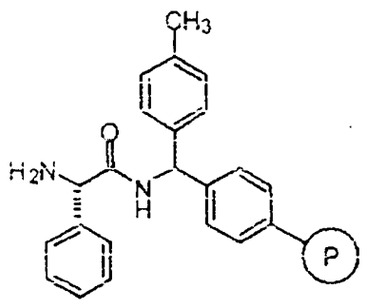
G) Síntesis de Fmoc-nVal-(dpsc)-Gli-OH:



A una solución de Fmoc-nVal-(dpsc)-Gli-Oalil (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 por medio de TLC luego de 90 minutos con el uso de 9:1 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 0,1M. La capa orgánica se trató luego con 50 ml de bisulfito de sodio y el sistema de dos fases se agitó durante 15 minutos. Se separaron las fases y el procedimiento se repitió dos veces más. La capa orgánica se secó y se concentró y se sometió a cromatografía cromatografía flash con acetato de etilo al 20% a 100% en hexanos. A esto le siguió solución al 9:1 de diclorometano: metanol. Las fracciones correspondientes al producto bruto se reunieron y concentraron para obtener un sólido blanco (3,99 g, 94%). El TLC en 9:1 diclorometano: metanol mostró dos manchas (cis y trans isómeros). NMR δ ppm (CD3OD): 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).

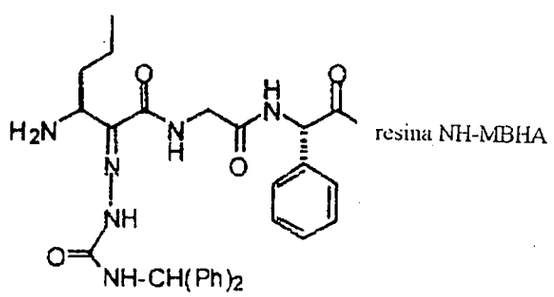
Paso 2. Síntesis de resina H-Phg-MBHA:

000528



La resina MBHA disponible en el mercado (2,6 g, 1,12 mmol/g, 2,91 mmol) se transfirió a un recipiente fritado de reacción de fase sólida de 250 mL equipado con una entrada de nitrógeno. Luego se lavó totalmente con porciones de 30 ml diclorometano, metanol, dimetilformamida y diclorometano y se acopló durante 18 horas al Fmoc-Phg-OH disponible en el mercado (2,17 g, 5,82 mmol) de acuerdo con el Procedimiento A con 99,82% de eficiencia. La resina se sometió luego a desprotección de Fmoc de acuerdo con procedimiento B. Un ensayo cuantitativo de ninhidreno en una pequeña alícuota dio una resina y una solución azul oscura, lo que indica el éxito de la reacción.

Paso 3 Síntesis de resina H-nVal(dpsc)-Gli-Ph4-MBHA:

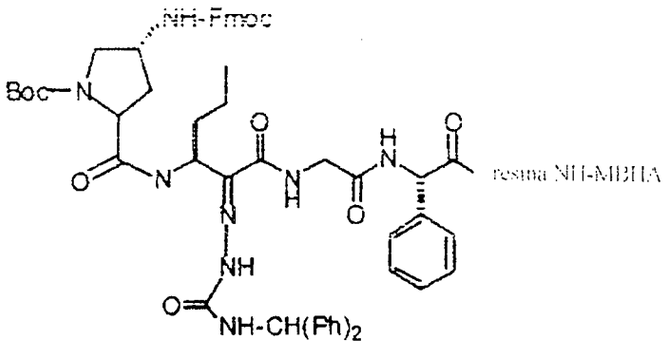


La resina obtenida en el paso II (2,6 g, 0,8 mmol/g, 2,91 mmol) se sometió a reacción con Fmoc-nVal-(dpsc)-Gli-Oalil (Paso IG) (5,82 mrnol, 3,77 g) de acuerdo con Procedimiento A. Luego de 18 horas, el análisis cuantitativo de ninhidreno indicó 99,91 de eficiencia de acoplamiento. La resina se sometió a Desprotección de Fmoc de acuerdo con procedimiento B. Un ensayo cualitativo

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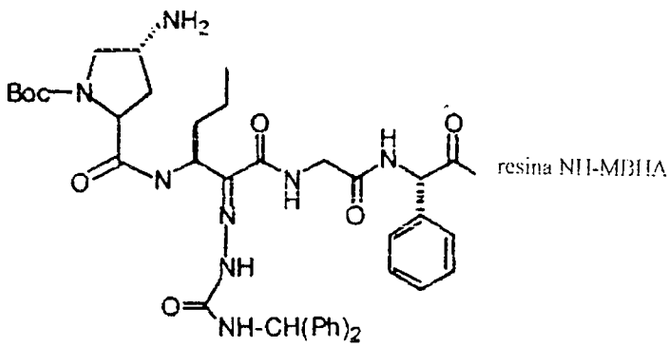
de ninhidreno en una pequeña alícuota dio resina y solución azul oscuro, lo que indicó el éxito de la reacción.

Paso 4 Síntesis de Resina Boc-Pro(4t-NHFmoc)-nVal(dpsc)-Gli-Phg-MBHA:



El compuesto resina H-nVal(dpsc)-Gli-Phg-MBHA (Paso 3 anterior) (600 mg, 0,8 mmol/g, 0,67 mmol) se transfirió a un tubo fritado de polipropileno y se acopló a Boc-Pro(4t-NHFmoc)-OH (Ejemplo VI, Paso 3) (610 mg, 1,34 mmol) de acuerdo con procedimiento A. Luego de 18 horas, el análisis cuantitativo de ninhidreno indicó 99,96% de eficiencia de acoplamiento.

Paso 5. Síntesis de resina Boc-Pro(4 t-NHP)-nVal(dpsc)-Gli-Phg-MBHA:

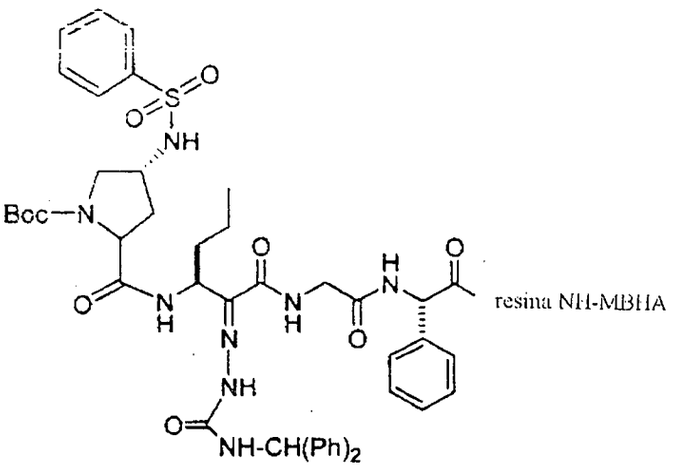


La resina del paso anterior (resina Boc-Pro(4t-NHFmoc)-nVal(dpsc)-Gli-PhgMBHA) se sometió a desprotección de Fmoc de acuerdo con procedimiento B. Un ensayo cualitativo de ninhidreno en

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una pequeña alícuota dio resina y solución azul oscuro, lo que indicó el éxito de la reacción.

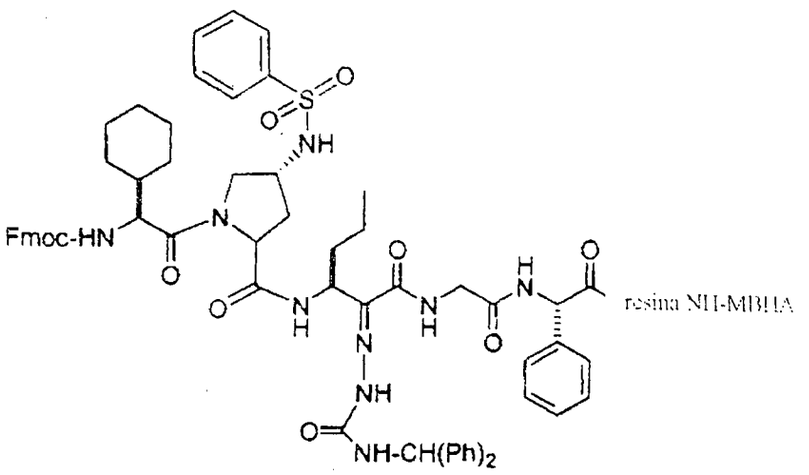
Paso 6. Síntesis de resina Boc-Pro(4t-$NHSO_2$.Bn)-nVal dpsc)-Gli-Phg-MBHA:



A la resina obtenida del paso anterior (resina Boc-Pro(4t-NH2)-nVal(dpsc)-Gli-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 ninhidreno mostró perlas sin color y solución lo que indicó el éxito de la reacción.

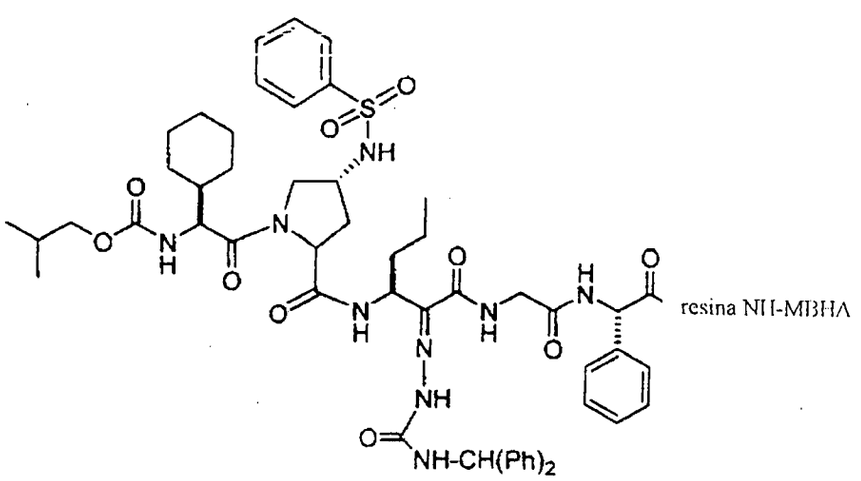
Paso 7 Síntesis de resina Fmoc-G(Chx)-Pro(4t-$NHSO_2$Bn)-nVal-(dasc)-Gli-Pha-MBHA:

000531



La resina obtenida en el paso anterior, (resina Boc-Pro(4t-$NHSO_2Bn$)-nVal(dpsc)Gli-Phg-MBHA) se sometió al procedimiento de desprotección Boc de acuerdo con Procedimiento C. Luego se acopló Fmoc-G(Chx) (0,17 g, 0,45 mmol) de acuerdo con procedimiento A. Luego de 18 horas el análisis cualitativo de ninhidreno mostró perlas sin color y el análisis cuantitativo de ninhidreno indicó 99,79% de eficiencia de acoplamiento.

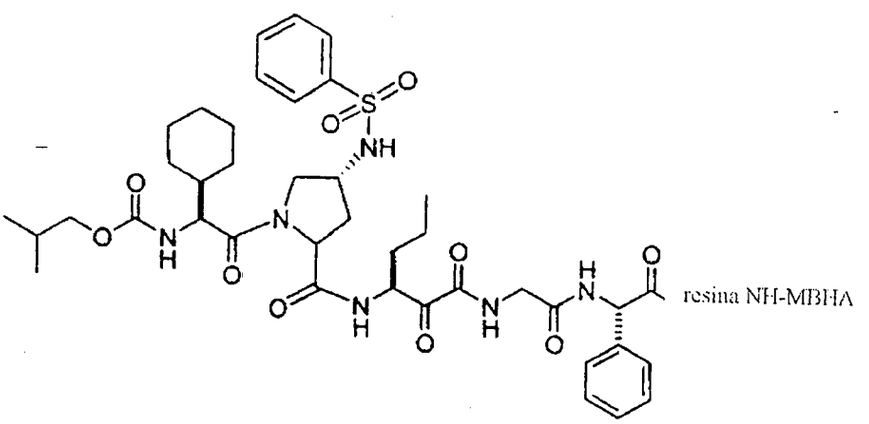
Paso 8. Síntesis de resina iBoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal dpsc)-Gli-Phg MBHA:



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La resina obtenida en el paso anterior (resina Fmoc-G(Chx)-Pro(4t-$NHSO_2Bn$)nVal(dpsc)-Gli-Phg-MBHA) se sometió a Desprotección de Fmoc de acuerdo con procedimiento B. Un ensayo de ninhidreno en una pequeña alícuota dio resina y solución azul oscuro, lo que indicó el éxito de la reacción. A la resina (0,2 g, 0,22 mmol) suspendida en 2 ml de 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 ninhidreno mostró perlas sin color y solución lo que indicó el éxito de la reacción.

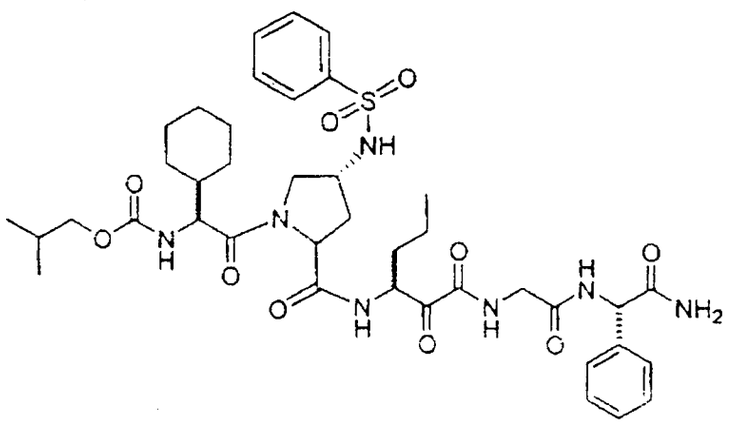
Paso 9. Síntesis de resina iBoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal CO)-Gli-Phg-MBHA:



El compuesto del paso anterior (resina iBoc-G(Chx)-Pro(4t-$NHSO_2Bn$)-nVal(dpsc)-Gli-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)-GliPhg-NH_2:

000533



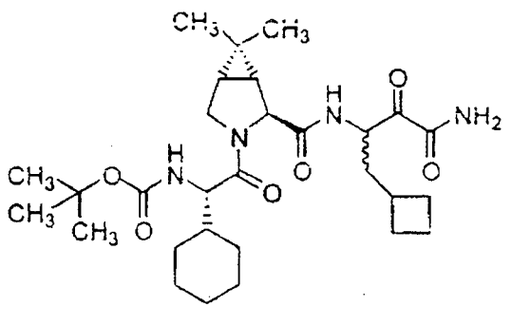
La resina del paso anterior (resina iBoc-G(Chx)-Pro(4t-NHSO$_2$Bn)-nVal(CO)Gli-Phg-MBHA) (100 mg) se sometió a condición de disociación de HF (Procedimiento E) para producir el producto bruto deseado. El material se purificó por HPLC con el uso de una columna de fase inversa de 2,2 x 25 cm, que contenía una resina C-18 formada por partículas de gel de un tamaño de 10 micrones con un tamaño de poros de 300 angstrom, eluyendo con un gradiente mediante el uso de acetonitrilo al 20-50% en agua. La HPLC analítica con el uso de una columna de fase inversa de 4,6 x 250 mm, que contenía una resina C-18 resina formada por partículas de gel de un tamaño de 5 micrones con un tamaño de poros de 300 angstrom, eluyendo con acetonitrilo al 25-75% (que contenía ácido trifluoroacético al 0.1 %) 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 Síntesis de la Fase de Solución:

A continuación se muestran los compuestos representativos para preparar compuestos adicionales de la invención, y los compuestos preparados mediante dichos procedimientos aparecen enumerados en la Tabla 5.

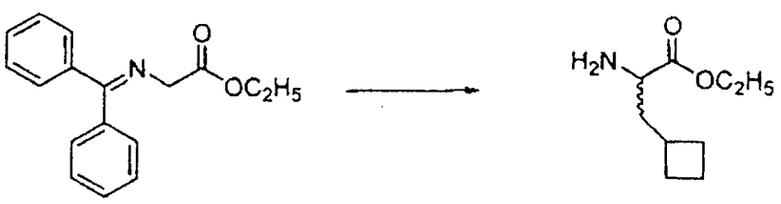
Ejemplo XXIII : Preparación de un compuesto de la fórmula XXIII:

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XXIII

Paso 1.

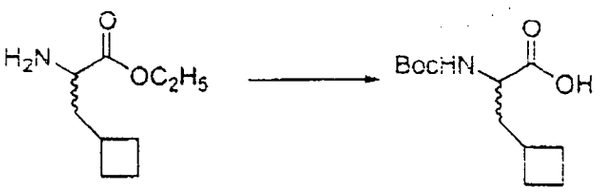


XXIIIa **XXXIIIb**

Una solución agitada de la cetimina **XXIIIa** (50 g, 187,1 mmol) en N_2 en THF anhidro (400 mL) se enfrió hasta -78 °C y se trató con una solución 1M de K-^{t}BuO (220 mL, 1,15 equiv.) en THF. La mezcla de reacción se entibió hasta 0 °C y se agitó durante 1 hr y se trató con ciclobutano de bromoetilo (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 capa acuosa se hizo básica hasta un pH -12-14 con NaOH (50 acuoso) y se extrajo con CH_2Cl_2 (3 x 300 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron para dar amina pura **(XXIIIb,** 18 g) como un aceite sin color.

Paso 2.

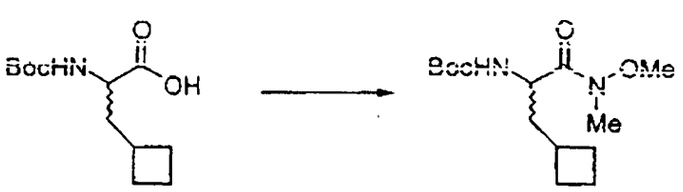
000535



XXIIIb XXIIIc

Una solución de 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 hr. 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 $LiOH \cdot H_2O$ (6,5 g, 158,5 mmol) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se concentró y la capa acuosa básica se extrajo con Et_2O. La capa acuosa se ácidoificó con HCl concentrado hasta un pH ~1-2 y se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron al vacío para producir **XXIIIc** como un aceite viscoso sin color que se usó durante el paso siguiente sin purificación adicional.

Paso 3.



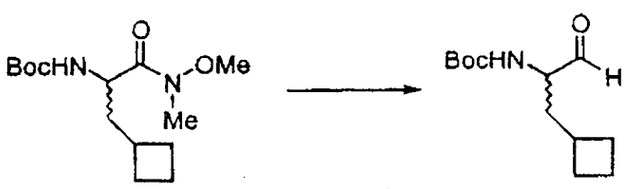
XXIIIc **XXIIId**

Una solución del ácido **XXIIIc** (15,0 g, 62 mmol) en CH_2Cl_2 (250 mL) se trató con reactivo BOP (41,1 g, 93 mmol), N-metil morfolina (27 mL), clorhidrato

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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 capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (3x300 ml). Las capas orgánicas combinadas se secaron ($MgSO_4$), se filtraron y se concentraron al vacío y se purificaron por cromatografía (SiO_2, EtOAc/Hex 2:3) para producir la amida **XXIIId** (15,0 g) como un sólido sin color.

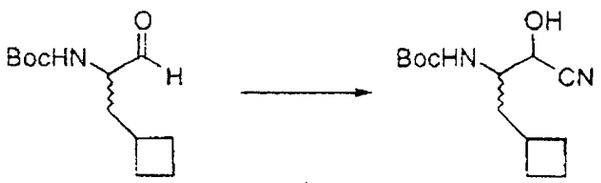
Paso 4.



XXIIId **XXIIIe**

Una solución de la amida **XXIIId** (15 g, 52,1 mmol) en THF anhidro (200 mL) se trató por goteo con una solución de $LiAlH_4$ (1M, 93 mL, 93 mmol) a 0°C. La mezcla de reacción se agitó a temperatura ambiente durante 1 hr y se inactivó cuidadosamente a 0°C con una solución de $KHSO_4$ (10% acuosa) y se agitó durante 0,5 h. La mezcla de reacción se diluyó con HCl acuoso (1M, 150 mL) y se extrajo con CH_2Cl_2 (3x200 mL), las capas orgánicas combinadas se lavaron con HCl acuoso (1M), $NaHCO_3$ saturado, salmuera, y se secaron ($MgSO_4$). La mezcla se filtró y se concentró al vacío para producir **XXIIIe** como un aceite viscoso sin color (14 g).

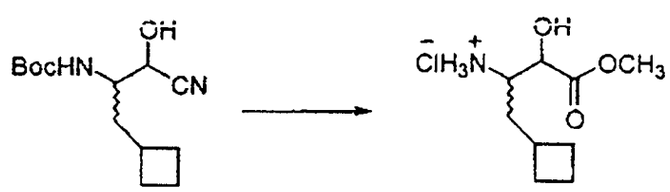
Paso 5.



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 (3x200 mL). Las capas orgánicas combinadas se lavaron con H_2O, salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron al vacío y se purificaron por medio de cromatografía (SiO_2, EtOAc/Hex 1:4) para producir **XXIIIf** (10,3 g) como un líquido sin color.

Paso 6.



XXIIIf **XXIIIg**

Se trató metanol saturado con HCl*, preparado mediante la formación de burbujas de gas de HCl a CH_3OH (700 ml) a 0°C, se trató con cianohidrina **XXIIIf** y se calentó a reflujo durante 24 h. La reacción se concentró al vacío para producir **XXIIIg,** que se usó en el paso siguiente sin purificación. * En forma

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alternativa también se puede usar HCl 6M preparado mediante el agregado de AcCl a metanol seco.

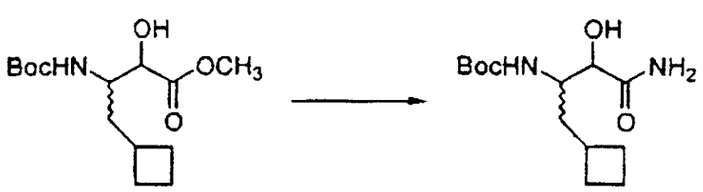
Paso 7.



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 (45,7g, 209 mmol) a -78 °C. La mezcla de reacción se agito, luego, a temperatura ambiente durante la noche y se diluyó con HCl (2 M, 200 mL) y se extrajo en CH_2Cl_2. Las capas orgánicas combinadas se secaron ($MgSO_4$) se filtraron y se concentraron al vacío y se purificaron por cromatografía (EtOAc/Hex 1:4) para producir éster de hidroxi **XXIIIh.**

Paso 8.



XXIIIh **XXIIII**

Una solución de éster metílico **XXIIIh** (3 g, 10,5 mmol) en THF/H_2O (1:1) se trató con LiOH•H2O (645 mg, 15,75 mmol) y se agitó a temperatura ambiente.

030539

durante 2 hr. La mezcla de reacción se ácidoificó 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 removieron con vacío y el residuo se diluyó con HCl acuoso (250 mL) y se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con $NaHCO_3$ acuoso saturado, se secaron ($MgSO_4$) se filtraron y concentraron al vacío para obtener **XXIIIi**, que se usó como estaba en los pasos siguientes. (En forma alternativa, también puede obtenerse **XXIIIi** directamente mediante 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.)

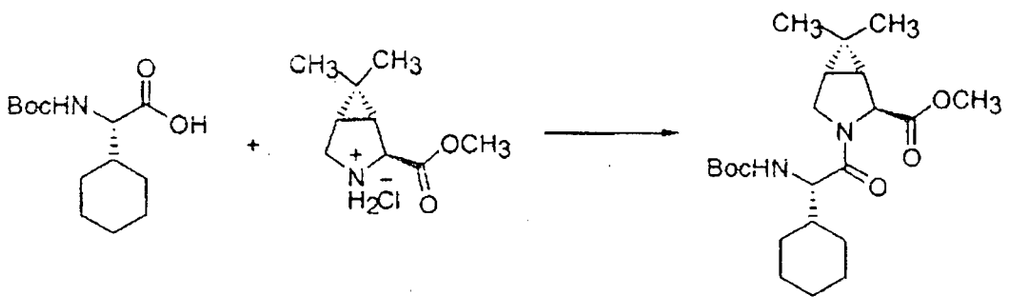
Paso 9.



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.

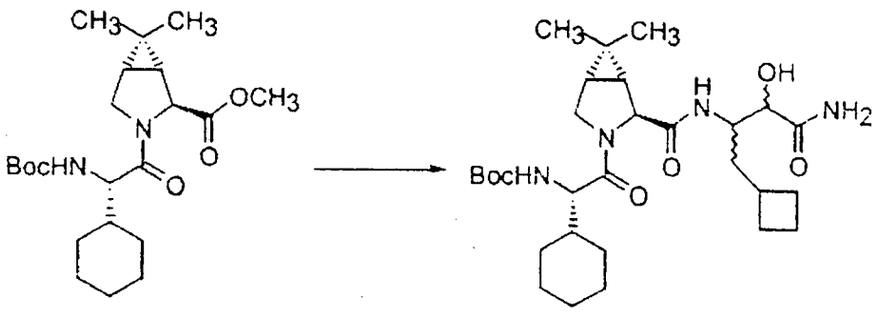


XXIIIk **XXIIII** **XXIIIm**

El amino éster **XXIIII** 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 por medio de la reacción del amino ácido con protección Boc con HCl metanólico.

Una solución del amino ácido comercial Boc-Chg-OH, **XXIIIk** (Senn chemicals, 6,64 g, 24,1 mmol) y clorhidrato de amina **XXIIII** (4,5 g, 22 mmol) en CH_2Cl_2 (100 mL) a 0°C se trató con Reactivo 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 (3x200 mL). Las capas orgánicas combinadas se lavaron con $NaHCO_3$ saturado (200 mL), se secaron ($MgSO_4$), se filtraron y se concentraron *al vacío,* y se sometieron a cromatografía (SiO_2, EtOAc/Hex 3:7) para obtener **XXIIIm** (6.0 g) como un sólido sin color.

Paso 11.



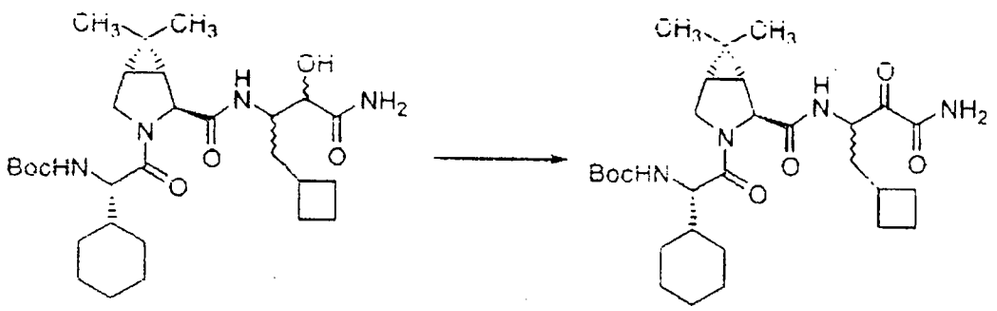
XXIIIm XXIIIn

Una solución de éster metílico **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 de ácido (1,5 g, 3,74 mmol) en DMF/CH_2Cl_2 (1:1 50 mL) se trató con 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 $NaHCO_3$ acuoso, HCl acuoso, salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron al vacío para obtener **XXIIIn** (2,08 g) como un sólido de color tostado.

Paso 12.

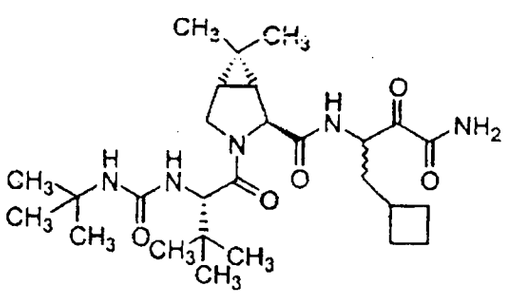
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XXIIIn **XXIII**

Una solución de 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 $NaHCO_3$ saturado, y salmuera. Las capas orgánica se secaron ($MgSO_4$), se filtraron y se concentraron al vacío y se purificaron por cromatografía (SiO_2, Acetona/Hexanos 3:7) para producir **XXIII** como un sólido sin color.

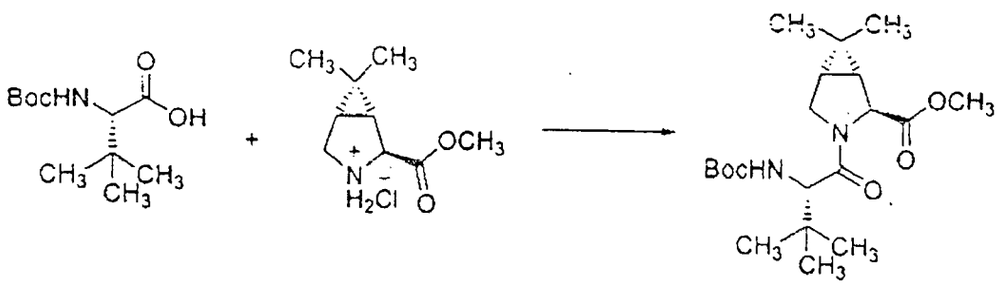
Ejemplo XXIV Preparación de un compuesto de la fórmula XXIV:



XXIV

Paso 1.

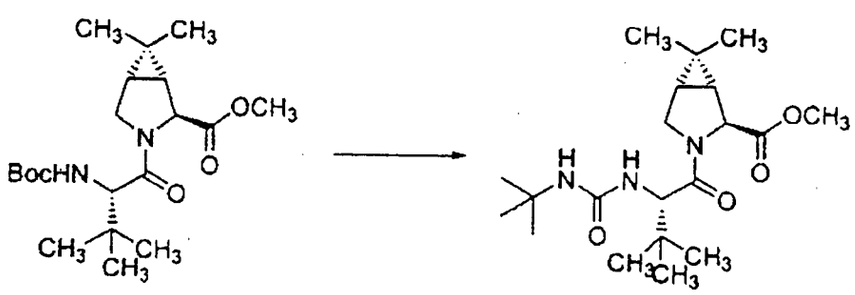
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XXIVa XXIIII XXIVb

Una solución de Boc-ter-Lue **XXIVa** (Fluka, 5,0 g 21,6 mmol) en CH_2Cl_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 BOP (11,6 g, 25,7 mrnol). La reacción se agitó a temperatura ambiente durante 24 h, se diluyó con HCl acuoso (1 M) y se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con HCl (acuoso, 1 M), $NaHCO_3$ saturado, salmuera, se secaron ($MgSO_4$), se filtraron y se concentraron al vacío y se purificaron por cromatografía (SiO_2, Acetona/Hexano 1:5) para producir **XXIVb** como un sólido sin color.

Paso 2.



XXIVb **XXIVc**

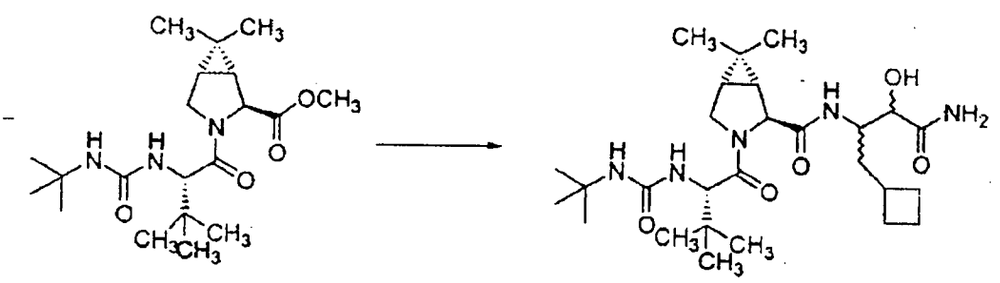
Una solución de éster metílico **XXIVb** (4,0 g, 10,46 mmol) se disolvió en HCl (solución 4M, dioxano) y se agitó a temperatura ambiente durante 3 h. La

030544

mezcla de reacción se concentró al vacío para obtener la sal de clorhidrato de amina usada en el paso siguiente.

Una solución de la sal de clorhidrato de amina (397 mg, 1,24 mmol) en CH_2Cl_2 (10 mL) se enfrió hasta -78°C y se trató con ter-butil isocianato (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 (1M) y se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con HCl acuoso (1M), $NaHCO_3$ saturado y salmuera. La capa orgánicas se secaron, se filtraron y se concentraron al vacío y el residuo se purificó por cromatografía (SiO_2, acetona/Hex 1:4) para producir **XXIVc** como un sólido sin color.

Paso 3.



XXIVc **XXIVd**

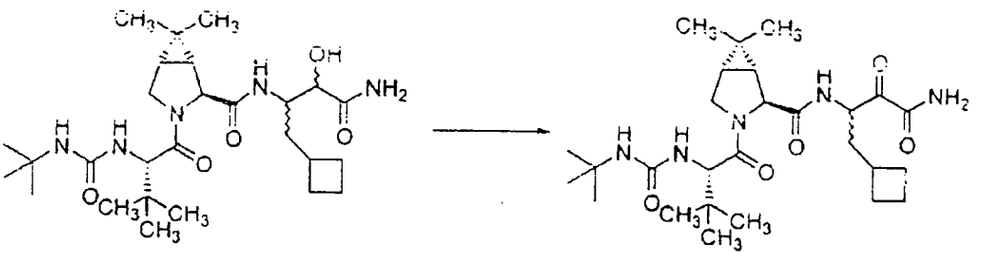
Una solución de éster metílico **XXIVc** (381 mg, 1,0 mmol) en THF/H_2O (1:1, 5 mL) se trató con $LiOH \cdot H_2O$ (62 mg, 1,5 mmol) y se agitó a temperatura ambiente durante 3 h. La mezcla de reacción se acidificó con HCl acuoso y se concentró al vacío para obtener el ácido libre.

Una solución de ácido (254,9 mg, 0,69 mmol) en DMF/CH_2Cl_2 (1:1, 5,0 mL) se trató con 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 capas orgánicas

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combinadas se extrajeron con $NaHCO_3$ acuoso, HCl acuoso, salmuera, se secaron ($MgSO_4$) se filtraron y se concentraron al vacío para obtener **XXIVd (470** mg) como un sólido de color tostado.

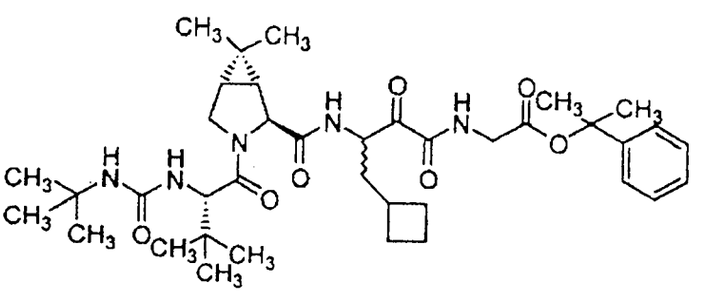
Paso 4.



XXIVd **XXIV**

Una solución de 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 $NaHCO_3$ saturado, y salmuera. La capa orgánica se secó ($MgSO_4$), se filtró, se concentró al vacío y se purificó por cromatografía (SiO_2, Acetona/Hexanos 3:7) para producir XXIV como un sólido sin color.

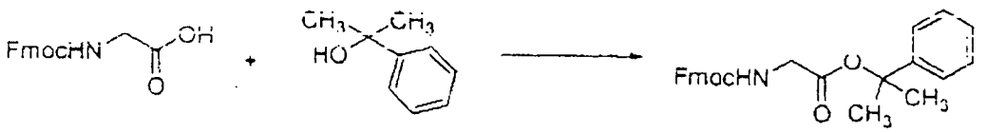
Ejemplo XXV Preparación de un compuesto de la fórmula XXV:



XXV

Paso 1.

030546



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 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 $NaHCO_3$ saturado. La capa orgánica se secó ($MgSO_4$), se filtró, se concentró al vacío, y se purificó por cromatografía (SiO_2, EtOAc/Hex 1:5) para producir éster **XXVI** (1,1 g) como un líquido viscoso sin color.

Paso 2.

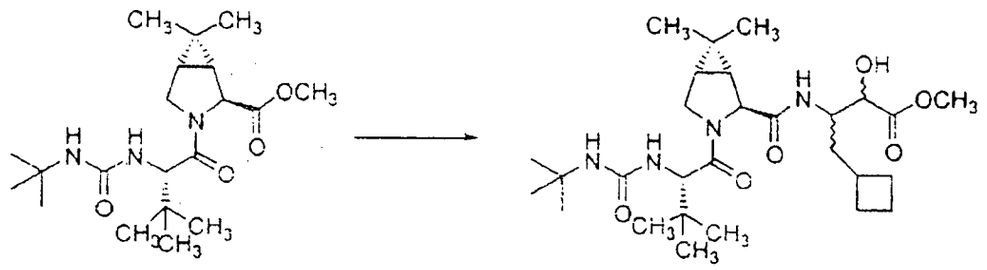


XXVc XXVd

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 por cromatografía (SiO_2, Acetona/Hexanos 1:10 a 1:1) para producir la amina **XXVd** (420 mg) como un líquido sin color.

Paso 3.

000547

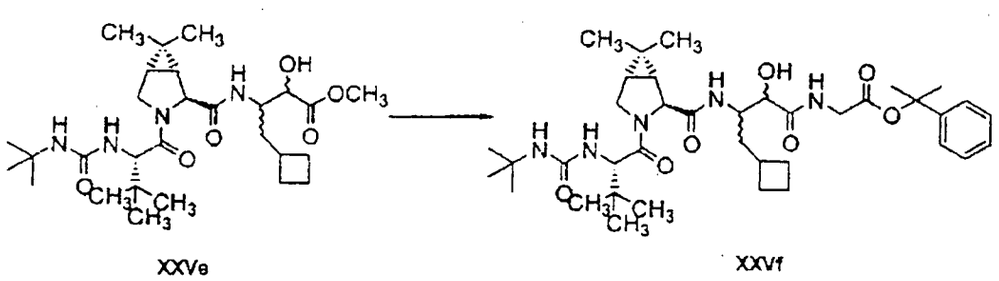


XXIVc XXVe

Una solución de éster metílico **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 de ácido (2,0 g, 5,5 mmol) en DMF/CH_2Cl_2 (1:1, 40,0 mL) a -10°C se trató con 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 (3x100 mL). Las capas orgánicas combinadas se extrajeron con $NaHCO_3$ acuoso, HCl acuoso, salmuera, se secaron ($MgSO_4$) se filtraron, se concentraron al vacío para obtener **XXVe** (3,17 g) como un sólido de color tostado que se utilizó sin ninguna purificación.

Paso 4.



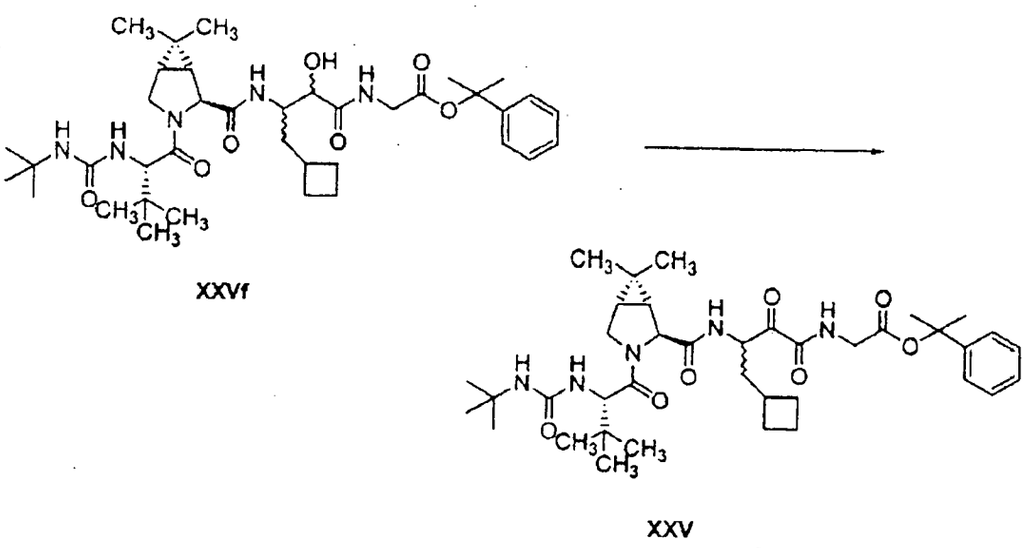
XXVe XXVf

000548

Una solución de éster metílico **XXVe** (2,5 g, 4,66 mmol) en $THF/H_2O/CH_3OH$ (1:1:1, 60 mL) se trató con $LiOH \cdot H_2O$ (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 de ácido (200,0 mg, 0,38 mmol) en DMF/CH_2Cl_2 (1:1, 6,0 mL) a -10°C se trató con 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 (3x30 mL). Las capas orgánicas combinadas se extrajeron con $NaHCO_3$ acuoso (2x30 mL), HCl acuoso, salmuera (30 mL), se secaron ($MgSO_4$) se filtraron, se concentraron al vacío para obtener **XXVf** (240 mg) como un sólido de color tostado.

Paso 5.



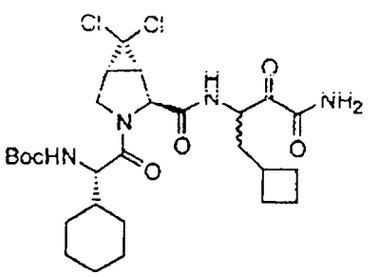
XXVf **XXV**

Una solución de **XXVf** (240 mg, 0,28 mrnol) 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 1:4) la

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mezcla de reacción se diluyó con $NaHCO_3$ saturado (20 mL) y $Na_2S_2O_3$ (solución al 10% acuosa, 20 mL). La mezcla de reacción se agitó durante 30 min. y se extrajo con CH_2Cl_2 (3x30 mL). Las capas orgánicas combinadas se extrajeron con $NaHCO_3$ saturado, salmuera, se secaron ($MgSO_4$) se filtraron, se concentraron al vacío y se purificaron por cromatografía (SiO_2, acetona/Hexanos 1:5) para producir **XXV** (122 mg) como un sólido sin color.

Ejemplo XXVI Preparación de un compuesto de la fórmula XXVI:



XXVI

Paso 1:



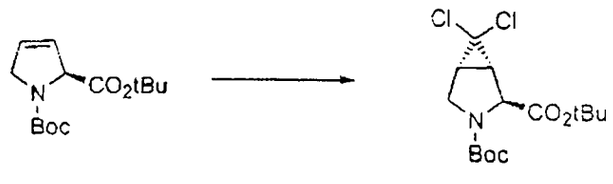
XXVIa **XXVIb**

A una solución agitada de N-Boc-3,4-dehidroprolina **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 mrnol) 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 concentrar al vacío. El residuo, de color marrón oscuro, se purificó por cromatografía flash en

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columna eluyendo con EtOAc/hexano al 10-25% para dar el producto **XXVIb** como un aceite amarillo pálido (5,29 g, 84%).

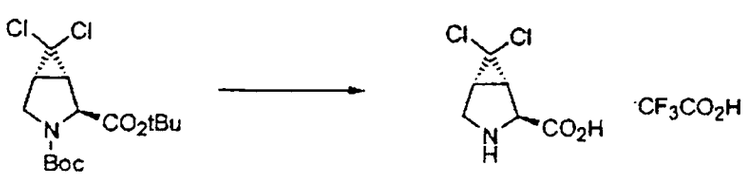
Paso 2:



XXVIb **XXVIc**

A una solución agitada de dehidroprolina **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 hidróxido de sodio acuoso al 50% (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 capas se separaron, la solución acuosa se extrajo con CH_2Cl_2/Et_2O (1:2, 3x600 mL). La solución orgánica se secó ($MgSO_4$) y se concentró. El residuo se purificó mediante cromatografía flash en columna mediante el uso de EtOAc/hexano al 5-20% para obtener 9,34 g (71 %) de **XXVII** como un sólido blanco grisáceo.

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 concentrar al vacío para dar un residuo marrón que se usó en el Paso 4 sin purificación adicional.

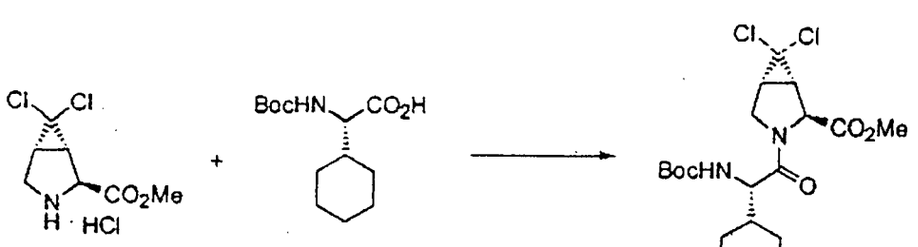
Paso 4



XXIIId **XXIIIe**

Se agregó ácido clorhídrico concentrado comercial (4.5 mL) 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:



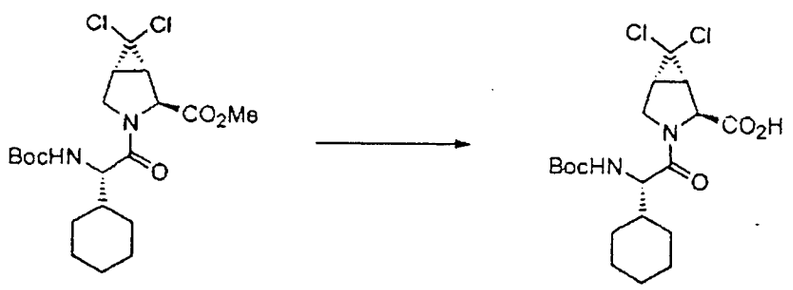
XXVIe **XXVIf** **XXVIg**

A una solución agitada de éster metílico de prolina **XXVIe** del Paso 4, N-Boc-ciclohexilglicina comercial **XXVIf** (10,2 g, 40,0 mmol) y [hexafluorofosfato de O-(7-azabenzotriazol-1il)-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).

000552

Luego de dejar entibiar hasta la temperatura ambiente junto con el baño de hielo durante la noche (18 h), la mezcla de reacción se diluyó con EtOAc (600 mL), H_3PO_4 al 5% (150 mL) y salmuera (150 mL). La solución orgánica se lavó con 5% H_3PO_4 (150 ML), $NaHCO_3$ saturado (2x200 mL) antes de que se seque ($MgSO_4$), se filtró y se concentró *al vacío*. El residuo se purificó mediante cromatografía flash en columna mediante el uso de EtOAc/hexano al 5-20% para obtener 3,84 g (32%, tres pasos) de **XXVIg** como un sólido blanco grisáceo.

Paso 6:

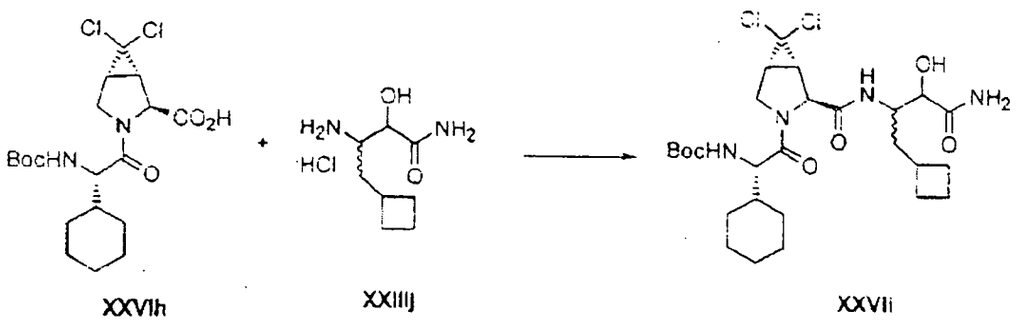


XXVIg **XXVIh**

La solución de éster metílico XXVIg (5,87g, 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 THF se removieron con presión reducida. La solución acuosa se acidificó hasta un pH ~2 con el uso de solución acuosa de HCl 1N (50 mL) y se saturó con sólido cloruro de sodio antes de extraer con EtOAc (3x150 mL). La solución orgánicas se combinaron, se secaron ($MgSO_4$), se filtró y se concentró al vacío para dar un sólido blanco XXVIh (5,8 g, cuantitativo).

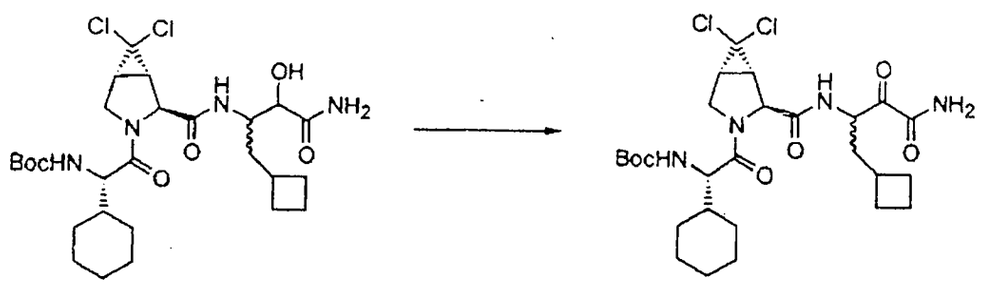
Paso 7:

000553



XXVIh XXIIIj XXVIi

El producto deseado XXIIIi se preparó de acuerdo con el procedimiento en el Ejemplo XXIII, Paso 11.

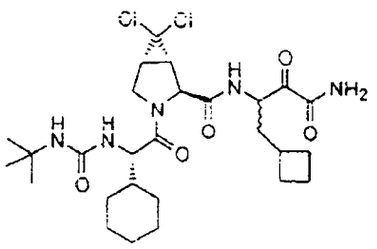


XXVII XXVI

Paso 8:

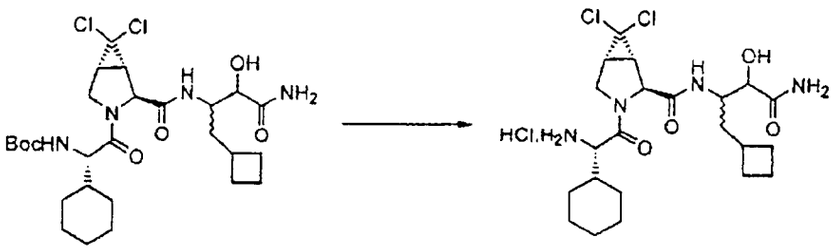
El producto deseado XXVI se preparó de acuerdo con el procedimiento en el Ejemplo XXIII, Paso 12.

Ejemplo XXVII: Preparación del compuesto de la fórmula XXVII:



XXVII

Paso 1

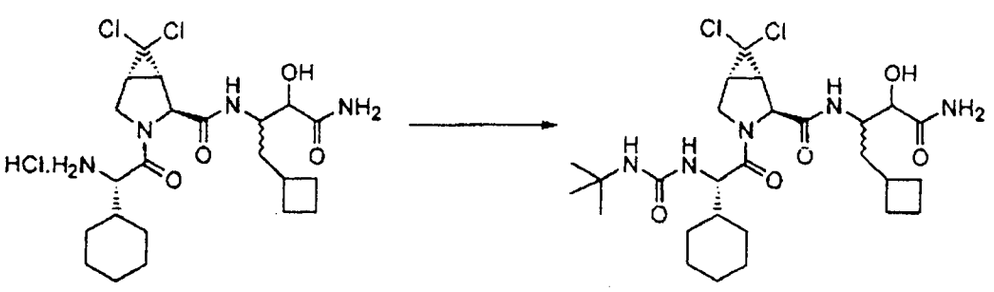


XXVIi

XXVIIa

El producto deseado XXVIIa se preparó de acuerdo con el procedimiento en el Ejemplo XXIII, Paso 9.

Paso 2



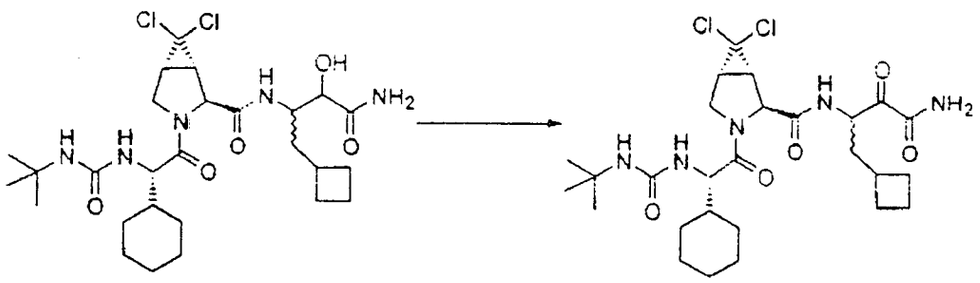
XXVIIa

XXVIIb

El producto deseado XXVIIb se preparó de acuerdo con el procedimiento en el Ejemplo XXIV, Paso 2.

000555

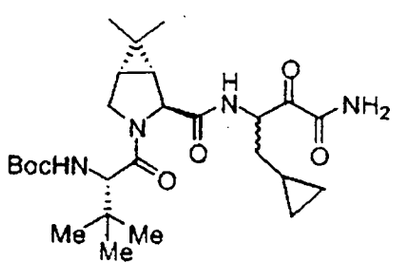
Paso 3



XXVIIb XXVII

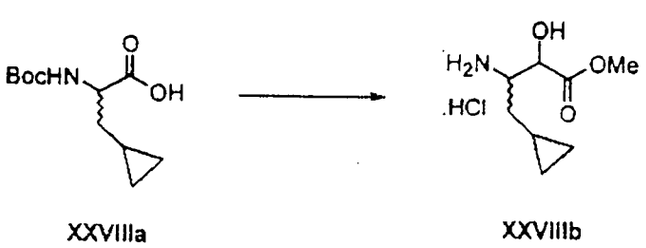
El producto deseado XXVII se preparó de acuerdo con el procedimiento en el Ejemplo XXIII, Paso 12.

Ejemplo XXVIII: Preparación de un compuesto de la fórmula XXVIII:



XXVIII

Paso 1:

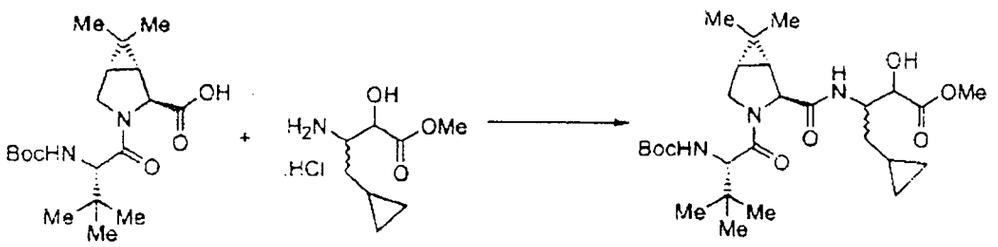


XXVIIIa XXVIIIb

008556

El intermediario XXVIIIb se preparó de acuerdo con el procedimiento en el Ejemplo XXIII, Pasos 3-6.

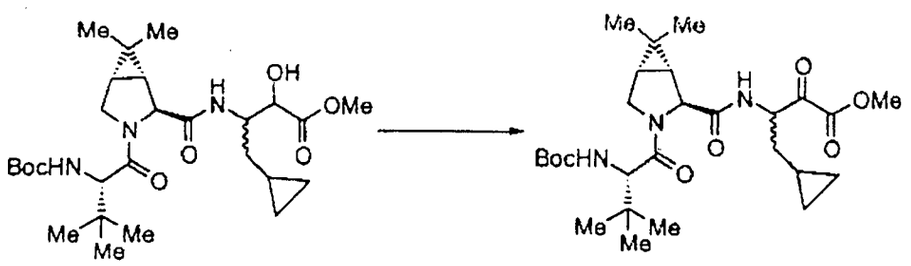
Paso 2:



XXVIIIc XXVIIIb XXVIIId

El ácido del Ejemplo XXIV, Paso 2 (**XXVIIIc**) (0,7 g) se sometió a reacción con el producto del Paso 1 anterior (0,436 g), HATU (0,934 g) y DIPEA (1,64 mL) en el modo que se describió anteriormente en el Ejemplo IX, Paso 2a para obtener 0,66 g del producto deseado **XXVIIId.**

Paso 3:

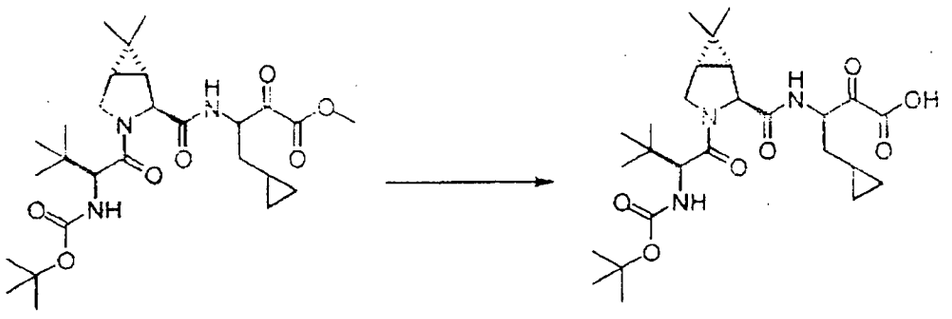


XXVIIId **XXVIIIe**

El producto del Paso 2 (0,5 g) se sometió a reacción con Reactivo de Dess-Martin (1 g) en el modo que se describió anteriormente en el Ejemplo XX, Paso 7. La Purificación mediante cromatografía flash en columna (EtOAc al 40%, Hexano, sílice) logró 0,35 g de producto **XXVIIIe.** Espectro de masa (LCMS) 522 (M+H+).

000557

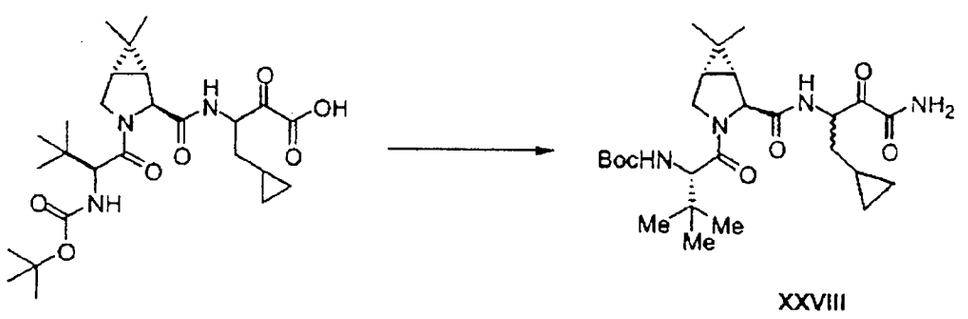
Paso 4:



XXVIIIe XXVIIIf

El producto del Paso 4 (0,3 g) se agregó una solución al 1/1 de H2O/MeOH (20 mL) y $NaHCO_3$ sólido (242 mg, 5 equiv.). Luego de agitar durante 18 horas a temperatura ambiente, la reacción se diluyó con EtOAc y las capas se separaron. La fase acuosa se acidificó hasta un pH 2 con HCl 1,0N y se extrajo con EtOAc. La capa de EtOAc se lavó con salmuera luego se secó sobre $MgSO_4$, se secó y se concentró al vacío para obtener el producto **XXVIIIf** como un polvo blanco (0,26 g). Espectro de masa (LCMS) 508 ($M+H^+$).

Paso 5:

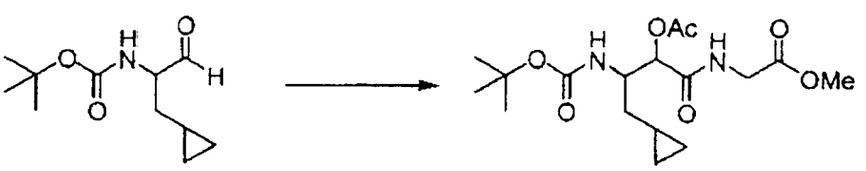


XXVIIIf XXVIII

El producto del Paso 5 (0,15 g) se disolvió en CH_2Cl_2 y se sometió a reacción con HATU (0,137 g), NH_4Cl (0,08 g, 5 equiv.) y DIPEA (0,53 mL). Luego

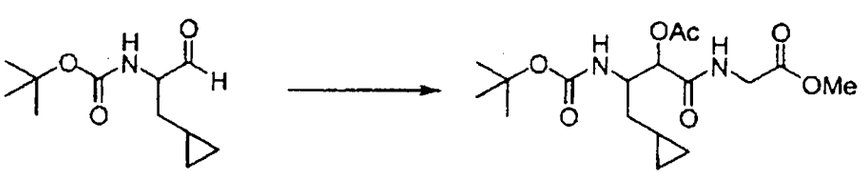
de 2 horas a temperatura ambiente, la reacción se diluyó con EtOAc, se lavó con a solución de ácido cítrico al 10%, luego una solución de $NaHCO_3$ saturado. La capa de EtOAc se lavó con salmuera luego se secó sobre $MgSO_4$, se filtró y se concentró para obtener una mezcla bruta. La purificación mediante cromatografía flash en columna (Acetona al 30%, Hexano, sílice) logró el producto deseado XXVIII (0,096g). Espectro de masa (LCMS) 507 ($M+H^+$).

Ejemplo XXIX: Preparación de un compuesto de la fórmula XXIX:



XXIXa

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 metilisocianoacetato (1,1 equiv., 1,9 mL). La reacción se entibió entonces en forma gradual hasta la temperatura ambiente. Luego de 18 horas (durante la noche), la reacción se diluyó con EtOAc y se lavó con una solución de $NaHCO_3$ saturado. La capa de EtOAc se lavó con salmuera luego se secó sobre $MgSO_4$, se filtró y se concentró al vacío para obtener una mezcla bruta. La purificación mediante cromatografía

033559

flash en columna (EtOAc al 30 a 40%, Hexano, sílice) logró el producto **XXIXa** (4,5 g).

Paso 2:

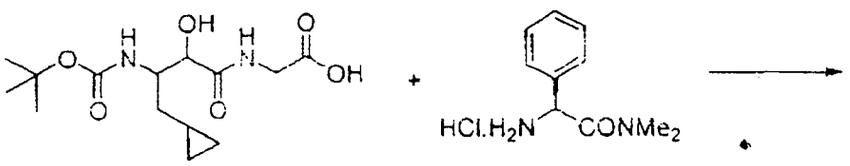


XXIXa **XXIXb**

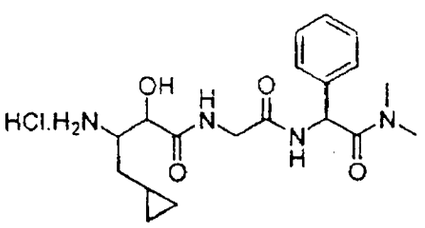
A una solución a 0°C de **XXIXa** (4.4g) en THF (100 mL) se agregó 26 mL (2,2 equiv.) de una solución de LiOH 1,0N. La reacción se agitó a esta temperatura durante 2 horas luego se entibió hasta la temperatura ambiente. Luego de 2 horas, la mezcla de reacción se acidificó hasta un pH 2 con una solución de HCl 1,0N. Se agregó EtOAc y las capas se separaron. La capa de EtOAc se lavó con salmuera luego se secó sobre $MgSO_4$, se filtraron y se concentraron al vacío para obtener el producto **XXIXb** (3,7g).

Paso 3:

000550



XXIXb **XV**

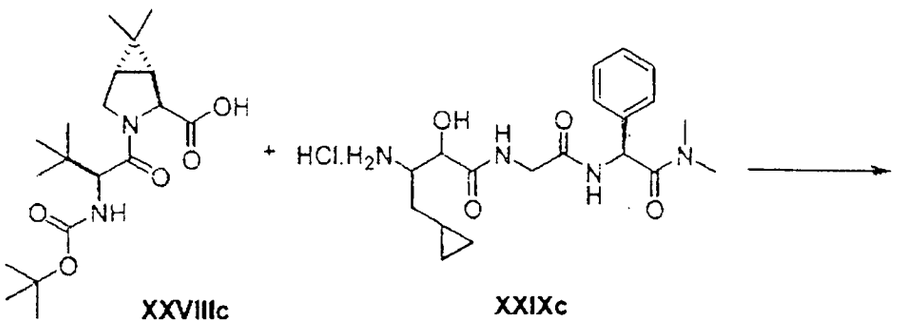


XXIXc

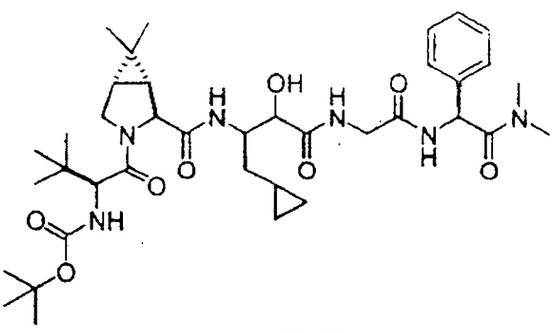
El ácido **XXIXb** se sometió a reacción con la amina del Ejemplo XV en el modo que se describió anteriormente en el Ejemplo XXI, Paso 4. El intermediario resultante se trató con HCl en el modo que se describió anteriormente en el Ejemplo XXIII, Paso 9 para obtener el producto **XXIXc**.

Paso 4:

000561



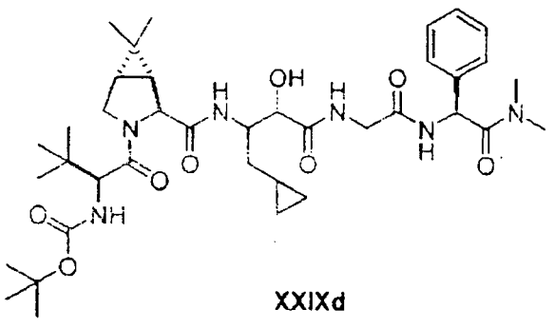
XXVIIIc **XXIXc**



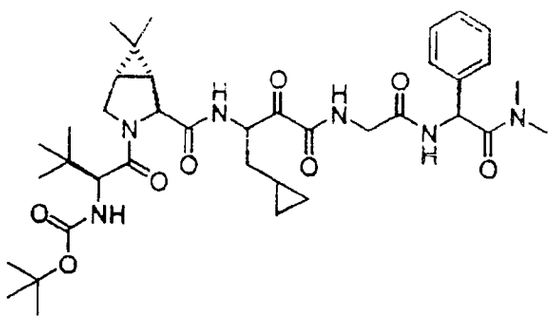
XXIXd

El ácido **XXVIIIc** (2,43 g) se disolvió en CH_2Cl_2 y se sometió a reacción con la amina **XXIXc** (2,47 g), HATU (2,5 g) y DIPEA (5,8 mL) en el modo que se describió anteriormente en el Ejemplo IX, Paso 2a para obtener, luego de la purificación mediante cromatografía flash en columna (MeOH al 4%, CH_2Cl_2, sílice), el producto deseado **XXIXd** (4,35 g). Espectro de masa (LCMS) 727 ($M+H^+$).

Paso 5:



XXIXd

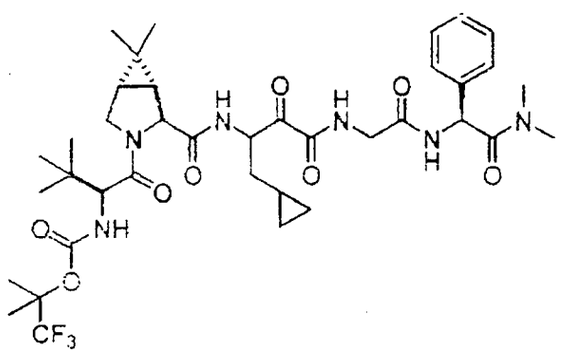


XXIX

El producto del Paso 4 (4,2 g) se sometió a reacción con Reactivo de Dess-Martin (6,4 g) en el modo que se describió anteriormente en el Ejemplo de Preparación XX, Paso 7. La purificación mediante cromatografía flash en columna (EtOAc al 100%, sílice) logró 3 g del producto final **XXIX**. Espectro de masa (LCMS) 725 ($M+H^+$).

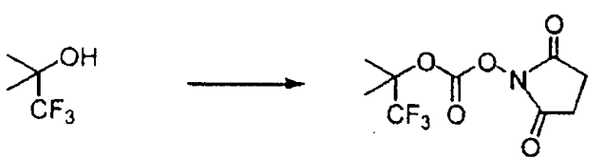
Ejemplo XXX: Preparación de un compuesto de la fórmula XXX:

003533



XXX

Paso 1:

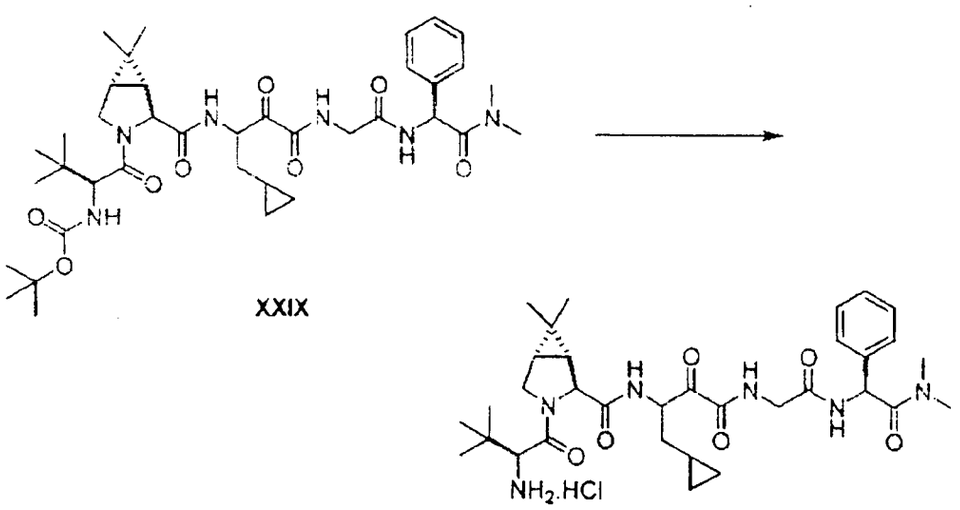


XXXa

El alcohol 2-(trifluorometil)propan-2-ol (1,28 g) se sometió a reacción con carbonato de N,N-disuccinimidilo (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 $NaHCO_3$, salmuera luego se secó sobre $MgSO_4$, se filtró y se concentró al vacío para obtener una mezcla bruta. La purificación mediante cromatografía flash en columna (EtOAc al 50%, Hexano, sílice) logró el producto deseado **XXXa** (0,3 g).

Paso 2:

033534



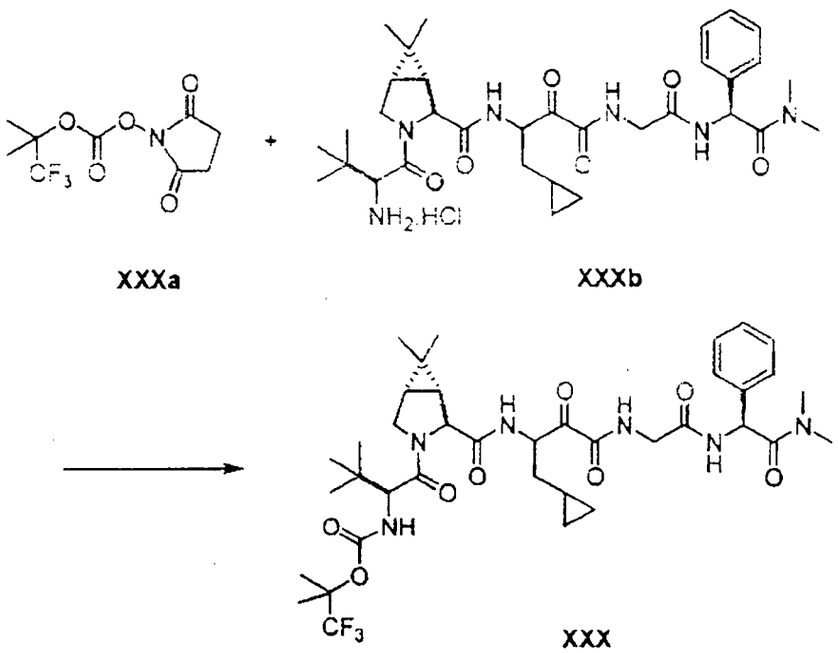
XXIX

XXXb

El producto del Ejemplo XXIX (0,3g) se trató con 100 mL de HCl 4,0N en dioxano. Luego de 1 h, se agregaron 200 mL de Et_2O y el precipitado resultante se filtró *hasta eliminarlo y* se secó al vacío para obtener el producto **XXXb** (0,27 g) como un polvo blanco. Espectro de masa (LCMS) 625 (M - HCl $+H^+$).

Paso 3:

033535



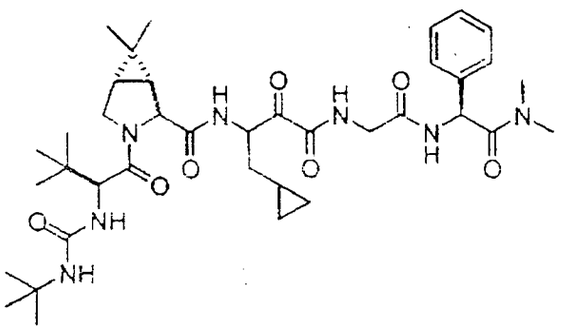
XXXa **XXXb**

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 $NaHCO_3$ luego salmuera. La capa de EtOAc se secó en $MgSO_4$, se filtró y se concentró al vacío para obtener una mezcla bruta. La purificación por cromatografía preparatoria (Acetona al 40%, Hexano, sílice) logró el producto deseado **XXX** (0,044 g). Espectro de masa (LCMS) 779 ($M+H^+$).

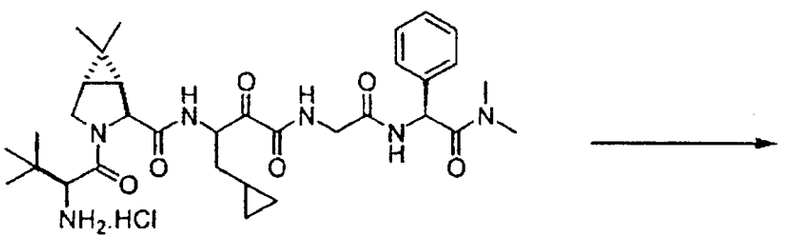
Ejemplo XXXI: Preparación de un compuesto de la fórmula XXXI:

033536

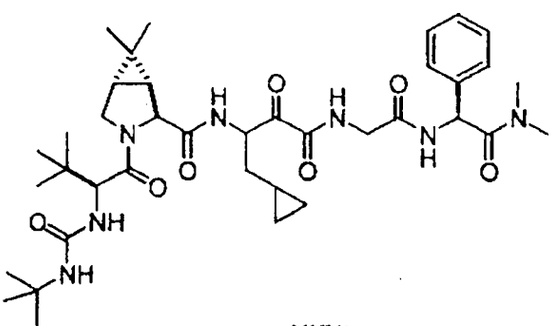


XXXI

Paso 1:



XXXb



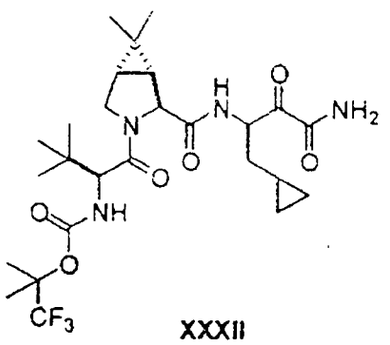
XXXI

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 1,5N, $NaHCO_3$ y salmuera. La capa de EtOAc se secó sobre $MgSO_4$, se filtró y se concentró al vacío para obtener una mezcla bruta. La purificación mediante

033537

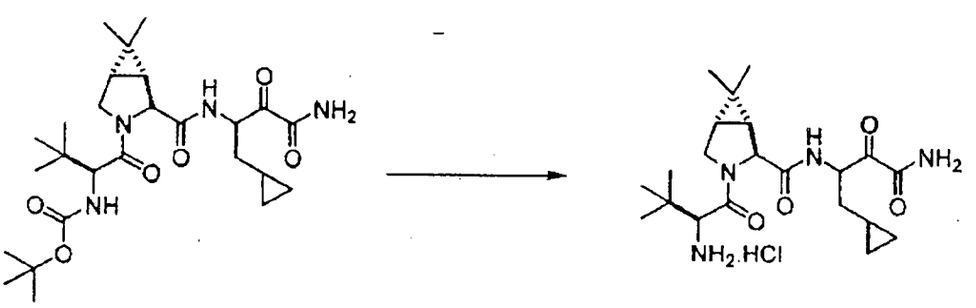
cromatografía preparatoria (EtOAc al 100%, sílice) logró el producto final **XXXI** (0,021 g). Espectro de masa (LCMS) 724 ($M+H^+$).

Ejemplo XXXII: Preparación de un compuesto de la fórmula XXXII:



XXXII

Paso 1:

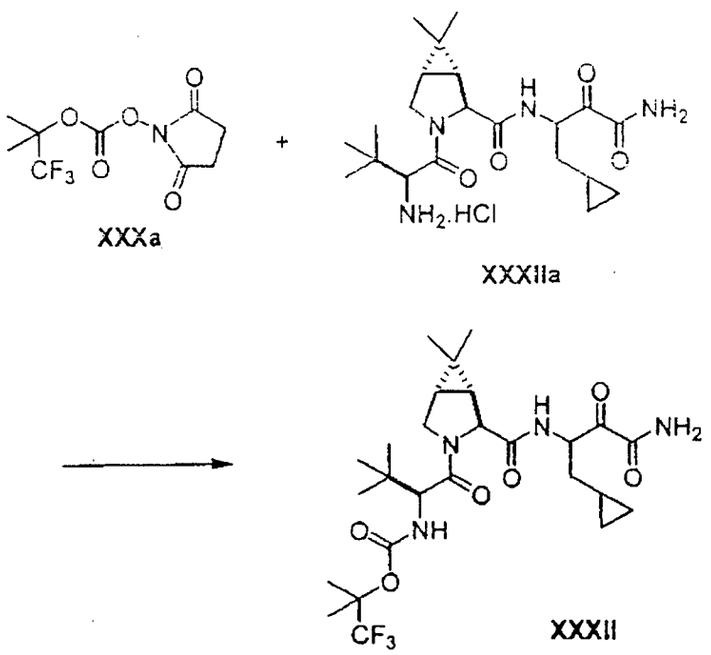


XXVIII **XXXIIa**

El producto del Ejemplo XXVIII se trató en el modo que se describió anteriormente en el Ejemplo de Preparación XXX, Paso 2 para obtener el producto XXXIIa. Espectro de masa (LCMS) 407 ($M - HCl + H^+$).

Paso 2:

000538



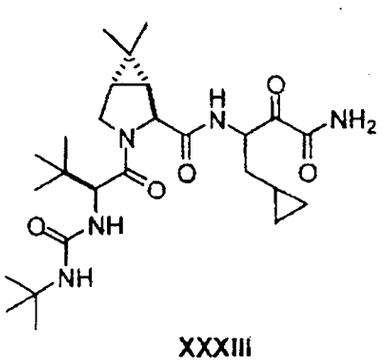
XXXa

XXXIIa

XXXII

La amina **XXXIIa** se sometió a reacción con **XXXa** en el modo que se describió anteriormente en el Ejemplo de Preparación XXX, Paso 3 para obtener el producto deseado XXXII. Espectro de masa (LCMS) 508 ($M+H^+$).

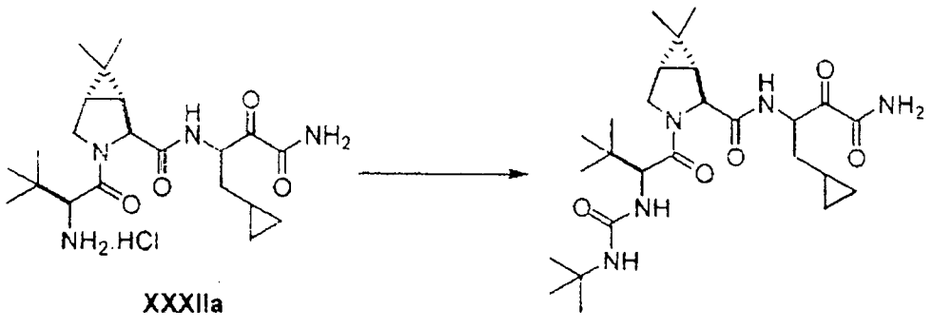
Ejemplo XXXIII: Preparación de un compuesto de la fórmula XXXIII:



XXXIII

Paso 1:

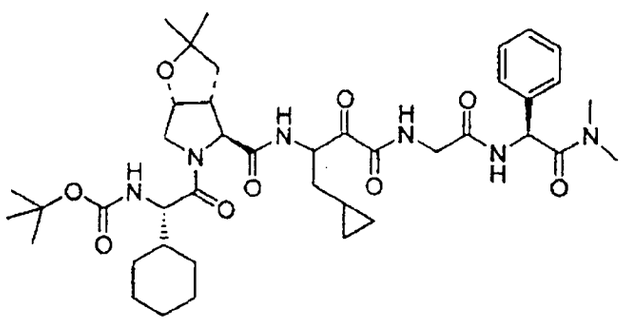
033539



XXXIIa XXXIII

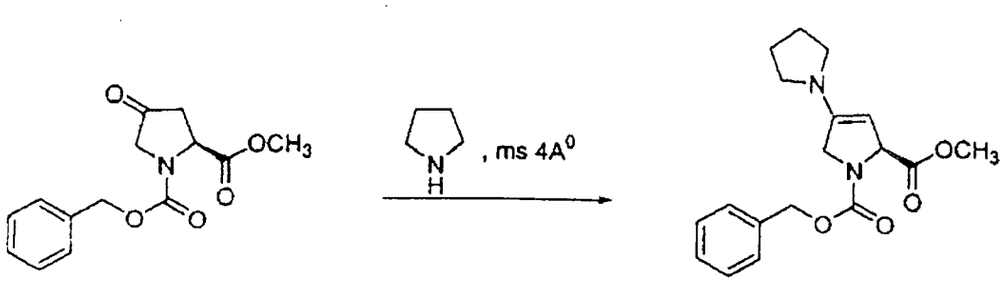
La amina **XXXIIa** se sometió a reacción con ter-butilisocianato en el modo que se describió anteriormente en el Ejemplo **XXXI**, Paso 1, para obtener el producto XXXIII. Espectro de masa (LCMS) 561 ($M+H^+$).

Ejemplo XXXIV: Preparación de un compuesto de la fórmula XXXIV:



XXXIV

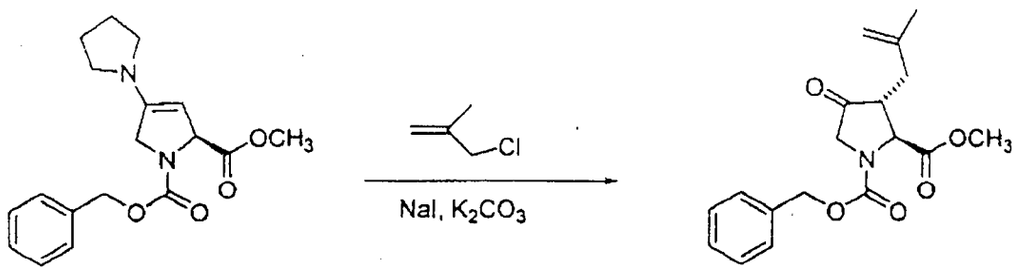
Paso 1:



033570

A la mezcla de éster (6,0 g) y tamiz molecular (5,2 g) en cloruro de metileno anhidro (35 mL) se agregó pirrolidina (5,7 mL, 66,36 mmoL). La suspensión de sólido en líquido resultante, de color marrón, se agitó a temperatura ambiente en N_2 durante 24 h, se filtró y se lavó con CH_3CN anhidro. El filtrado combinado se concentró para dar el producto deseado.

Paso 2:



A una solución de el producto del paso anterior en CH_3CN (35 mL) se agregó K_2CO_3 anhidro, cloruro de metalilo (2,77g, 30,5 mmoL), NaI (1,07g, 6,7 mmoL). La suspensión de sólido en líquido resultante se agitó a temperatura ambiente en N_2 durante 24 h. Se agregaron 50 mL de agua helada con hielo seguido de solución de $KHSO_4$ 2N hasta que el pH fue 1. Se agregó EtOAc (100 mL) y la mezcla se agitó durante 0,75 h. Se recolectó la capa orgánica combinada y se lavó con salmuera, se secó sobre $MgSO_4$, y se evaporó para lograr el producto deseado.

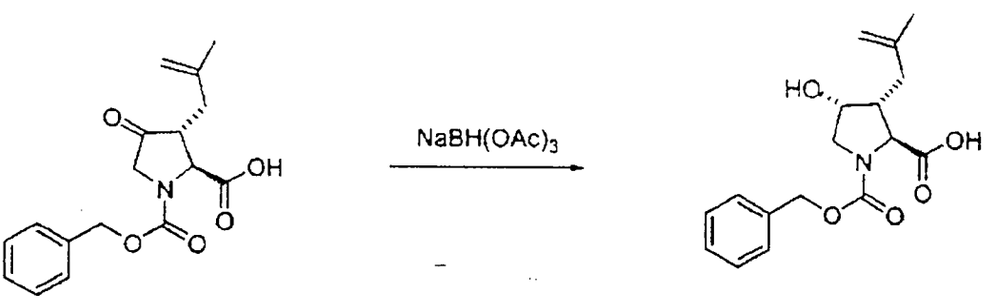
Paso 3:



055571

El producto del paso precedente (2,7 g, 8,16 mmoL) se disolvió en dioxano (20 mL) y se trató con LiOH 1N preparado recientemente (9 mL). La mezcla de reacción se agitó a temperatura ambiente en N_2 durante 20 h. La mezcla de reacción se absorbió en EtOAc y se lavó con H_2O. La fase acuosa combinada se enfrió hasta los 0°C y se acidificó hasta un pH 1,65 mediante el uso de HCl 1N. La mezcla turbia se extrajo con EtOAc (2 x 100 mL). La capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, se concentró para dar el ácido deseado (3,40 g).

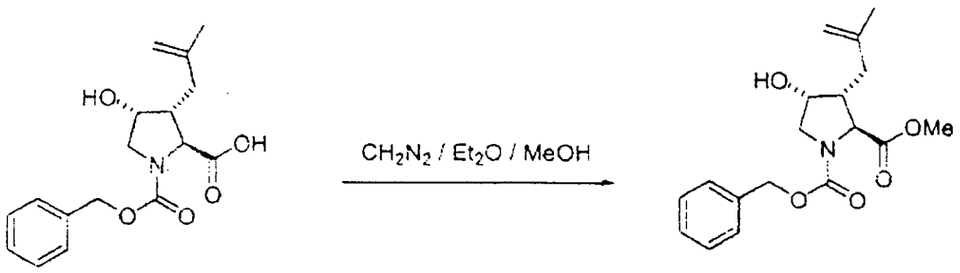
Paso 4:



A una suspensión de $NaBH(OAc)_3$ (3,93 g, 18,5 mmoL) en CH_2Cl_2 (55 mL) se agregó una solución del producto del paso precedente en CH_2Cl_2 anhidro (20 mL) y ácido acético (2 mL). La suspensión de sólido en líquido se agitó a temperatura ambiente durante 20 h. Se agregó agua helada con hielo (100 mL) a suspensión de sólido en líquido y se agitó durante 1/2 hr. La capa orgánica se separó, se filtró, se secó y se evaporó para lograr el producto deseado.

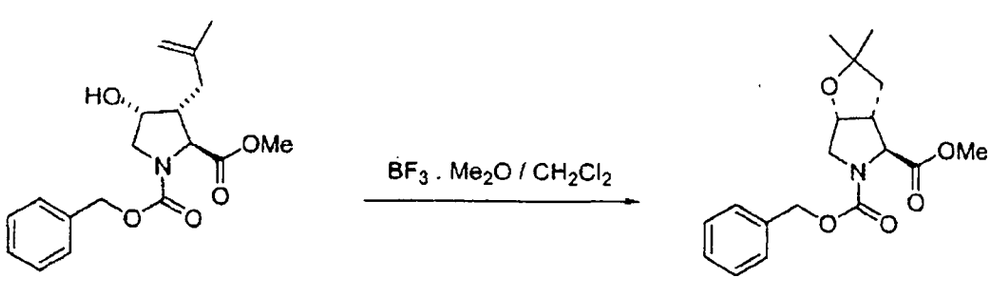
Paso 5:

033572



A una solución de el producto del paso precedente (1,9 g) en MeOH (40 mL) se trató con el exceso de solución de CH_2N_2 / Et2O y se agitó durante la noche. La mezcla de reacción se concentró hasta secarse para obtener un residuo bruto. El residuo se sometió a cromatografía en gel de sílice, eluyendo con un gradiente de EtOAc / hexano para obtener 1.07 g de el producto puro deseado.

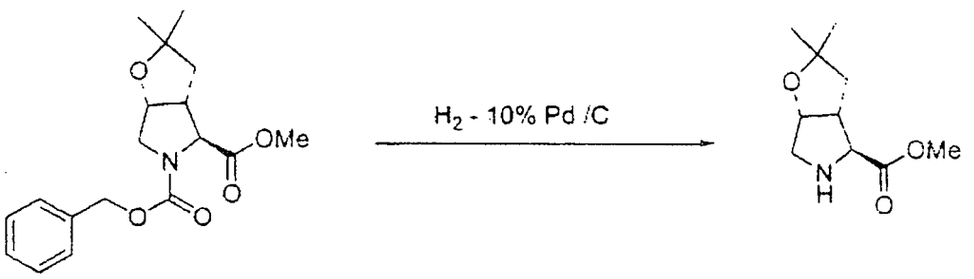
Paso 6:



A una solución del producto del paso precedente (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 $NaHCO_3$ saturado (30 mL) y se agitó durante 1/2 hr. La capa orgánica se separó y la capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, se concentró para dar el residuo bruto. El residuo se sometió a cromatografía en gel de sílice eluyendo con un gradiente de EtOAc / hexano para obtener 0,88 g de el compuesto deseado.

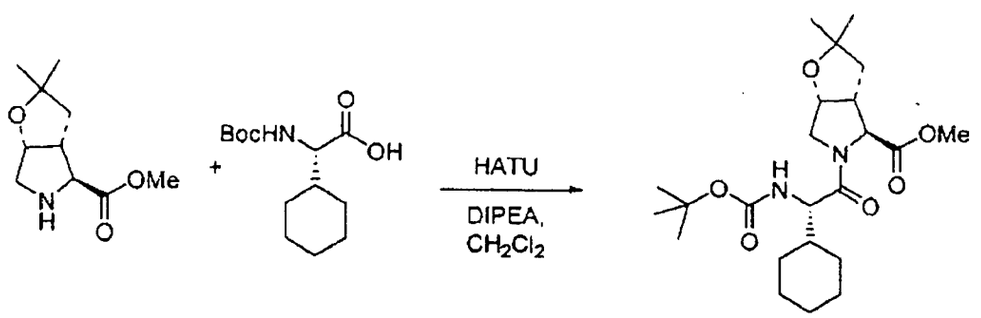
033573

Paso 7:



A una solución de el producto (0,92 g) del paso precedente en MeOH (30 mL) se agregó Pd/C al 10% (0,16 g) a temperatura ambiente y se hidrogenó a temperatura ambiente en Presión de 1 atm. La mezcla de reacción se agitó durante 4 h y se concentró hasta secar para obtener el compuesto deseado.

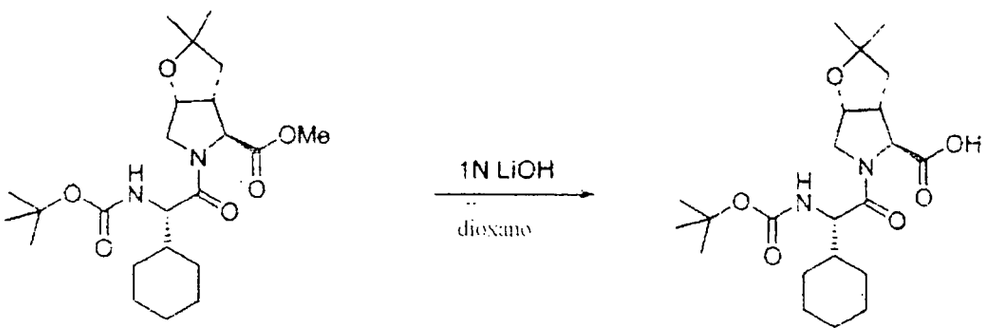
Paso 8:



El producto deseado se preparó de acuerdo con el procedimiento en el Ejemplo XXIII, Paso 10.

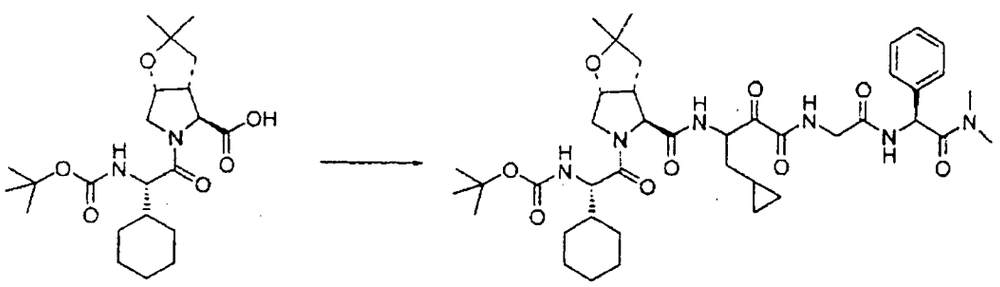
Paso 9:

003574



El producto ácido se preparó de acuerdo con el procedimiento en el Ejemplo XXIV, Paso 3.

Paso 10:

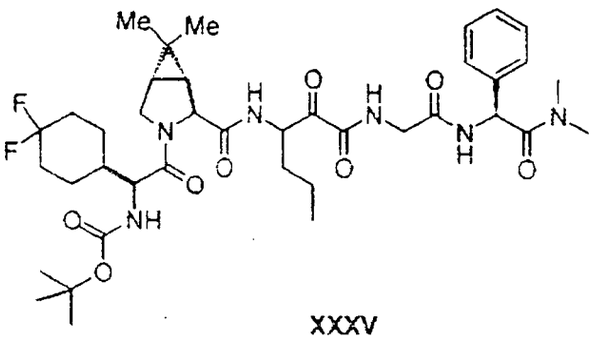


XXXIV

El producto deseado XXXIV se preparó de acuerdo con el procedimiento en el Ejemplo XXIX, Pasos 4-5.

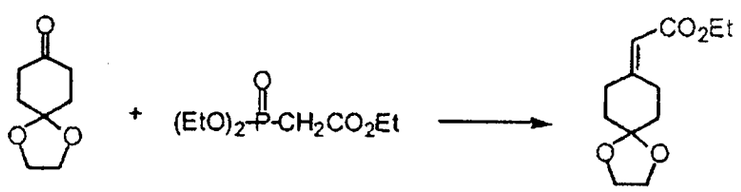
Ejemplo XXXV: Preparación de un compuesto de la fórmula XXXV:

033575



XXXV

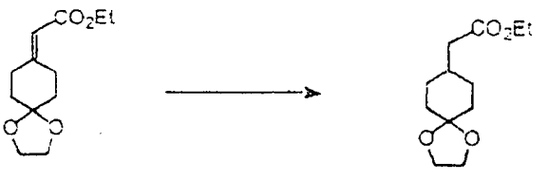
Paso 1:



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 cetal de 1,4-ciclohexanodiona etileno (15,6 g) en THF (50 mL) se agregó por goteo, y la solución resultante se agitó a temperatura ambiente durante 18 horas. La mezcla de reacción se enfrió, entonces, hasta 0°C, se trató con cold ácido cítrico acuoso, y la mezcla se extrajo con EtOAc. El extracto se lavó con $NaHCO_3$ acuoso saturado, luego salmuera; luego se secó sobre anhidro Na_2SO_4, se filtró, y el filtrado se evaporó. El residuo se sometió a cromatografía en gel de sílice, eluyendo con un gradiente de CH_2Cl_2/EtOAc para obtener el compuesto del título (21 g), 92% de rendimiento. Espectro de masa (FAB) 227,3 ($M+H^+$).

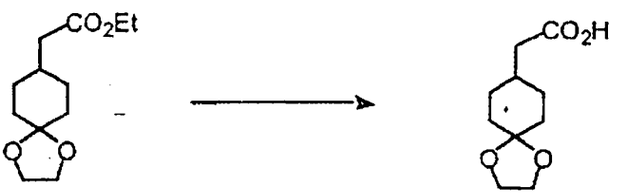
000576

Paso 2:



El producto del paso precedente (20 g) se disolvió en EtOH (150 mL) y se trató con Pd/C al 10% en 1 atm de hidrógeno durante 3 días. La mezcla se filtró y el filtrado se evaporó para obtener el compuesto del título (20.3 g), 100 % de rendimiento. Espectro de masa (FAB) 229.2 ($M+H^+$).

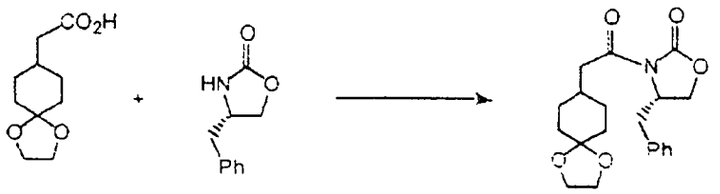
Paso 3:



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 cold agua (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 anhidro Na_2SO_4, se filtró, y el filtrado se evaporó para obtener el compuesto del título (17.1 g), 97% de rendimiento. Espectro de masa (FAB) 201.2 ($M+H^+$).

Paso 4:

000577

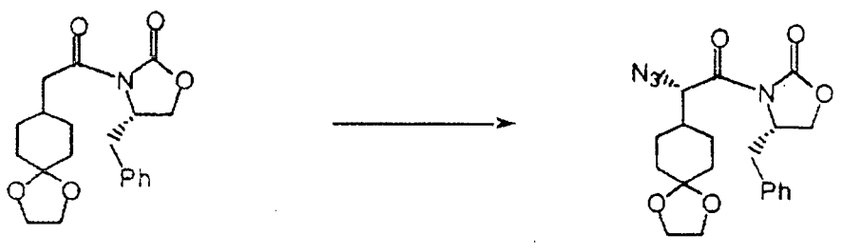


1. El producto del paso precedente (3,0 g) se disolvió en Et_2O (150 mL), se trató con Et_3N (2,1 mL), y la solución se enfrió hasta -78°C. Se agregó cloruro de pivaloilo (1,85 mL) por goteo, y luego de 0,25 horas de agitación adicional, la reacción se dejó entibiar hasta 0°C durante 0,75 hora, y luego se enfrió nuevamente hasta -78°C para obtener una solución de anhídrido mezclado durante la reacción en 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 se agregó una solución 1,6M (9,38 mL) de n-butillitio en hexano por goteo. Luego de un adicional de 0,33 horas de agitar 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 horas. La capa orgánica se separó, la fase acuosa se extrajo con Et_2O, se lavaron las capas orgánicas con salmuera, se secaron sobre anhidro Na_2SO_4, se filtraron, y el filtrado se evaporó. El residuo se sometió a cromatografía en gel de sílice, eluyendo con un gradiente de hexano/EtOAc (9:1) para obtener el compuesto del título (5,0 g), 93% de rendimiento. Espectro de masa (FAB) 360.4 ($M+H^+$).

Paso 5:

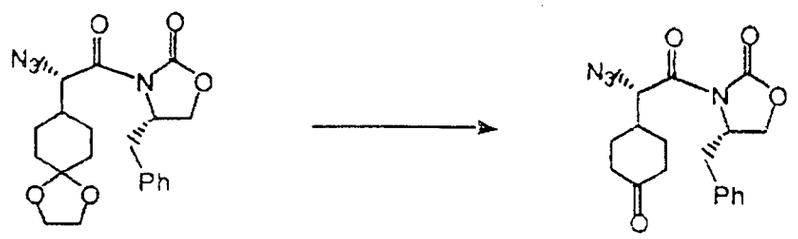
000578



El producto del paso precedente (2,7 g) se disolvió en THF (25 mL), se enfrió hasta -78°C, se transfirió a través de una cánula a una solución de bis(trimetilsilil)amida de potasio/tolueno 0,5M (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 trisililo (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 se agitó durante 16 horas. La reacción se diluyó con EtOAc (300 mL), y se lavó con NaCl acuoso al 5%. La fase acuosa se extrajo con EtOAc, las fases orgánicas combinadas se lavaron con $NaHCO_3$ acuoso saturado, luego con salmuera; luego se secó sobre Na_2SO_4 anhidro, se filtró, y el filtrado se evaporó. El residuo se sometió a cromatografía en gel de sílice, eluyendo con EtOAc/hexano (1:3) para obtener el compuesto del título (2,65 g), 88% de rendimiento.

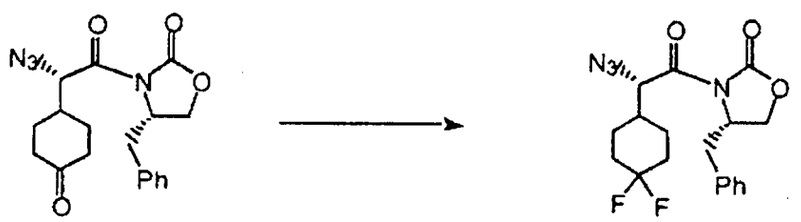
Paso 6:

000579



El producto del paso precedente (11,4 g) se disolvió en ácido fórmico al 95% (70 mL) y se calentó hasta 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 $NaHCO_3$ acuoso saturado, luego con salmuera; luego se secó sobre Na_2SO_4 anhidro, se filtró, y se evaporó el filtrado. El residuo se sometió a cromatografía en gel de sílice para obtener el compuesto del título (8,2 g).

Paso 7:

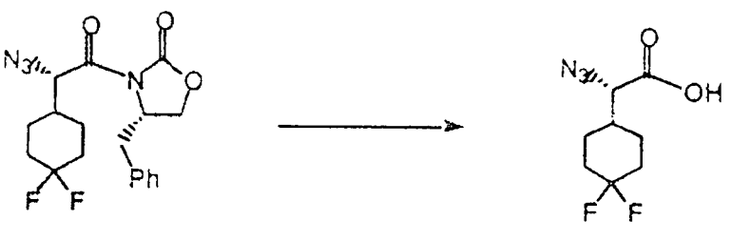


El producto del paso precedente (8,2 g) se disolvió en CH_2Cl_2 (16 mL) y se trató con trifluoruro de dietilaminosulfuro (DAST, 7,00 mL) a temperatura ambiente durante 3 horas. La reacción se vertió sobre hielo/agua (200 cc), y se extrajo con CH_2Cl_2. El extracto se lavó con $NaHCO_3$ acuoso saturado, luego con salmuera; luego se secó sobre Na_2SO_4 anhidro, se filtró, y el filtrado se evaporó. El residuo se sometió a cromatografía en gel de sílice, eluyendo con

033580

EtOAc/hexano (15:85) para obtener el compuesto del título (4.5 g), 52% de rendimiento.

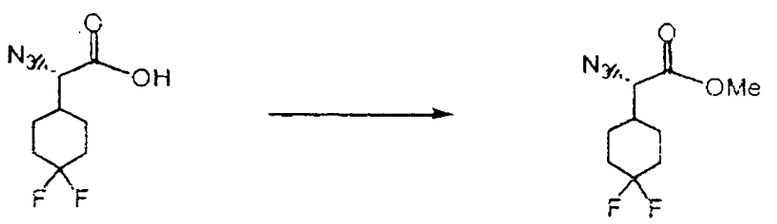
Paso 8:



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 H_2O_2 al 30% (3,95 mL), y luego con LiOH-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 $NaHCO_3$ 0,5N (100 mL). La mezcla se concentró al vacío hasta la 1/2 del volumen, se diluyó con agua (a 500 mL), y se extrajo con CH_2Cl_2 (4 x 200 mL). La fase acuosa 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 evaporó para obtener el compuesto del título (1,95 g), 91% de rendimiento, que se usó directamente en el paso siguiente.

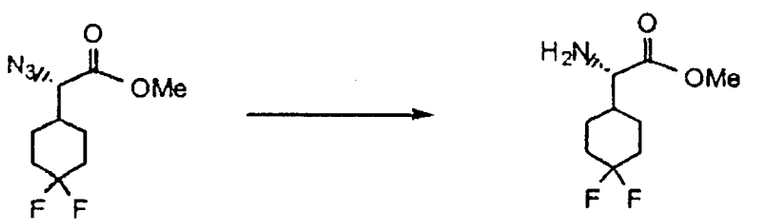
Paso 9:

000581



El producto del Ejemplo precedente (2,6 g) se disolvió en Et_2O (50 mL) y se trató por goteo con una solución de CH_2N_2 en Et2O hasta que la solución permaneció amarilla. La solución se agitó durante 18 horas, luego se evaporó al vacío para obtener el compuesto del título (2,8), que se usó directamente en el paso siguiente.

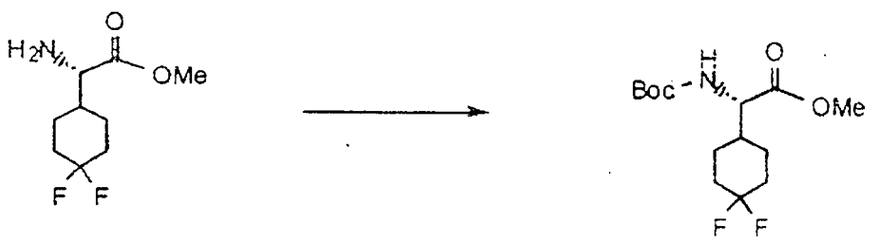
Paso 10:



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% Pd/C (3,3 g, tipo Degussa E101) en 1 atm de hidrógeno durante 1,5 horas. La mezcla se filtró y el filtrado se evaporó para obtener el compuesto del título (2.1 g) como la sal del ácido fórmico, que se usó directamente en el paso siguiente.

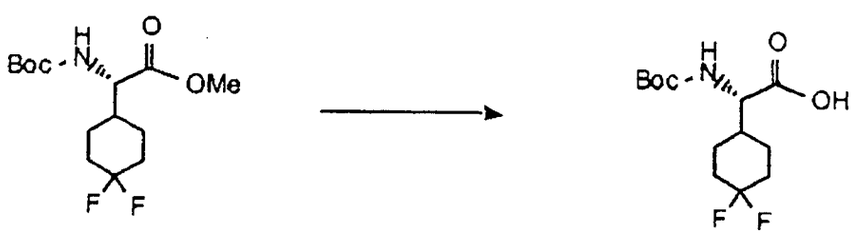
Paso 11:

000582



El producto del paso precedente (2,1 g) se disolvió en 1,4-dioxano (100 mL) y dicarbonato de di-ter-butilo (1,9 g) se agregó, seguido de diisopropiletilamina (2,9 mL). La solución se agitó durante 18 horas, y se concentró al vacío. El residuo se trató con KH_2PO_4 acuoso al 5% y la mezcla extrajo con EtOAc. El extracto se lavó con salmuera; luego se secó sobre $MgSO_4$ anhidro, se filtró, y el filtrado se evaporó. El residuo se sometió a cromatografía en gel de sílice, eluyendo con un gradiente de CH_2Cl_2/Et_2O para obtener el compuesto del título (2,5 g), 99% de rendimiento. Espectro de masa (FAB) 307,9 ($M+H^+$).

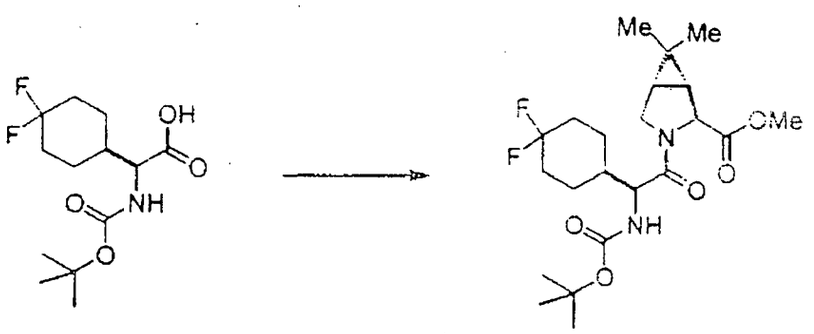
Paso 12:



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 obtener el compuesto del título (2,3 g), 96% de rendimiento. Espectro de masa (FAB) 294.0 ($M+H^+$).

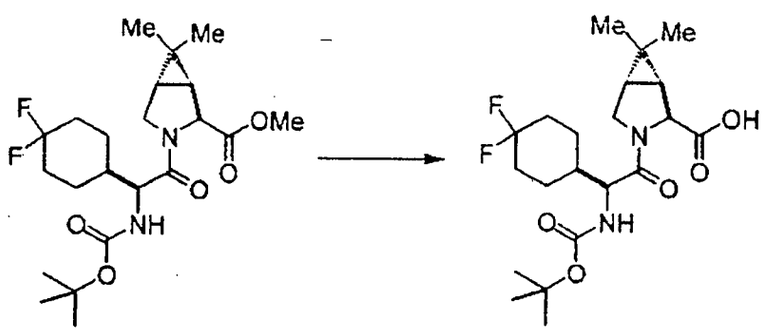
033583

Paso 13:



El producto deseado se preparó de acuerdo con el procedimiento en el Ejemplo XXIII, Paso 10.

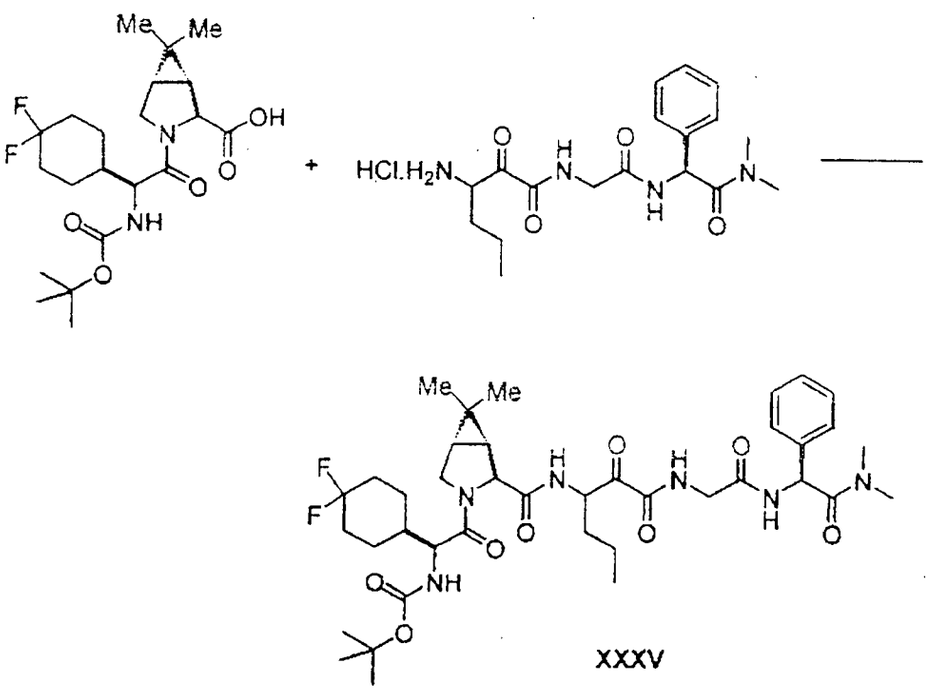
Paso 14:



El producto ácido deseado se preparó de acuerdo con el procedimiento en el Ejemplo XXIV, Paso 3.

Paso 15:

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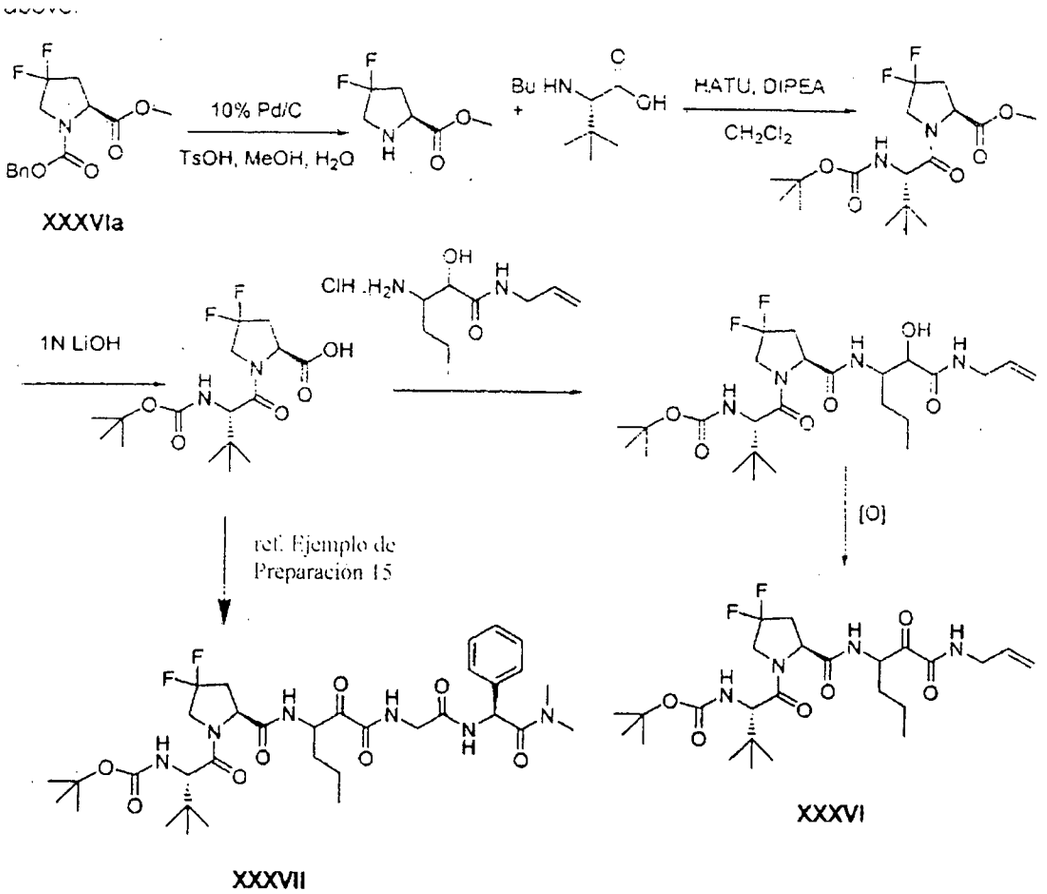
XXXV

El producto ácido deseado se preparó de acuerdo con el procedimiento en el Ejemplo XXIX, Paso 4.

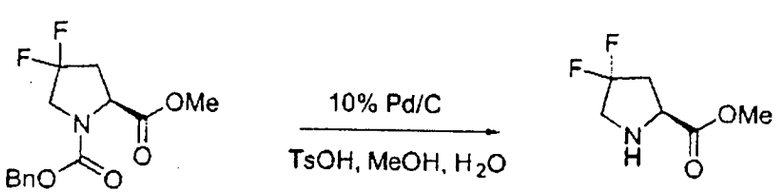
Ejemplo XXXVI. Preparación del compuestos de las fórmulas XXXVI y XXXVIII:

Los compuestos de las fórmulas XXXVI y XXXVIII se prepararon de acuerdo con el esquema que sigue y utilizando el Ejemplo de Preparación 11 a 15 anteriores.

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El compuesto de la fórmula XXXVIb se preparó a partir de un compuesto de la fórmula XXXVIa como sigue mediante procedimientos conocidos:



XXXVIa **XXXVIb**

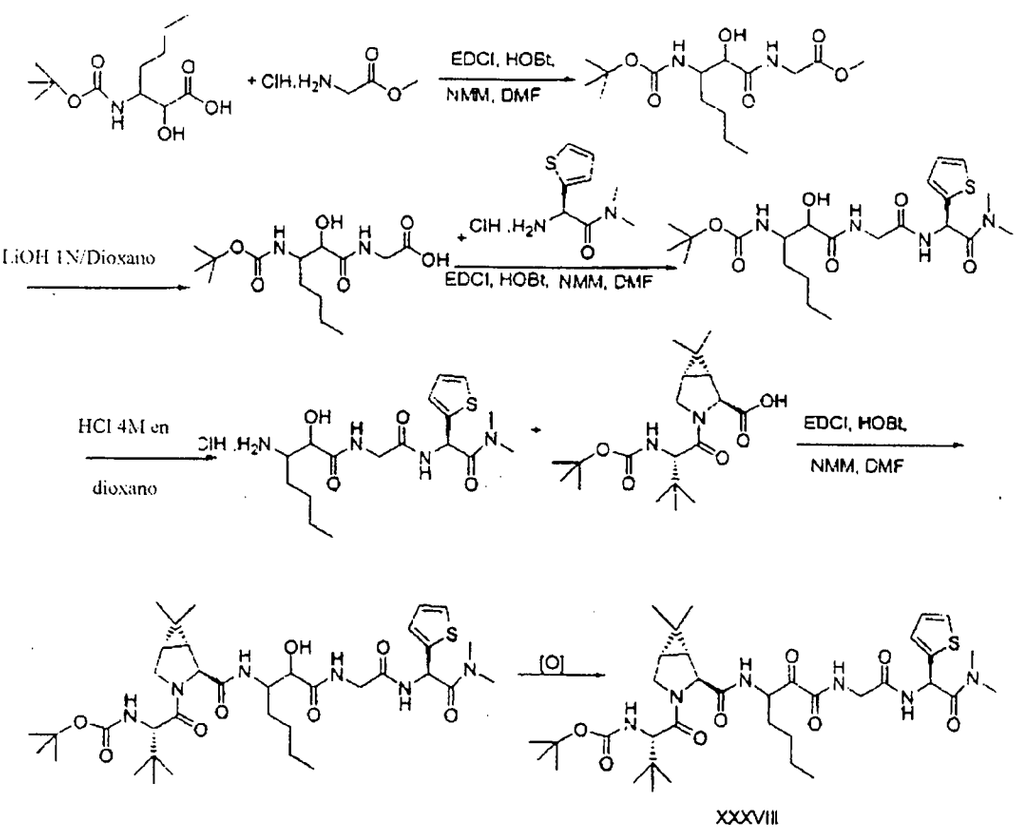
A una solución del compuesto XXXVIa (6,58 g, 22 mmol) en 100 mL de MeOH se agregó 10% Pd/C (0,8 g) y ácido p-toluen sulfónico (4,2 g). La mezcla de reacción se sometió a hidrogenación a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de celite y se lavó con exceso de

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MeOH. El filtrado combinado se concentró al vacío para suministrar el compuesto del título XXXVIb como una goma. La conversión de XXXVIb a XXXVI y XVII siguió la vía que se muestra en el esquema anterior y de acuerdo con el Ejemplo de Preparación 11-15.

Ejemplo XXXVIII. Preparación de un compuesto de la fórmula XXXVIII:

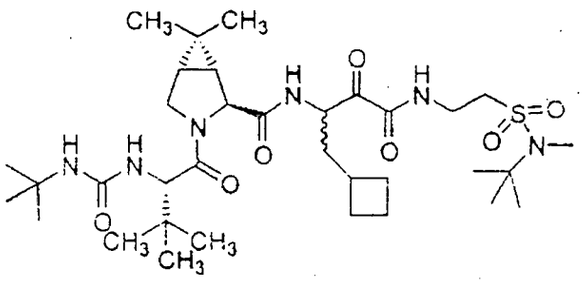
Un compuesto de la fórmula XXXVIII se preparó con la utilización del siguiente esquema y siguiendo el Ejemplo de Preparación 11 a 15 que se describieron anteriormente.



XXXVIII

Ejemplo XXXIX Síntesis del compuesto de la fórmula XXXIX:

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XXXIX

Paso 1:



XXXIXa XXXIXb

Una solución del cloruro de sulfonilo XXXIXa preparado mediante el procedimiento de H. Mcklwaen (J. Chem. Soc 1941, 75) se agregó por goteo 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 por cromatografía (SiO_2, Hex/Acetona 4:1) para obtener la sulfonamida XXXIXb como un aceite sin color.

Paso 2:



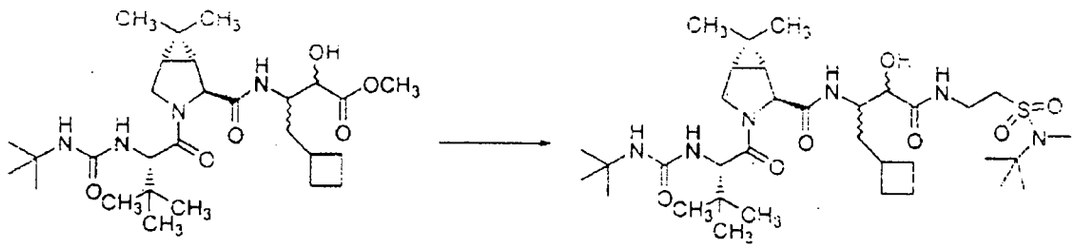
XXXIXb XXXIXc

Una solución de la amina protegida por Cbz XXXIXb se disolvió en metanol y se trató con 5 mol% de Pd /C (5% p/p) y se hidrogenó a 60 psi. La

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mezcla de reacción se filtró a través de un tapón de celite y se concentró al vacío para obtener la amina libre XXXIXc que se solidificó en reposo.

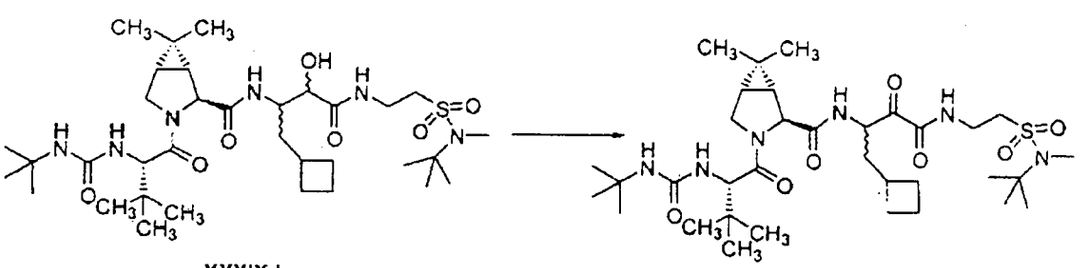
Paso 3:



XXVe XXXIXd

La hidroxi sulfonamida XXXIXd se sintetizó de un modo similar al procedimiento de la síntesis de XXVf con la excepción de que se reemplazó la amina XXVd por XXXIXc. La mezcla de reacción bruta se usó directamente durante la reacción siguiente.

Paso 4:



XXXIXd XXXIX

La hidroxi amida XXXIXd se oxidó a un compuesto XXXIX mediante el uso del reactivo de Dess-Martin siguiendo el procedimiento para la síntesis de XXV (paso 5). La mezcla bruta se purificó por cromatografía (SiO_2, Acetona/Hexano 3:7) para obtener XXXIX como un sólido sin color.

Ensayo para evaluar la actividad de inhibición de la proteasa de HCV:

Ensayo Espectrofotométrico: El ensayo espectrofotométrico para la proteasa serina de HCV se realizó en los compuestos de la invención a través del

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procedimiento que se describe en R. Zhang *y sus colaboradores*, *Analytical Biochemistry*, 270 (1999) 268-275, cuya descripción se incorpora aquí a modo de referencia. El ensayo basado en la proteólisis de los substratos del éster cromogénico es apropiado para el monitoreo continuo de la actividad de proteasa NS3 de HCV. Los substratos derivaron del lado P de la secuencia de unión NS5A-NS5B (Ac-DTEDVVX(Nva), en la cual X= A o P), cuyos grupos carboxilo terminal C se esterificaron con uno de cuatro alcoholes cromofóricos diferentes (3- ó 4-nitrofenol, 7-hidroxi-4-metil-cumarina, o 4-fenilazofenol). A continuación se presenta la síntesis, caracterización y aplicación de estos novedosos substratos de éster espectrofotométrico a la selección de alto rendimiento y la evaluación cinética detallada de los inhibidores de proteasa NS3 de HCV.

Materiales y Métodos:

Materiales: Los reactivos químicos para los buffers relacionados con el ensayo se obtuvieron de Sigma Chemical Company (St. Louis, Missouri). Los reactivos para la síntesis de péptidos fueron de Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) y Perseptive Biosystems (Framingham, Massachusetts). 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 UV de 96 receptáculos se obtuvieron de Corning (Corning, New York). El bloque de pre-calentado fue de USA Scientific (Ocala, Florida) y el aparato para vórtex con placa de 96 receptáculo fue de Labline Instruments (Melrose Park, Illinois). Un lector de placa de microtitulación Spectramax Plus con monocronómetro se obtuvo de Molecular Devices (Sunnyvale, California).

Preparación de las Enzimas: La proteasa heterodimérica recombinante NS3/NS4A de HCV (cepa 1a) se preparó mediante el uso de los procedimientos

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publicados con anterioridad (D. L. Sali, y sus colaboradores, *Biochemistry*, 37 (1998) 3392-3401). Las concentraciones de proteínas se determinaron mediante el método de coloreado con Biorad mediante el uso de los estándares de proteasa de HCV recombinante cuantificados anteriormente a través del análisis de amino ácidos. Antes de iniciar el ensayo, se intercambió el buffer de almacenamiento de las enzimas (fosfato de sodio 50 mM pH 8,0, NaCl 300 mM, glicerol al 10%, maltosida de laurilo al 0,05% y DTT 10 mM) para el buffer del ensayo (MOPS 25 mM pH 6,5, NaCl 300 mM, glicerol al 10%, maltosida de laurilo al 0,05% 5 µM de EDTA y 5 µM de DTT) con el uso de una columna pre-envasada Biorad Bio-Spin P-6.

Síntesis y Purificación del Substrato: La síntesis de los substratos se realizó como se informó en R. Zhang y sus colaboradores (anterior) y se inició mediante el anclaje de Fmoc-Nva-OH a la resina de cloruro de 2-clorotritilo con el uso de un protocolo estándar (K. Barlos y sus colaboradores, Int. J. Pept. Protein Res., 37 (1991), 513-520). Los péptidos se montaron posteriormente, mediante el uso de la química de Fmoc, ya sea en forma manual o en un sintetizador de péptidos automático ABI modelo 431. Los fragmentos N-acetilados y totalmente protegidos de péptido se disociaron de la resina, ya sea mediante ácido acético al 10% (HOAc) y trifluoroetanol al 10% (TFE) en diclorometano (DCM) durante 30 minutos, o mediante ácido trifluoroacético al 2% (TFA) en DCM durante 10 min. El filtrado y el lavado de DCM combinados se evaporaron azeotrópicamente (o se extrajeron en forma reiterada mediante solución acuosa de Na_2CO_3) para remover el ácido utilizado en la disociación. La fase de DCM se secó en Na_2SO_4 y se evaporó.

Los substrato de éster se ensamblaron con el uso de procedimientos estándar de acoplamiento de ácido-alcohol (K. Holmber y sus colaboradores, *Acta Chem. Scand.*, B33 (1979) 410-412). Los fragmentos de péptido se

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disolvieron en piridina anhidra (30-60 mg/ml) a la cual se agregaron 10 equivalentes molares de cromoforo y una cantidad catalítica (0,1 eq) de ácido para-toluensulfónico (pTSA). Se agregó diclorohexilcarbodiimida (DCC, 3 eq) para iniciar las reacciones de acoplamiento. La formación del producto se monitoreó por HPLC y se encontró completa luego de una reacción de 12-72 horas a temperatura ambiente. El solvente de piridina se evaporó al vacío y se eliminó en forma adicional mediante evaporación azeotrópica con tolueno. El éster péptido se desprotegió con TFA al 95% en DCM durante dos horas y se extrajo tres veces con éter etílico anhidro para remover el exceso de cromoforo. El substrato desprotegido se purificó por HPLC de fase inversa en una columna de C3 o C8 con un gradiente de acetonitrilo al 30% a 60% (con el uso de seis volúmenes de columna). El rendimiento general que siguió a la purificación por HPLC fue de aproximadamente 20-30%. La masa molecular se confirmó por espectroscopia de masa con ionización con electrospray. Los substratos se almacenaron en forma de polvo seco luego de disecar.

Espectro de los Substratos y los Productos: El especto de los substratos y los correspondientes productos cromóforos se obtuvieron en el buffer de ensayo de pH 6,5. Se determinaron los coeficientes de extinción en la longitud de onda pico óptima en cubetas de 1 cm (340 nm para 3-Np y HMC, 370 nm para PAP y 400 nm para 4-Np) mediante el uso de diluciones múltiples. La longitud de onda pico óptima se definió como la longitud de onda que producía la diferencia fraccional máxima en la absorbancia entre el substrato y el producto (OD producto - OD substrato)/OD substrato).

Ensayo de proteasa: Los ensayos de proteasa se realizaron a 30°C con el uso de una mezcla de reacción de 200 µl en una placa de microtitulación de 96 receptáculos. Las condiciones del buffer del ensayo (MOPS 25 mM pH 6,5, NaCl 300 mM, glicerol al 10%, maltosida de laurilo al 0,05% 5 µM de EDTA y 5 µM de

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DTT) se optimizaron para el heterodímero NS3/NS4A (D. L. Sali y sus colaboradores, ref anterior)). Normalmente, se colocaron mezclas de 150 µl de buffer, substrato e inhibidor en los receptáculos (concentración final de DMSO 4% v/v) y se le permitió preincubar a 30°C durante aproximadamente 3 minutos. Luego se usaron cincuenta µls de proteasa precalentada (12 nM, 30°C) en buffer del ensayo, para iniciar la reacción (volumen final 200 µl). Las placas se monitorearon mientras duró el ensayo (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) mediante el uso de un lector de placa para microtitulación Spectromax Plus equipado con un monocrómetro (los resultados apropiados pueden obtenerse con lectores de placas que utilizan filtros de corte). La disociación proteolítica del enlace de éster entre el Nva y el cromóforo se monitoreó en la longitud de onda apropiada contra un blanco sin enzimas como control para la hidrólisis no enzimática. La evaluación los parámetros cinéticos del substrato se realizó en un rango de concentración de 30 veces el substrato (~6-200 µM). Las velocidades iniciales se determinaron mediante el uso de regresión lineal y las constantes cinéticas se obtuvieron al adaptar los datos a la ecuación de Michaelis-Menten con el uso del análisis de regresión no lineal (Mac Curve Fit 1.1, K. Raner). Las cifras de los resultados (k_{cat}) se calcularon con la suposición de que la enzima era totalmente activa.

Evaluación de Inhibidores e Inactivadores: Las constantes de inhibición (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 enzima y substrato mediante el trazado de un gráfico de v_o/v_i versus concentración del inhibidor ($[I]_o$) de acuerdo con la ecuación redispuesta de Michaelis-Menten para la cinética de inhibición competitiva: $v_o/v_i = 1 + [I]_o$ y $[S]_o/ K_m$)), en la cual V_o es la velocidad inicial no

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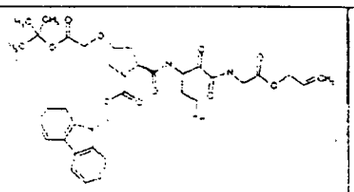
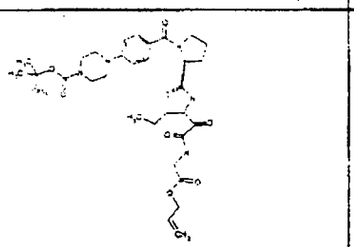
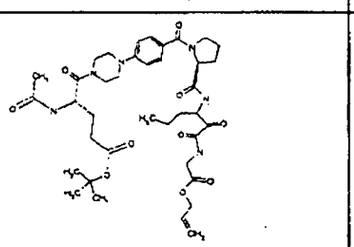
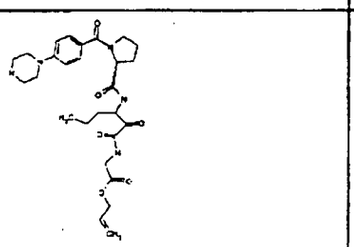
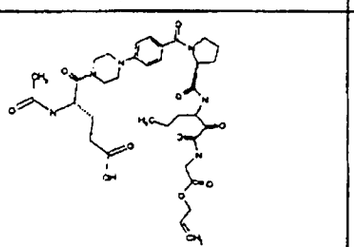
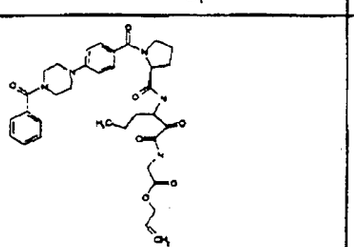
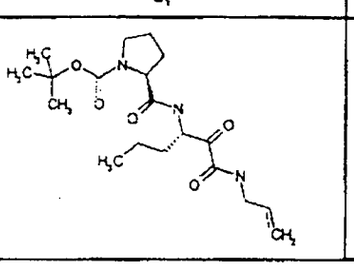
inhibida. V_i es la velocidad inicial en presencia del inhibidor en cualquier concentración dada de inhibidor ($[I]_o$) y $[S]_o$ es la concentración de substrato utilizada. Los datos resultantes se adaptaron con el uso de regresión lineal y la inclinación resultante, $1/(Ki^*(1+[S]_o/K_m)$, se utilizó para calcular el valor de Ki*.

Los valores de Ki* obtenidos para los diferentes compuestos de la presente invención se suministran en las Tablas mencionadas anteriormente en las cuales los compuestos se han dispuesto en el orden de los rangos de los valores de Ki*. A partir de estos resultados experimentales, resultaría aparente para aquellos con experiencia en el arte que los compuestos de la invención tienen una excelente utilidad como inhibidores de la proteasa serina NS3.

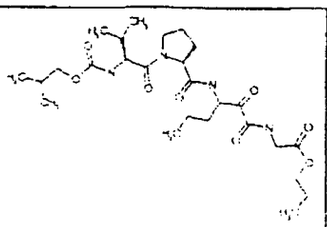
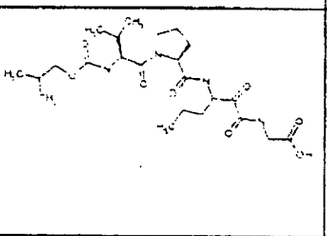
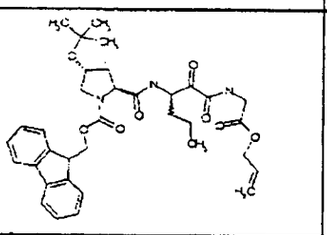
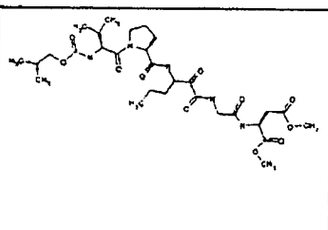
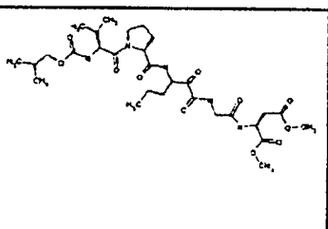
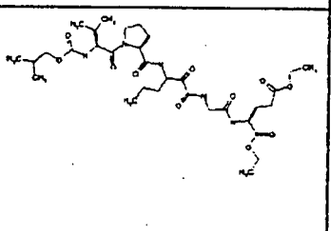
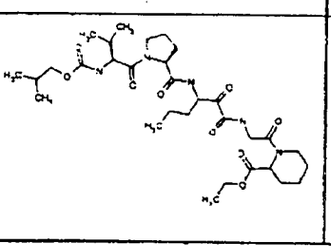
Mientras que la invención se ha descrito en forma conjunta con las realizaciones específicas que se establecieron anteriormente, muchas alternativas, modificaciones y otras variaciones de la misma resultarán aparentes para aquellos con experiencia común en el arte. Todas dichas alternativas, modificaciones y variaciones caen dentro del espíritu y el alcance de la presente invención.

Tabla 2

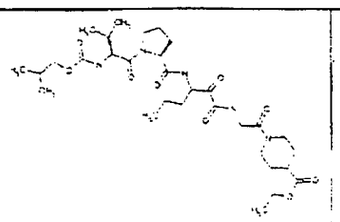
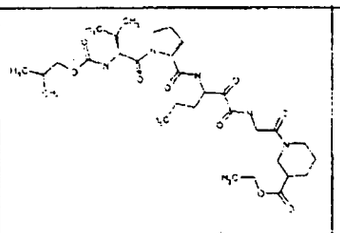
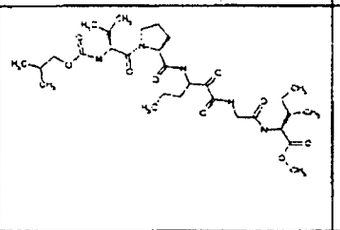
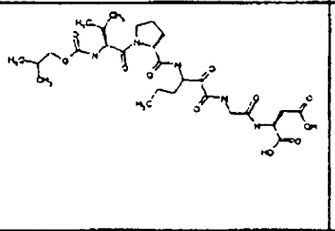
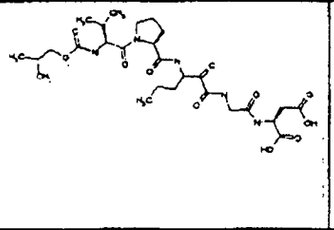
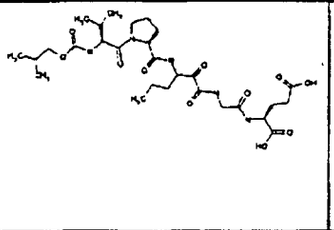
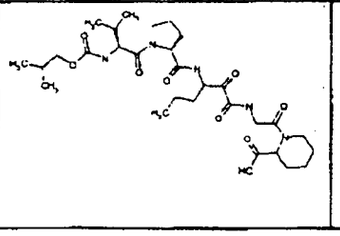
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Ej. #	ESTRUCTURA	Peso Molecular
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4		527.6259
5		698.7799
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7		381.476

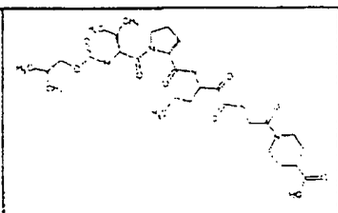
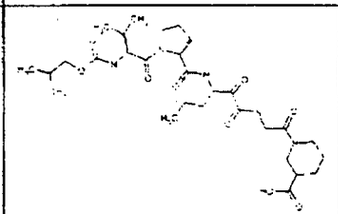
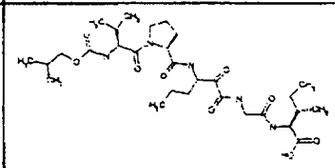
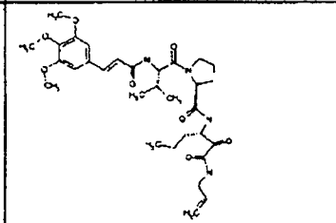
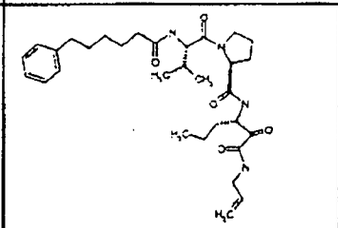
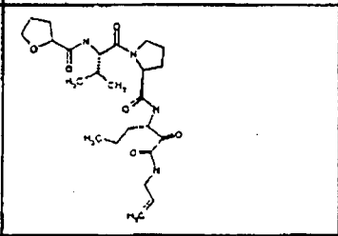
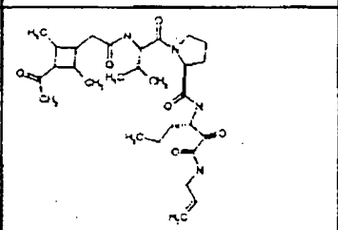
033535

8		540.6626
9		498.5813
10		633.7482
11		641.7249
12		641.7249
13		683.8061
14		637.7802

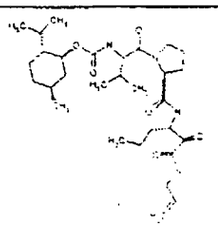
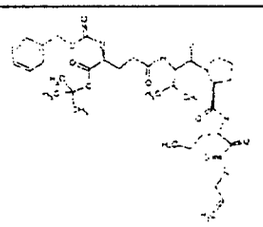
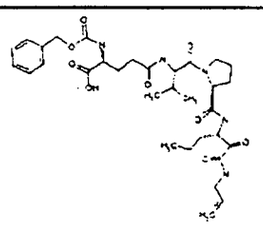
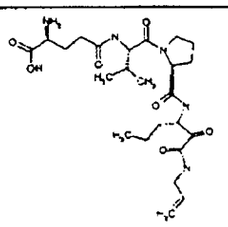
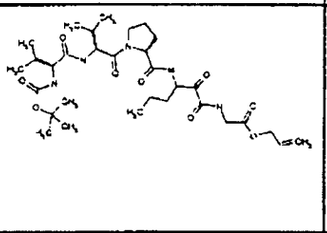
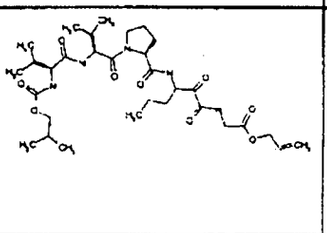
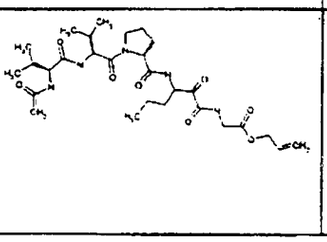
033535

15		637.7802
16		637.7802
17		625.769
18		613.6707
19		613.6707
20		627.6978
21		609.726

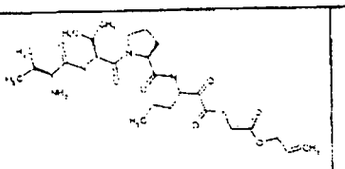
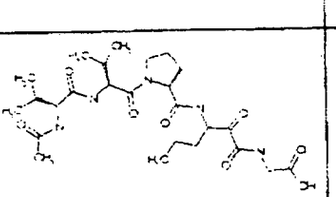
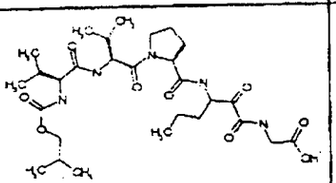
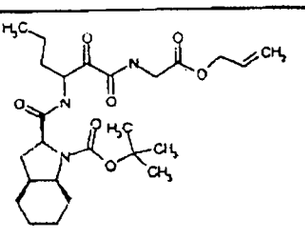
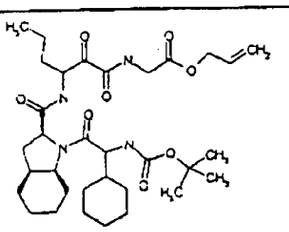
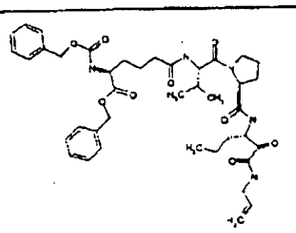
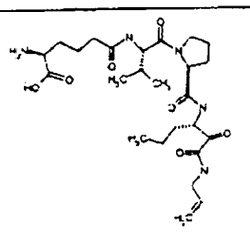
033597

22		609.726
23		609.726
24		611.742
25		600.7183
26		554.7361
27		478.5937
28		546.7132

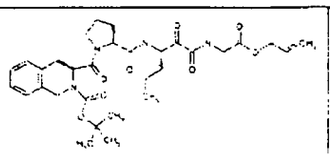
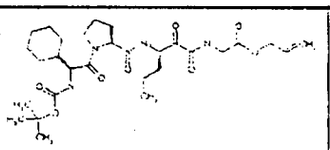
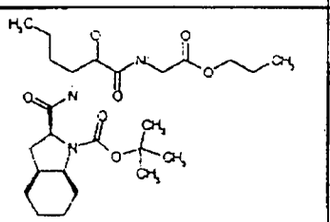
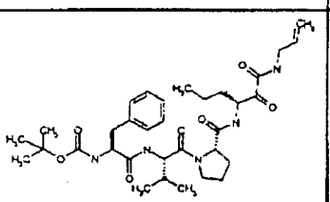
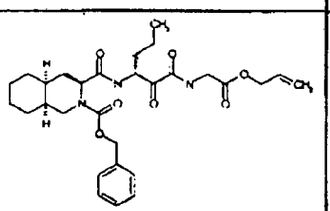
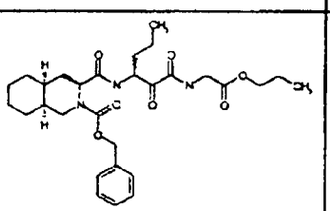
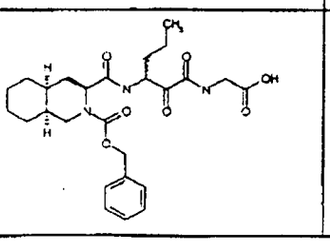
000598

29		562.7562
30		699.8519
31		643.7435
32		509.6077
33		637.7802
34		637.7802
35		579.6995

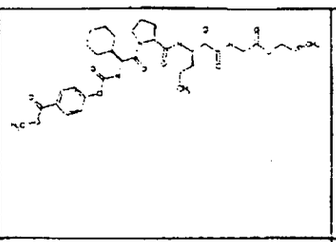
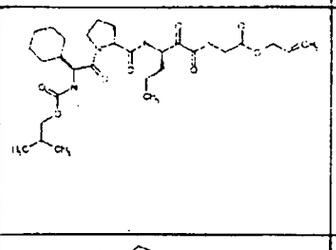
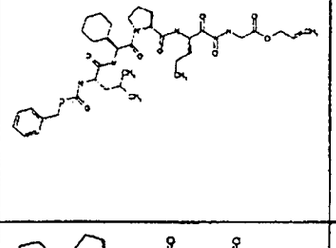
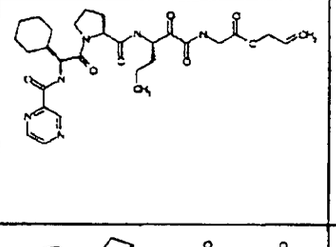
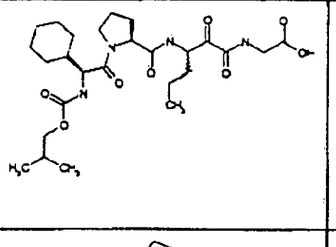
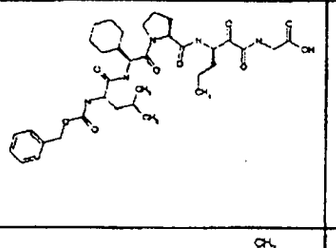
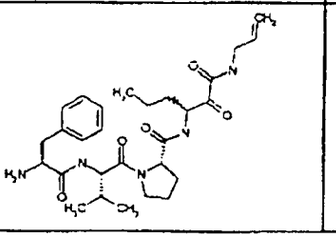
000599

36		537.6619
37		539.6342
38		597.7149
39		493.6055
40		632.8044
41		747.8965
42		523.6348

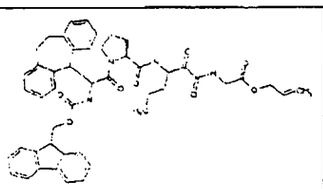
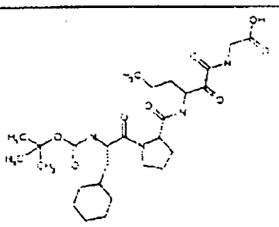
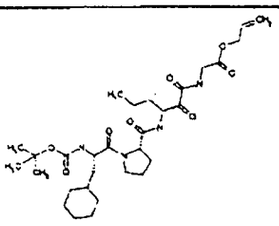
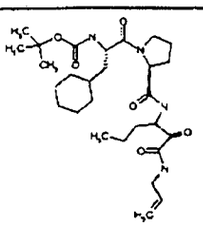
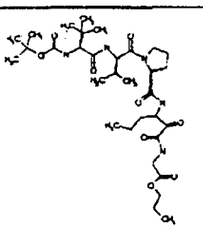
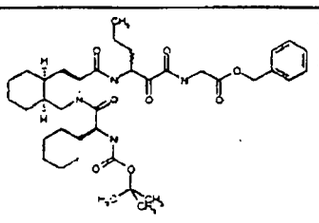
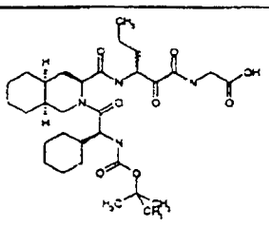
000300

43		598.7024
44		578.712
45		495.6214
46		627.7878
47		541.6501
48		543.666
49		501.5847

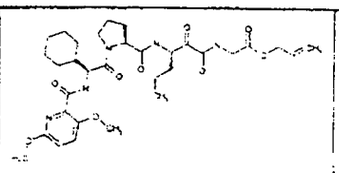
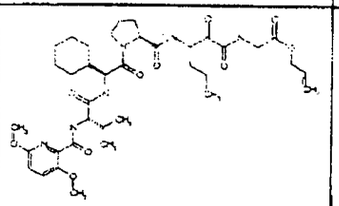
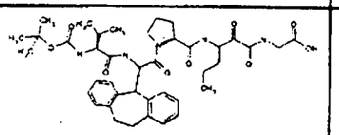
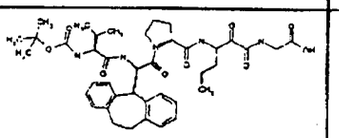
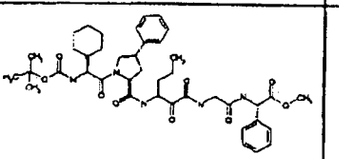
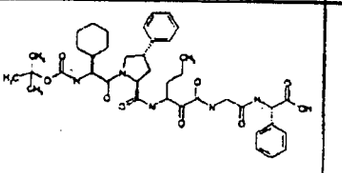
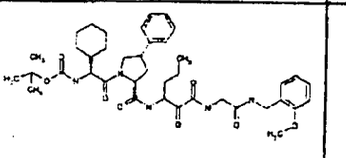
000301

50		656.7394
51		578.712
52		725.8901
53		584.6782
54		538.6467
55		685.8248
56		527.6695

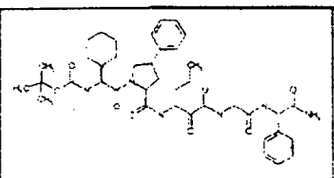
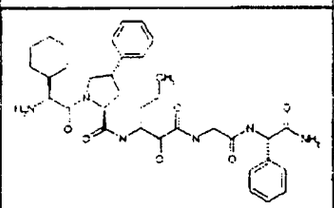
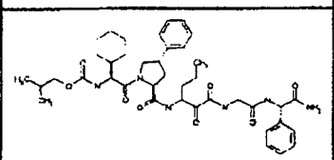
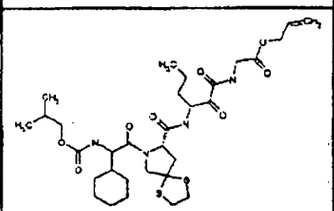
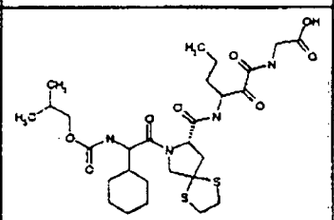
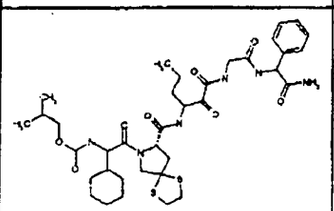
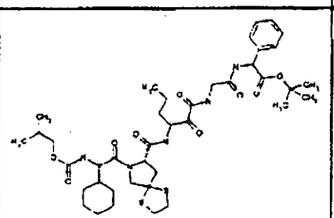
033302

57		810.9557
58		552.6737
59		592.7391
60		534.702
61		653.8232
62		696.892
63		606.7662

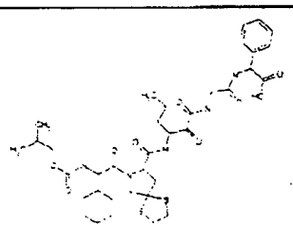
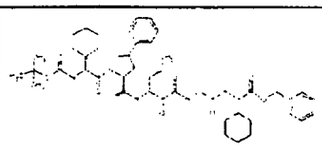
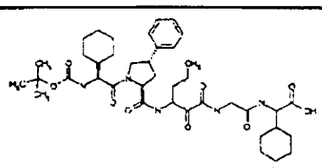
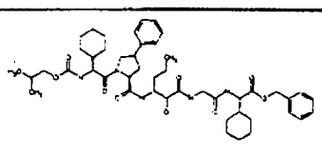
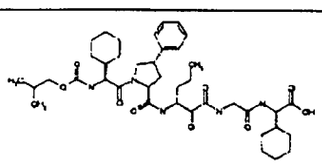
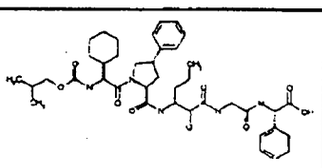
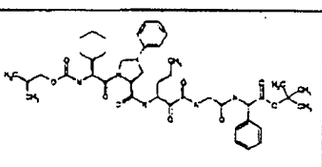
000303

64		643.7435
65		742.8771
66		747.8965
67		747.8965
68		761.9236
69		747.8965
70		733.913

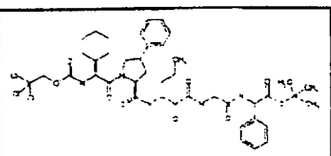
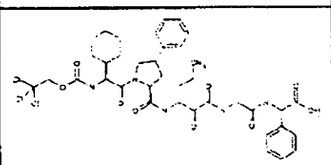
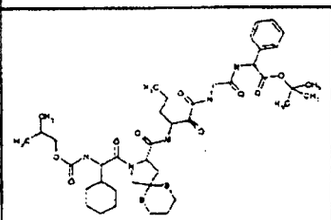
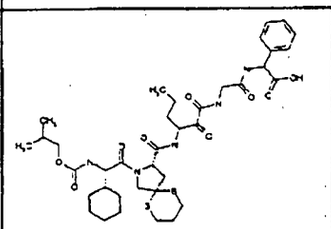
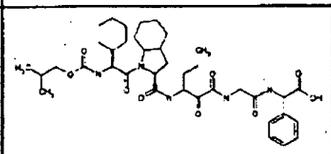
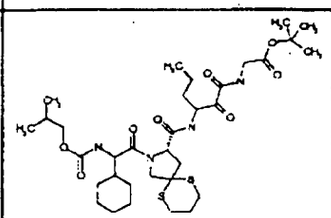
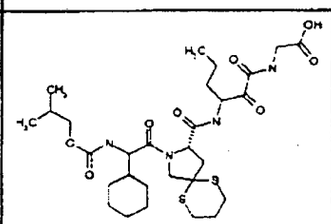
033304

71		746.9118
72		646.7935
73		746.9118
74		668.8782
75		628.8129
76		760.9792
77		818.0723

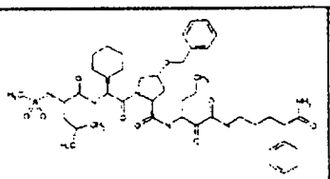
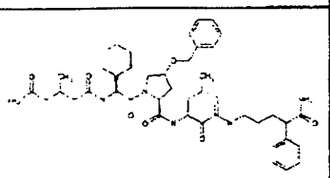
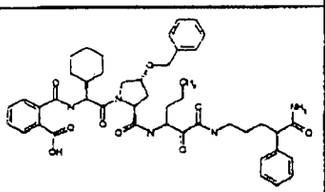
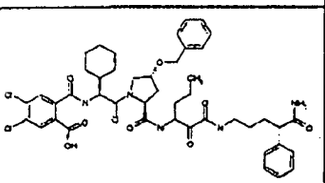
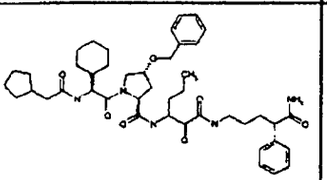
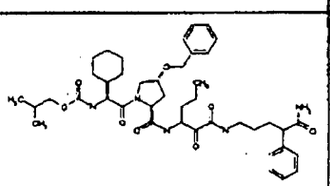
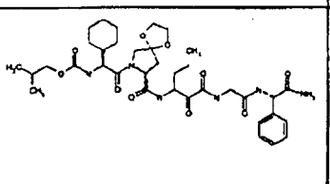
000305

78		761.964
79		844.0702
80		753.9443
81		844.0702
82		753.9443
83		747.8965
84		804.0049

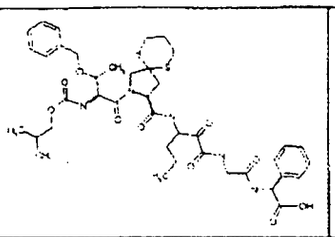
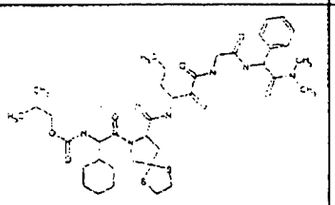
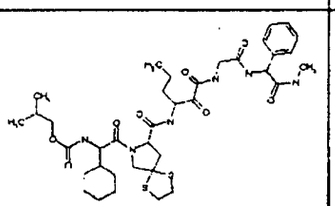
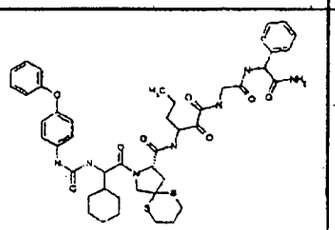
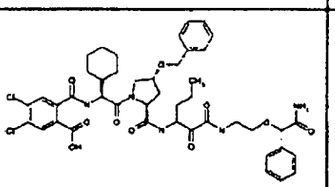
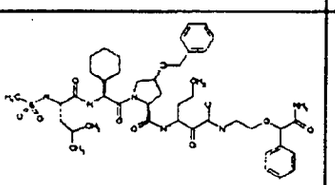
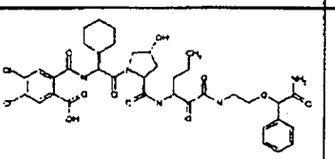
000306

85		879.2858
86		823.1774
87		832.0994
88		775.9911
89		725.8901
90		698.9483
91		642.84

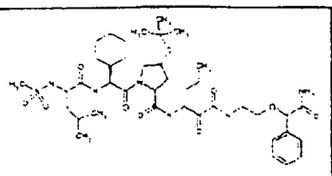
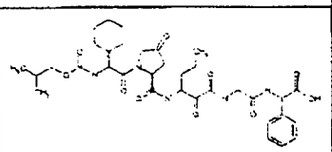
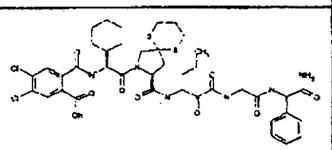
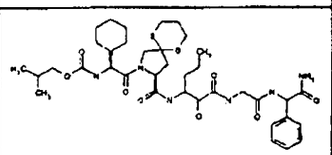
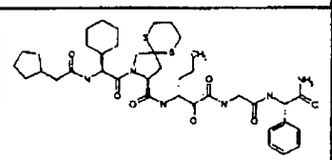
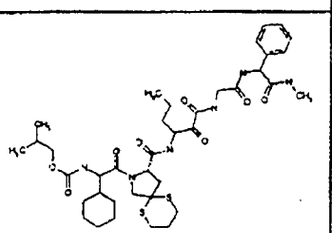
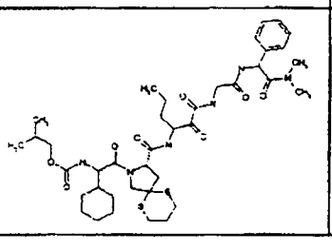
000307

92		853.0995
93		789.9778
94		809.9682
95		878.8583
96		772.006
97		761.9672
98		728.85

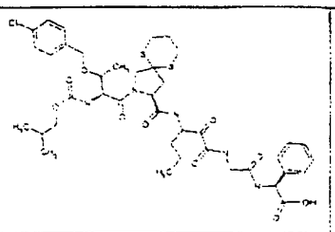
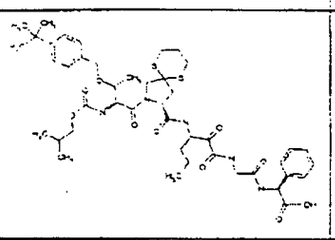
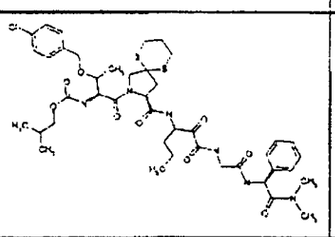
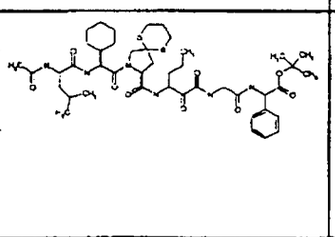
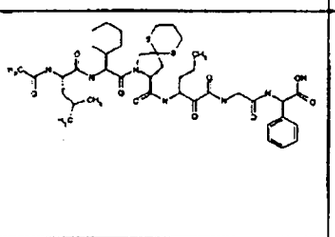
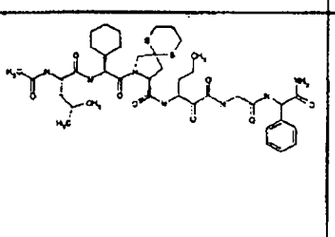
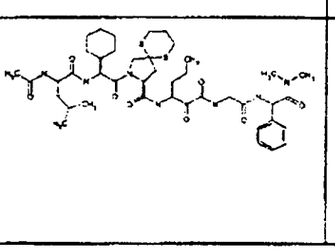
030308

99		828.0239
100		789.0334
101		775.0063
102		886.1102
103		880.8306
104		855.0718
105		790.7047

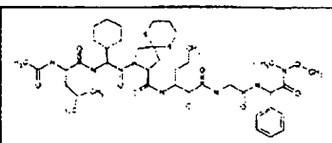
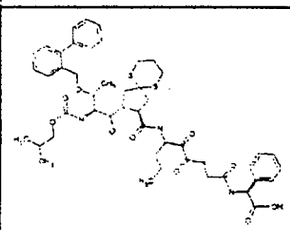
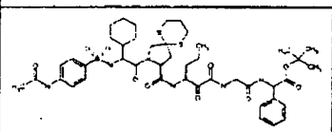
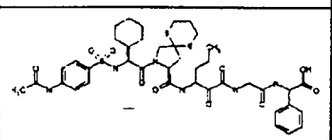
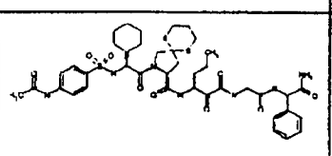
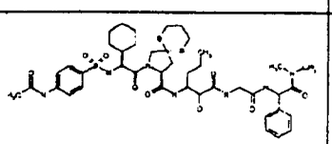
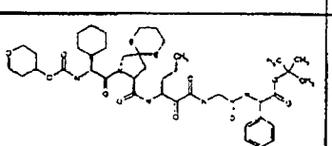
000309

106		821.0543
107		685.7812
108		891.8973
109		775.0063
110		785.0452
111		789.0334
112		803.0605

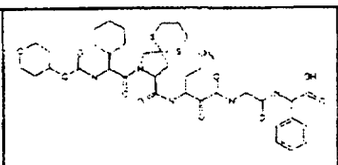
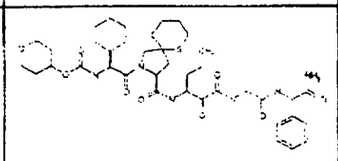
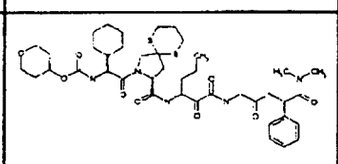
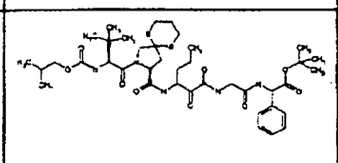
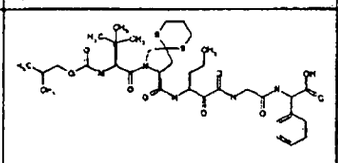
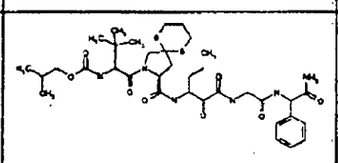
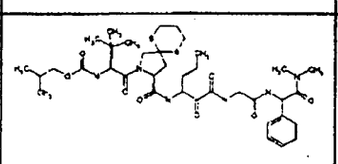
030510

113		862.4689
114		884.1323
115		889.5384
116		887.1794
117		831.071
118		830.0863
119		858.1405

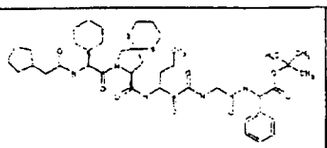
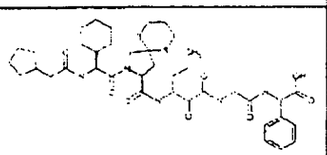
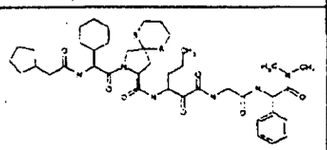
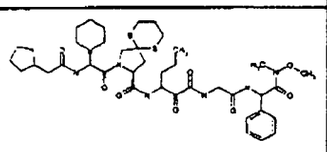
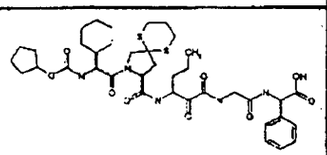
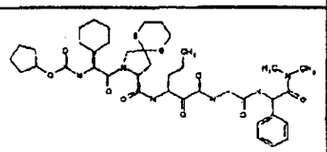
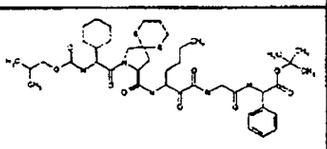
000511

120		874.1399
121		904.1227
122		929.195
123		873.0867
124		872.1019
125		900.1561
126		860.11

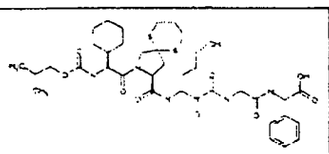
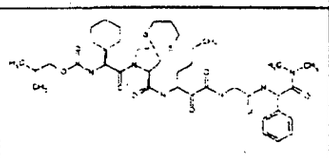
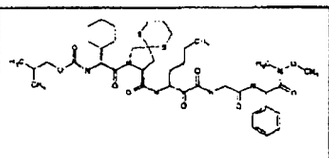
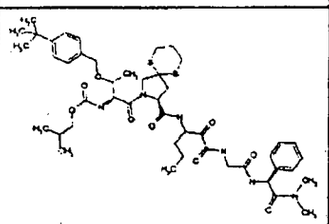
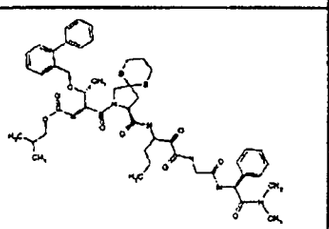
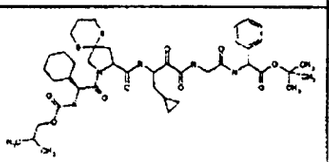
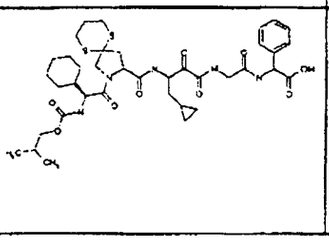
000312

127		804.0016
128		803.0169
129		831.071
130		806.0612
131		749.9528
132		748.9681
133		777.0223

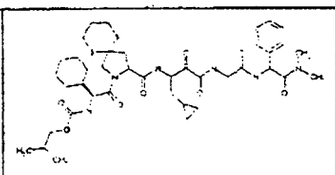
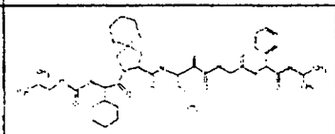
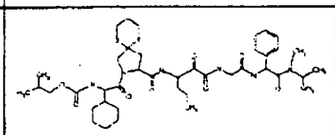
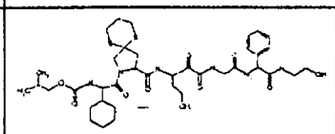
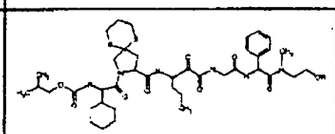
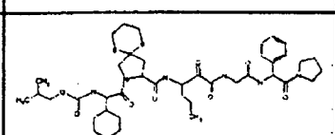
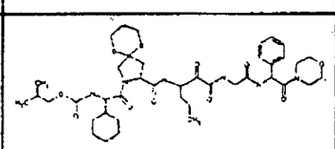
000513

134		842.1382
135		786.0299
136		813.0994
137		829.0988
138		788.0022
139		815.0717
140		846.1265

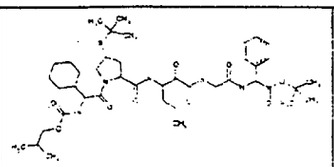
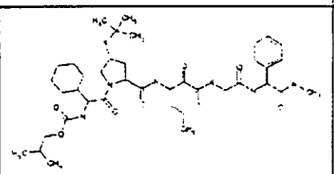
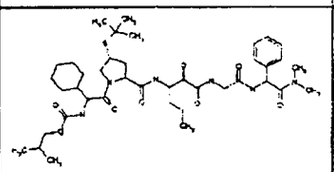
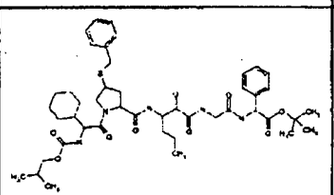
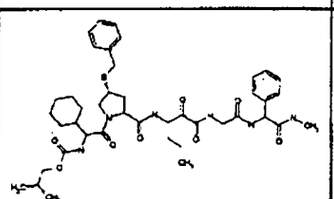
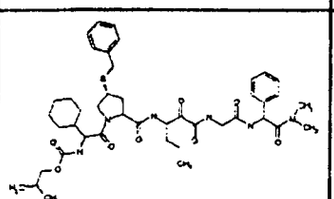
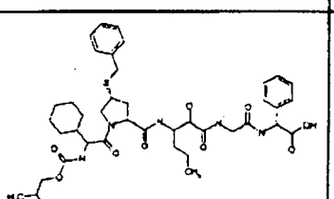
000314

141		790.0181
142		817.0876
143		833.087
144		911.2017
145		931.1921
146		844.1106
147		788.0022

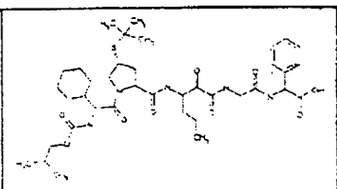
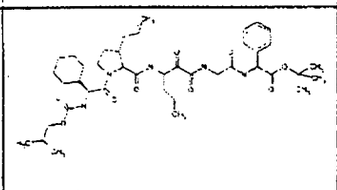
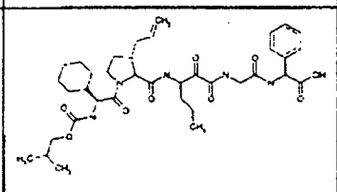
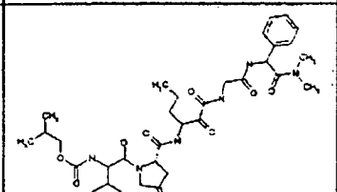
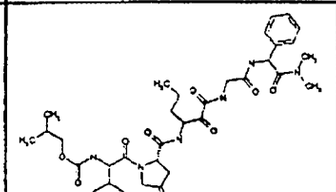
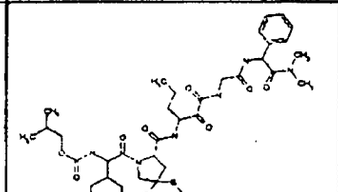
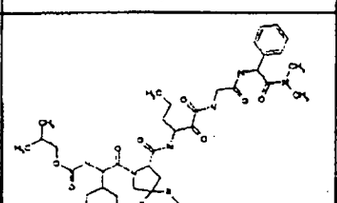
000315

148		815.0717
149		817.0876
150		831.1147
151		819.0599
152		833.087
153		829.0988
154		845.0981

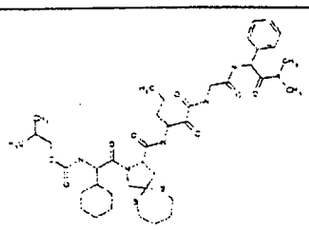
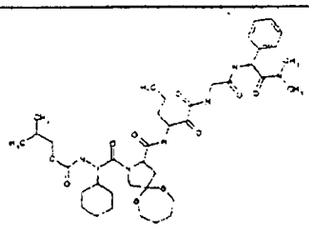
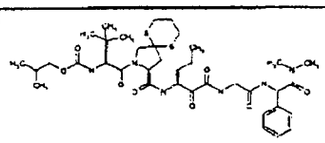
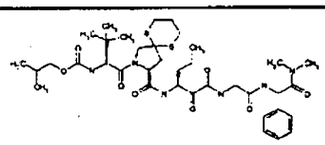
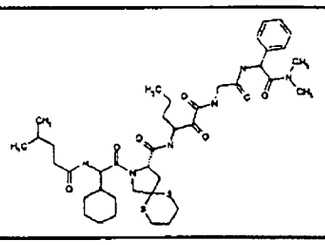
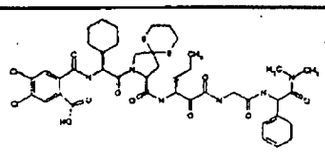
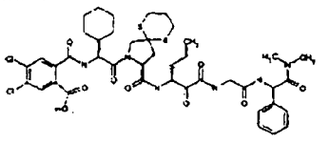
033516

155		816.0784
156		773.0125
157		787.0396
158		850.0959
159		807.03
160		821.0571
161		793.9876

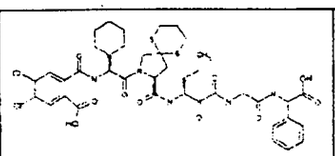
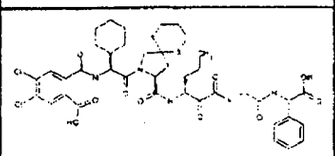
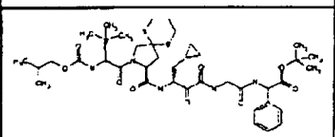
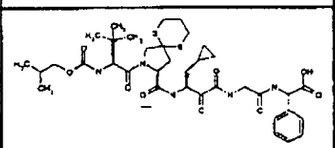
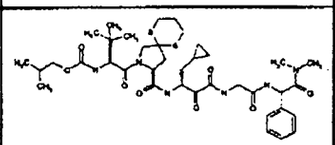
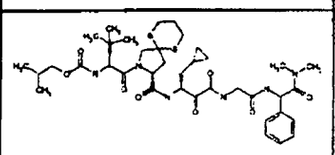
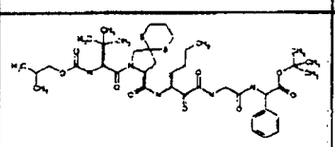
000517

162		759.9701
163		767.9714
164		711.863
165		712.8506
166		712.8506
167		817.0876
168		817.0876

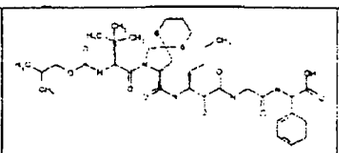
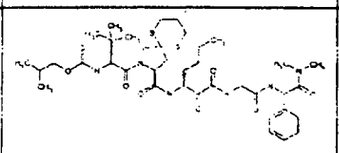
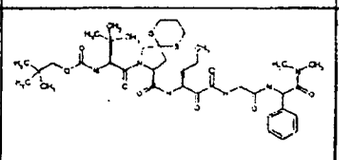
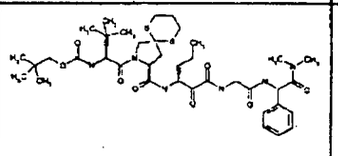
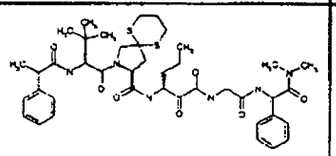
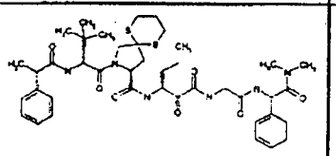
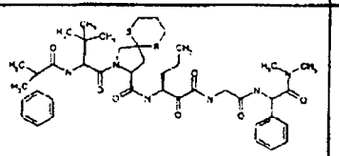
000318

169		817.0876
170		817.0876
171		777.0223
172		777.0223
173		801.0882
174		919.9515
175		919.9515

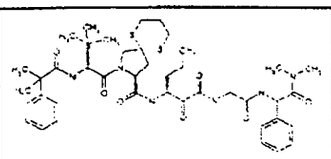
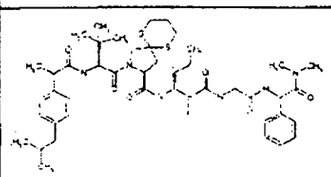
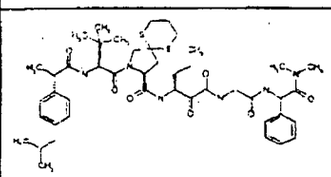
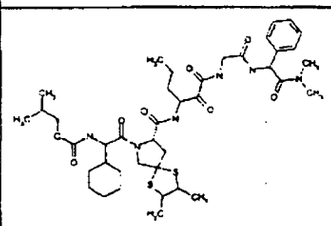
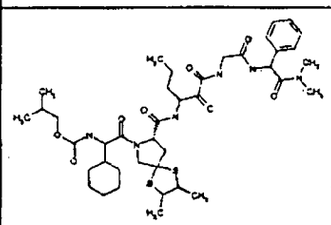
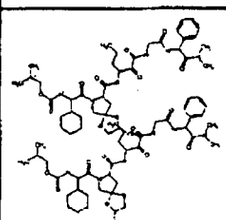
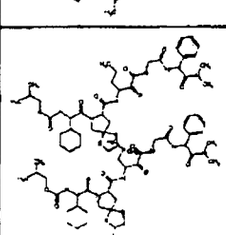
000319

176		892.8821
177		892.8821
178		818.0723
179		761.964
180		789.0334
181		789.0334
182		820.0883

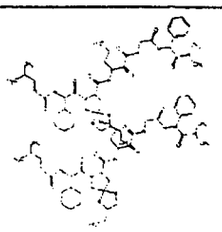
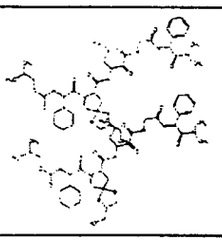
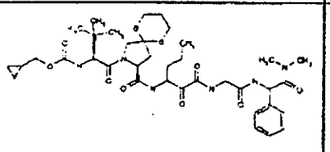
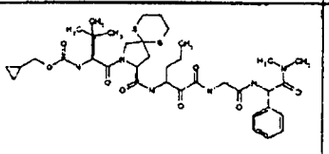
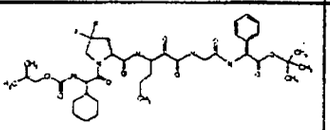
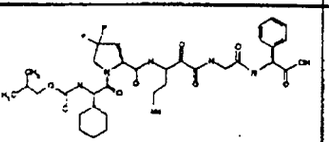
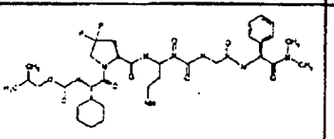
000320

183		763.9799
184		791.0494
185		791.0494
186		791.0494
187		809.0674
188		809.0674
189		823.0945

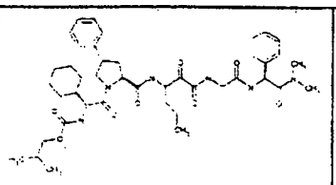
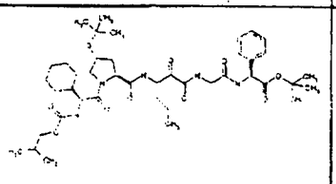
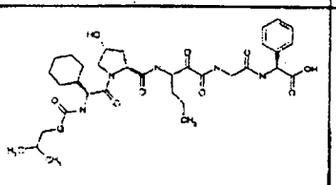
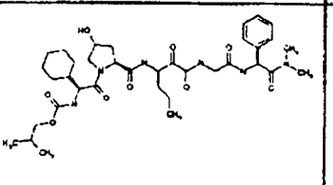
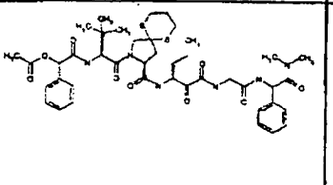
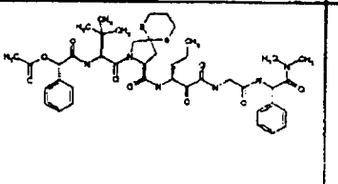
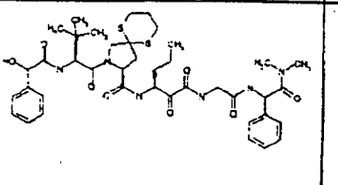
000321

190		823.0945
191		865.1758
192		865.1758
193		817.0876
194		817.0876
195		1606.121
196		1606.121

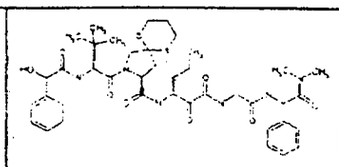
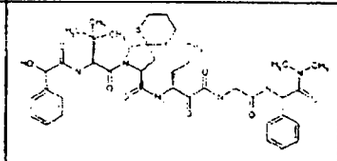
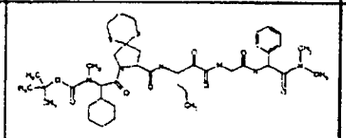
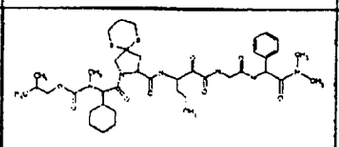
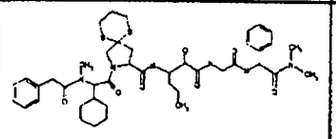
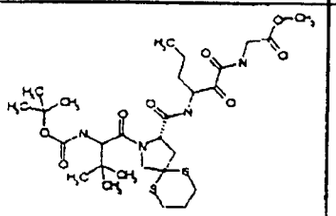
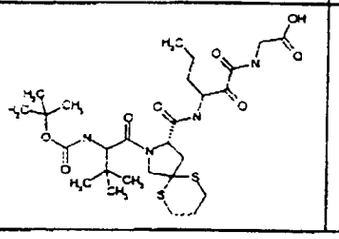
000322

197		1638.12
198		1638.12
199		775.0063
200		775.0063
201		763.887
202		707.7786
203		734.848

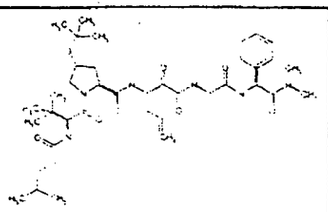
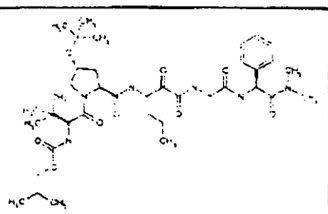
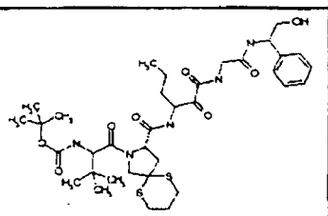
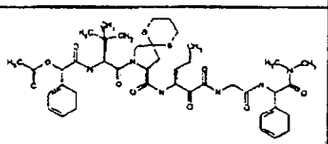
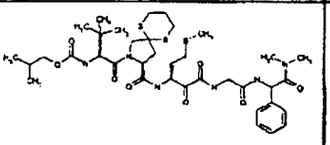
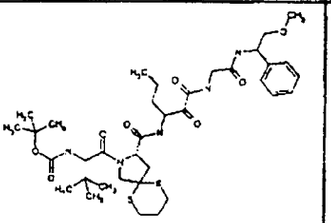
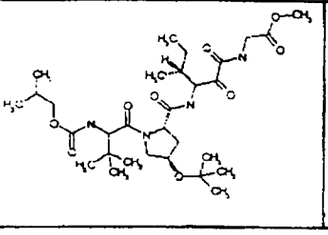
000523

204		774.9659
205		800.0139
206		687.7971
207		714.8666
208		853.0774
209		853.0774
210		811.0398

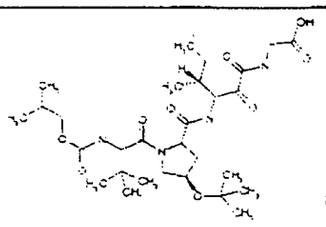
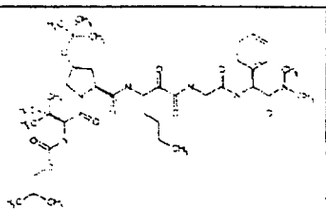
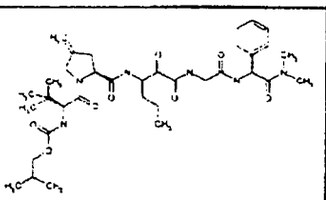
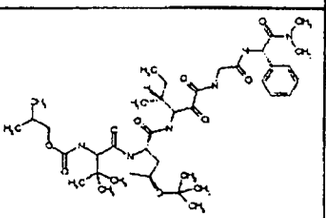
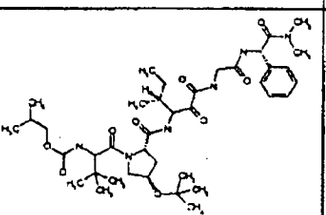
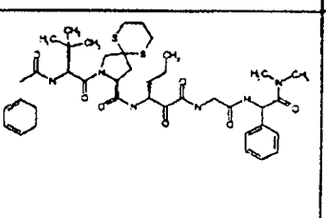
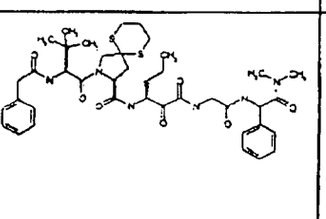
000524

211		811.0398
212		811.0398
213		817.0876
214		817.0876
215		835.1057
216		630.8288
217		616.8018

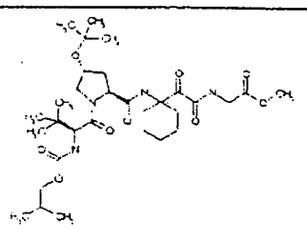
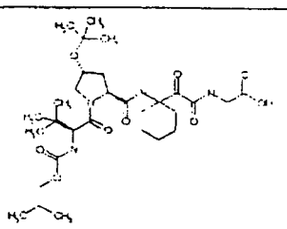
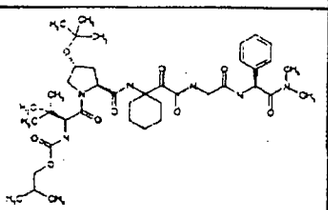
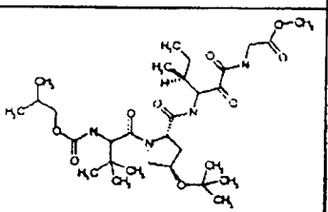
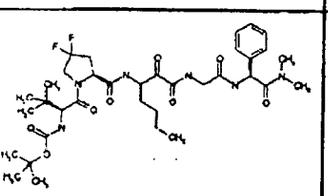
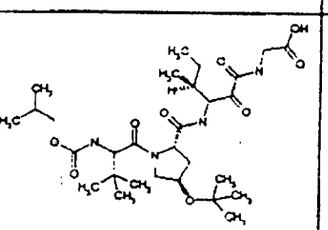
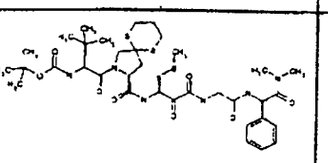
000325

218		742.9208
219		744.9367
220		735.9694
221		853.0774
222		809.0862
223		749.9965
224		612.7703

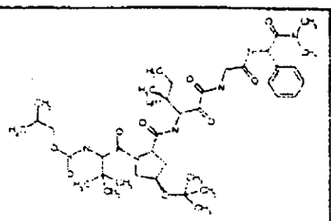
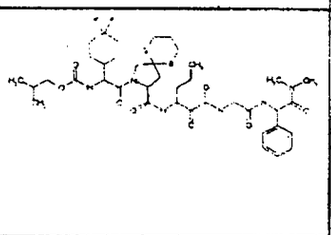
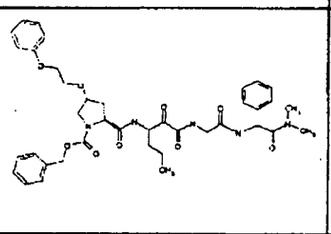
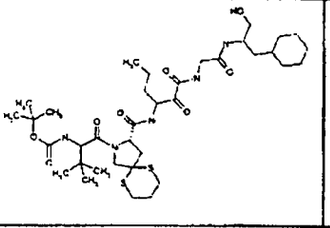
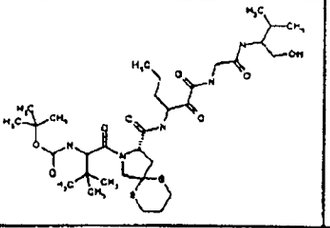
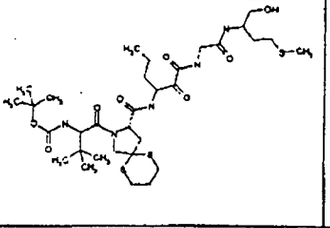
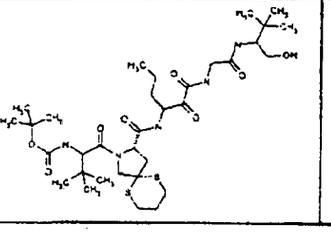
030326

225		598.7432
226		758.9638
227		684.8401
228		758.9638
229		758.9638
230		795.0404
231		795.0404

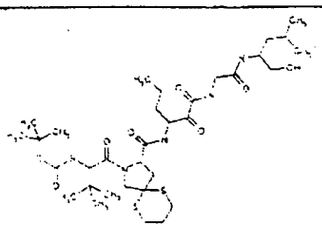
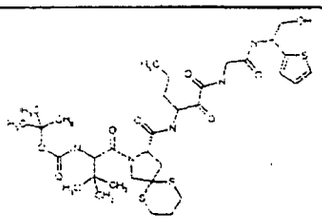
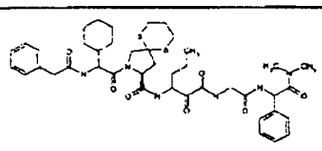
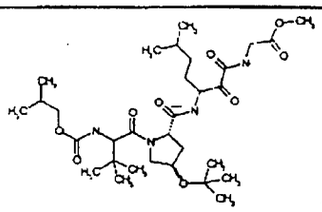
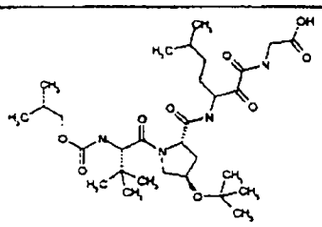
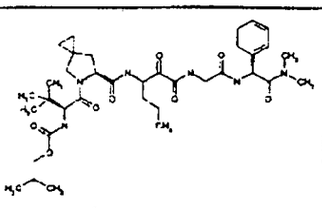
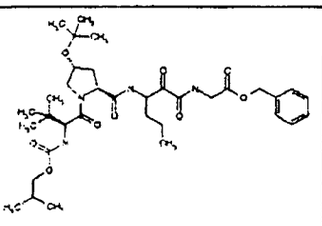
000327

232		624.7815
233		610.7544
234		770.9749
235		612.7703
236		722.8369
237		598.7432
238		795.0592

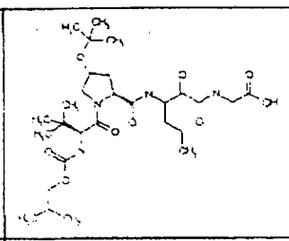
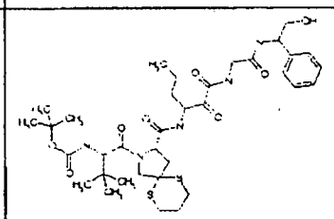
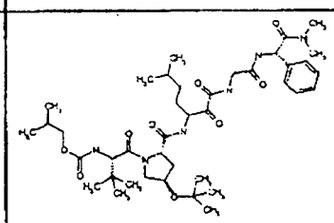
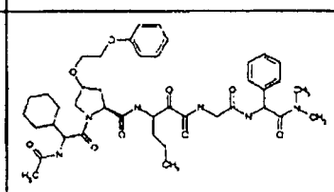
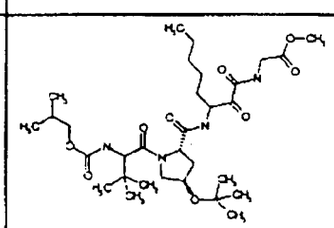
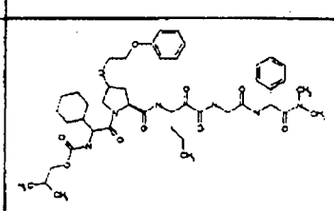
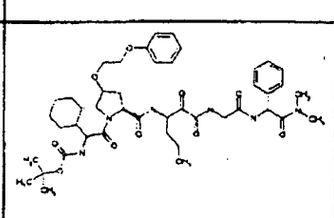
000328

239		758.9638
240		839.0414
241		729.8375
242		756.0443
243		701.9518
244		734.0159
245		715.9789

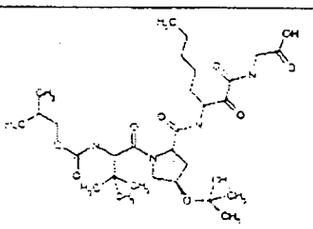
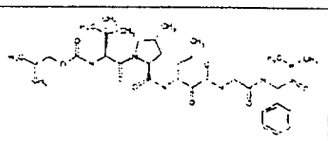
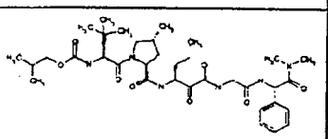
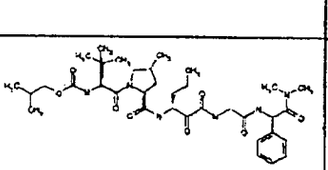
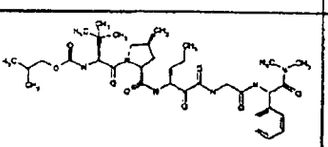
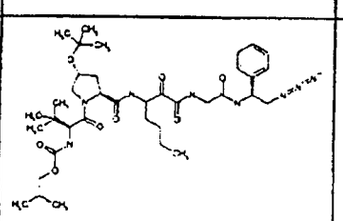
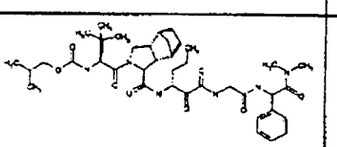
000329

246		715.9789
247		741.9951
248		821.0786
249		626.7974
250		612.7703
251		698.8672
252		674.842

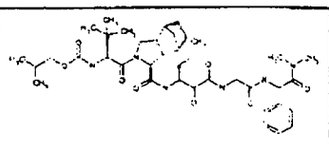
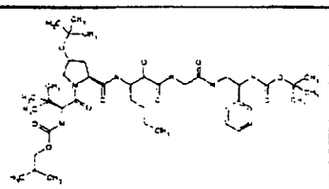
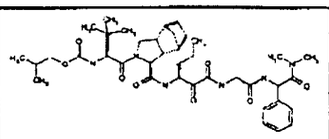
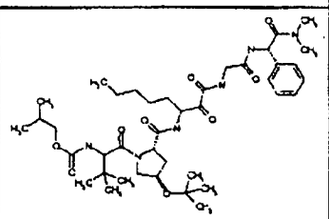
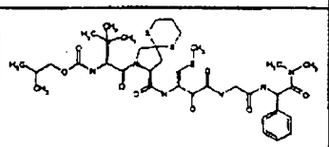
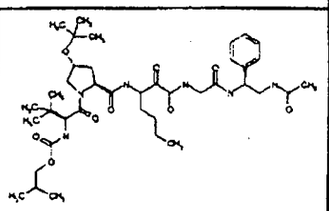
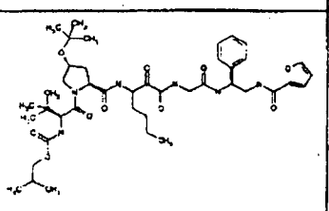
000330

253		584.7162
254		735.9694
255		772.9909
256		776.9383
257		626.7974
258		835.0189
259		835.0189

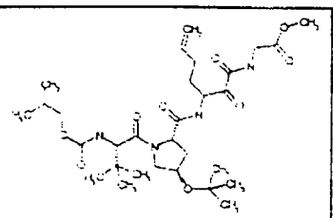
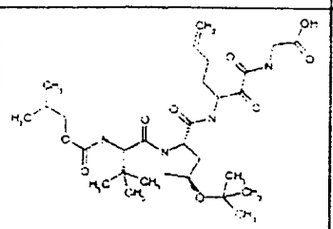
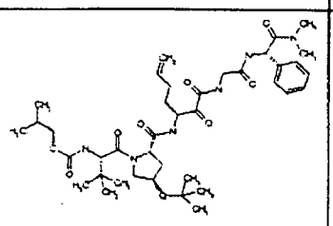
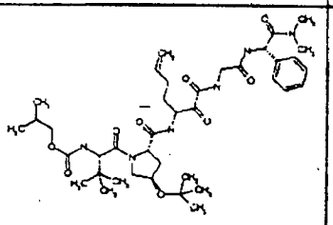
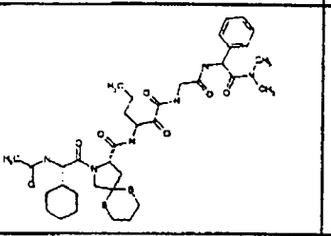
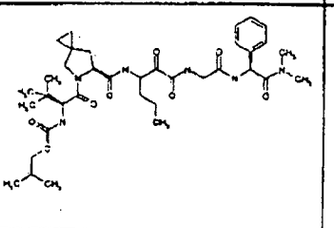
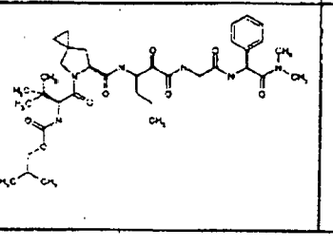
000331

260		612.7703
261		686.856
262		686.856
263		686.856
264		686.856
265		742.9236
266		738.9325

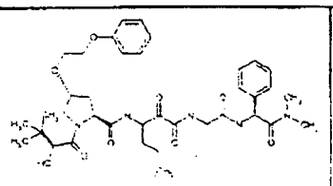
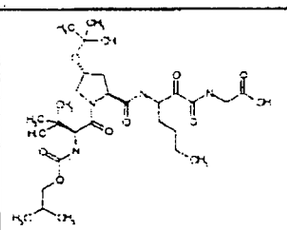
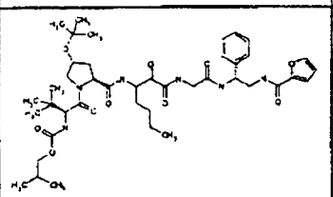
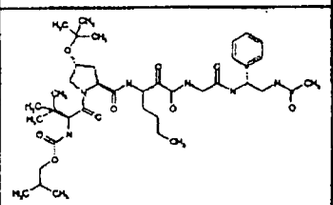
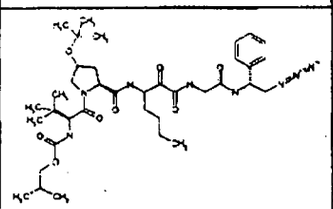
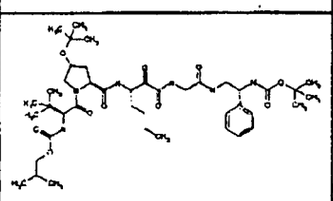
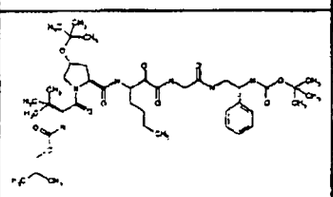
000332

267		738.9325
268		817.0444
269		738.9325
270		772.9909
271		795.0592
272		758.9638
273		810.9966

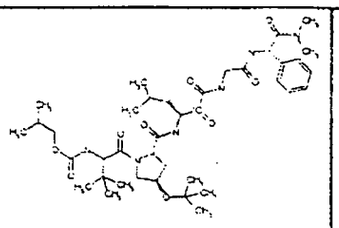
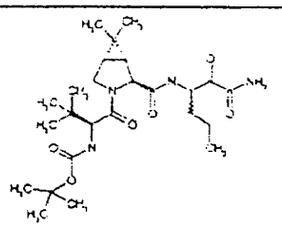
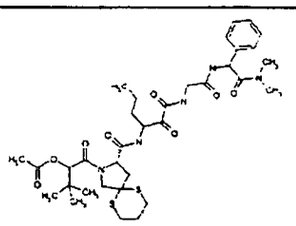
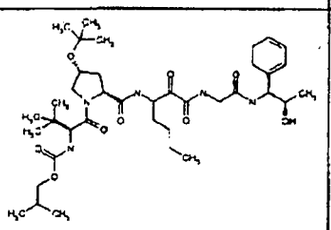
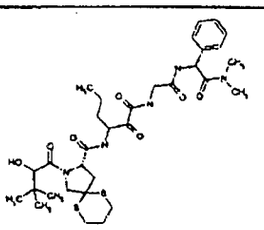
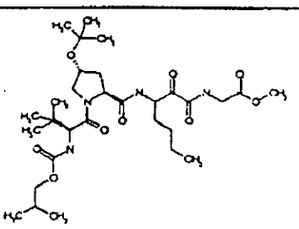
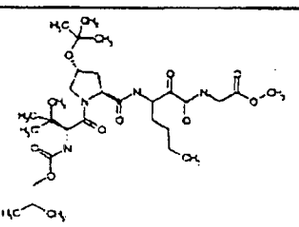
000533

274		610.7544
275		596.7273
276		756.9479
277		756.9479
278		744.9799
279		698.8672
280		698.8672

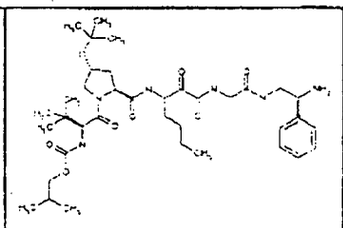
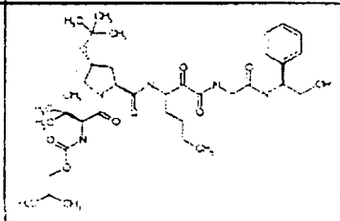
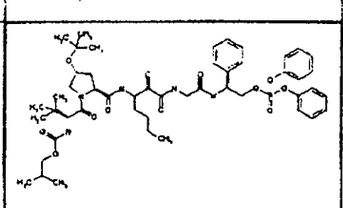
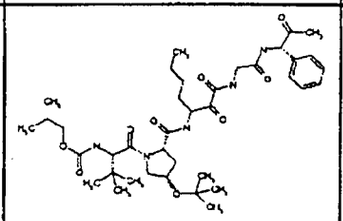
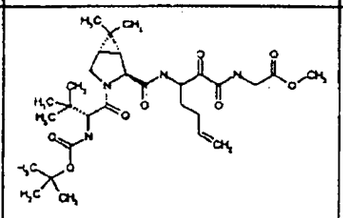
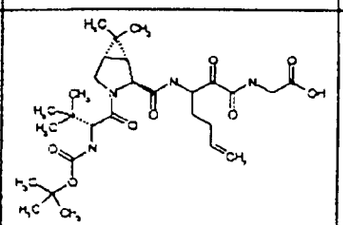
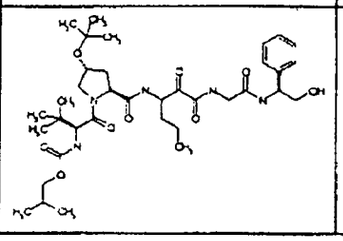
000534

281		709.8471
282		598.7432
283		810.9966
284		758.9638
285		742.9236
286		817.0444
287		817.0444

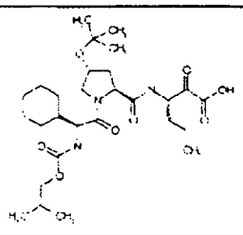
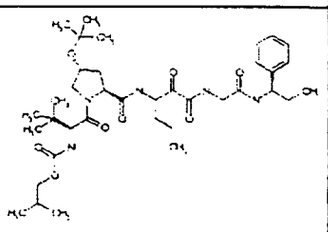
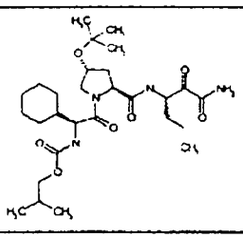
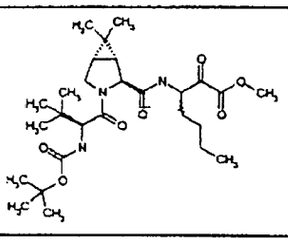
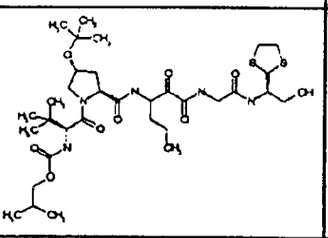
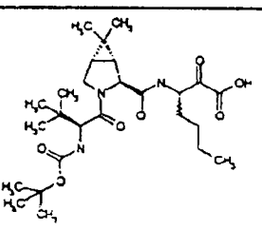
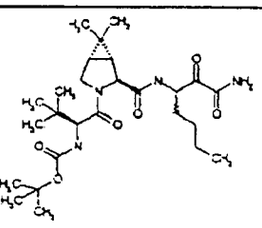
000535

288		759.9526
289		494.6367
290		719.9263
291		731.938
292		677.8887
293		612.7703
294		612.7703

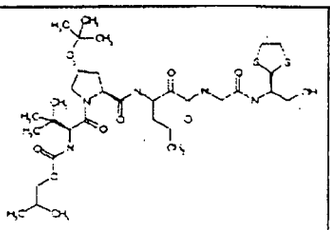
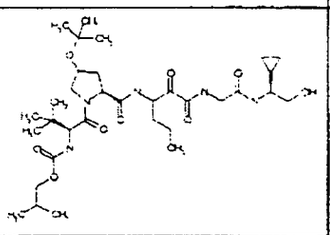
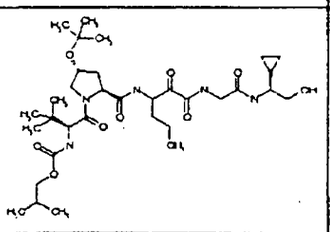
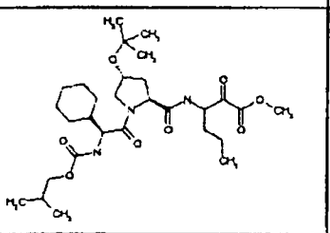
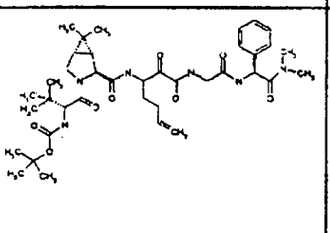
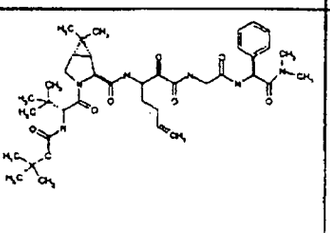
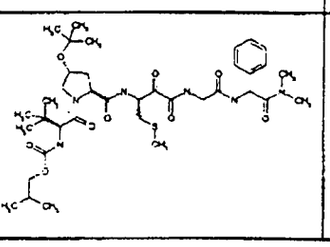
000336

295		716.9261
296		717.9109
297		950.0884
298		729.9221
299		578.712
300		564.6849
301		703.8838

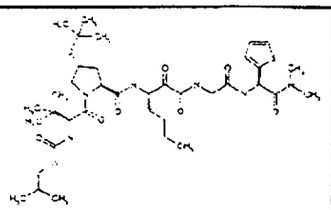
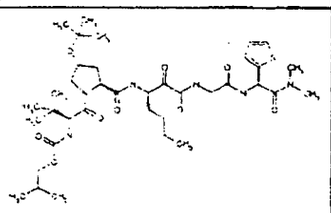
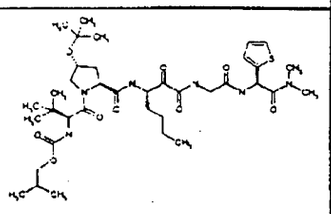
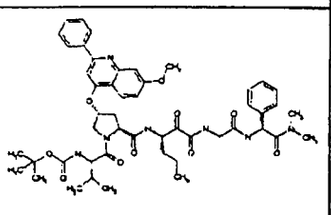
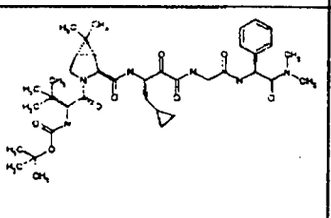
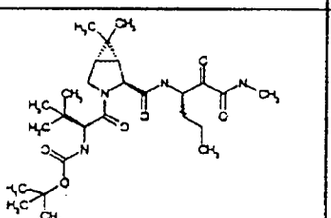
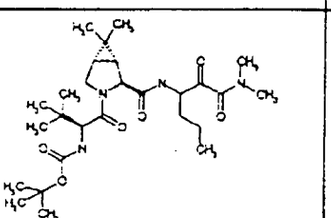
000337

302		553.7021
303		703.8838
304		552.7173
305		523.6756
306		731.9783
307		509.6485
308		508.6638

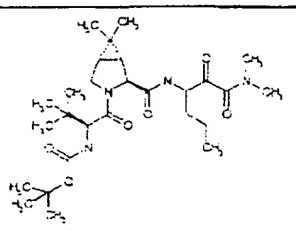
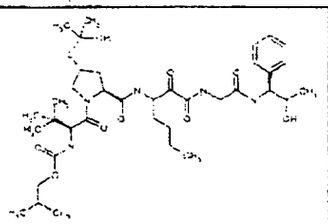
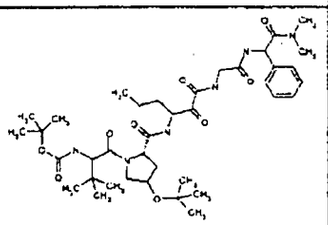
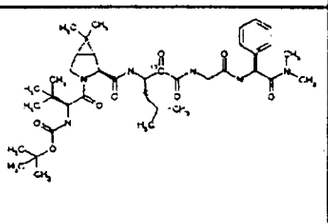
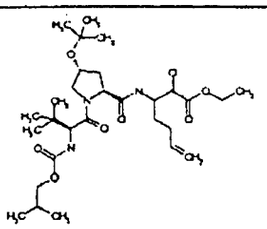
000338

309		731.9783
310		667.8503
311		667.8503
312		567.7292
313		724.9054
314		724.9054
315		762.9736

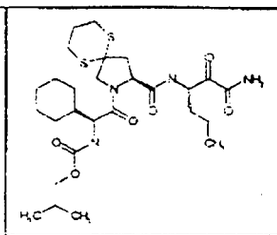
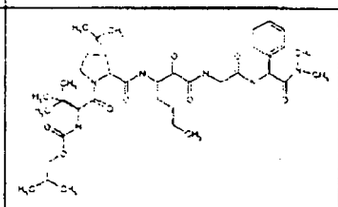
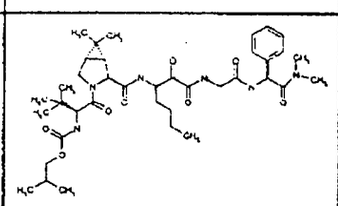
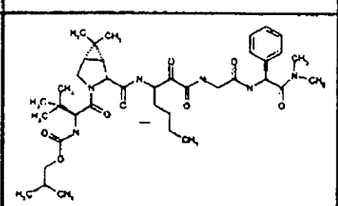
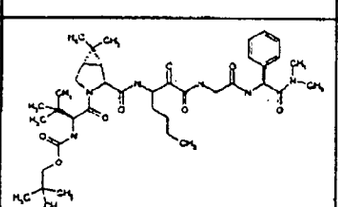
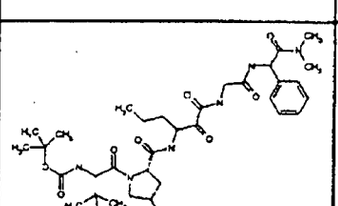
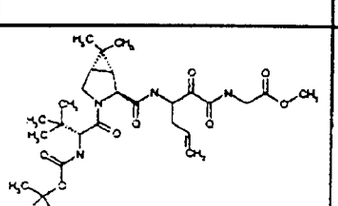
000339

316		764.9896
317		764.9896
318		764.9896
319		908.0734
320		724.9054
321		508.6638
322		522.6909

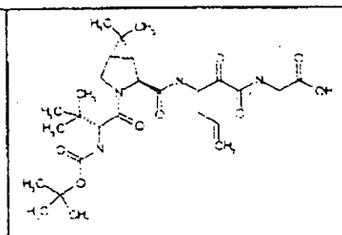
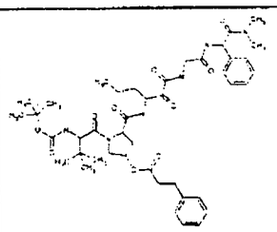
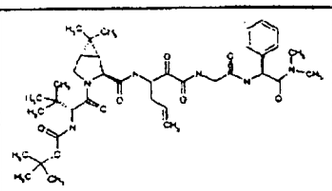
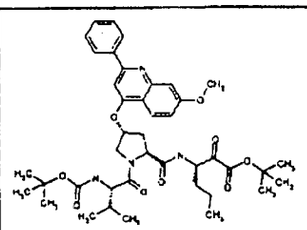
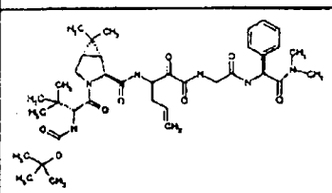
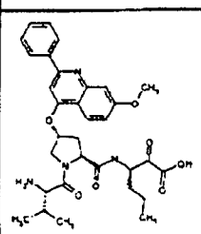
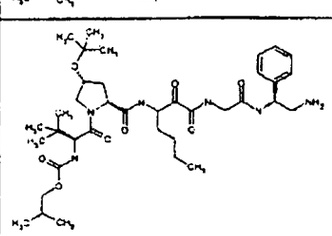
000540

323		522.6909
324		731.938
325		744.9367
326		727.9102
327		567.7292

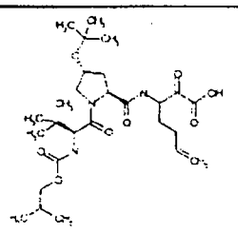
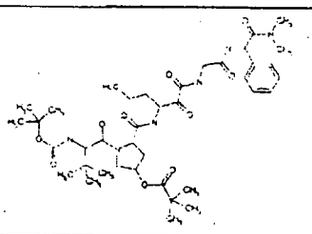
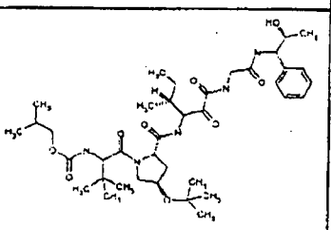
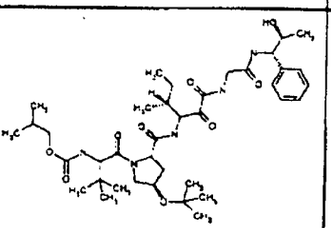
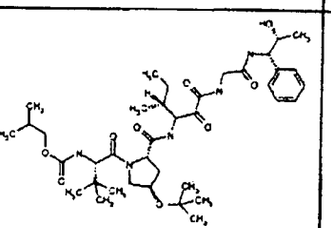
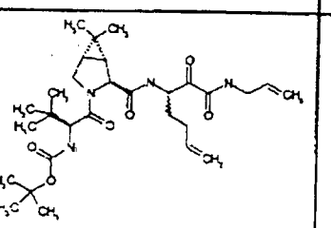
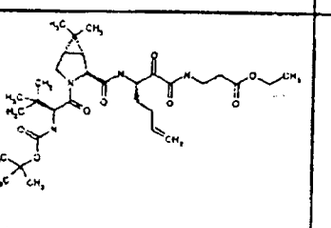
000541

328		584.8029
329		726.9214
330		726.9214
331		726.9214
332		740.9484
333		688.8284
334		564.6849

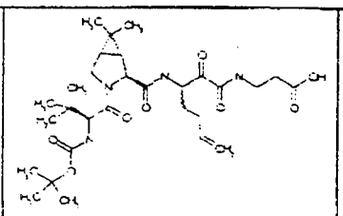
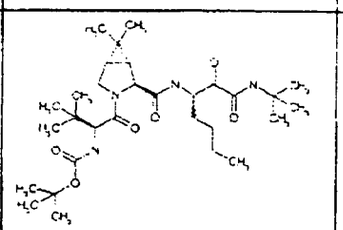
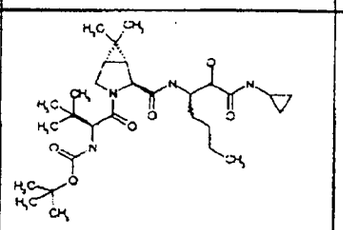
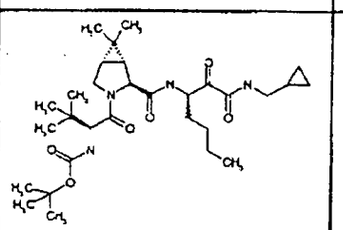
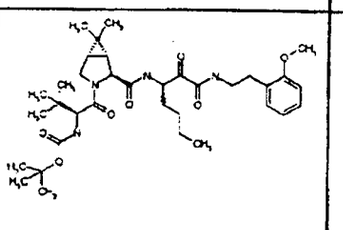
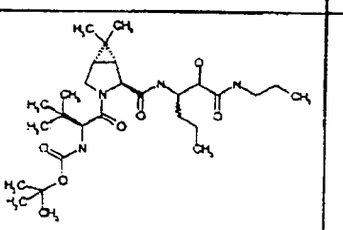
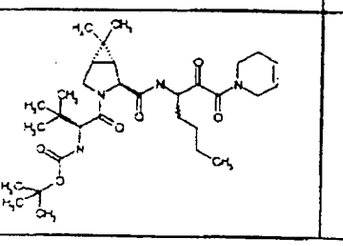
000342

335		550.6578
336		820.9918
337		710.8784
338		746.9089
339		710.8784
340		590.6823
341		716.9261

000343

342		539.675
343		772.9473
344		731.938
345		731.938
346		731.938
347		546.7132
348		606.7662

000544

349		578.712
350		564.7722
351		548.7291
352		562.7562
353		642.8432
354		536.718
355		574.7673

000345

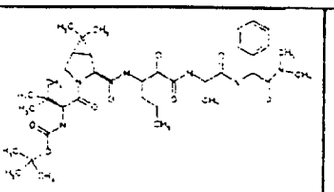
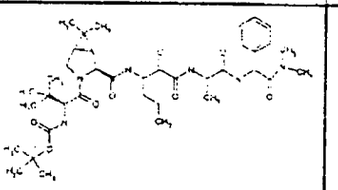
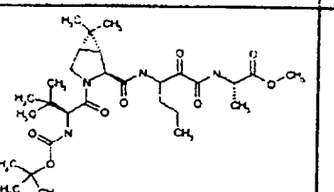
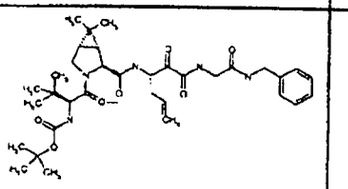
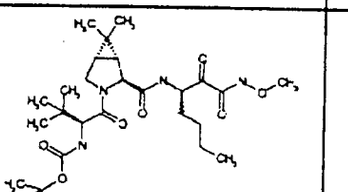
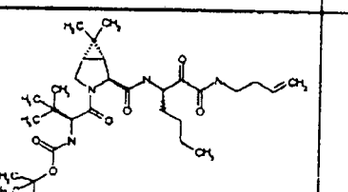
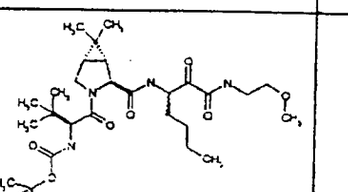
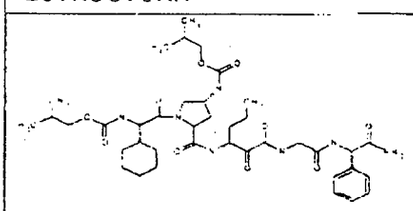
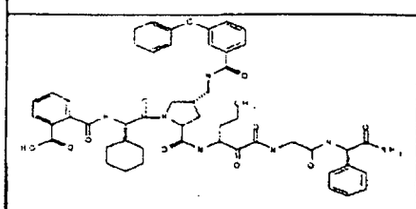
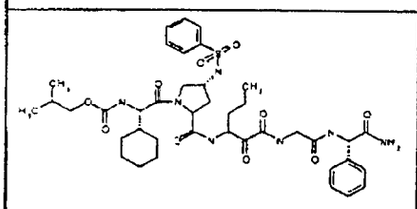
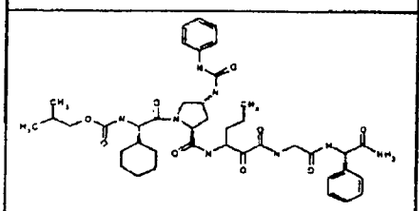
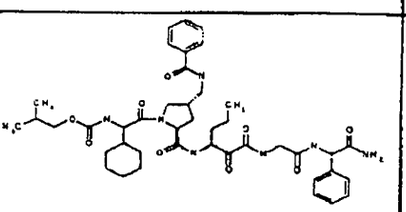
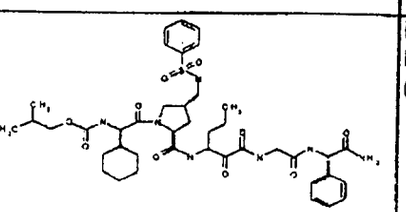
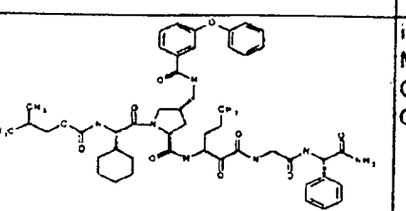
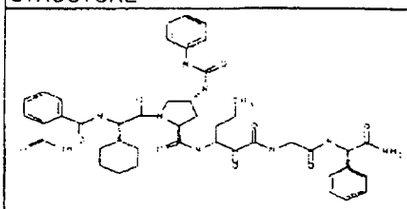
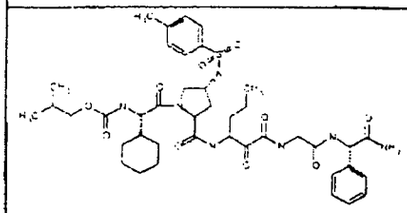
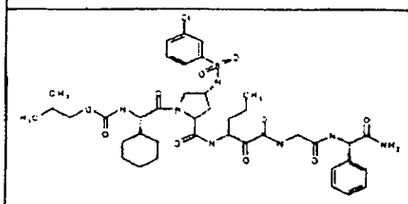
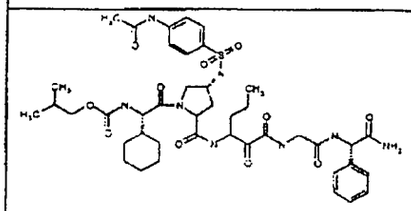
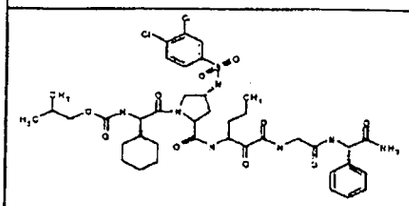
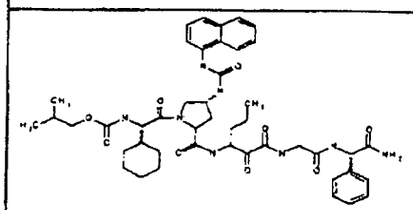
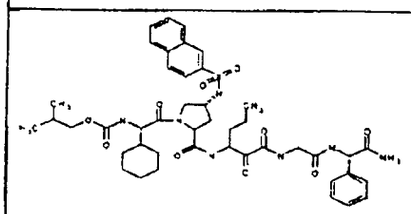
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Tabla 4

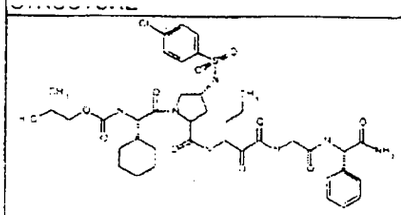
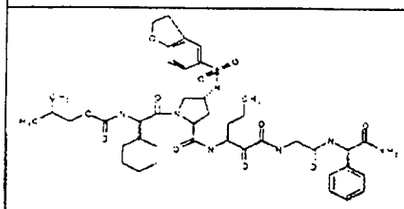
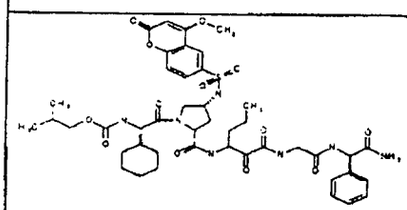
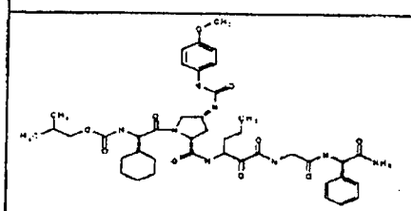
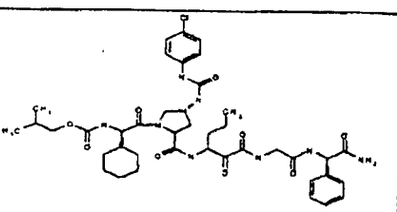
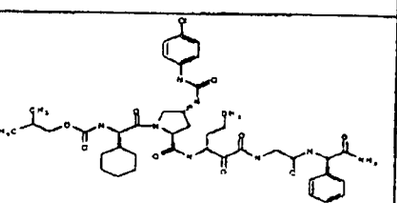
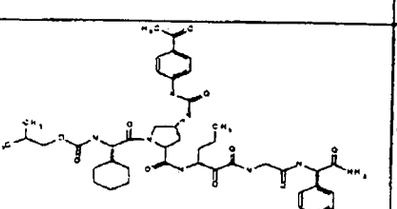
000346

ESTRUCTURA	NOMBRE	Rango 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

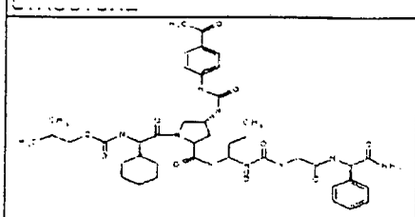
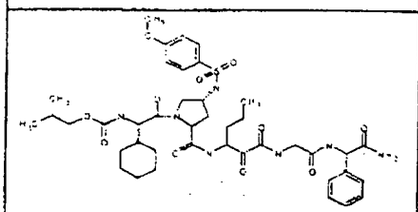
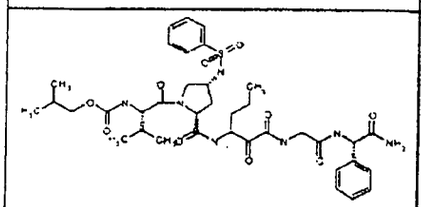
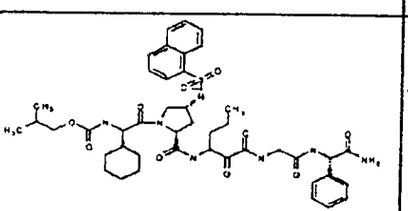
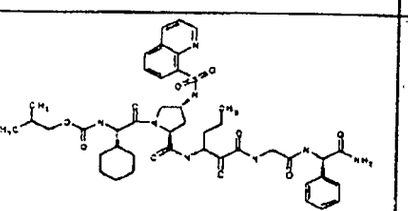
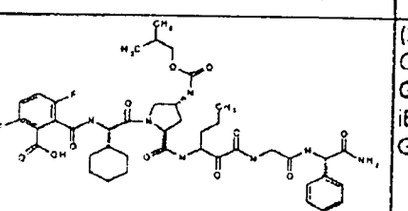
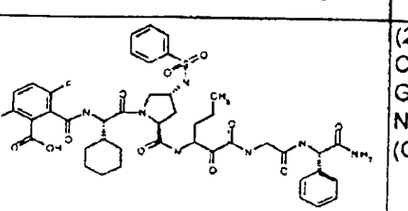
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ESTRUCTURA	NOMBRE	Rango Ki*
	(2-CO2)PhCO-G(chx)-P(4t-UreaPh)-nV-(CO)-G-G(ph)-Am	C
	iBoc-G(Chx)-P(4t-NHSO2-(4Me)Ph)-nV(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-(3Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-(4-NHAc)Ph)-nV-(CO)-G-G(Ph)-Am	A
	iBoc-G(Chx)-P(4t-NHSO2-(3,4-diCl)Ph)-nV-(CO)-G-G(Ph)-Am	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

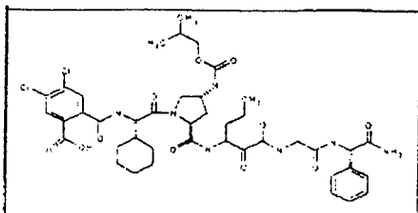
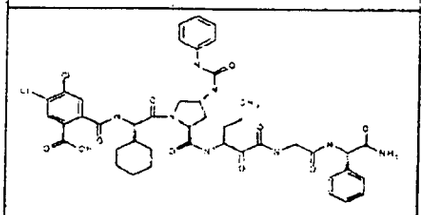
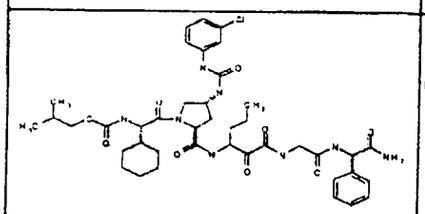
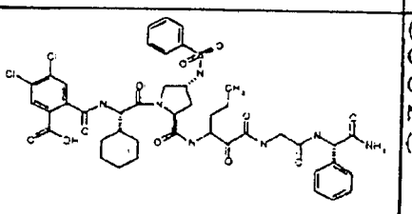
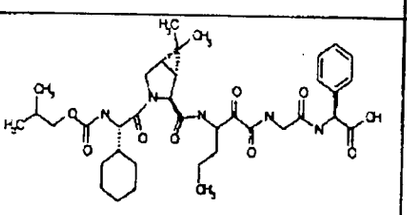
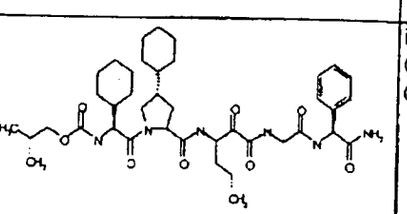
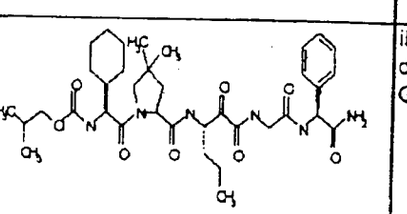
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ESTRUCTURA	NOMBRE	Rango Ki*
	iBoc-G(Chx)-P(4t-NHSO2-(4Cl)Ph)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-5(2,3-dihidrobenzofuran))-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-NHSO2-6(4-Ome)Cumarin)-nV-(CO)-G-G(Ph)-Am	B
	iBoc-G(Chx)-P(4t-Urea-Ph(4-OMe))-nV-(CO)-G-G(Ph)-Am	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

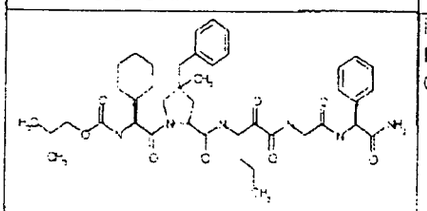
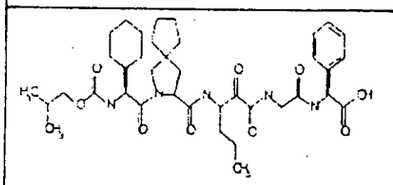
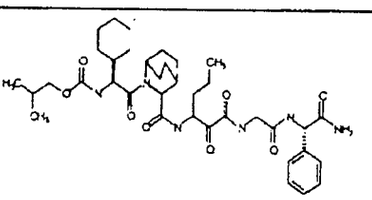
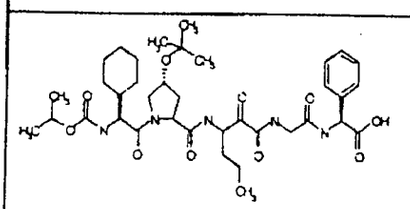
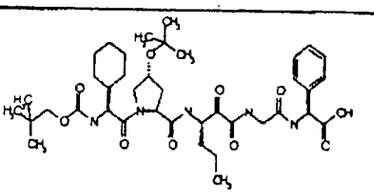
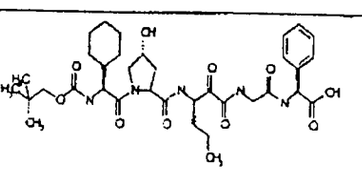
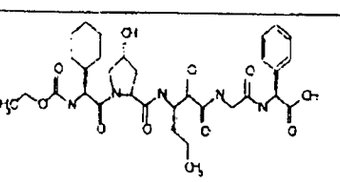
000349

ESTRUCTURA	NOMBRE	Rango 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

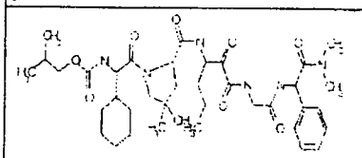
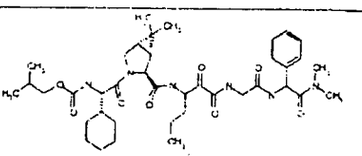
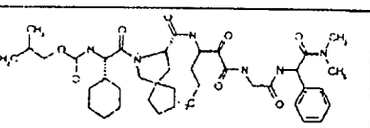
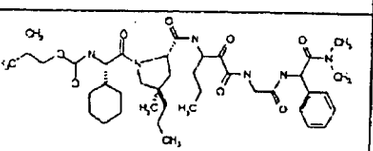
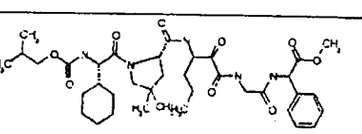
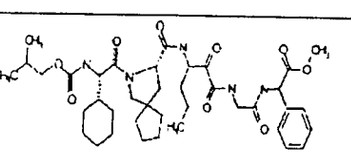
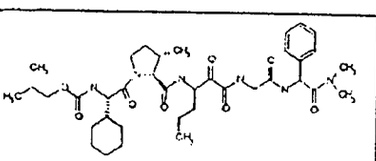
000.59

ESTRUCTURA	NOMBRE	Rango 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

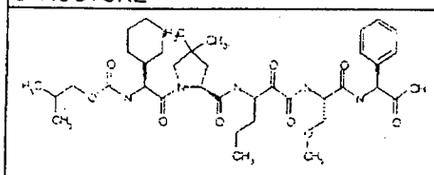
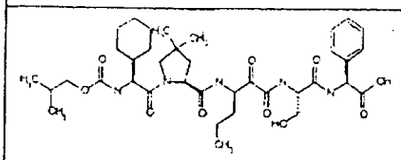
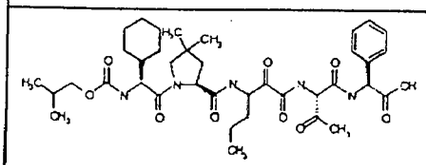
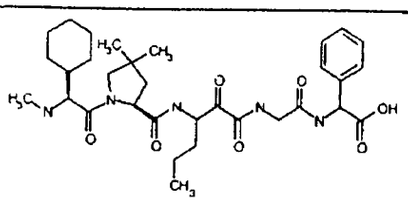
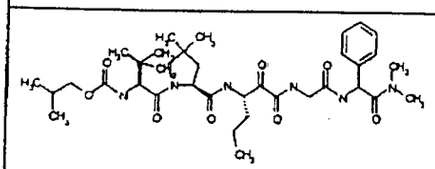
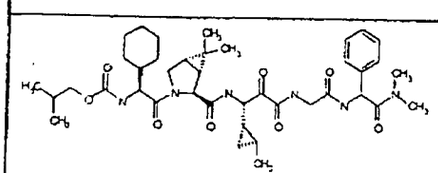
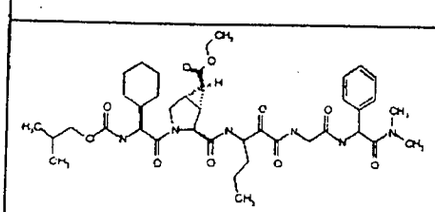
000651

ESTRUCTURA	NOMBRE	Rango 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

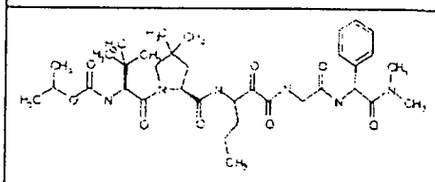
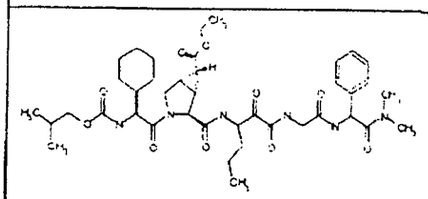
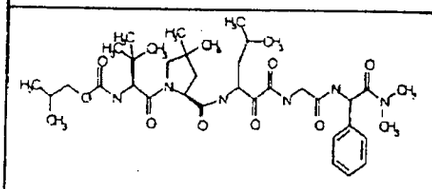
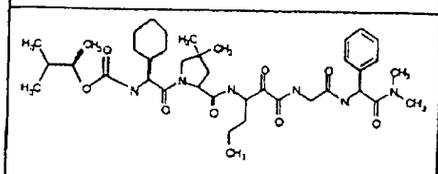
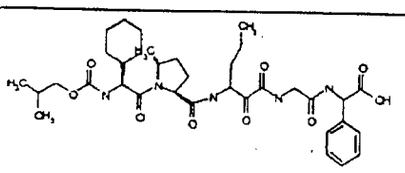
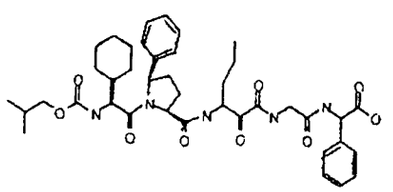
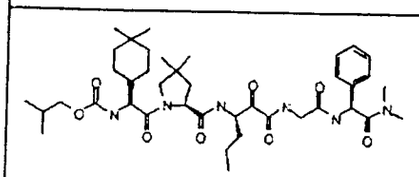
000352

ESTRUCTURA	NOMBRE	Rango 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

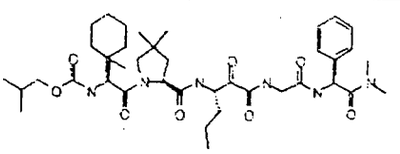
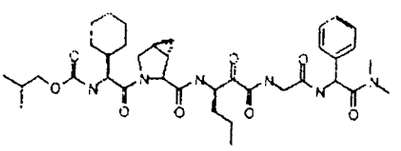
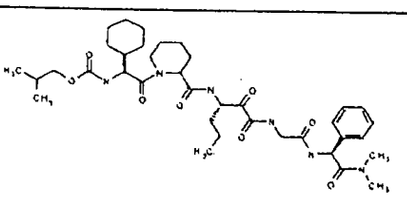
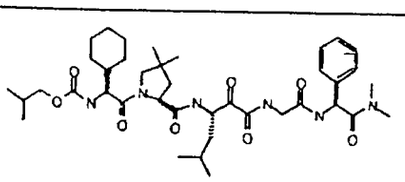
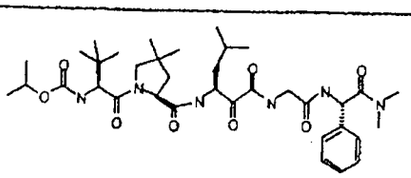
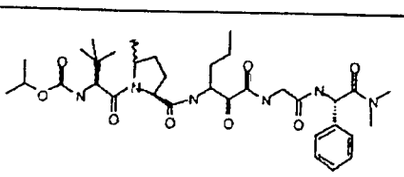
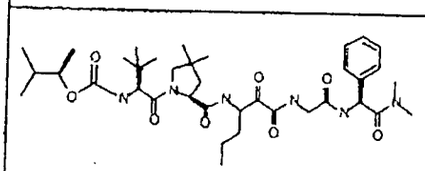
000353

ESTRUCTURA	NOMBRE	Rango 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

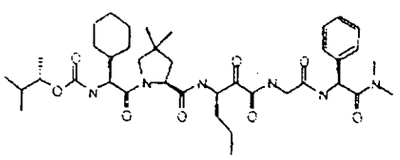
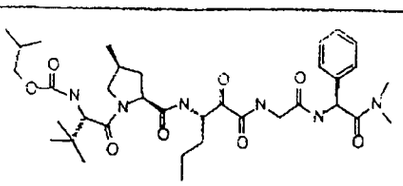
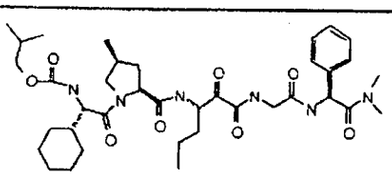
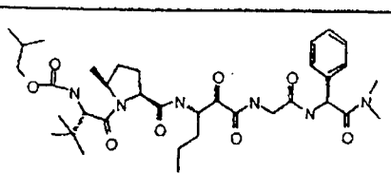
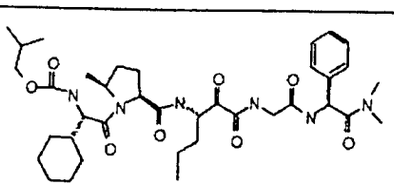
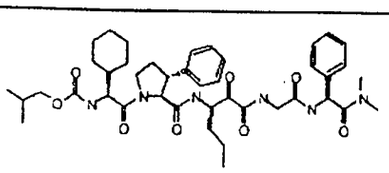
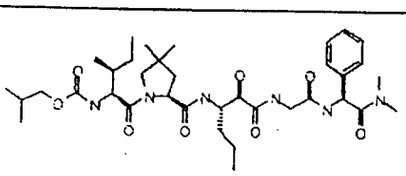
000354

ESTRUCTURA	NOMBRE	Rango Ki
	iPoc-G(tBu)-P(4,4-diMe)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(5R-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

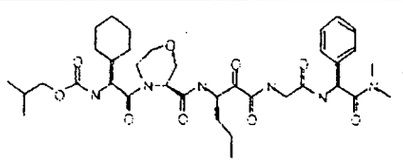
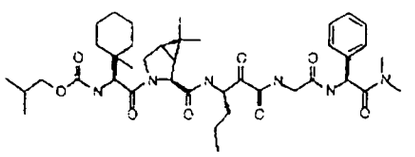
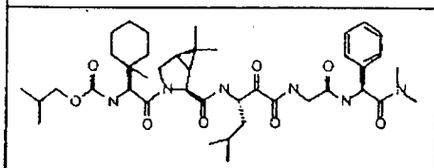
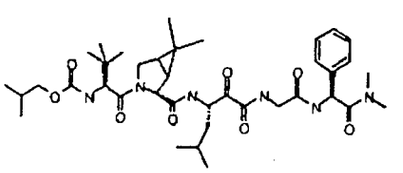
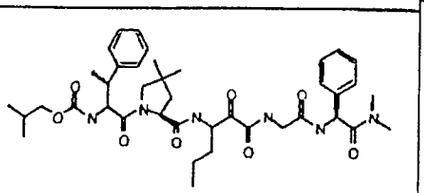
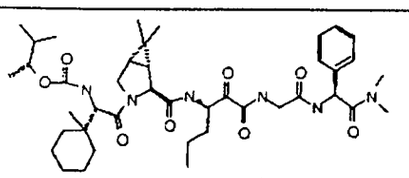
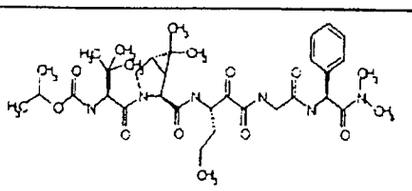
000355

ESTRUCTURA	NOMBRE	Rango 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

000656

ESTRUCTURA	NOMBRE	Rango 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

000357

ESTRUCTURA	NOMBRE	Rango 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-eritro-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

000358

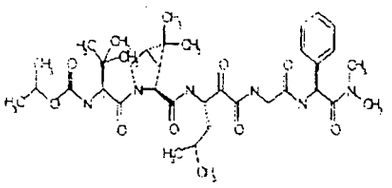
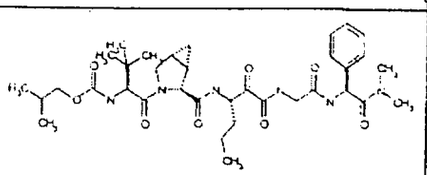
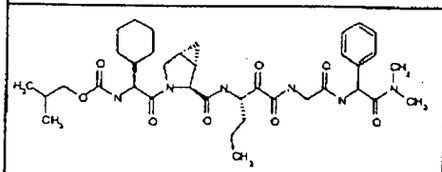
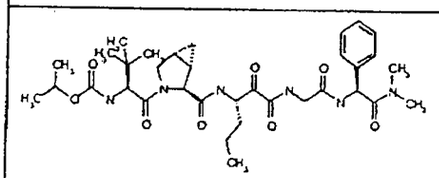
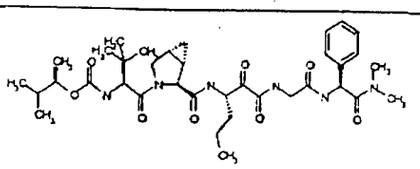
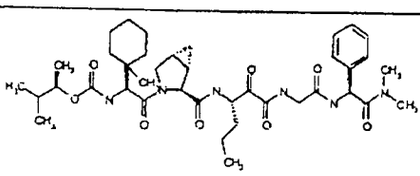
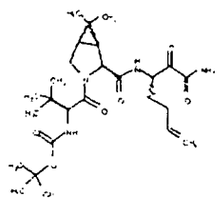
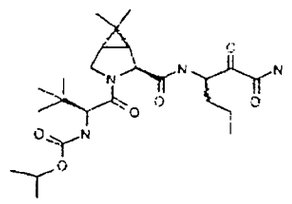
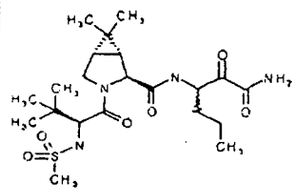
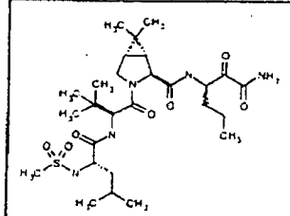
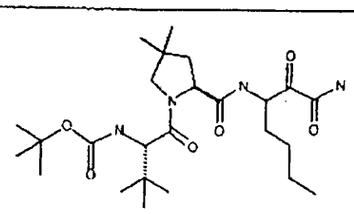
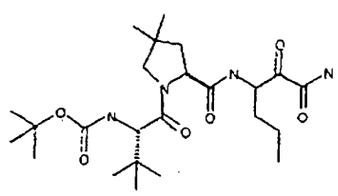
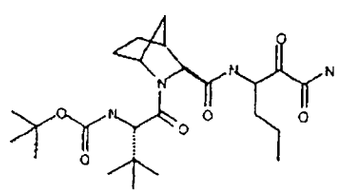
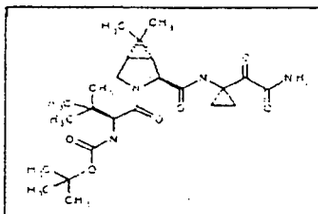
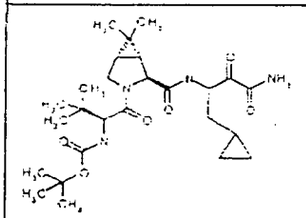
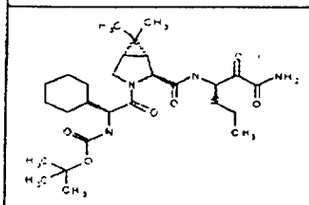
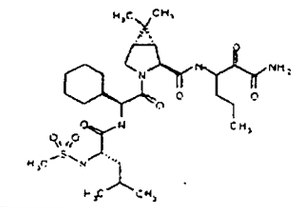
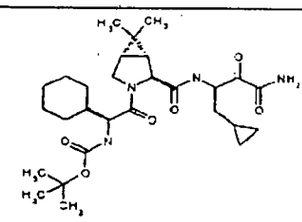
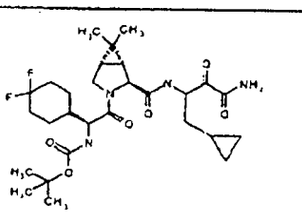
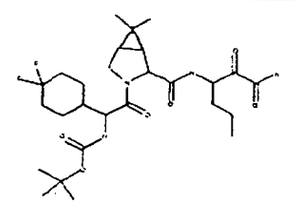
ESTRUCTURA	NOMBRE	Rango Ki*
	iPoc-G(tBu)-P[3,4-(diMe-ciclopropil)]-L-(CO)-G-G(Ph)N(Me)2	A
	iBoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iBoc-G(Chx)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	iPoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(tBu)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A
	((R)-1-Me)iBoc-G(1-MeChx)-P(3,4-CH2)-nV-(CO)-G-G(Ph)-N(Me)2	A

Tabla 5

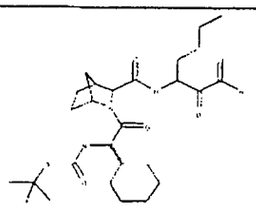
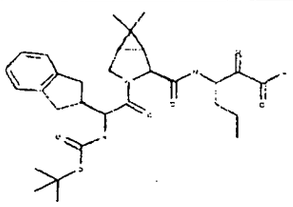
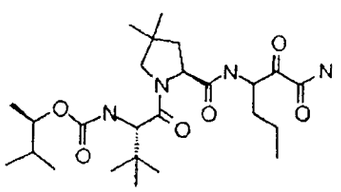
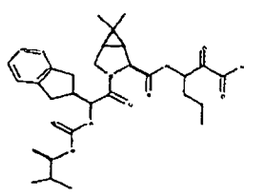
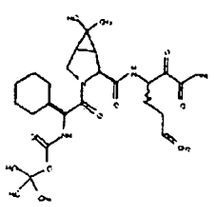
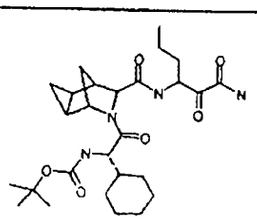
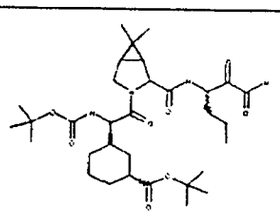
000359

Estructura	PM	Rango Ki*
	507	B
	481	B
	473	C
	586	B
	497	C
	483	C
	481	C

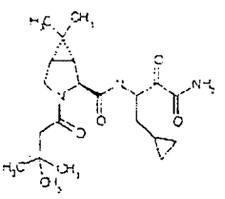
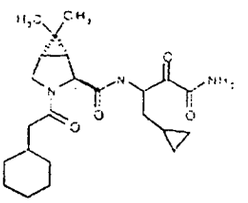
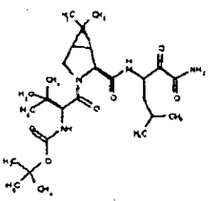
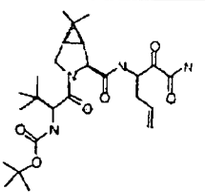
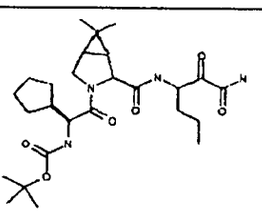
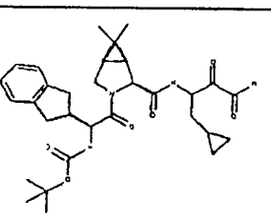
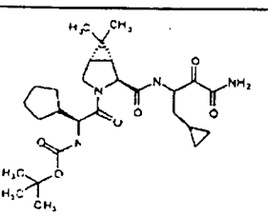
000350

	479	B
	507	A
	521	A
	612	A
	533	A
	569	A
	557	B

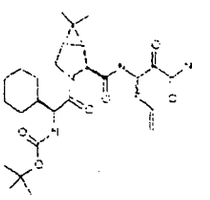
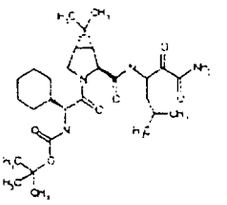
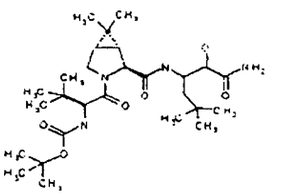
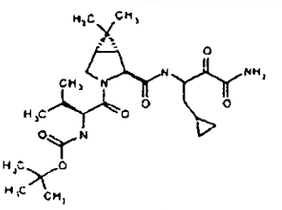
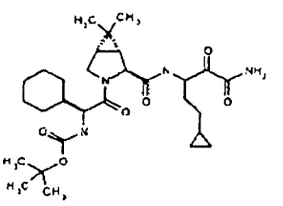
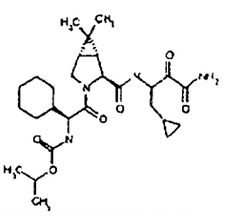
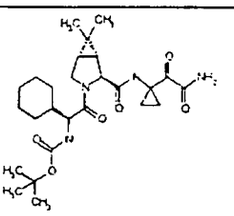
000661

	521	C
	555	A
	497	C
	569	B
	533	B
	519	C
	621	B

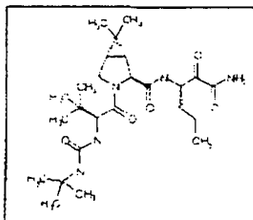
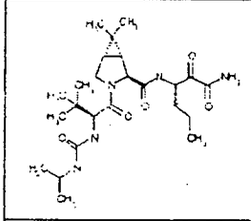
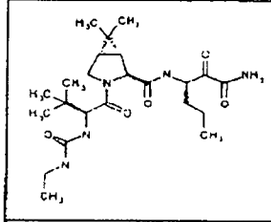
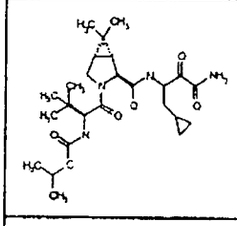
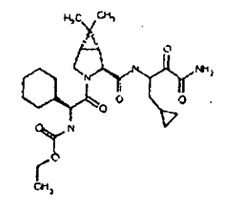
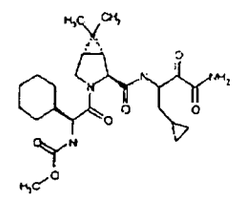
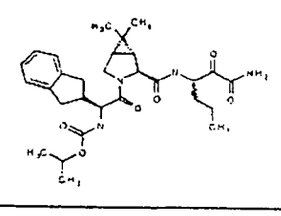
000352

	392	C
	418	C
	509	B
	493	C
	507	B
	567	A
	519	A

030353

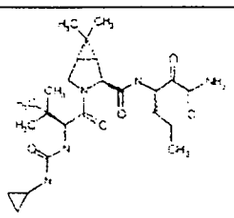
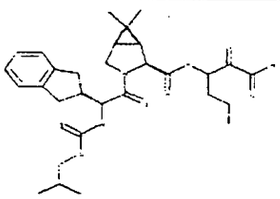
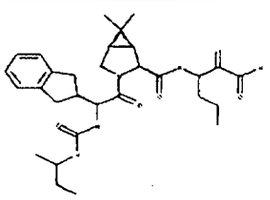
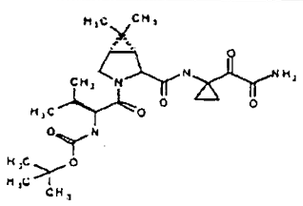
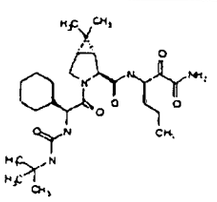
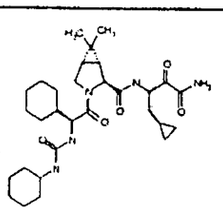
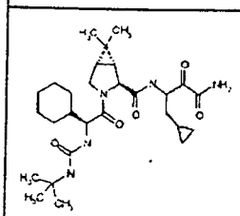
	519	B
	535	B
	523	C
	493	B
	547	B
	519	A
	505	C

000554

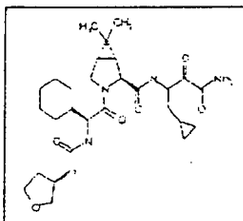
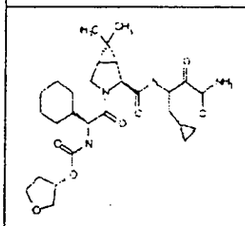
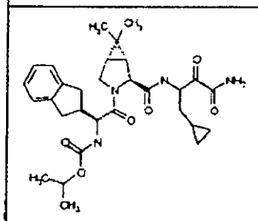
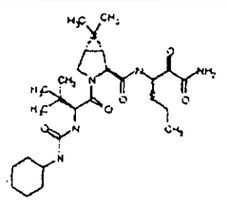
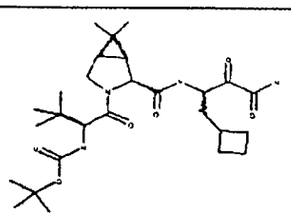
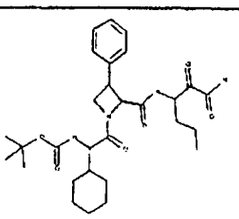
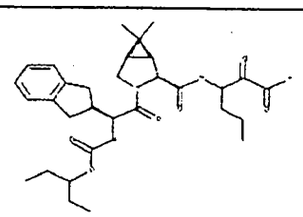
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03-3340

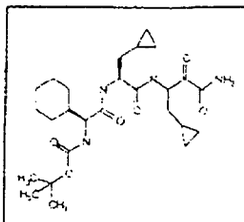
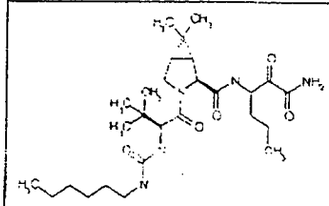
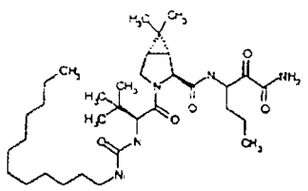
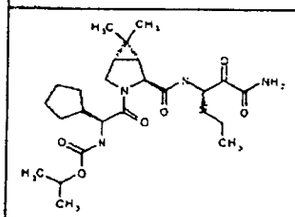
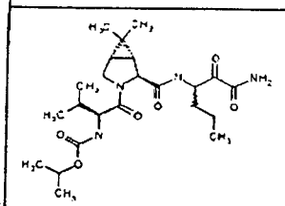
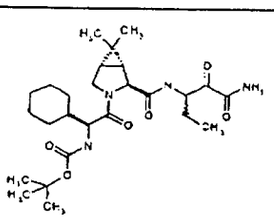
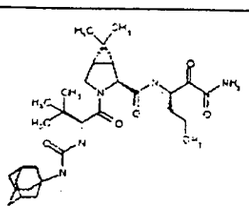
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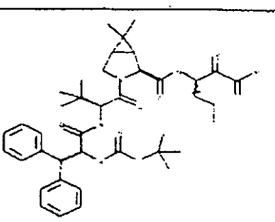
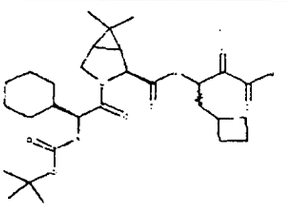
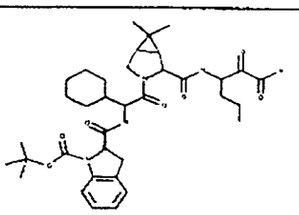
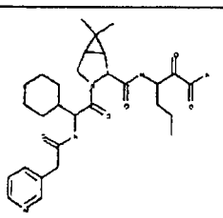
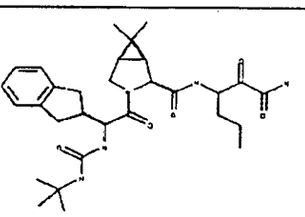
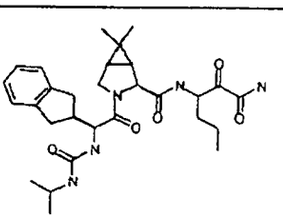
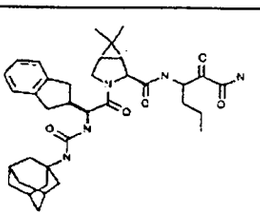
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	520	B
	521	A
	543	C
	569	B

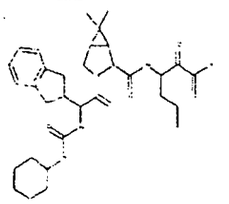
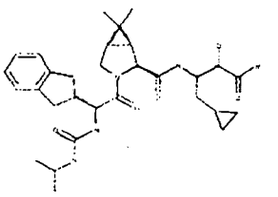
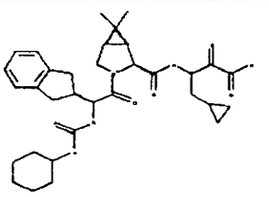
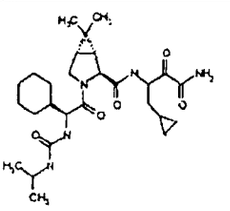
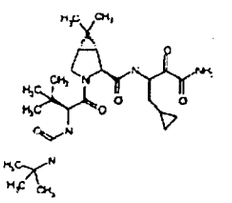
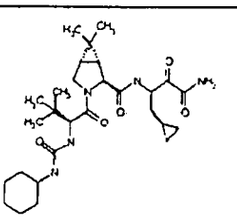
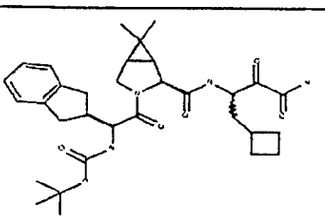
000557

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	606	C
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	467	C
	507	B
	572	A

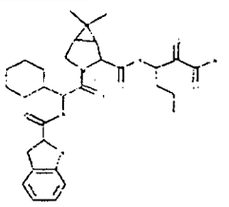
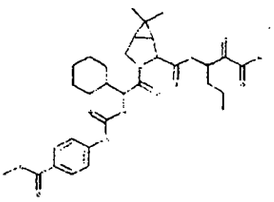
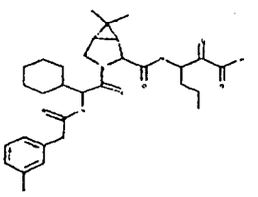
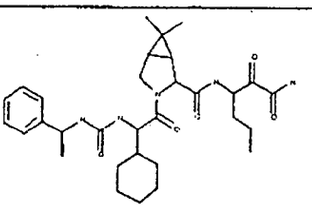
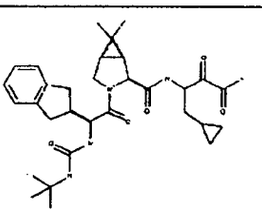
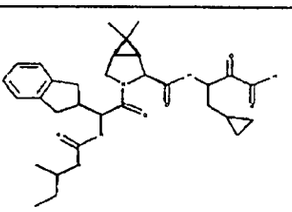
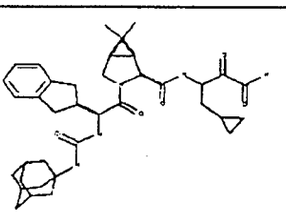
000368

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	540	C
	554	B
	540	B
	632	B

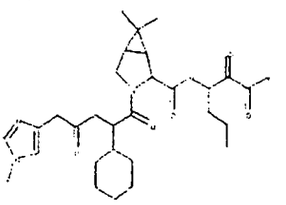
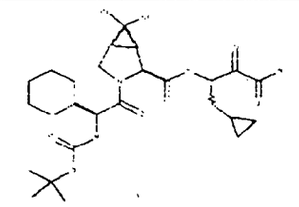
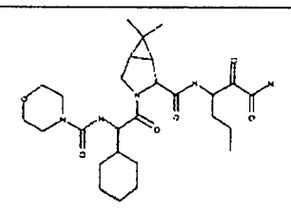
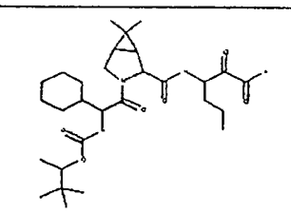
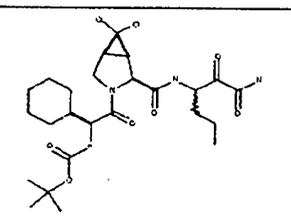
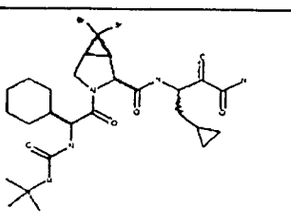
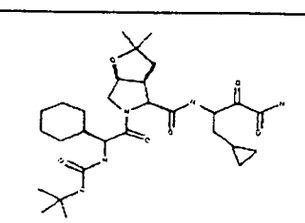
000139

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	592	A
	518	A
	506	A
	532	A
	581	B

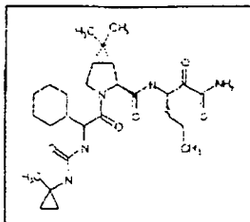
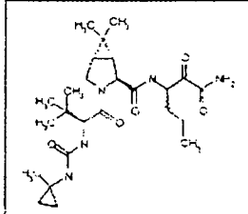
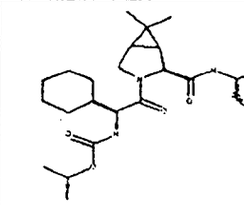
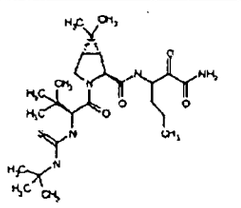
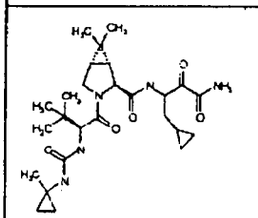
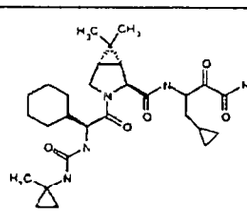
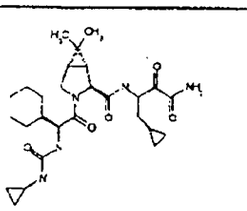
030370

	566	C
	599	B
	553	B
	568	B
	566	A
	566	A
	644	A

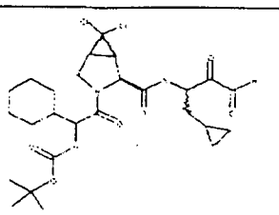
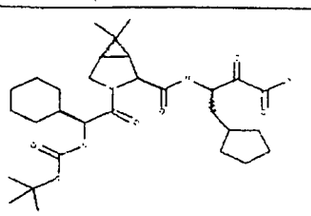
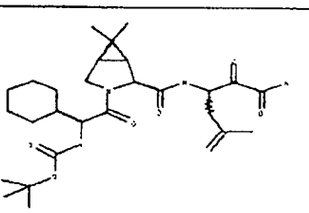
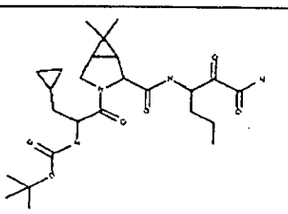
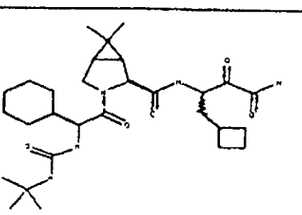
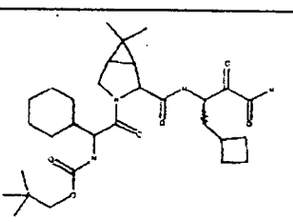
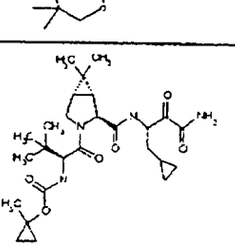
030371

	543	C
	574	A
	534	C
	549	B
	562	A
	662	A
	563	B

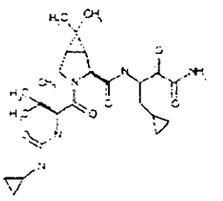
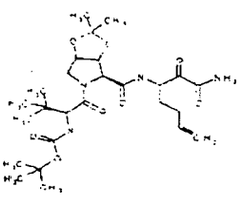
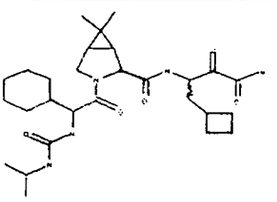
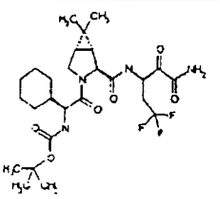
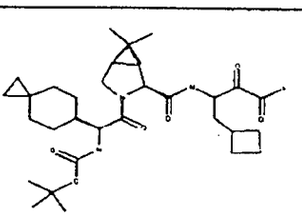
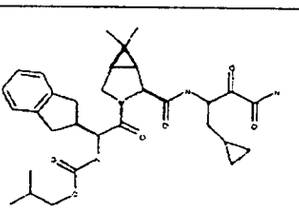
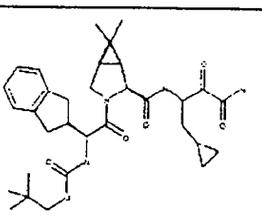
000372

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	530	B
	516	B

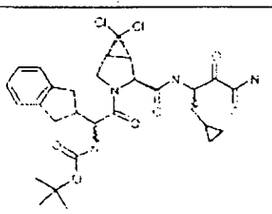
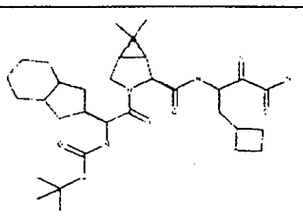
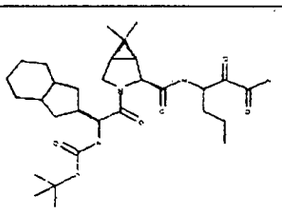
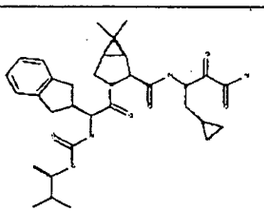
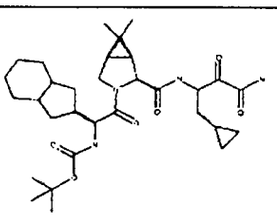
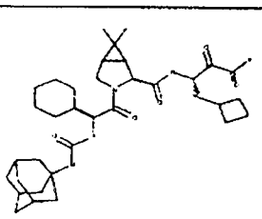
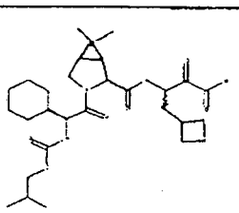
000373

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	533	B
	493	C –
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	561	A
	505	B

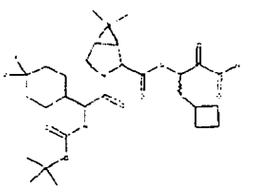
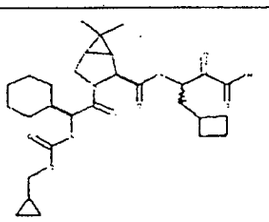
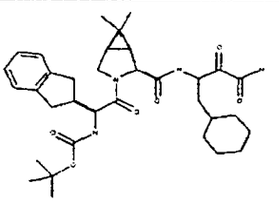
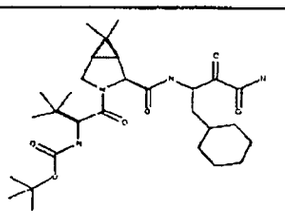
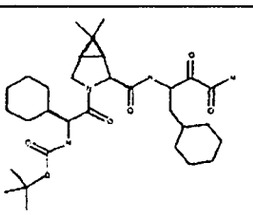
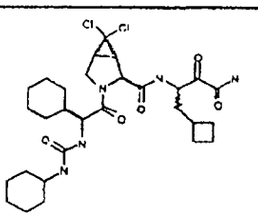
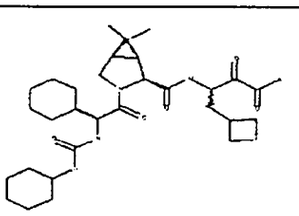
000374

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	573	A
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	581	A

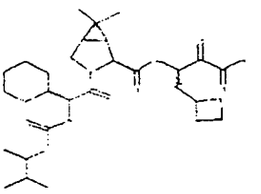
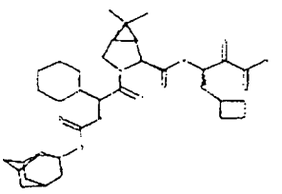
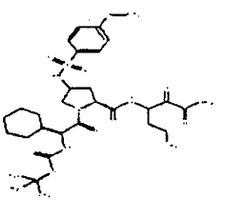
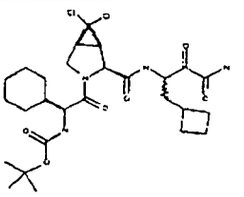
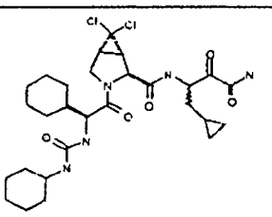
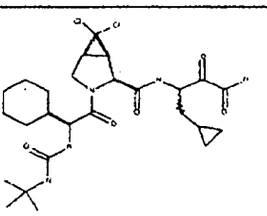
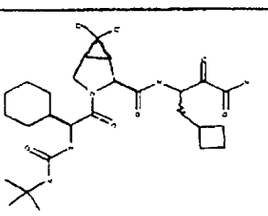
000375

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	561	B
	581	A
	573	A
	624	A
	547	A

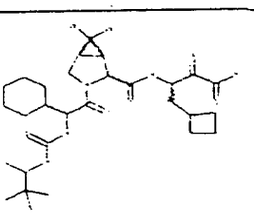
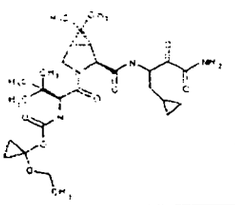
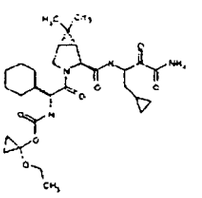
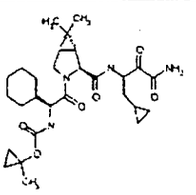
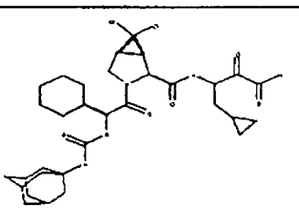
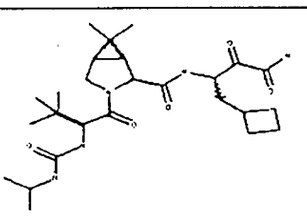
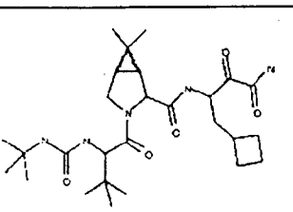
000376

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	609	C
	549	C
	575	C
	613	A
	573	A

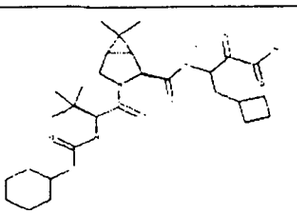
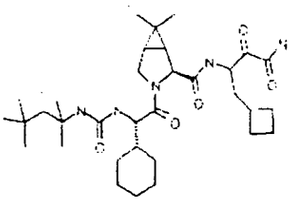
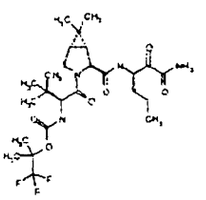
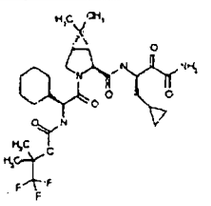
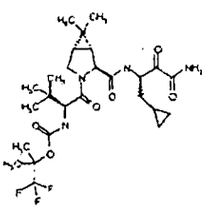
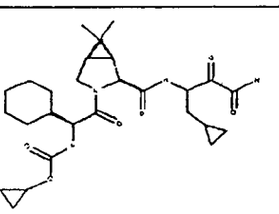
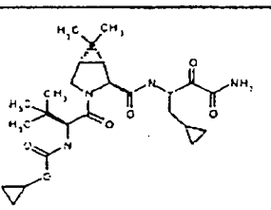
030377

	581	A
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	666	C
	588	A–
	599	A
	573	A
	587	A

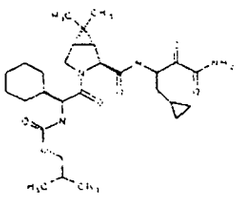
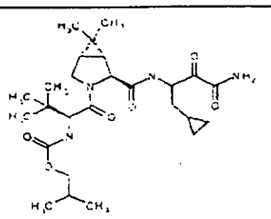
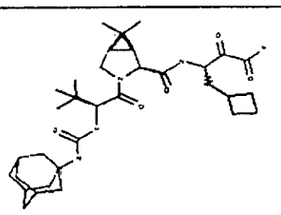
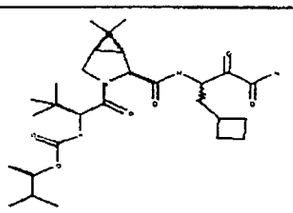
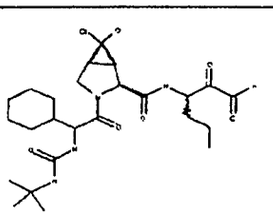
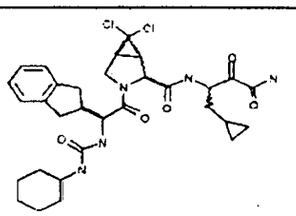
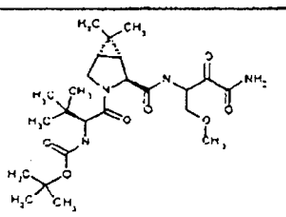
000378

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	561	A
	531	A
	651	A
	506	A
	520	A

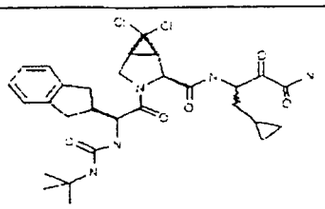
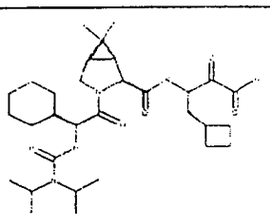
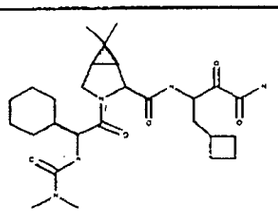
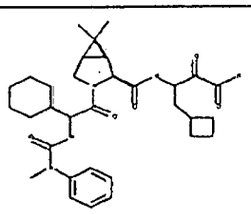
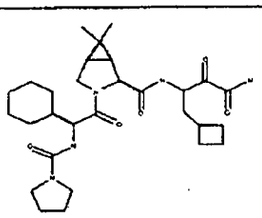
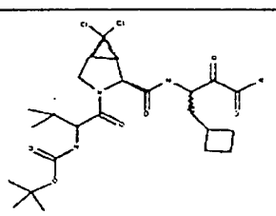
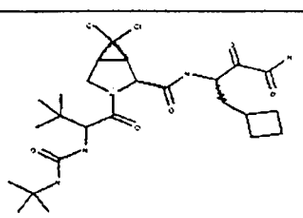
033379

	548	A
	602	A
	549	B
	587	A
	561	A
	517	B
	491	B

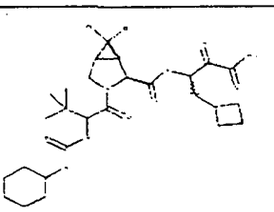
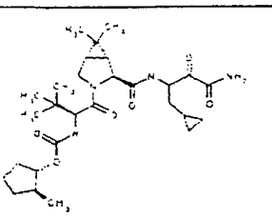
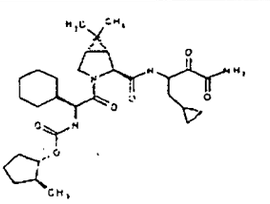
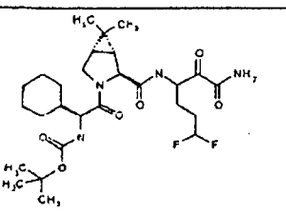
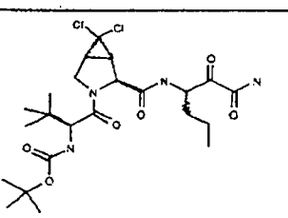
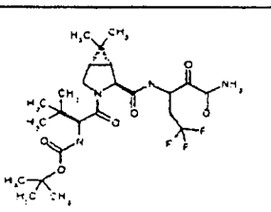
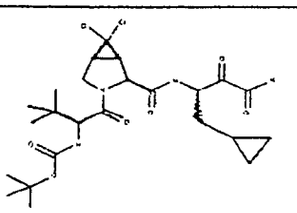
000380

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	535	A
	561	A
	633	A
	497	C

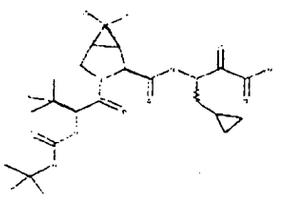
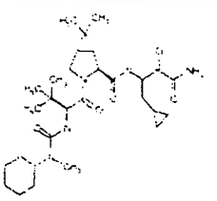
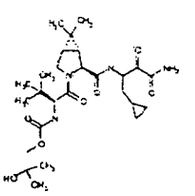
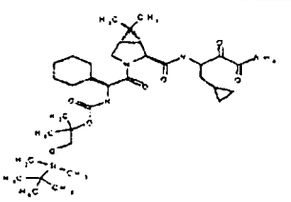
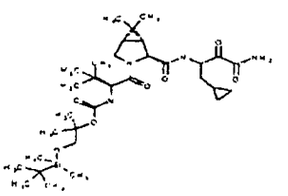
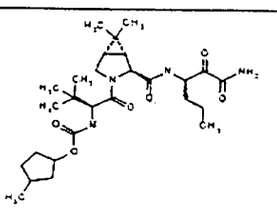
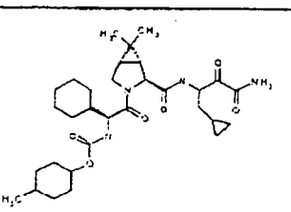
033581

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	518	B
	580	C
	544	B
	562	A
	561	A

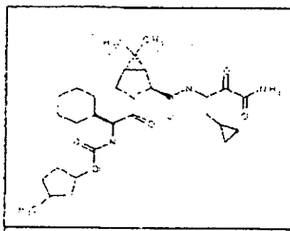
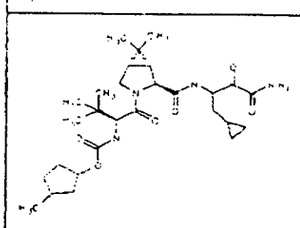
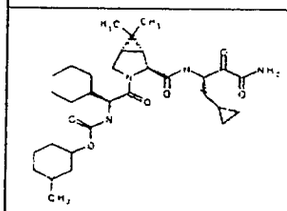
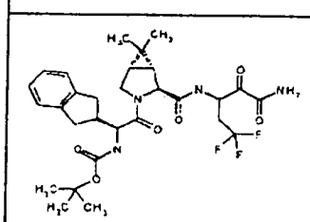
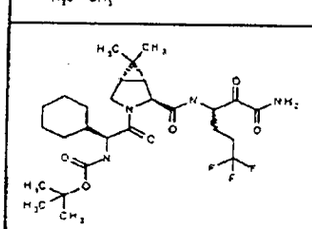
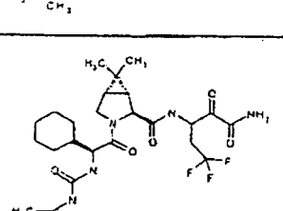
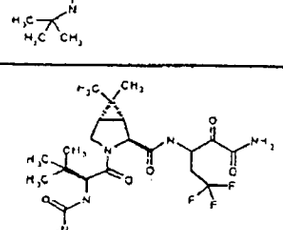
000382

	587	A
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	559	A
	557	C
	535	A
	535	B
	547	A

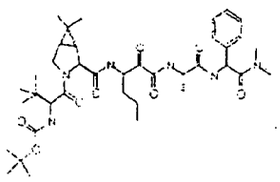
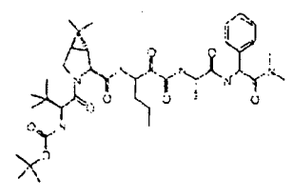
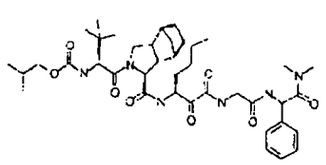
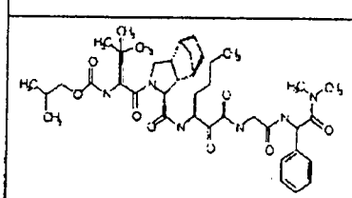
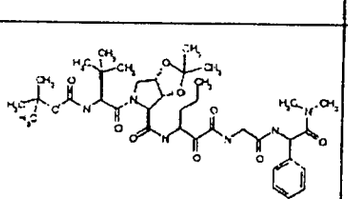
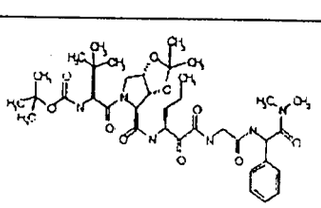
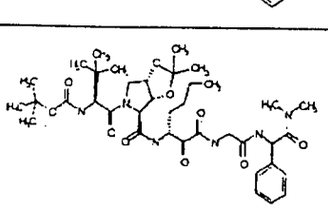
000383

	546	A
	546	B
	523	B
	663	C
	637	C
	521	B
	573	B

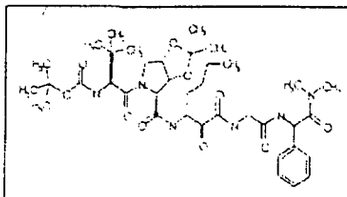
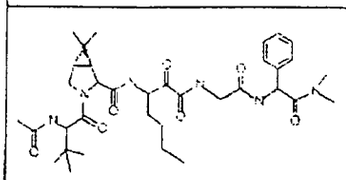
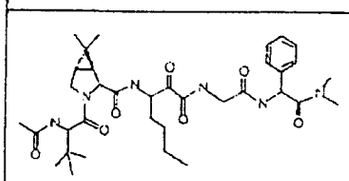
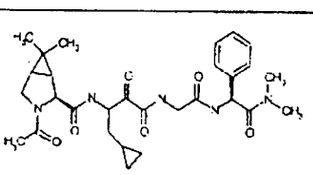
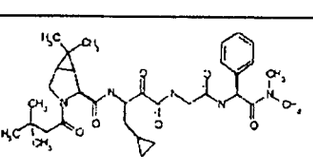
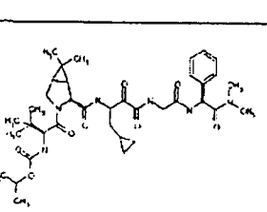
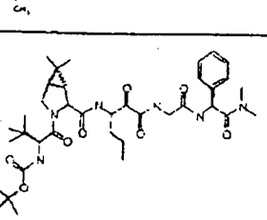
000384

	559	A
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	573	B
	595	B
	575	A
	560	B
	534	C

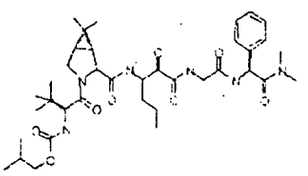
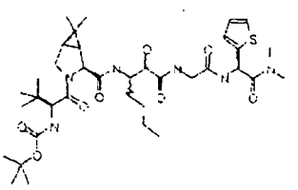
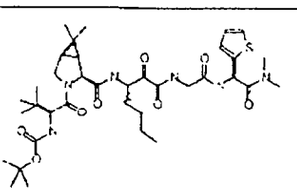
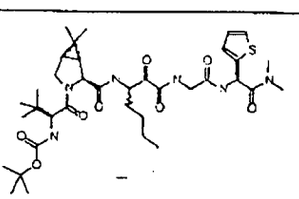
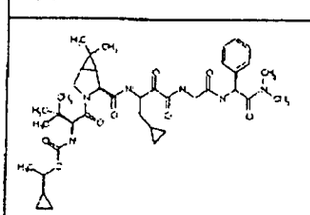
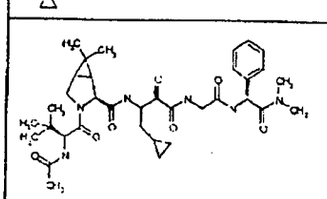
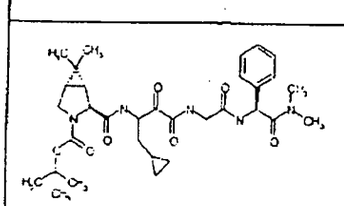
000385

Estructura	PM	Rango Ki*
	727	A
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	753	C
	753	B
	745	A
	745	A
	759	C

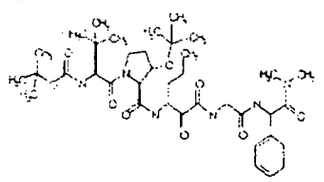
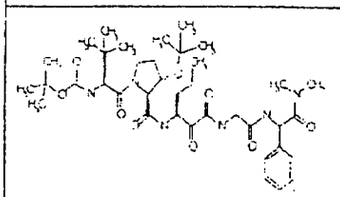
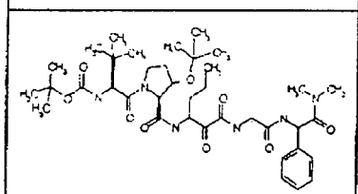
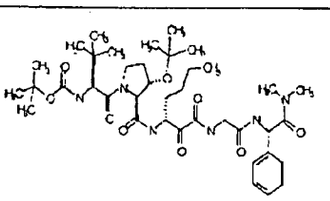
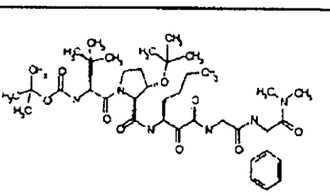
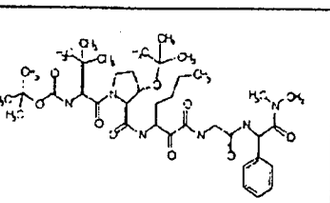
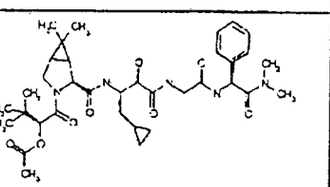
000388

	759	B
	669	B
	669	A
	554	C
	610	B
	711	A
	713	A

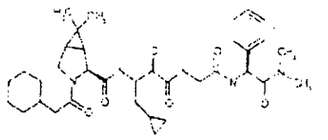
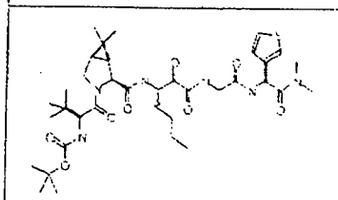
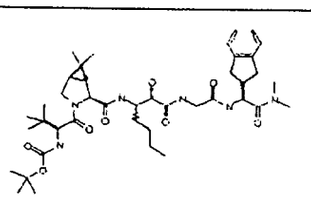
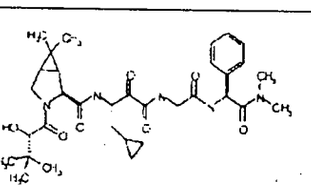
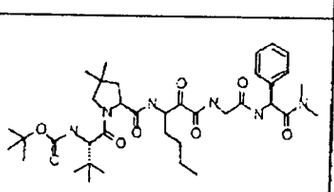
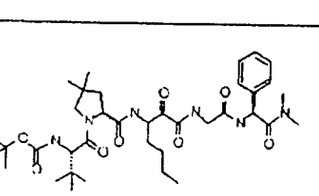
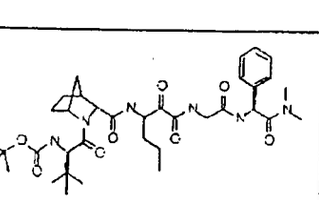
000387

	713	A
	732	A
	733	A
	733	A
	737	A
	667	A
	612	C

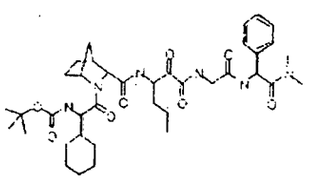
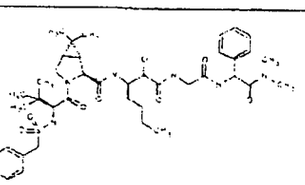
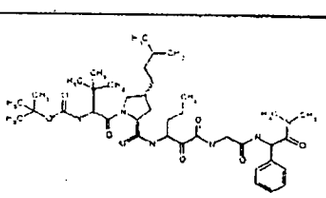
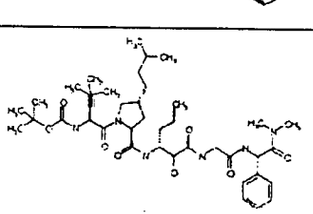
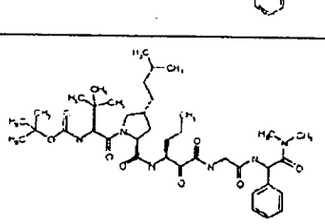
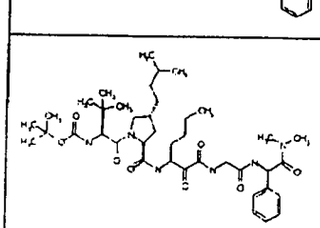
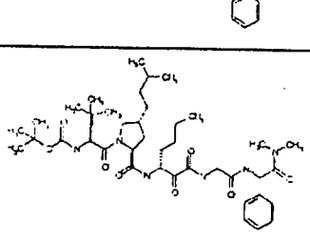
030388

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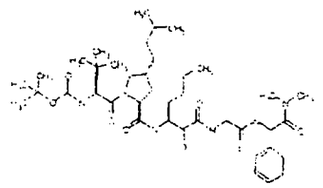
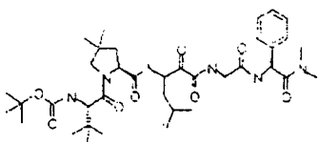
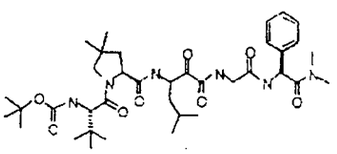
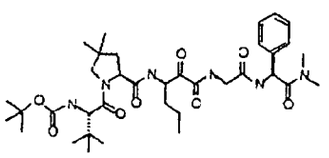
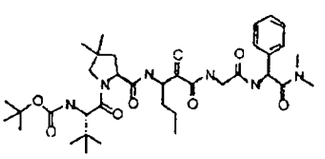
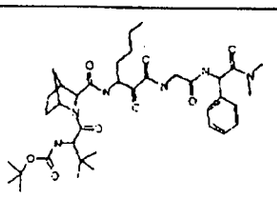
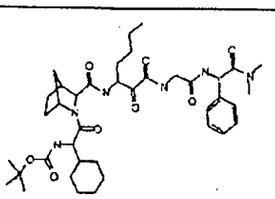
030389

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	715	A
	699	B

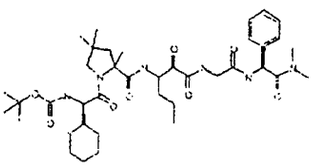
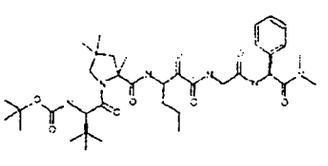
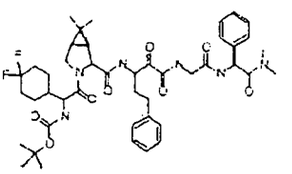
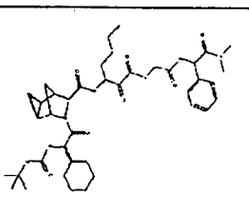
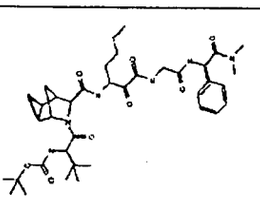
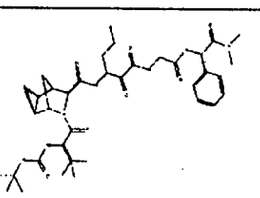
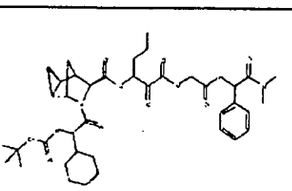
030390

	725	A
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	743	B
	743	C
	743	A
	757	B
	757	C

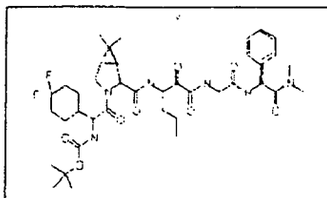
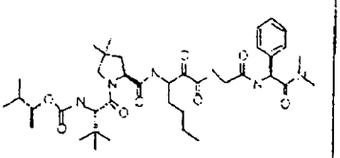
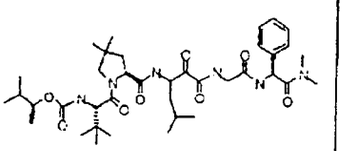
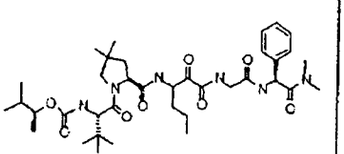
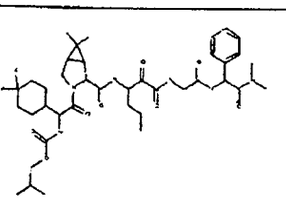
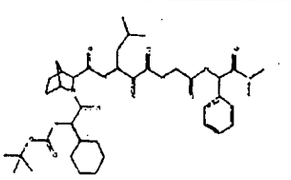
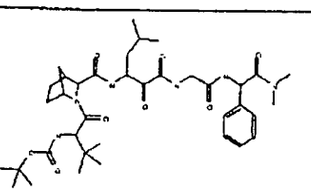
080391

	757	B
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	715	A
	701	C
	701	A
	713	A
	739	A

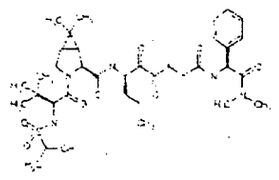
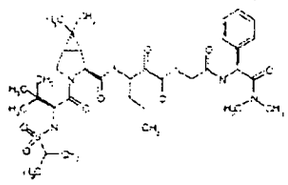
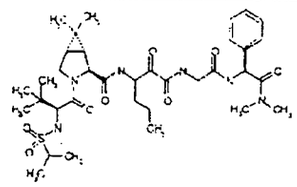
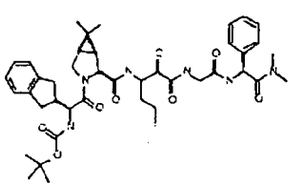
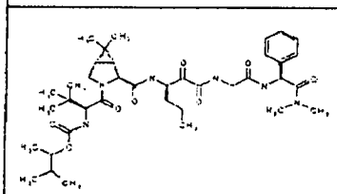
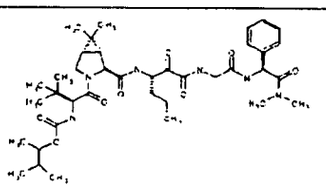
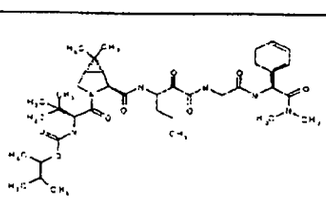
030392

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	837	B
	751	A
	725	C
	711	C
	737	A

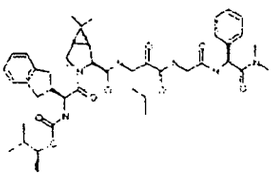
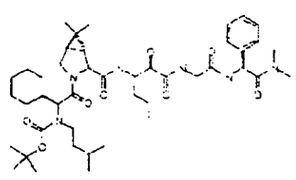
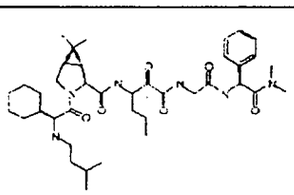
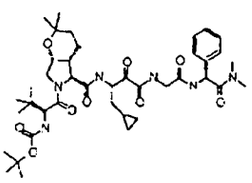
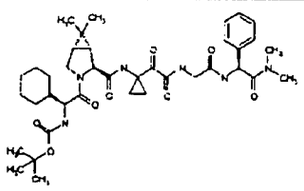
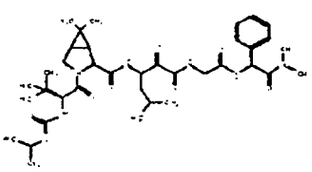
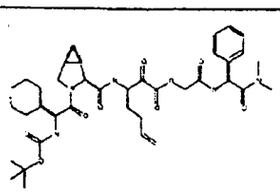
030393

	775	A
	729	A
	729	A
	715	A
	775	A
	739	A
	713	A

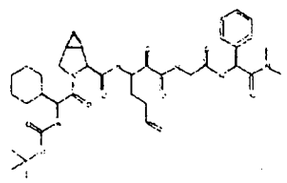
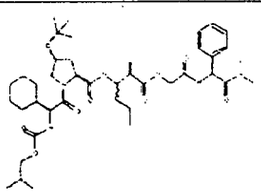
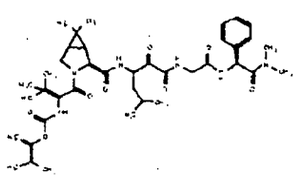
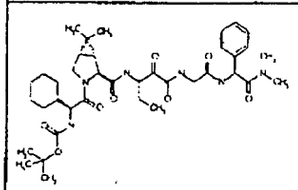
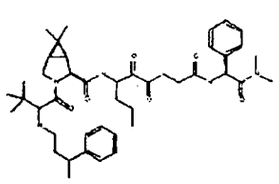
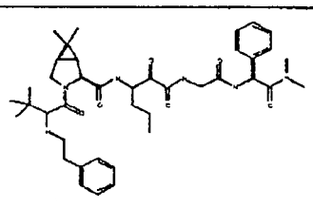
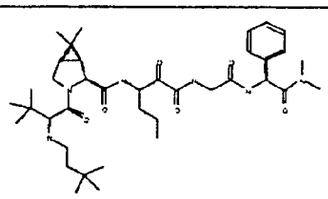
030394

	719	A
	719	A
	719	A
	773	A
	727	A
	727	A
	727	A

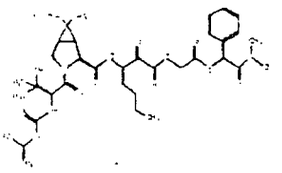
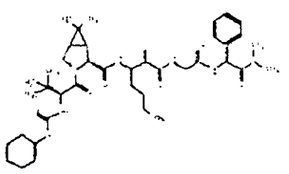
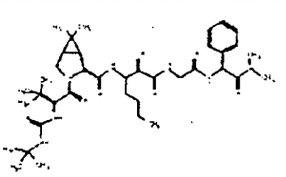
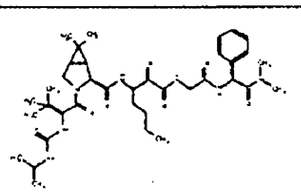
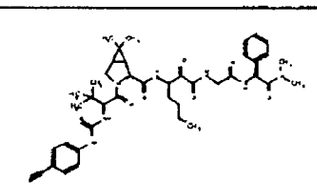
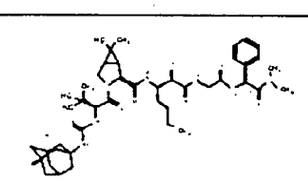
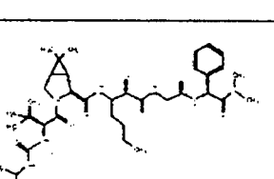
030395

	767	A
	809	C
	709	A
	769	B
	723	C
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	723	A

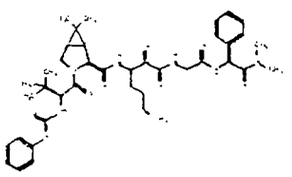
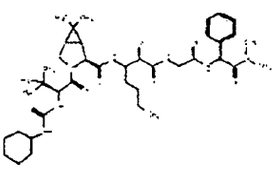
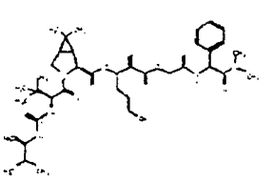
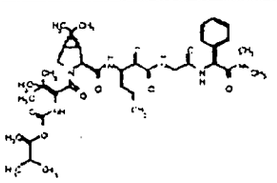
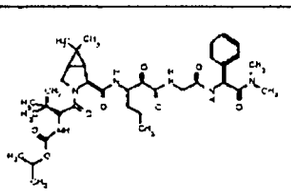
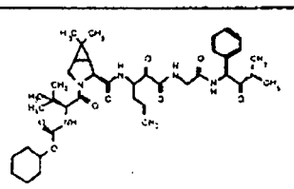
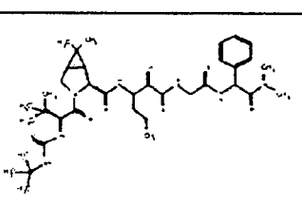
030396

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	745	A
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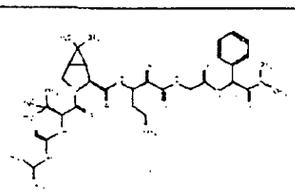
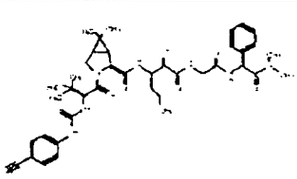
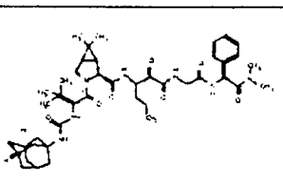
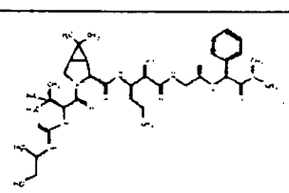
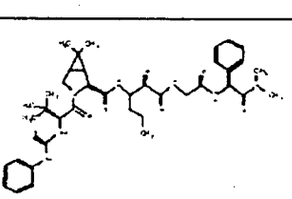
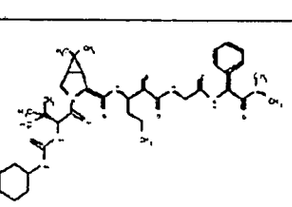
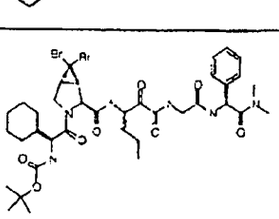
000697

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	712	A
	771	B
	804	A
	726	A

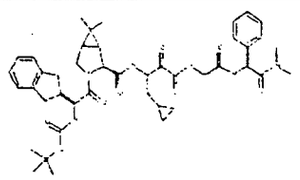
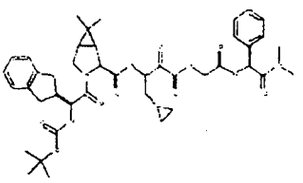
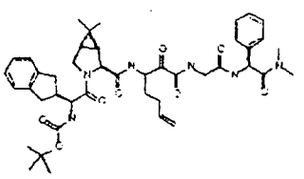
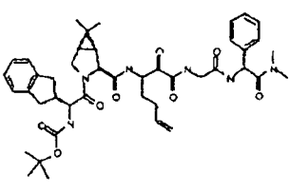
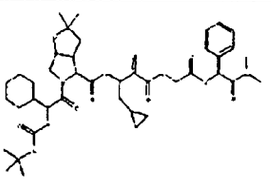
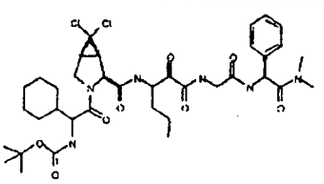
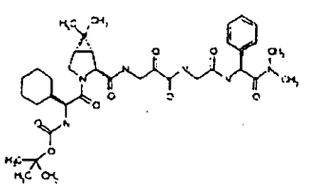
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	752	A
	741	A
	727	A
	699	A
	739	A
	712	A

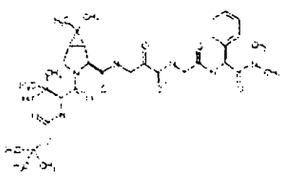
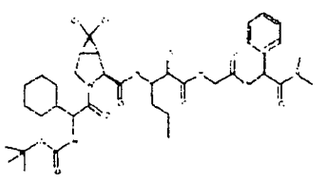
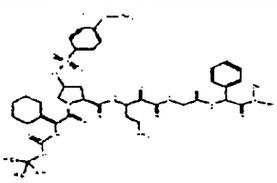
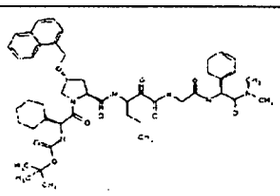
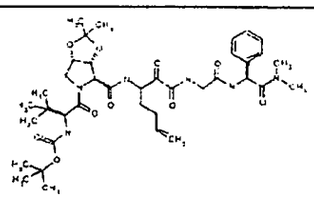
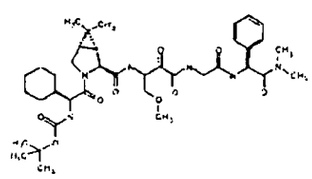
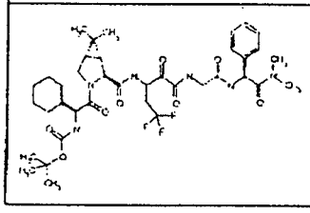
000599

	698	A
	757	B
	790	A
	712	A
	732	A
	738	A
	869	A

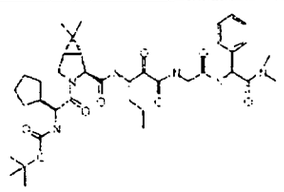
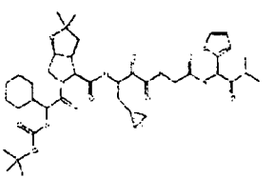
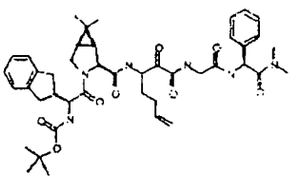
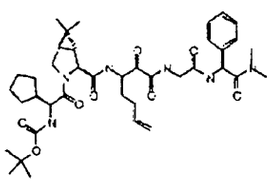
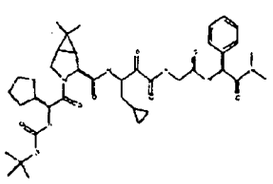
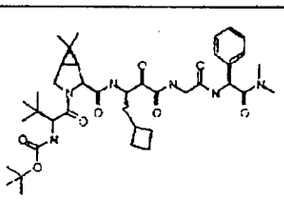
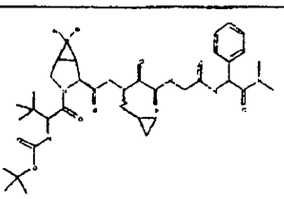
030700

	795	A
	795	A
	795	A
	785	A
	781	A
	780	A
	697	C

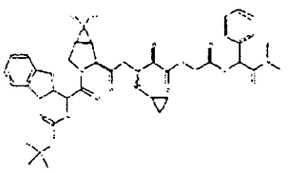
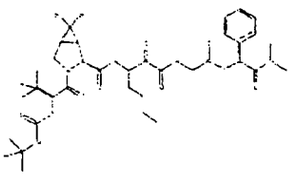
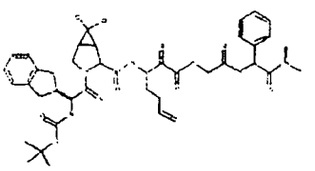
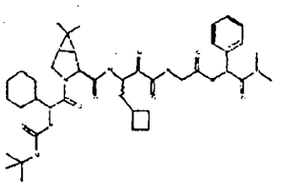
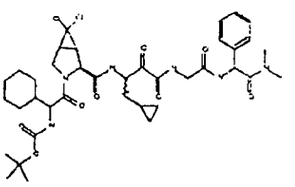
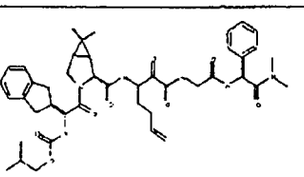
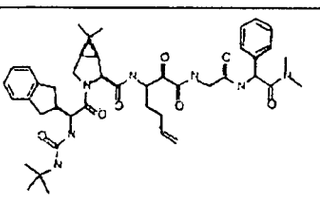
000701

	671	C
	780	A
	834	A
	855	A
	757	B
	741	B
	779	B

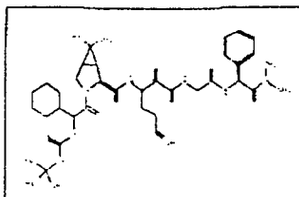
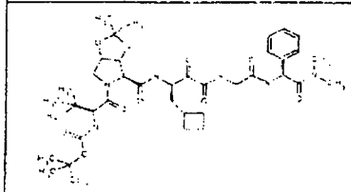
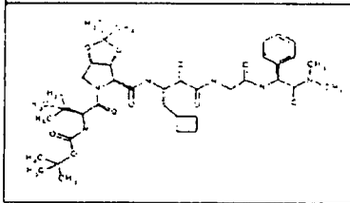
000702

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	787	A
	785	A
	737	A
	737	A
	739	A
	855	A

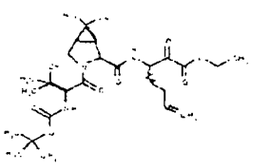
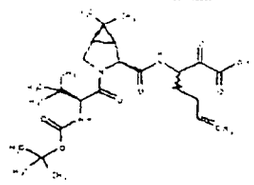
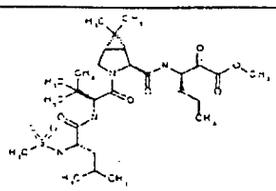
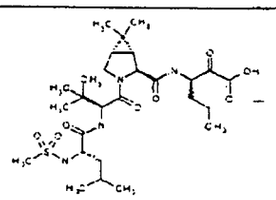
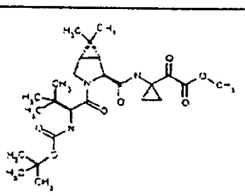
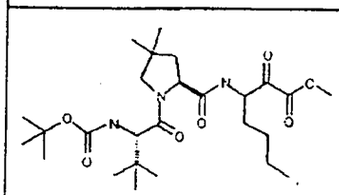
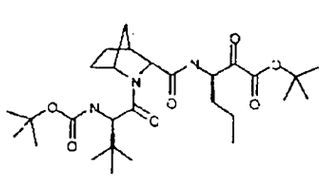
000703

	820	A
	857	A
	826	A
	765	A
	792	A
	799	A
	764	A

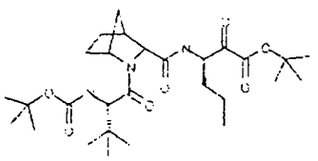
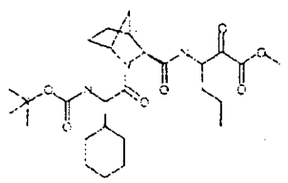
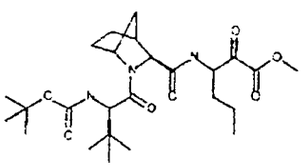
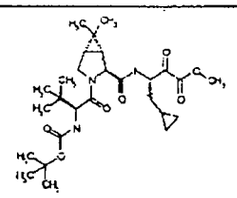
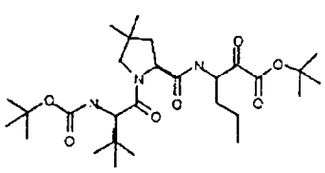
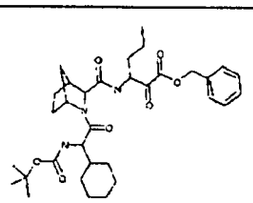
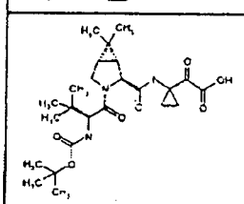
000704

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	771	A
	771	A

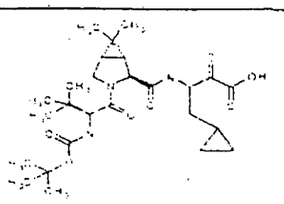
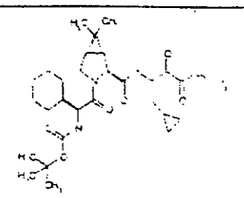
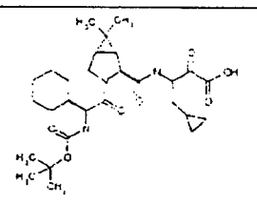
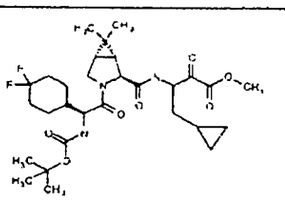
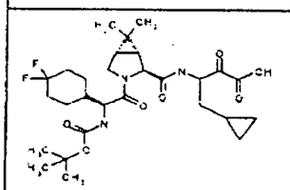
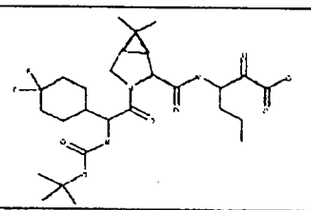
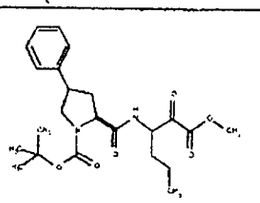
000706

ESTRUCTURA	PM	Rango Ki*
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	601	C
	587	B
	494	C
	512	C
	538	C

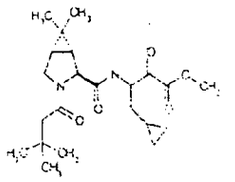
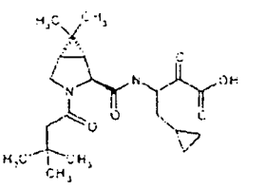
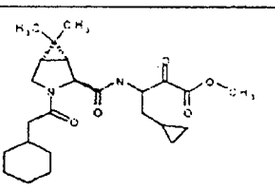
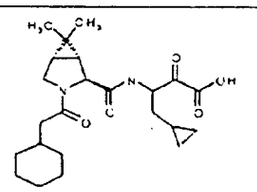
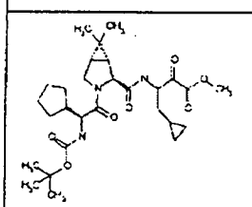
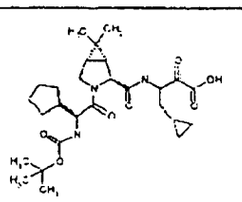
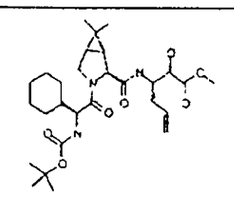
000707

	538	C
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	496	C
	522	C
	540	C
	596	C
	480	C

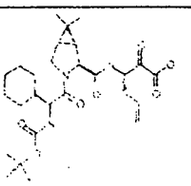
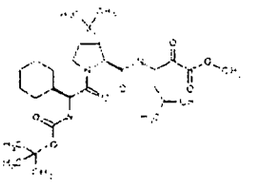
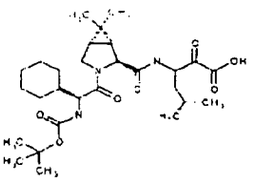
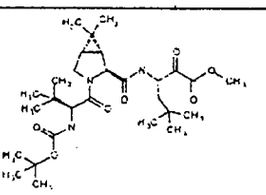
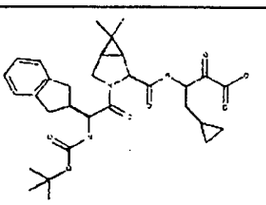
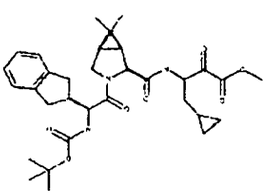
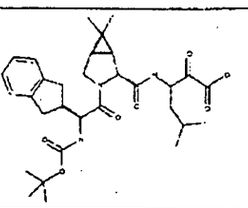
000708

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	534	B
	584	C
	570	B
	558	C
	433	C

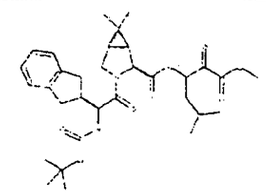
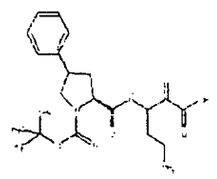
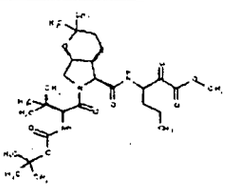
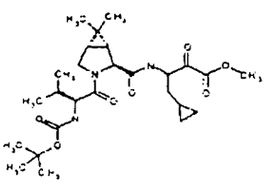
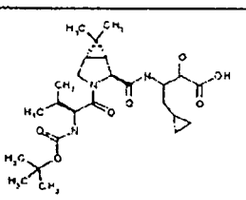
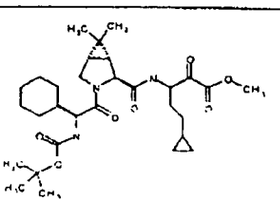
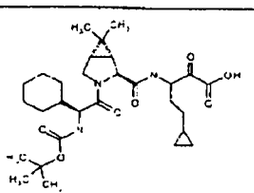
000709

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	534	C
	520	B
	534	C

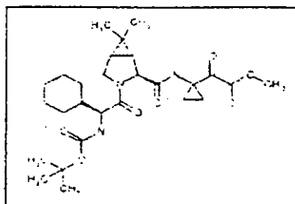
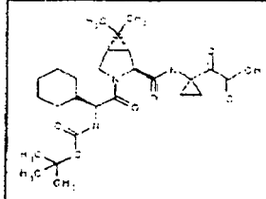
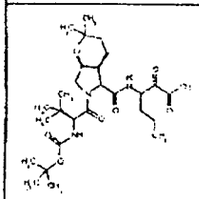
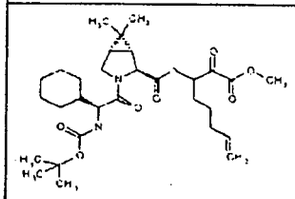
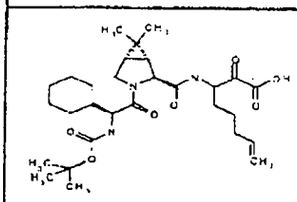
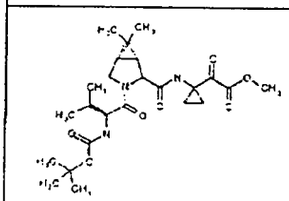
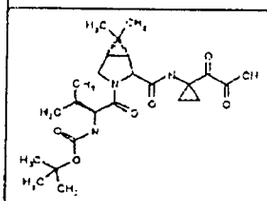
000710

	520	B
	550	C
	536	C
	538	C
	568	B
	582	C
	570	C

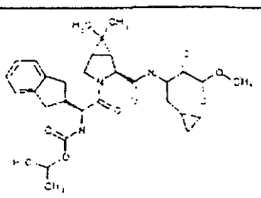
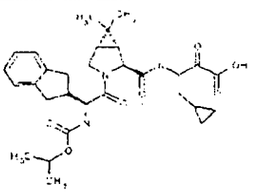
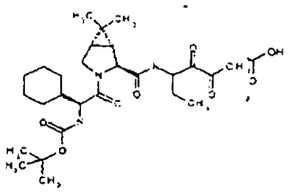
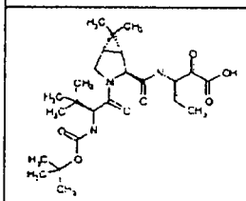
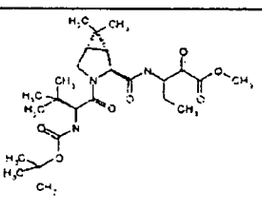
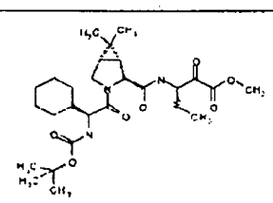
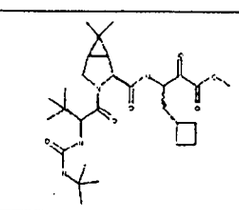
000711

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	418	C
	554	C
	508	C
	494	B
	562	C
	548	A

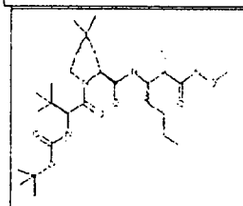
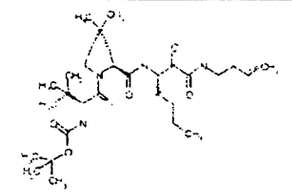
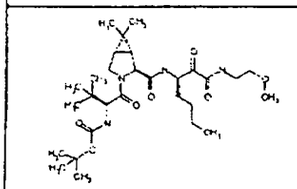
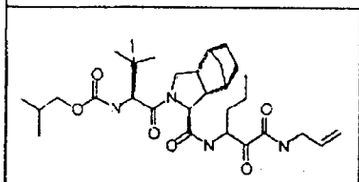
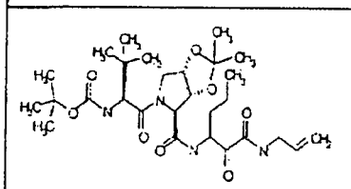
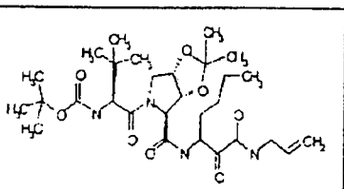
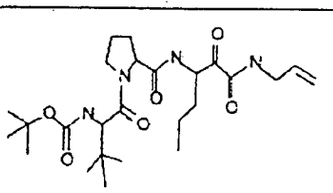
000712

	520	C
	506	C
	540	C
	562	C
	548	B
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	466	C

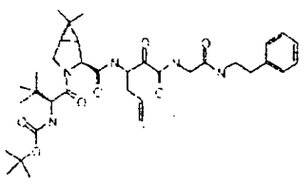
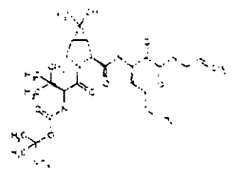
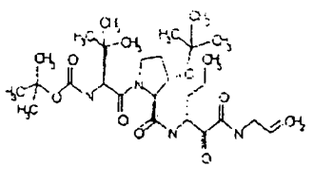
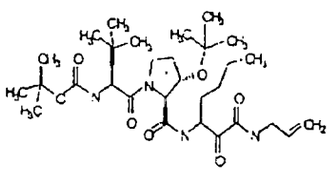
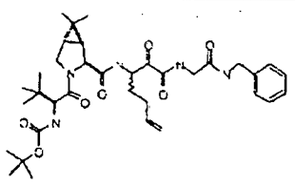
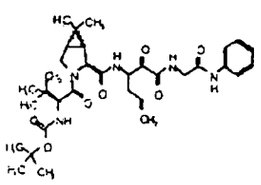
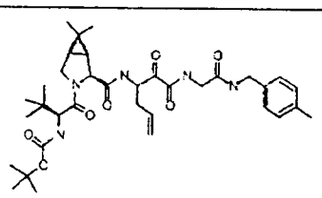
030713

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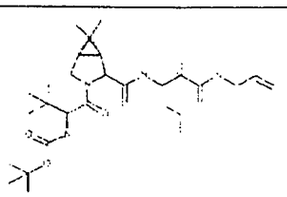
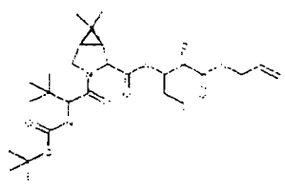
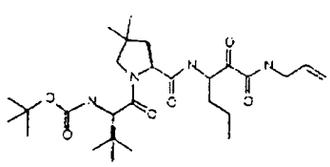
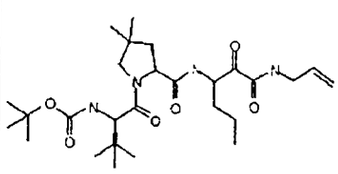
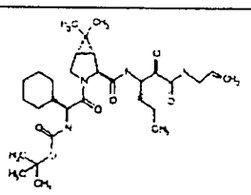
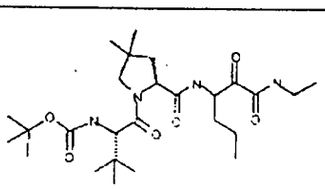
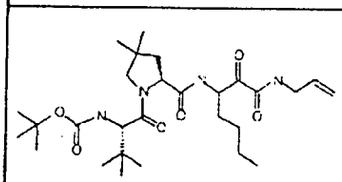
030714

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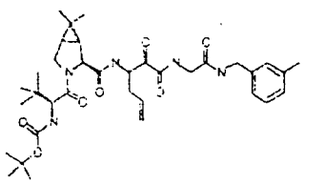
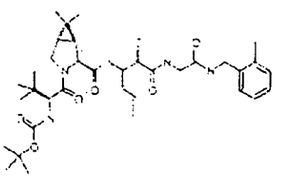
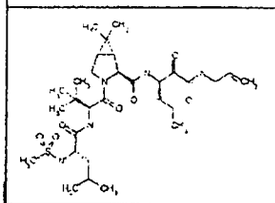
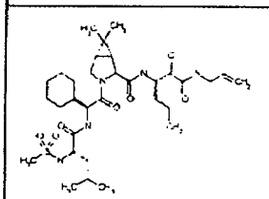
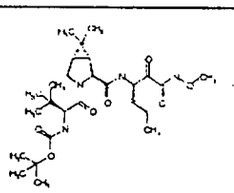
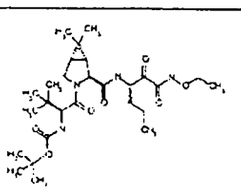
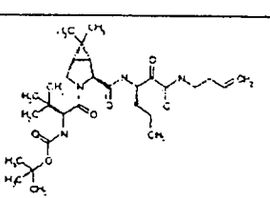
030715

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	626	B
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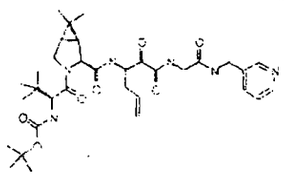
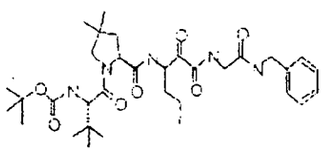
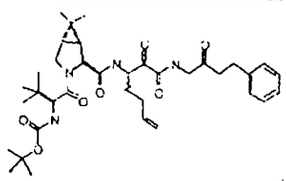
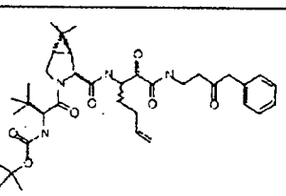
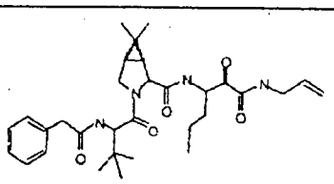
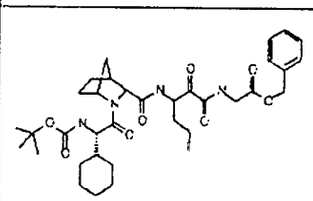
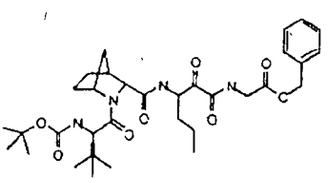
030716

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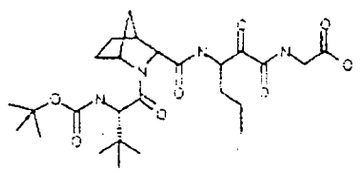
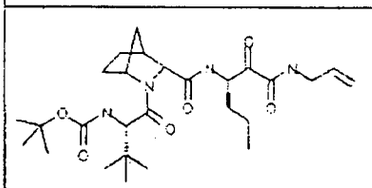
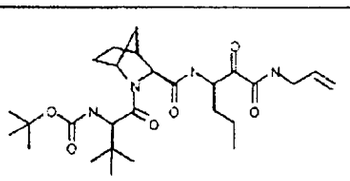
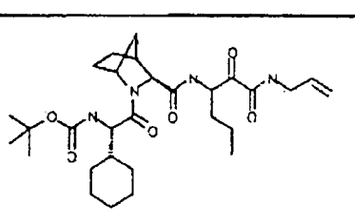
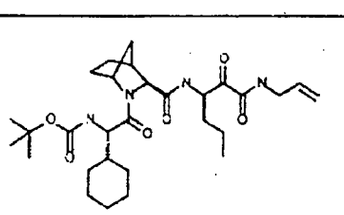
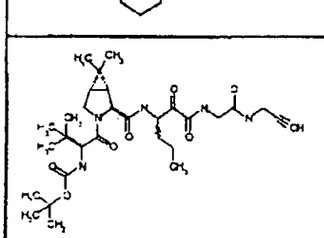
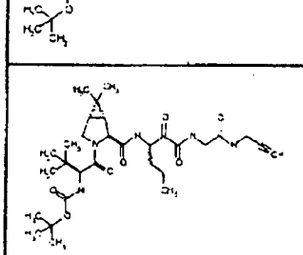
000717

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	539	C
	549	C

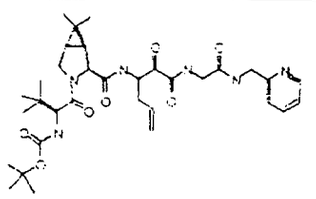
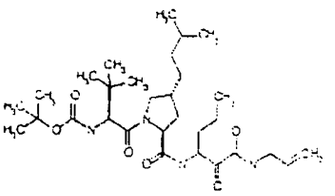
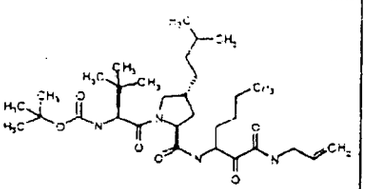
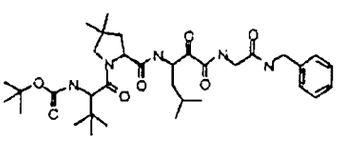
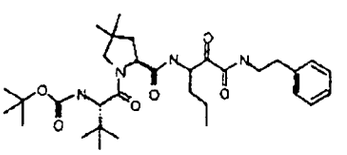
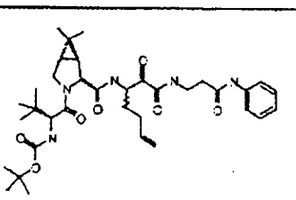
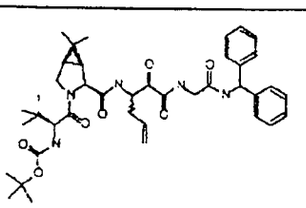
030718

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	629	C

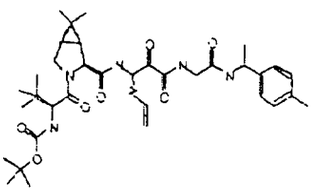
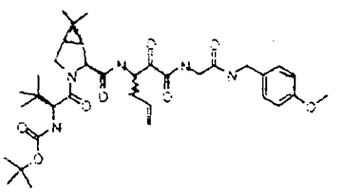
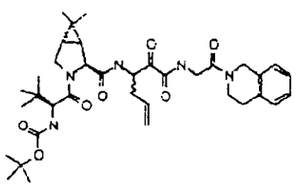
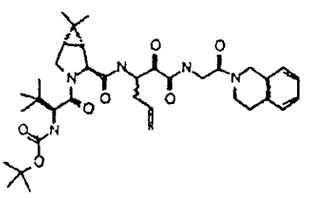
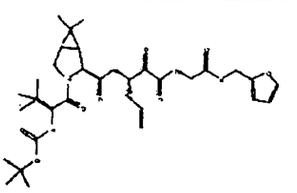
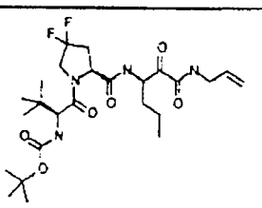
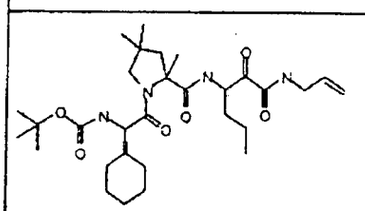
000719

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	590	B
	590	B

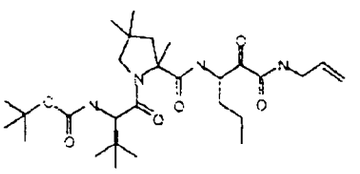
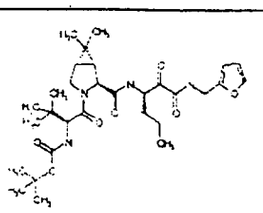
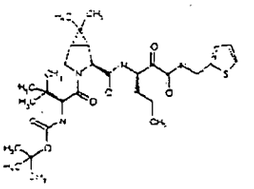
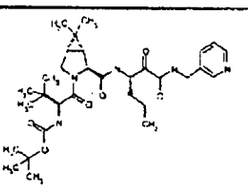
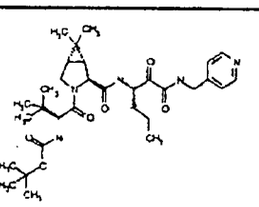
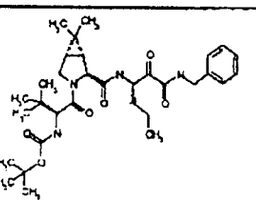
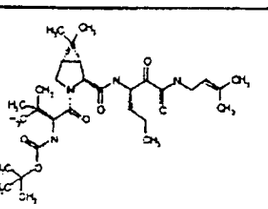
030720

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	716	B

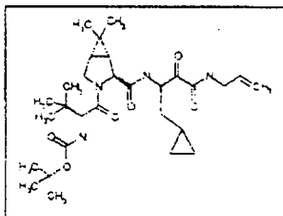
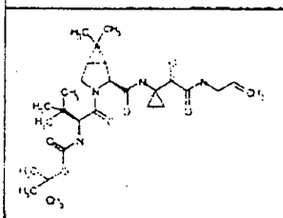
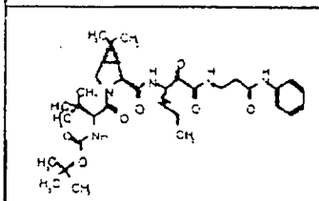
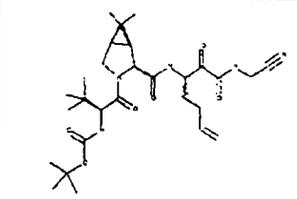
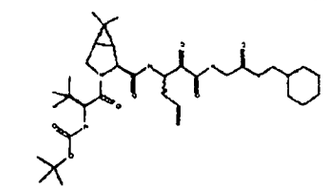
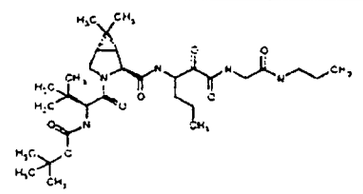
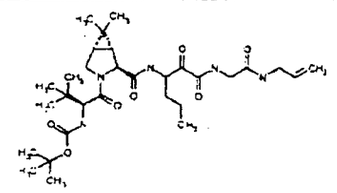
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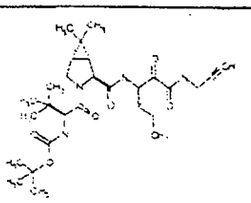
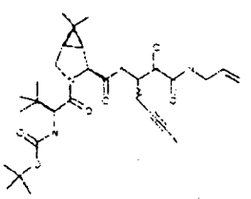
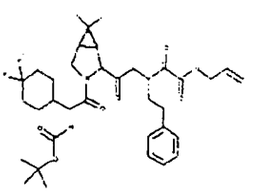
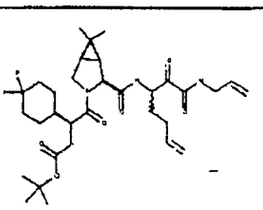
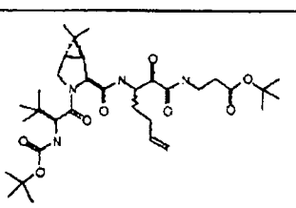
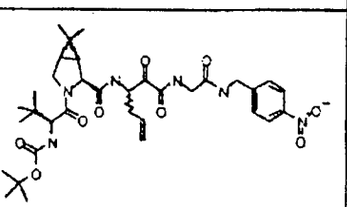
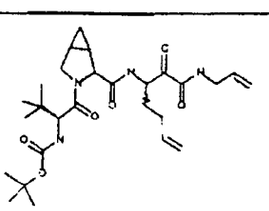
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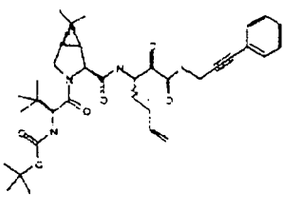
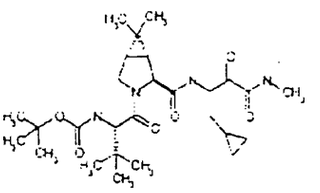
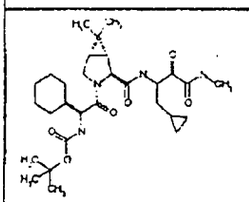
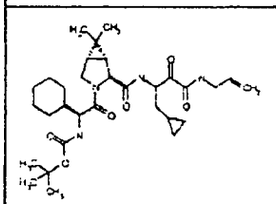
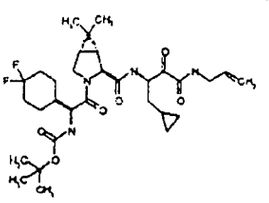
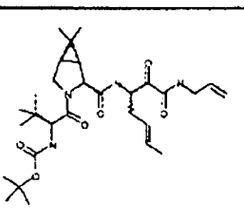
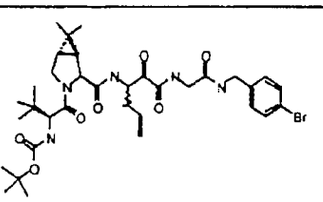
939723

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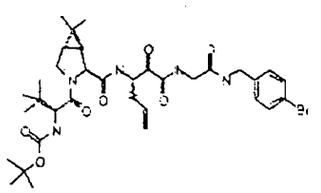
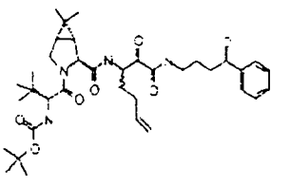
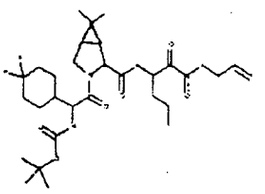
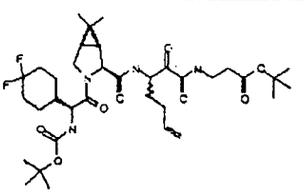
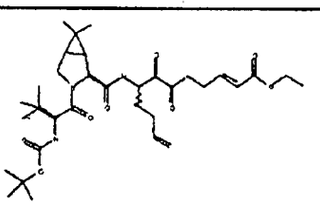
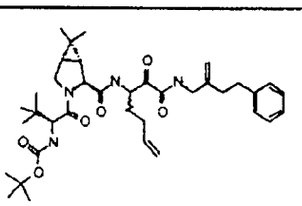
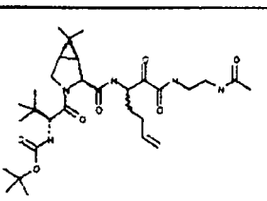
030724

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	519	C

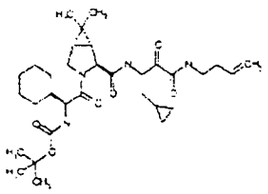
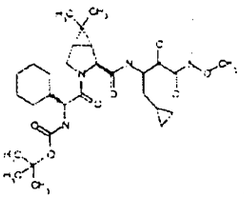
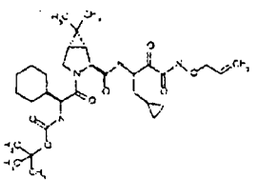
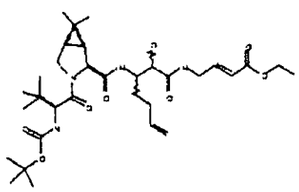
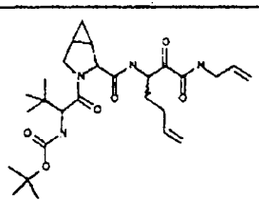
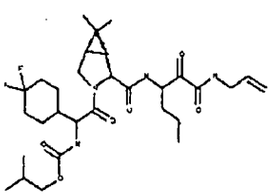
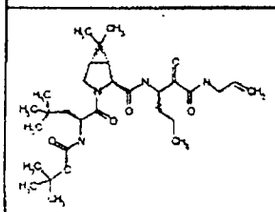
030725

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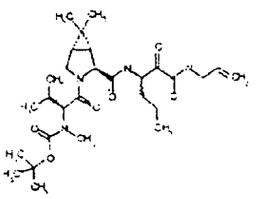
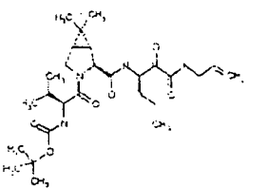
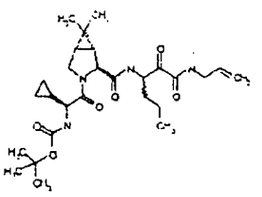
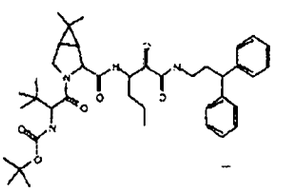
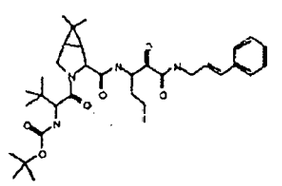
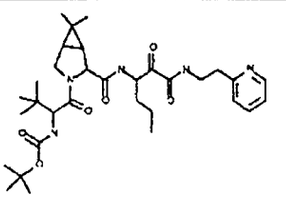
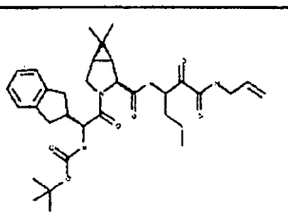
000726

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	592	B

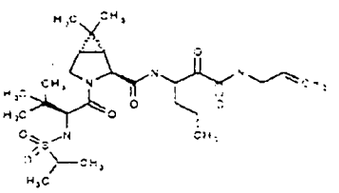
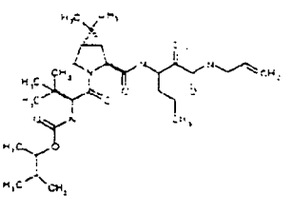
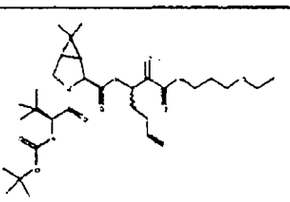
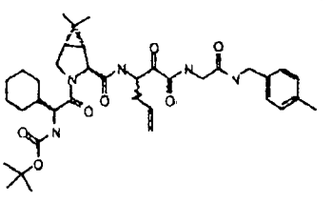
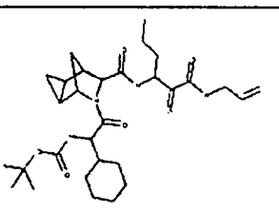
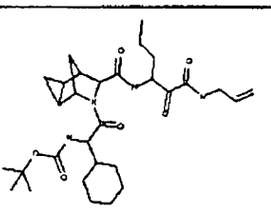
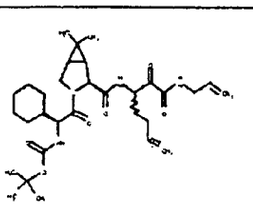
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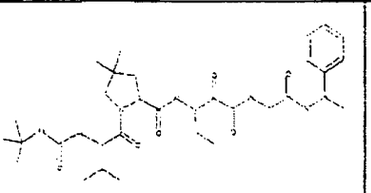
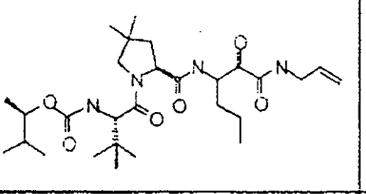
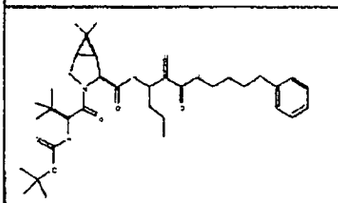
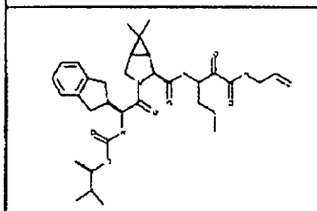
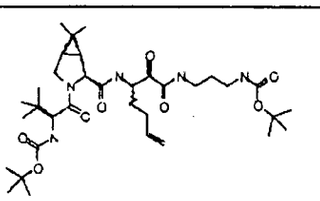
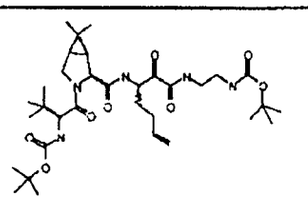
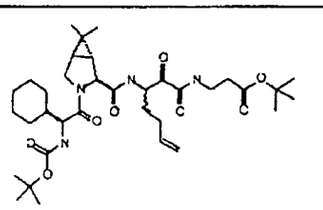
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	519	C
	597	B
	549	C

000728

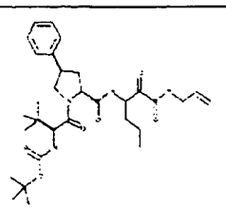
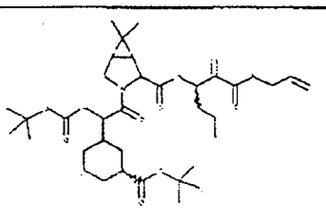
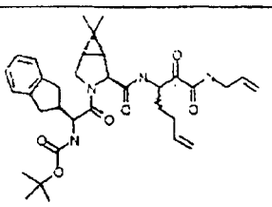
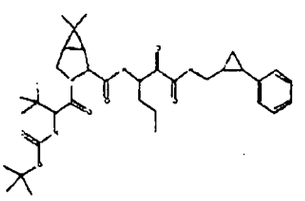
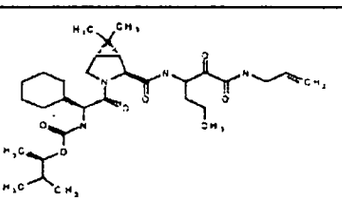
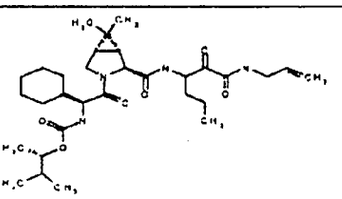
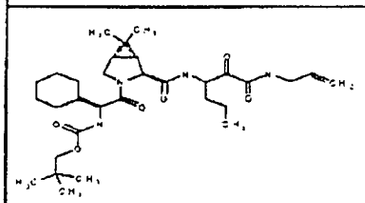
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000729

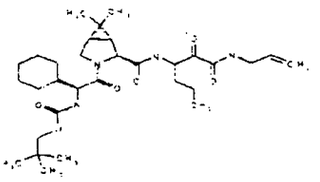
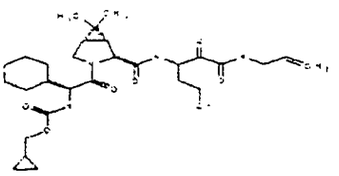
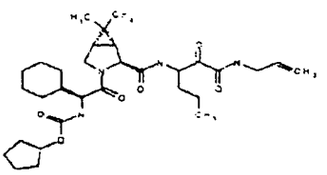
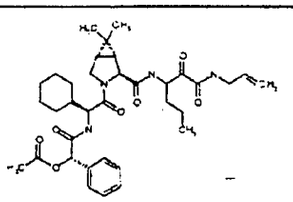
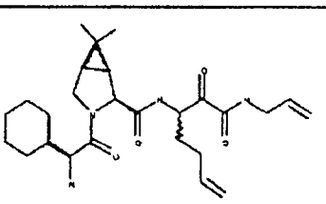
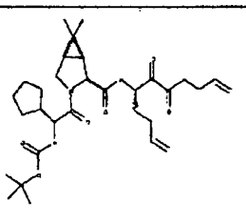
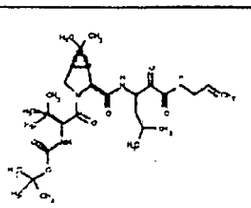
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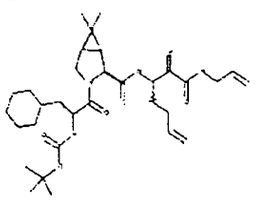
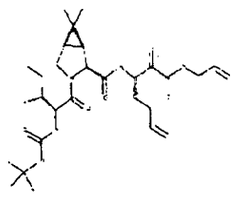
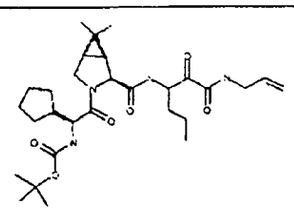
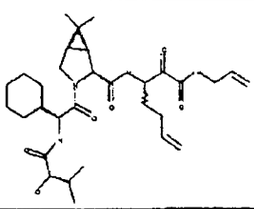
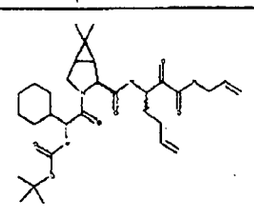
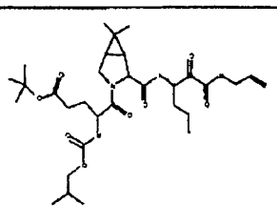
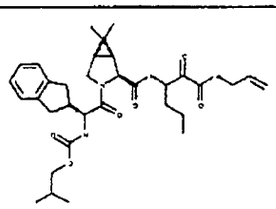
030731

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	625	C
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	575	B
	575	B

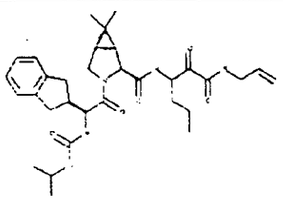
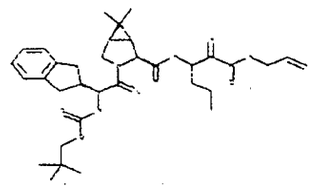
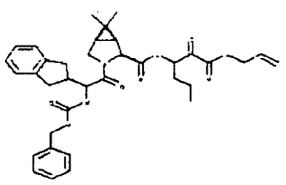
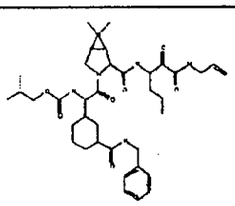
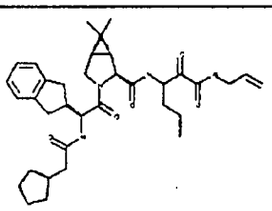
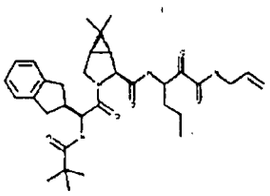
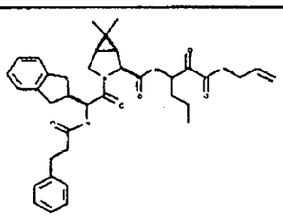
000732

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	573	B
	637	B
	473	C
	559	B
	549	C

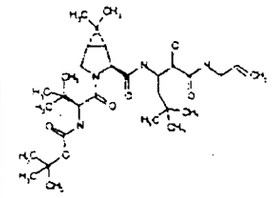
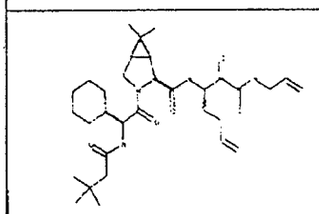
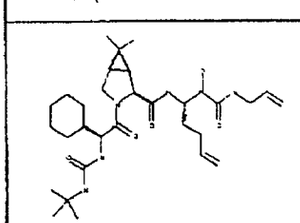
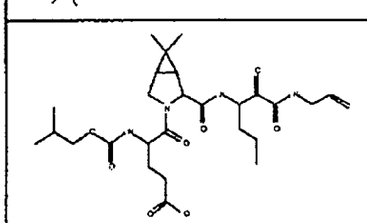
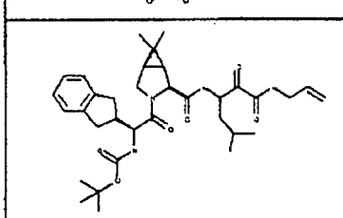
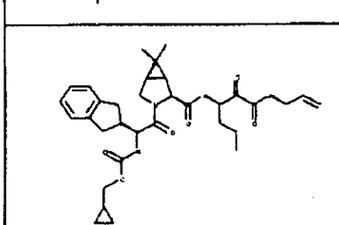
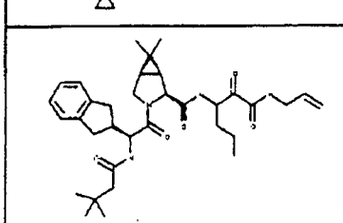
000733

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	547	B
	573	C
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	607	C
	595	B

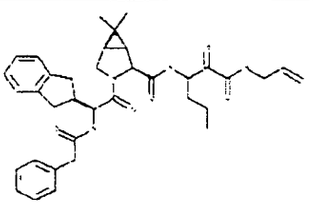
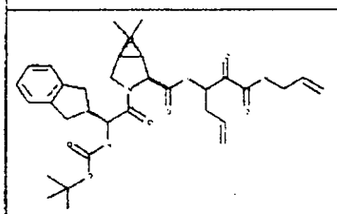
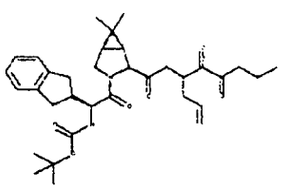
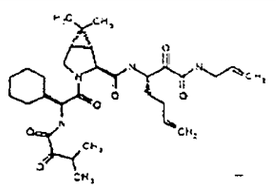
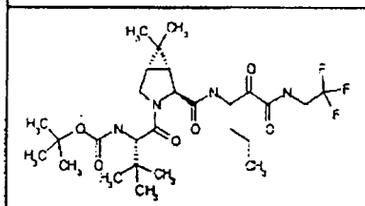
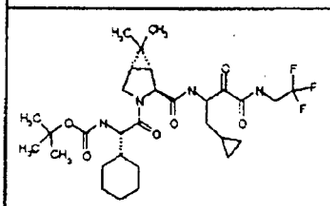
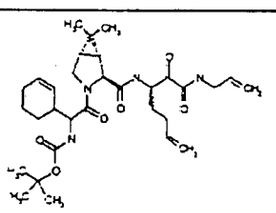
000734

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	629	C
	694	C
	605	C
	579	C
	627	C

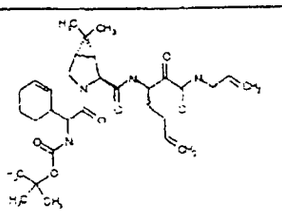
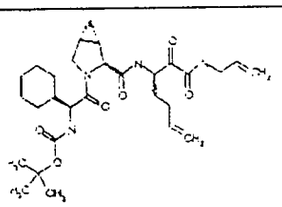
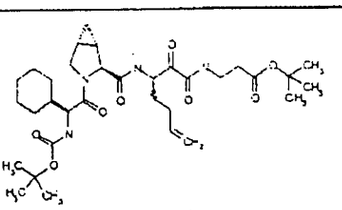
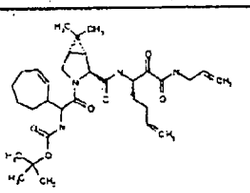
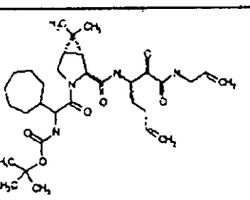
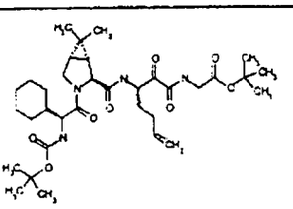
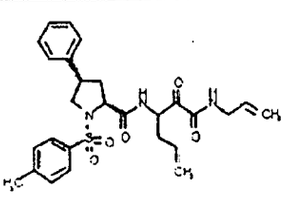
000735

	563	C
	571	C
	572	B
	551	C
	609	C
	593	B
	593	C

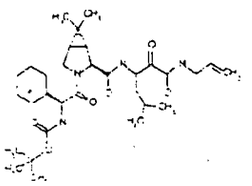
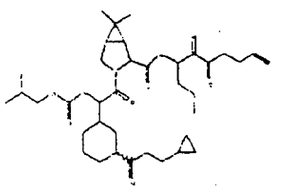
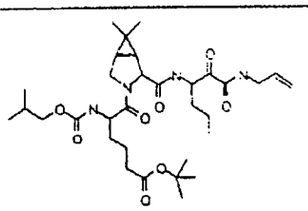
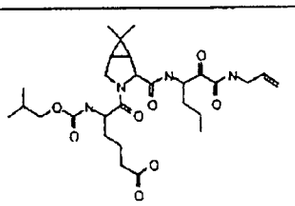
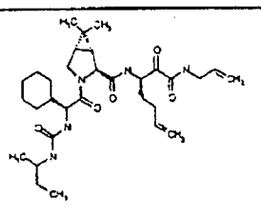
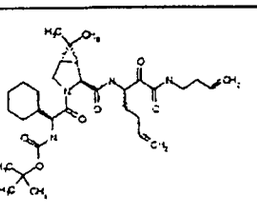
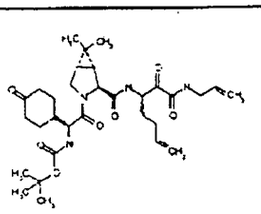
030736

	613	C
	593	B
	581	C
	571	B
	577	C
	615	C
	571	C

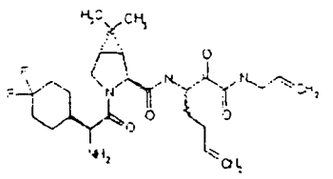
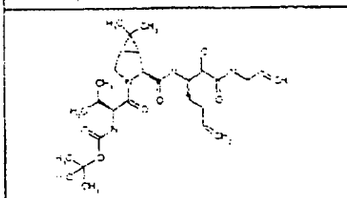
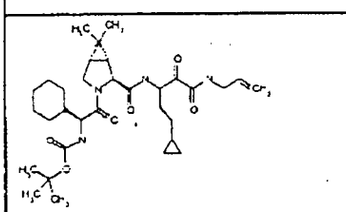
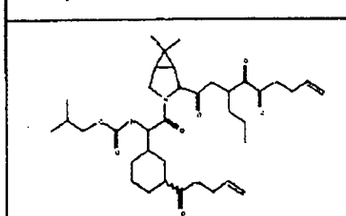
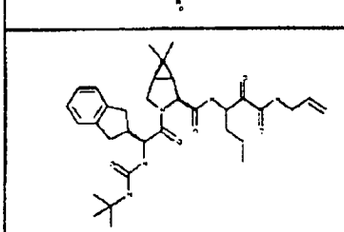
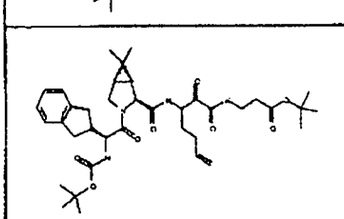
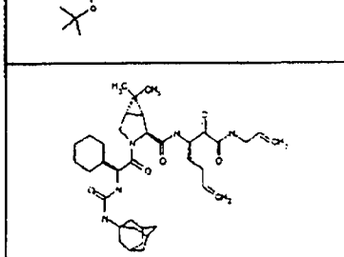
030737

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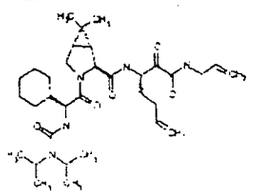
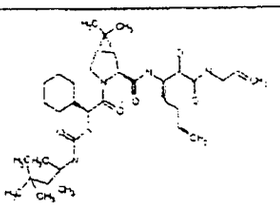
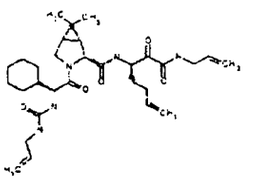
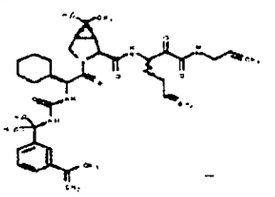
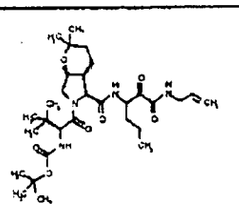
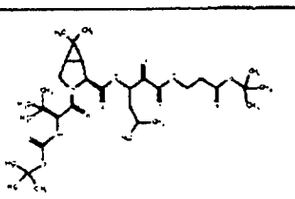
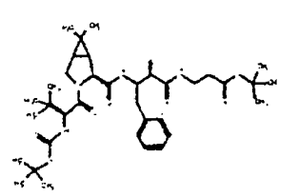
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	587	A
	587	B

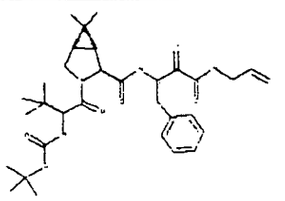
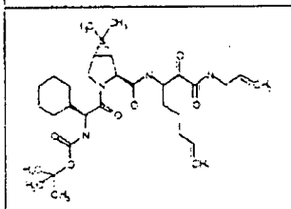
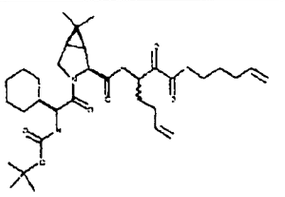
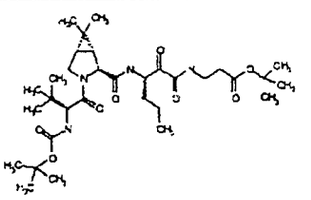
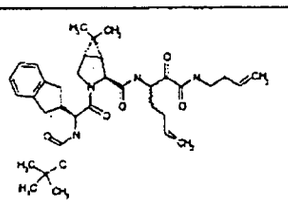
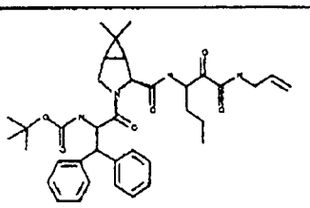
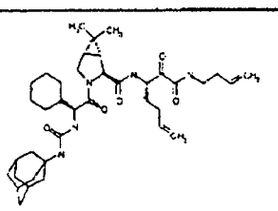
033739

	509	C
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	587	B
	644	C
	594	B
	695	B
	650	B

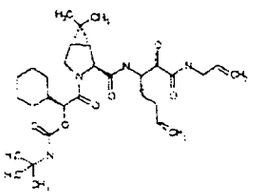
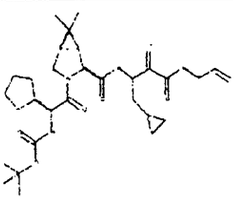
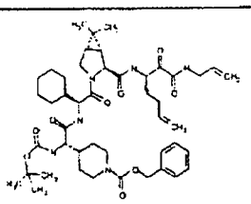
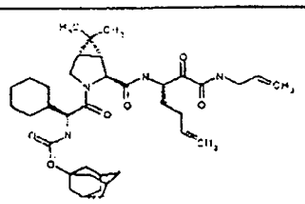
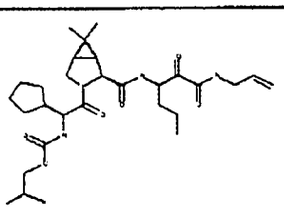
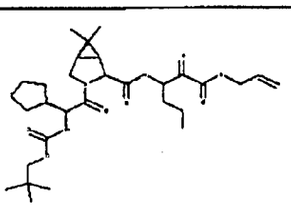
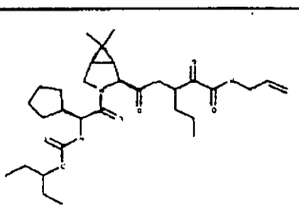
030740

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	556	B
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	579	C
	637	C
	671	C

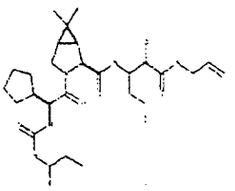
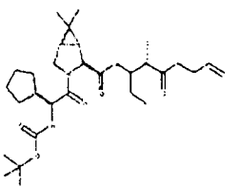
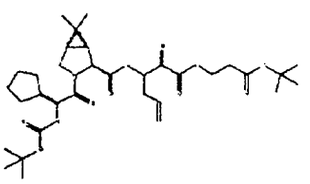
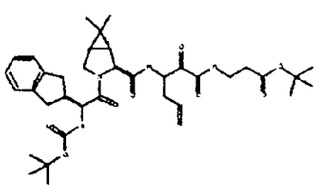
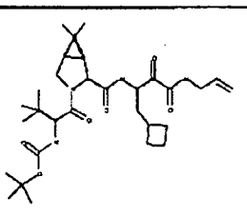
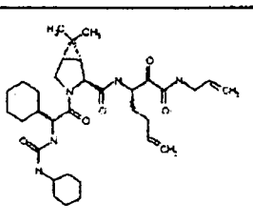
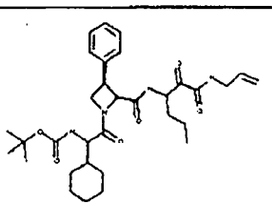
030741

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	664	B

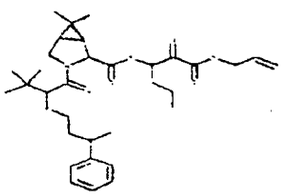
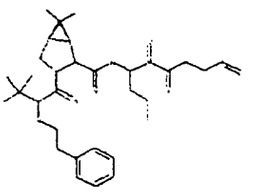
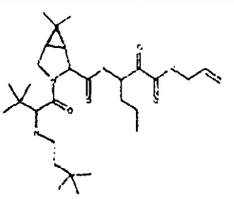
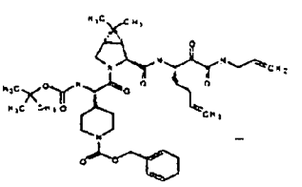
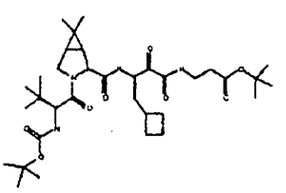
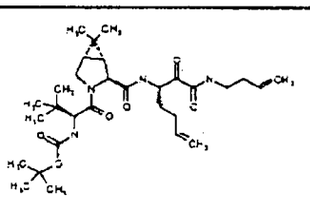
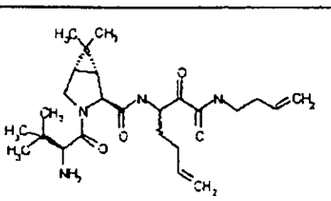
000742

	573	C
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	847	B
	651	B
	547	C
	561	B
	561	B

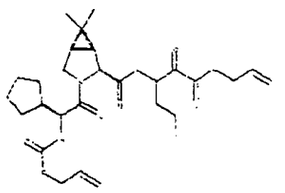
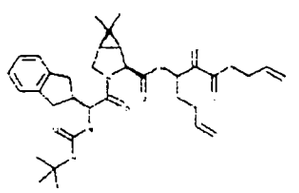
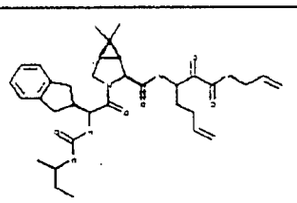
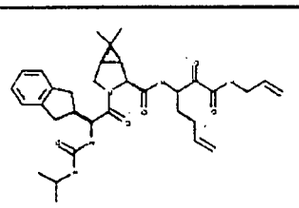
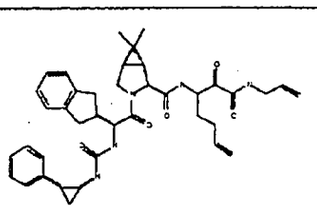
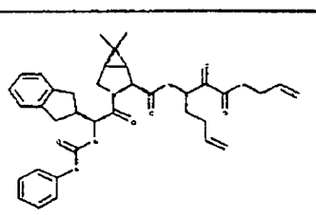
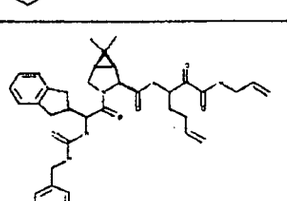
030743

	546	C
	545	C
	633	B
	681	C
	561	C
	598	B
	583	C

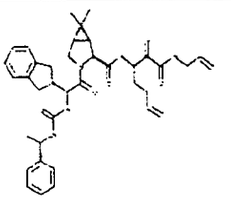
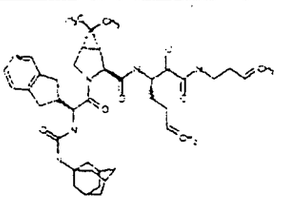
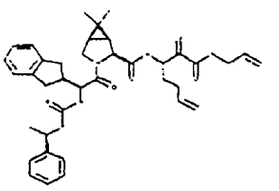
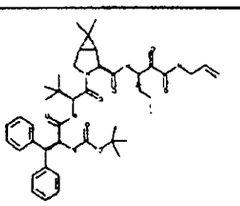
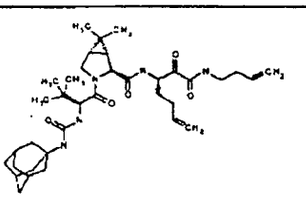
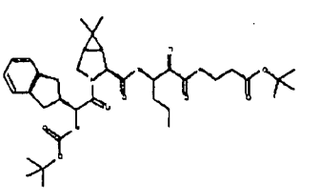
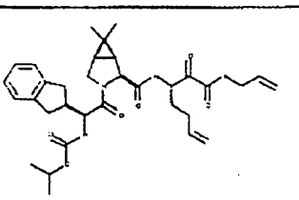
030744

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	539	C
	519	C
	708	B
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	561	B
	461	C

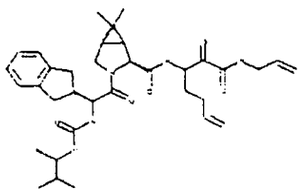
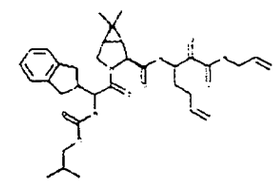
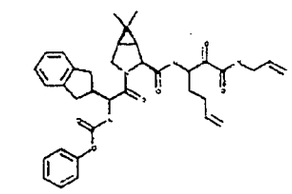
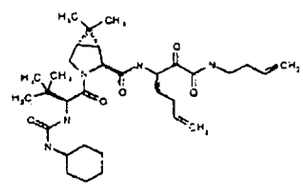
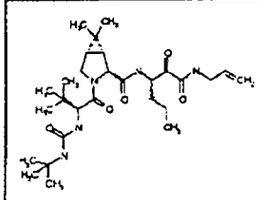
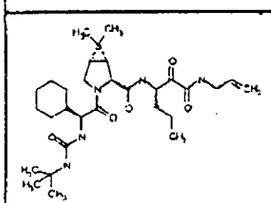
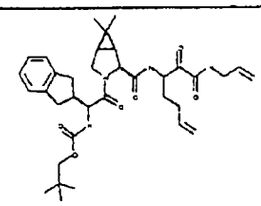
030745

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	666	C
	626	B
	640	B

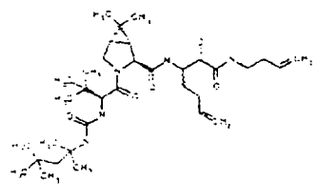
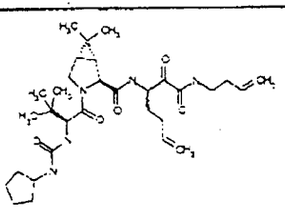
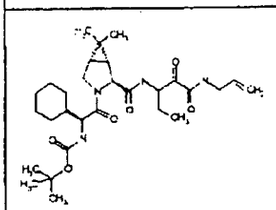
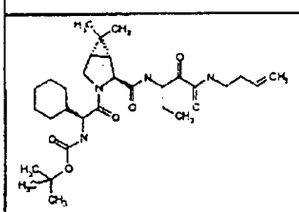
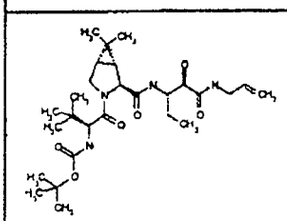
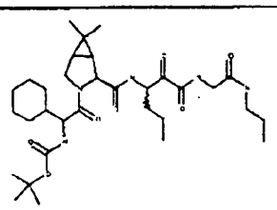
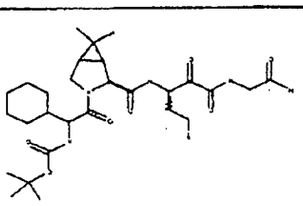
030746

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	654	B
	758	C
	638	A
	683	B
	593	A

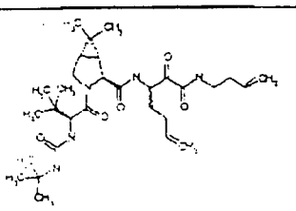
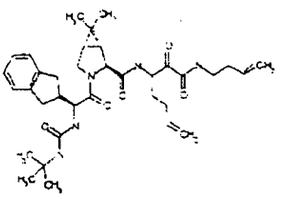
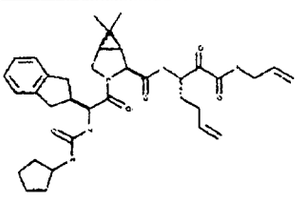
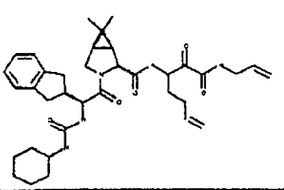
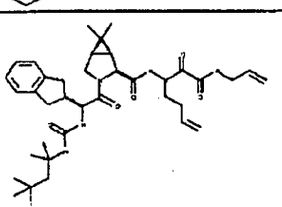
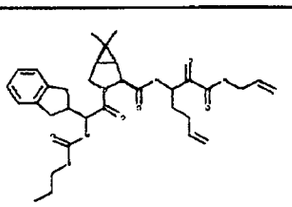
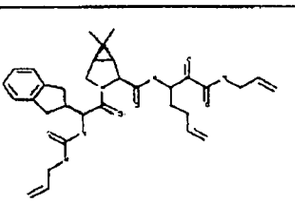
030747

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	607	B
	627	B
	586	A
	534	B
	560	C
	621	A

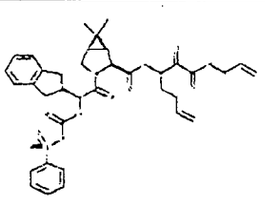
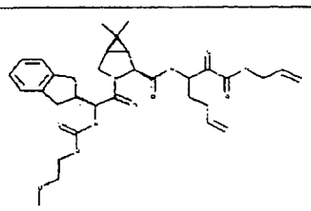
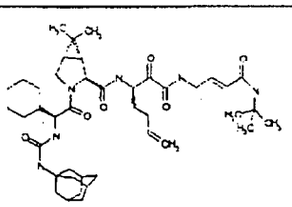
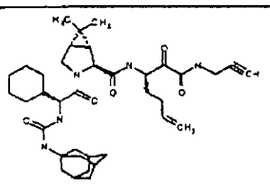
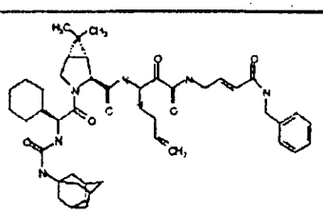
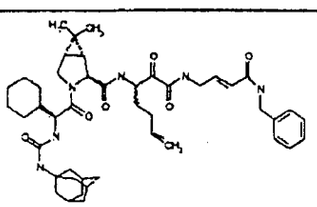
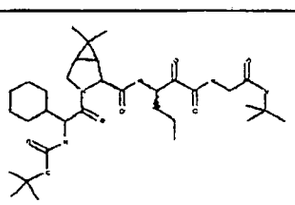
030748

	616	B
	572	A
	547	C
	561	C
	521	C
	620	B
	578	B

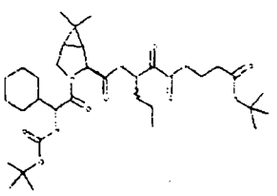
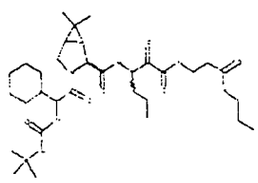
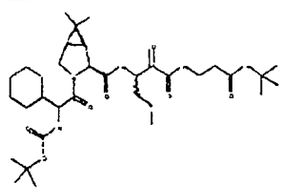
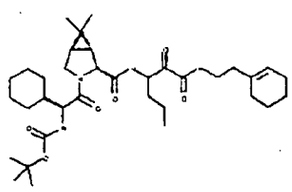
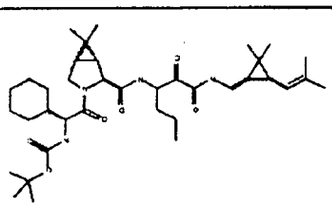
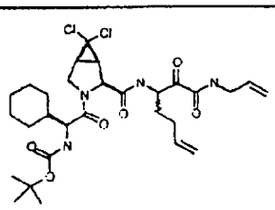
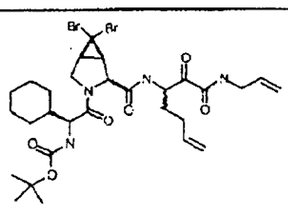
000749

	560	A
	620	A
	618	B
	632	B
	662	B
	592	B
	590	B

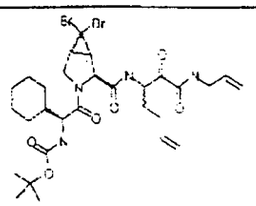
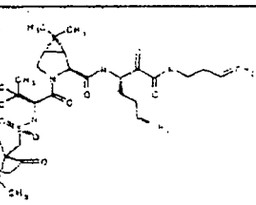
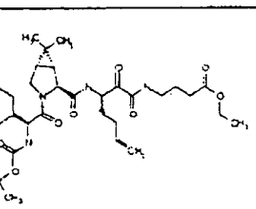
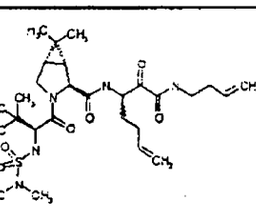
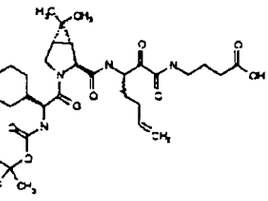
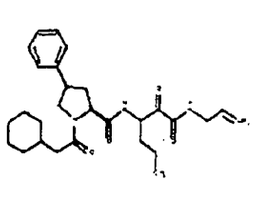
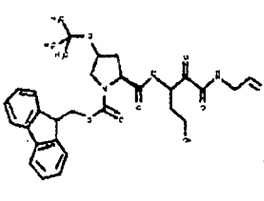
030750

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	609	B
	749	B
	648	A
	783	B
	783	B
	634	C

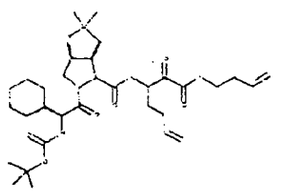
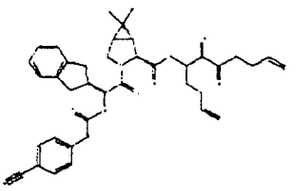
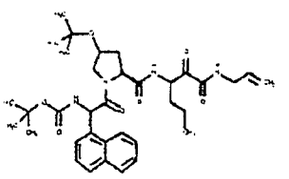
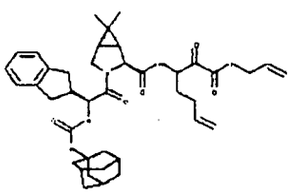
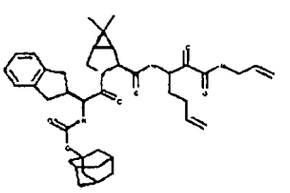
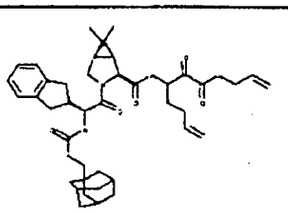
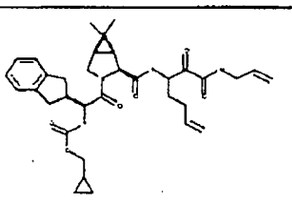
030751

	648	C
	634	C
	649	C
	629	C
	657	C
	614	A
	702	B

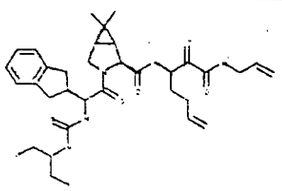
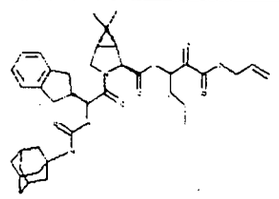
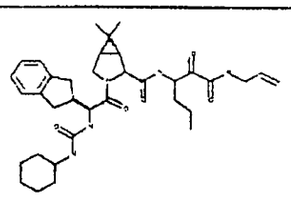
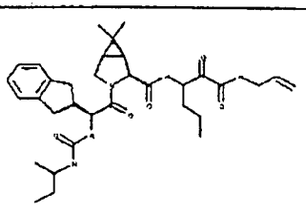
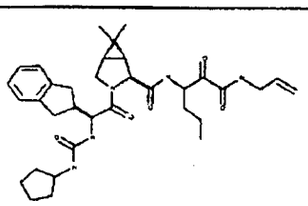
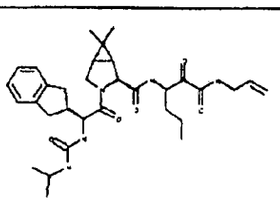
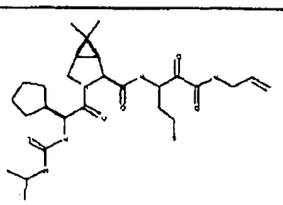
030752

	702	A
	675	B
	647	B
	568	C
	619	C
	482	C
	576	C

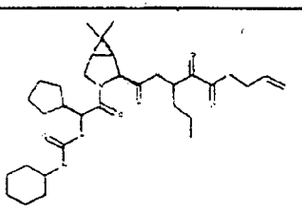
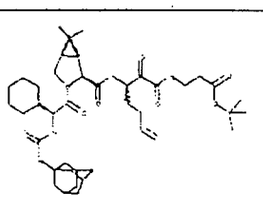
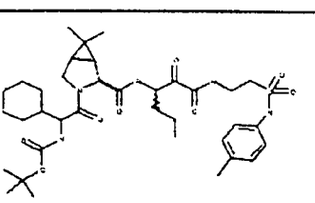
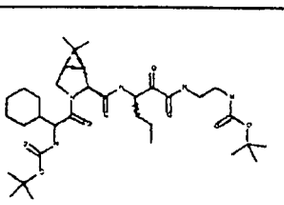
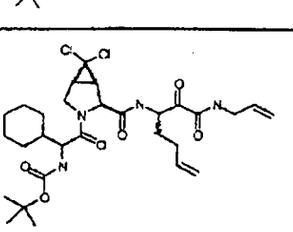
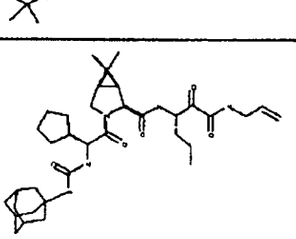
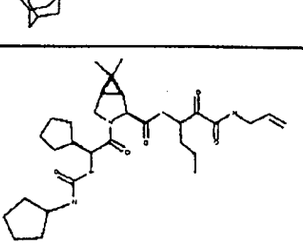
030753

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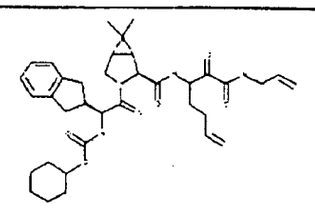
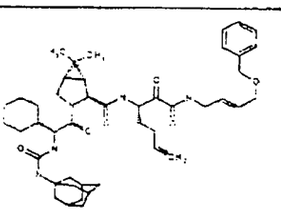
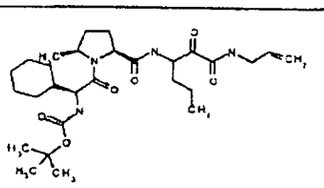
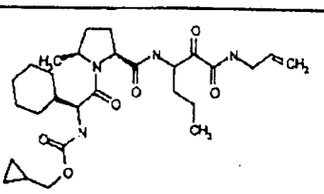
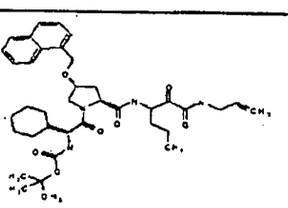
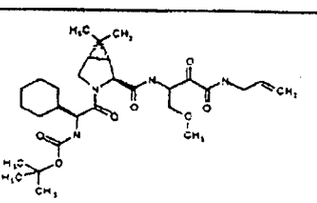
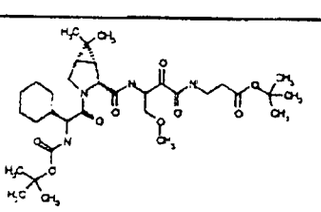
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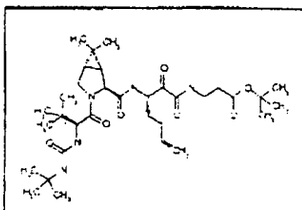
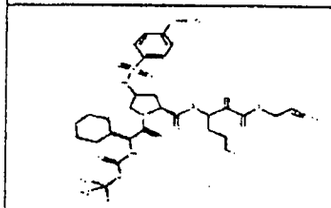
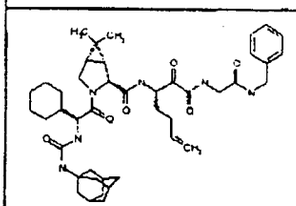
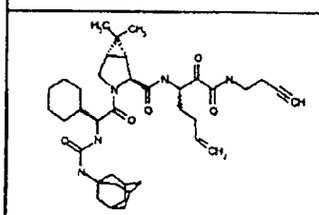
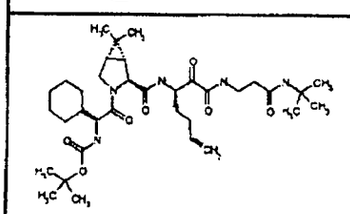
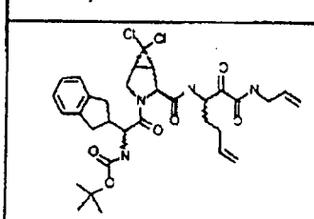
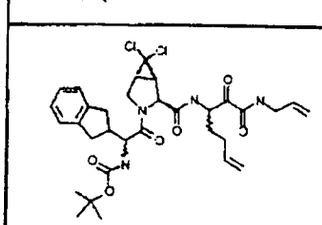
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	664	B
	614	B
	624	B
	558	B

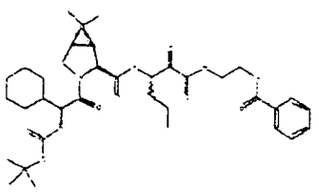
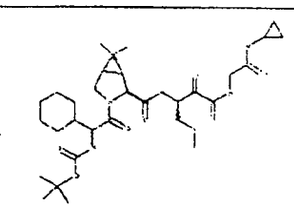
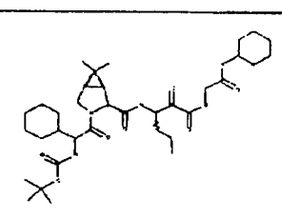
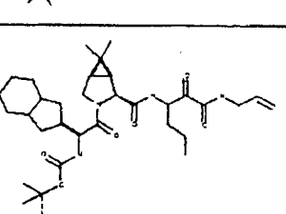
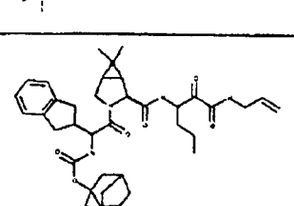
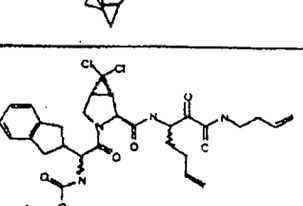
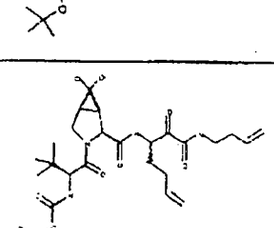
030756

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	563	B
	651	A

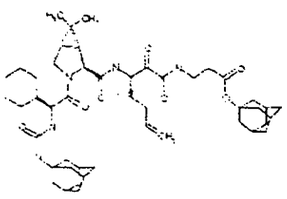
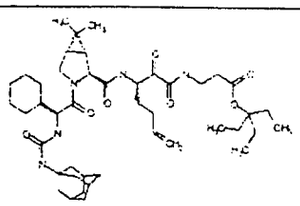
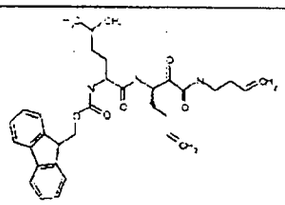
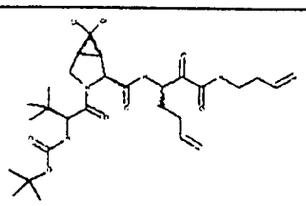
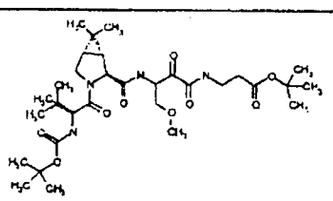
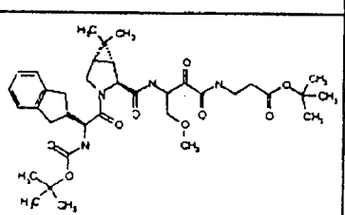
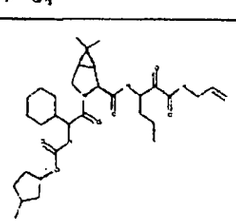
000757

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	757	A
	662	A
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	648	A
	648	C

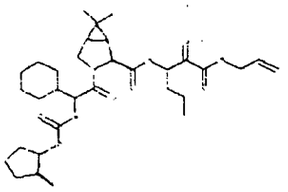
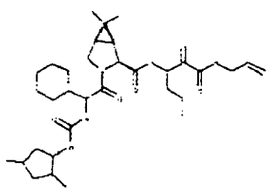
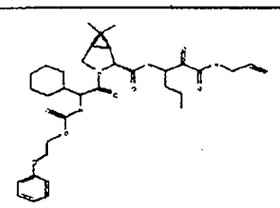
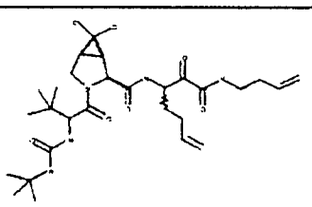
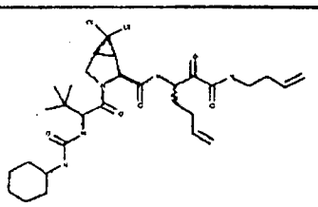
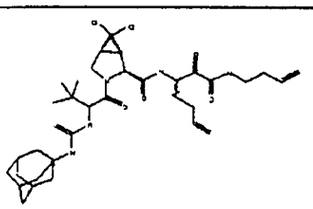
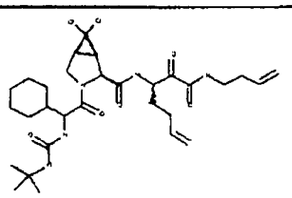
000758

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	601	B
	673	B
	662	A
	602	A

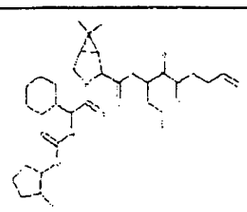
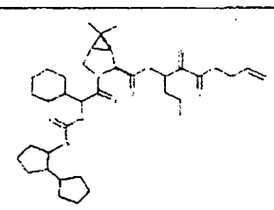
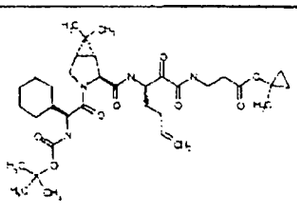
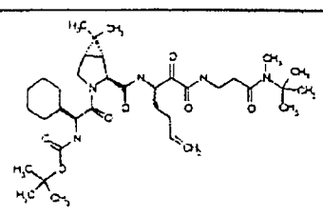
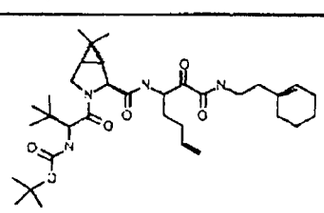
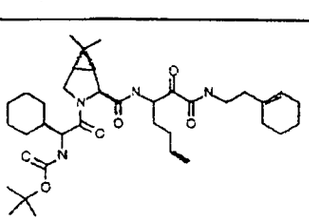
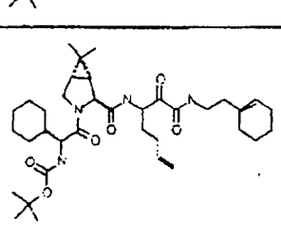
000759

	816	C
	780	B
	560	C
	602	C
	625	B
	685	B
	587	A

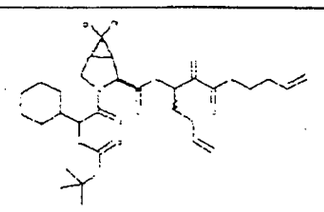
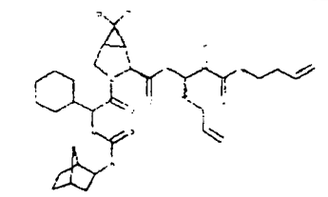
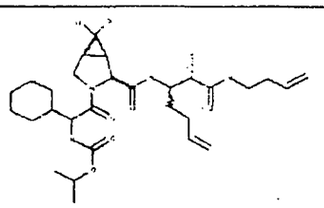
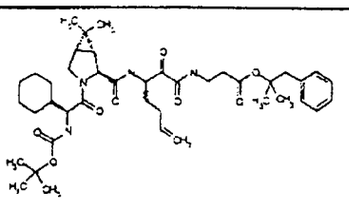
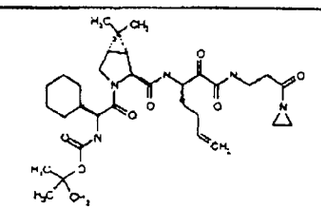
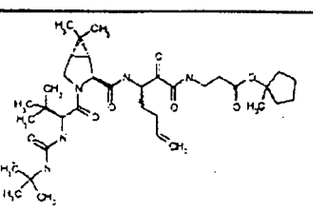
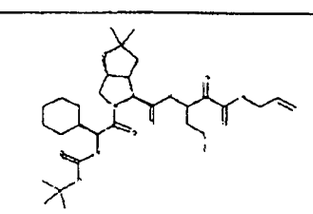
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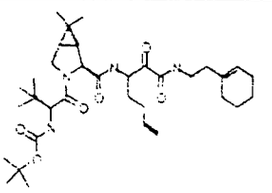
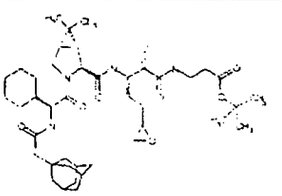
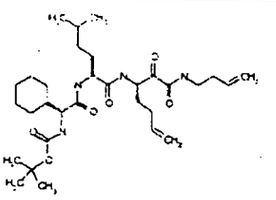
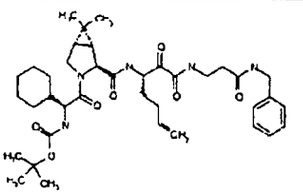
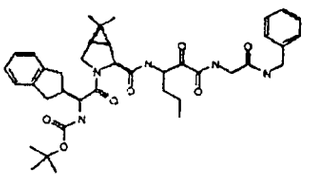
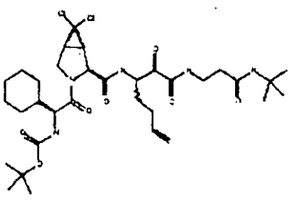
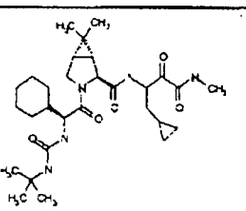
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	628	A

000761

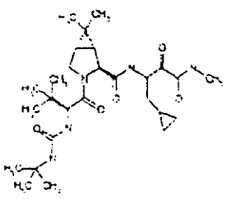
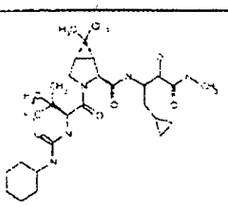
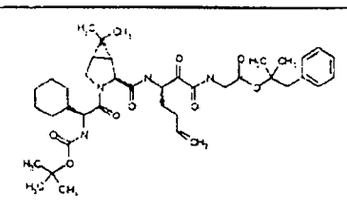
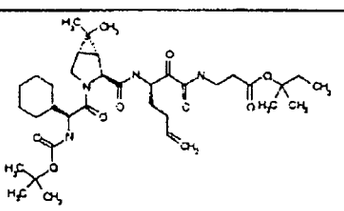
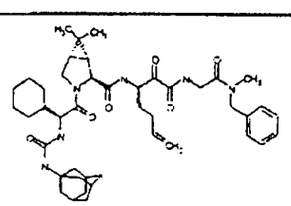
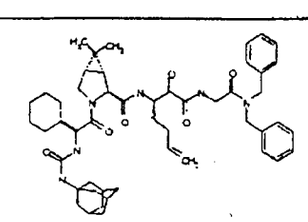
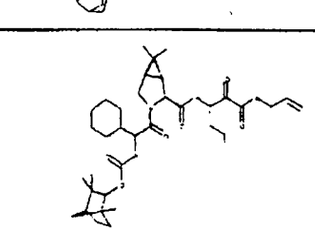
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	615	B
	641	B
	641	B

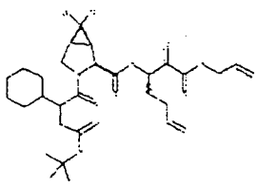
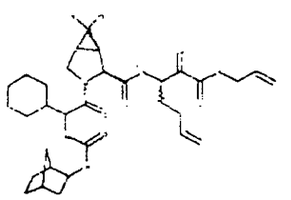
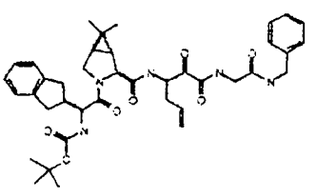
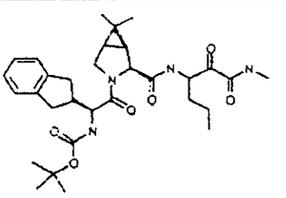
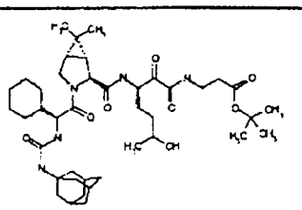
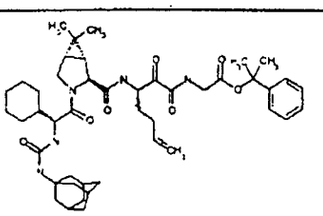
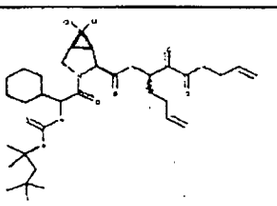
000762

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	737	B
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	660	A
	591	C

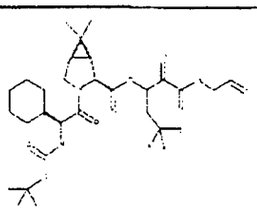
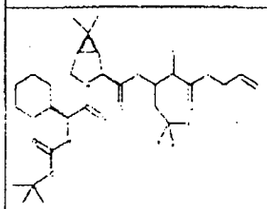
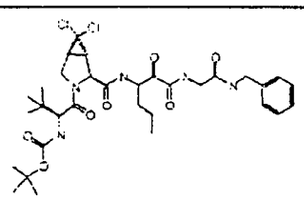
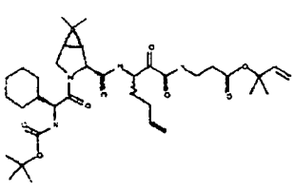
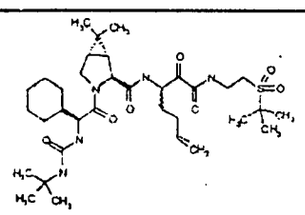
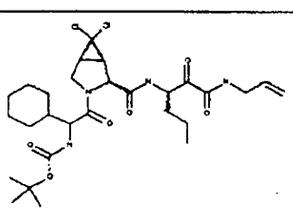
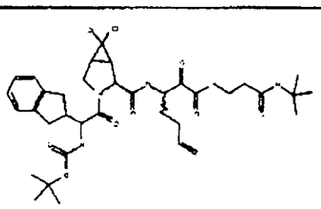
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000764

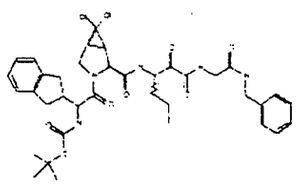
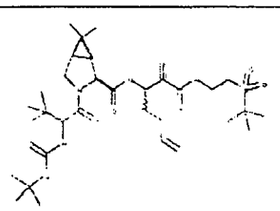
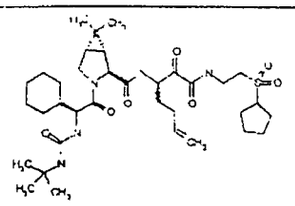
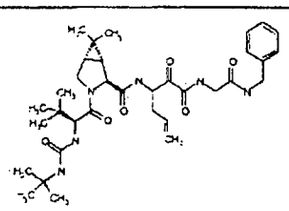
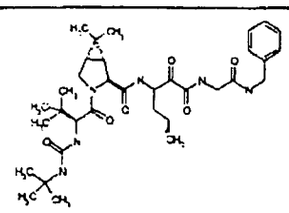
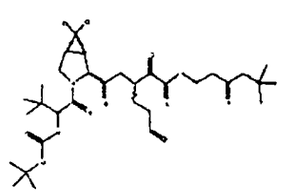
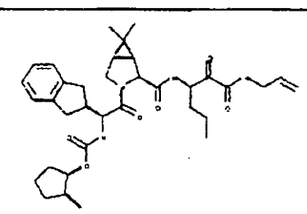
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	771	B
	847	C
	641	A

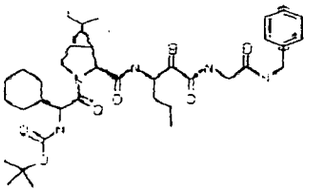
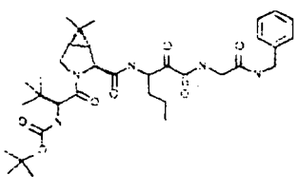
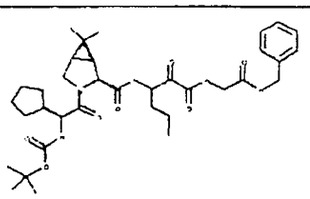
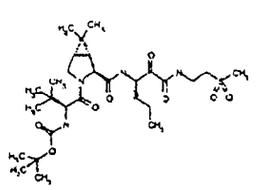
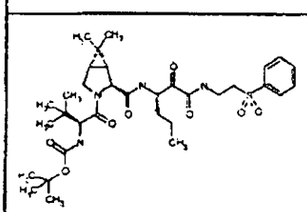
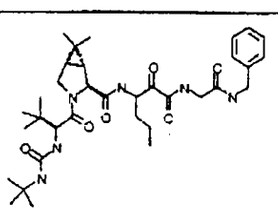
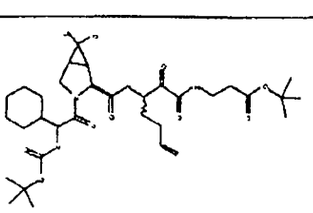
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	700	A
	569	A
	756	B
	786	A
	669	B

000766

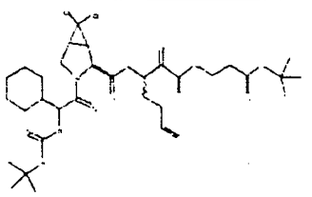
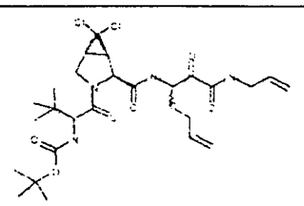
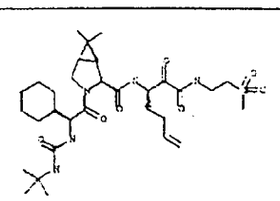
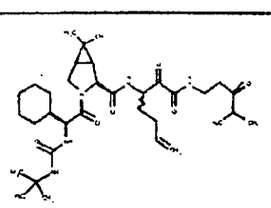
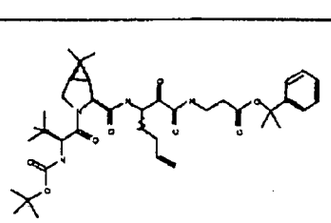
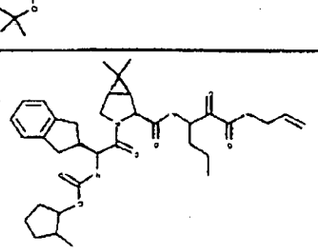
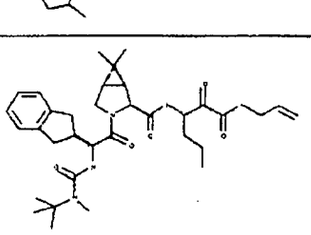
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	601	B
	683	A
	673	A
	680	A
	602	A
	735	A

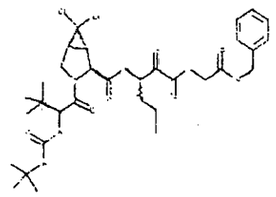
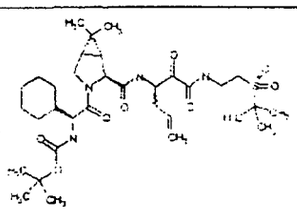
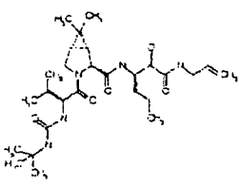
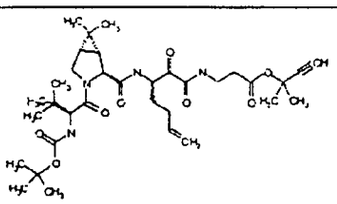
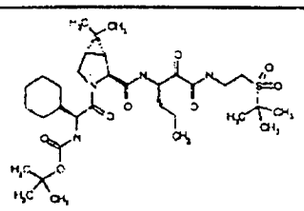
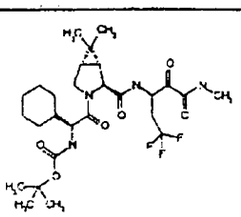
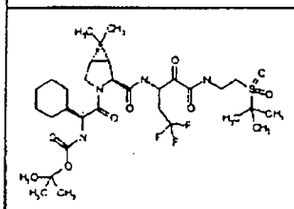
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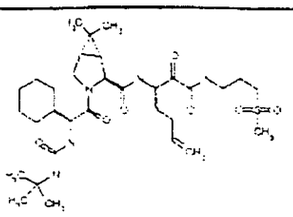
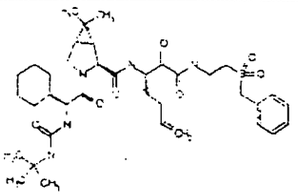
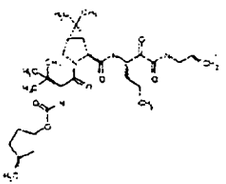
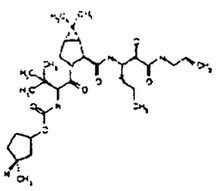
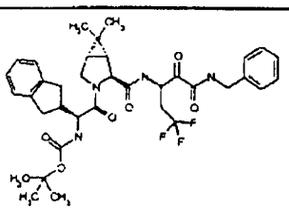
	743	A
	655	B
	692	A
	639	A
	639	A
	675	A
	621	A

	668	A
	642	A
	654	A
	601	C
	663	B
	641	A
	702	A

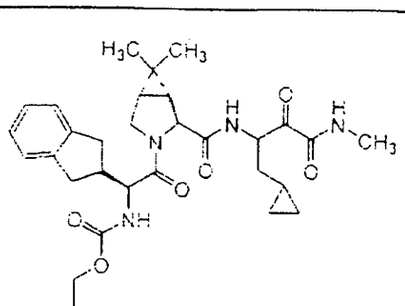
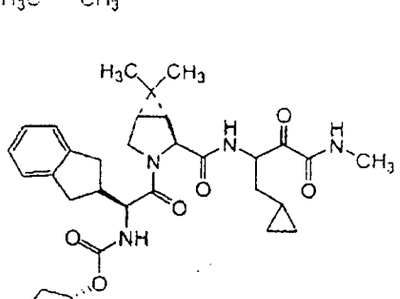
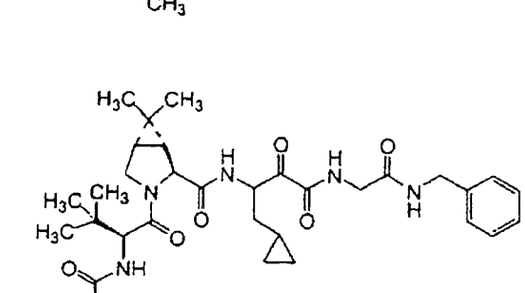
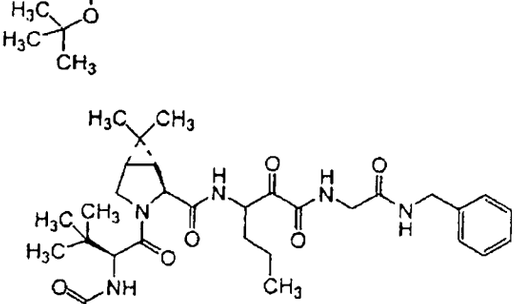
030739

	701	A
	588	B
	638	A
	630	A
	697	A
	621	A
	608	B

	682	A
	667	B
	520	B
	645	B
	669	C
	575	A
	709	B

	652	B
	714	A
	561	B
	561	B
	685	B

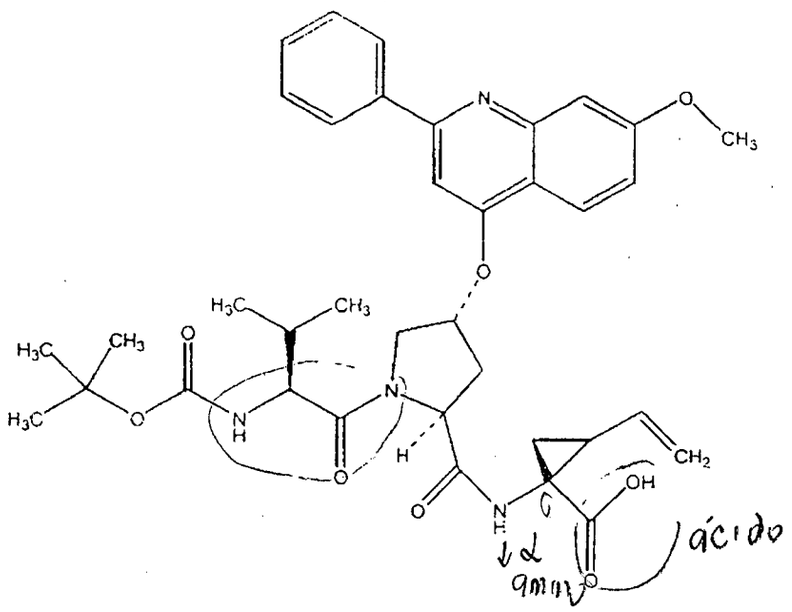
000772

ESTRUCTURA	PM	Rango Kᵢ*
	580	A
	606	A
	653	A
	667	A

REIVINDICACIONES

000773

1. Un compuesto, que incluye enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos y una prodrogá de dicho compuesto, y sus sales aceptables para uso farmacéutico o los solvatos de dicho compuesto, o de dicha prodroga, dicho compuesto posee la estructura que se muestra en la Fórmula I:



Fórmula I

en la cual:

Y se selecciona del grupo que consiste de los siguientes grupos funcionales: 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 condición de que Y puede ser 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 condición de que X^{11} puede sustituirse 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, arilureído, halógeno, ciano, o nitro, con la condición de que dicho alquilo, alcoxi, y arilo pueden sustituirse en forma opcional con grupos funcionales seleccionados en forma independiente de X^{12};

R^1 es COR^5 o $B(OR)_2$, en los cuales R^5 es H, OH, OR^8, NR^9R^{10}, CF_3, C_2F_5, C_3F_7, CF_2R^6, R^6, o COR^7 en el cual R^7 es H, OH, ORB, CHR^9R^{10}, o NR^9R^{10}, en el cual R^6, R^8, R^9 y R^{10} se seleccionan en forma independiente del grupo que consiste de H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, cicloalquilo, arilalquilo, heteroarilalquilo, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]$ $pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pCOR^{11}$, $[CH(R^{1'})]_pCH(OH)R^{11}$, $CH(R^{1'})CONHCH(R^{2'})COO$ R^{11}, $CH(R^{1'})CONHCH(R^{2'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})R'$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})COO$ R^{11}, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})COO$ R^{11}, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONR^{12}R^{13}$, $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})COO$ R^{11} y $CH(R^{1'})CONHCH(R^{2'})CONHCH(R^{3'})CONHCH(R^{4'})CONHCH(R^{5'})$ $CONR^{12}R^{13}$, en las cuales $R^{1'}$, $R^{2'}$, $R^{3'}$, $R^{4'}$, $R^{5'}$, R^{11}, R^{12}, R^{13}, y R', se seleccionan en forma independiente del grupo que consiste de H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo y heteroaralquilo;

Z se selecciona de O, N, CH o CR;

W puede estar presente o ausente, y si W está presente, W se selecciona de C=O, C=S, C(=N-CN), o SO_2;

Q puede estar presente o ausente, y cuando Q está presente, Q es CH, 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 se enlaza directamente a L;

A es O, CH_2, $(CHR)_p$, $(CHR\text{-}CHR')_p$, $(CRR')_p$, NR, S, SO_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 1 como G está enlazado a;

J puede estar presente o ausente, y cuando J está presente, J es $(CH_2)_p$, $(CHR)_p$, o $(CRR')_p$, SO_2, NH, NR u O; y cuando J está ausente, G está presente y E está enlazado directamente a N que se muestra en la Fórmula I enlazado a J;

L puede estar presente o ausente, y cuando L está presente, L es CH, CR, O, S o NR; y cuando L está ausente, entonces M puede estar presente o ausente; y si M está presente cuando L está ausente, entonces M se enlaza en forma directa e independiente a E, y J se enlaza directa e independientemente a E;

M puede estar presente o ausente, y cuando M está presente, M es O, NR, S, SO_2, $(CH_2)_p$, $(CHR)_p$ $(CHR\text{-}CHR')_p$, o $(CRR')_p$;

p es un número de 0 a 6; y

R, R', R^2, R^3 y R^4 se seleccionan en forma independiente del grupo que consiste de H; alquilo de C_1-C_{10}; alquenilo de C_2-C_{10}; cicloalquilo de C_3-C_8;

heterocicloaiquilo de C_3-C_4 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 a ocho átomos de carbono, y de cero a seis átomos de oxígeno, nitrógeno, sulfuro o fósforo, y dicho alquilo es de uno a seis átomos de carbono; arilo; heteroarilo; alquil-arilo; y alquil-heteroarilo;

donde dichos grupos funcionales alquilo, heteroalquilo, alquenilo, heteroalquenilo, arilo, heteroarilo, cicloalquil y heterocicloalquilo pueden sustituirse en forma apropiada para la química, donde dicho término "substituido" se refiere a una sustitución opcional y apropiada para la química de uno o más grupos funcionales seleccionados del grupo que consiste de 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, e hidroxamato;

además donde dicha unidad N-C-G-E-L-J-N representa una estructura de anillo cíclico de cinco o seis elementos con la condición de que cuando dicha unidad N-C-G-E-L-J-N representa una estructura de anillo cíclico de cinco elementos, o cuando la estructura de anillo bicíclico de la Fórmula I comprende N, C, G, E, L, J, N, A, Q, y M representa una estructura de anillo cíclico de cinco elementos, entonces la estructura de anillo cíclico de cinco elementos carece de un grupo carbonilo como parte del anillo cíclico.

2. El compuesto de la reivindicación 1, en el cual R^1 es COR^5, y R^5 es H, OH, $COOR^8$ o $CONR^9R^{10}$.

3. El compuesto de la reivindicación 2, en el cual R^1 es $COCONR^9R^{10}$, y R^9 es H; and R^{10} es H, R^{14}, $[CH(R^{1'})]_pCOOR^{11}$, $[CH(R^{1'})]_pCONR^{12}R^{13}$, $[CH(R^{1'})]_pSO_2R^{11}$, $[CH(R^{1'})]_pSO_2N\ R^{12}R^{13}$, $[CH(R^{1'})]_pCOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$,

$CH(R^{1'})C\emptyset NHCH(R^{2'})$ $CONR^{12}R^{13}$, o $CH(R^{1'})CONHCH(R^{2'})(R')$, donde R^{14} es H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo, alquenilo, alquinil o heteroaralquil.

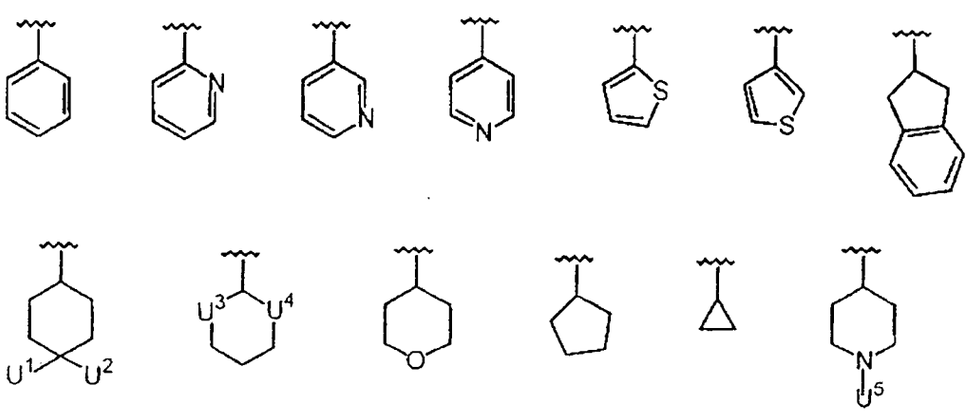
4. El compuesto de la reivindicación 3, en el cual R^{10} es H, R^{14}, $CH(R^{1'})COOR^{11}$, $CH(R^{1'})CH(R^{1'})COOR^{11}$, $CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})CONR^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})SO_2R^{11}$, $CH(R^{1'})CH(R^{1'})SO_2N$ $R^{12}R^{13}$, $CH(R^{1'})CH(R^{1'})COR^{11}$, $CH(R^{1'})CONHCH(R^{2'})COOR^{11}$, $CH(R^{1'})CONHCH(R^{2'})$ $CONR^{12}R^{13}$, o $CH(R^{1'})CONHCH(R^{2'})(R')$, donde $R^{1'}$ es H o alquilo, y $R^{2'}$ es fenilo, fenilo sustituido, fenilo sustituido por un heteroátomo, tiofenilo, cicloalquilo, piperidilo o piridilo.

5. El compuesto de la reivindicación 4, en el cual $R^{1'}$ es H.

6. El compuesto de la reivindicación 5, en el cual R^{11} es H, metilo, etilo, alilo, terbutilo, bencilo, α-metilbencilo, α,α-dimetilbencilo, 1-metilciclopropilo o 1-metilciclopentilo;

R' es hidroximetilo o $CH_2CONR^{12}R^{13}$;

R2' se selecciona en forma independiente del grupo que consiste de:



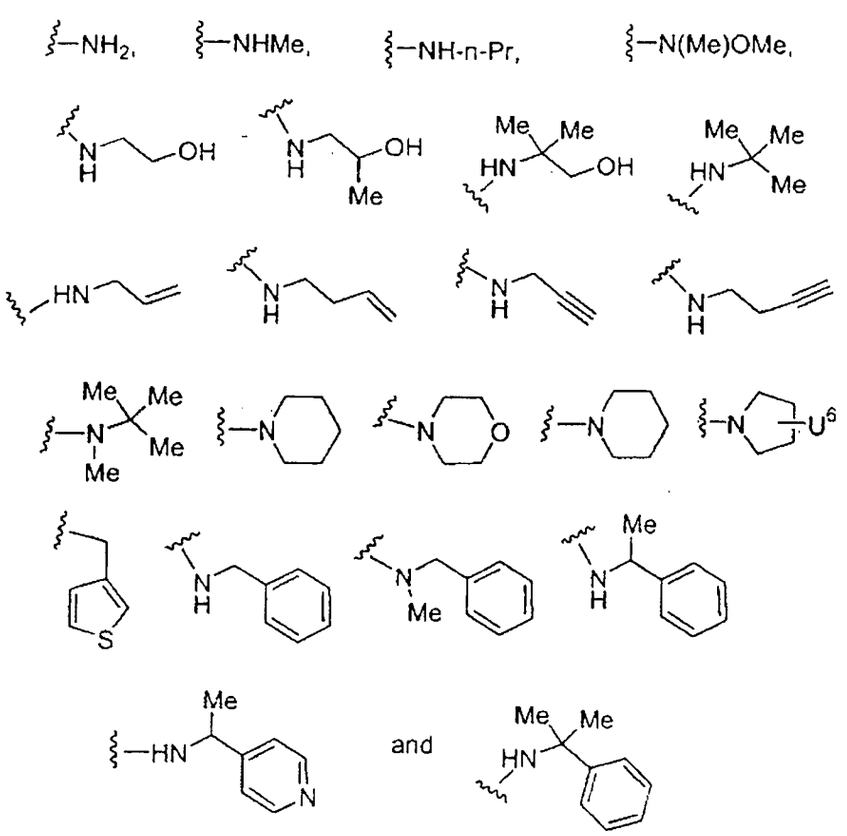
en el cual

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, 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 grupos funcionales que consisten de alquilo, sulfonilo, aril-sulfonilo, heteroalquil sulfonilo, heteroaril sulfonilo, alquil carbonilo, aril carbonilo, heteroalquil carbonilo, heteroaril carbonilo, alcoxicarbonilo, ariloxicarbonilo, heteroariloxicarbonilo, alquilaminocarbonilo, arilaminocarbonilo, heteroarilaminocarbonilo, o una combinación de estos;

y $NR^{12}R^{13}$ se selecciona del grupo que consiste de:



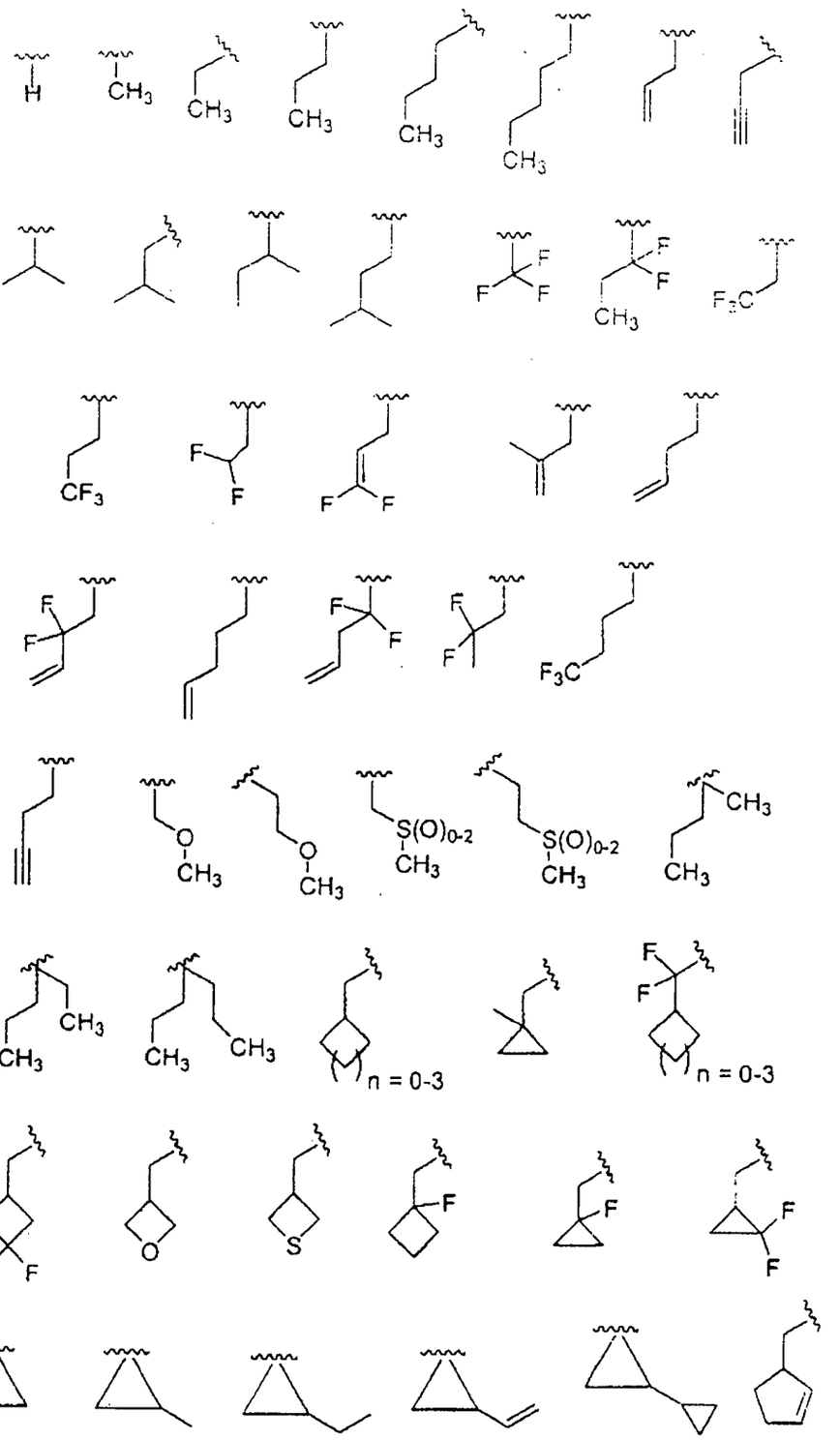
000779

donde U^6 es H, OH o CH_2OH;

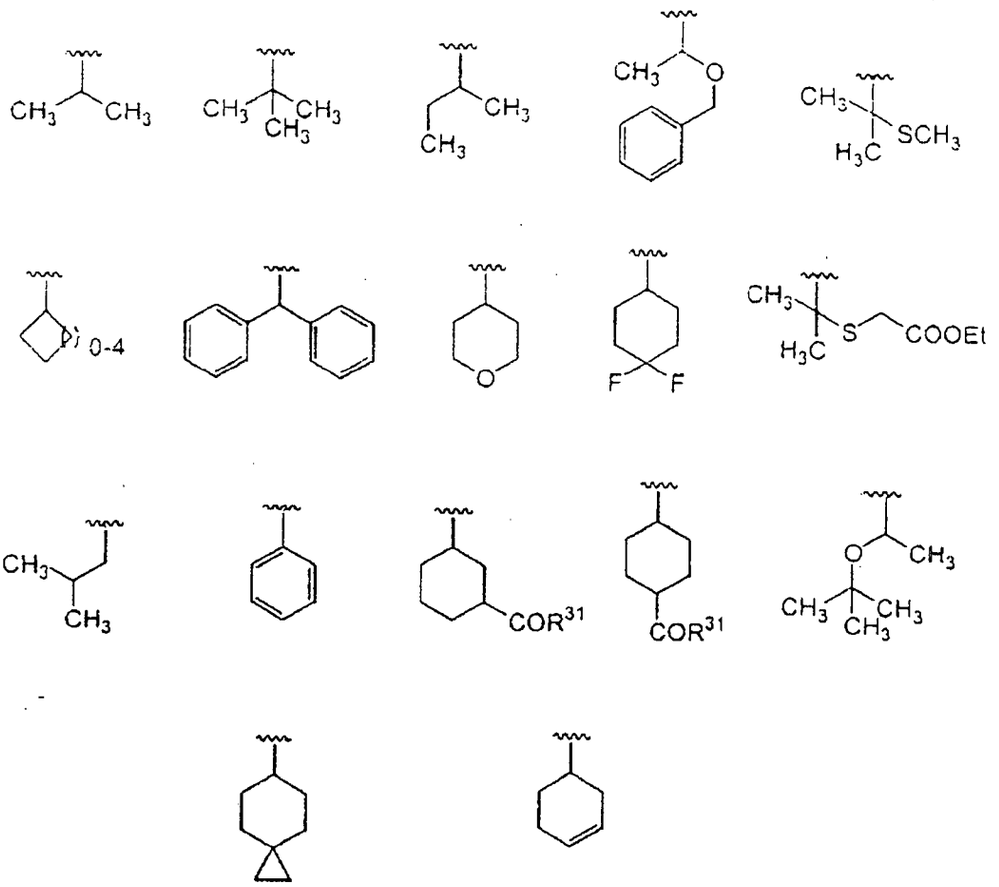
R^{14} se selecciona, con preferencia, del grupo que consiste de: H, Me, Et, *n*-propilo, metoxi, ciclopropilo, *n*-butilo, 1-but-3-inilo, bencilo, α-metilbencilo, fenetilo, alilo, 1-but-3-enilo, OMe, ciclopropilmetilo

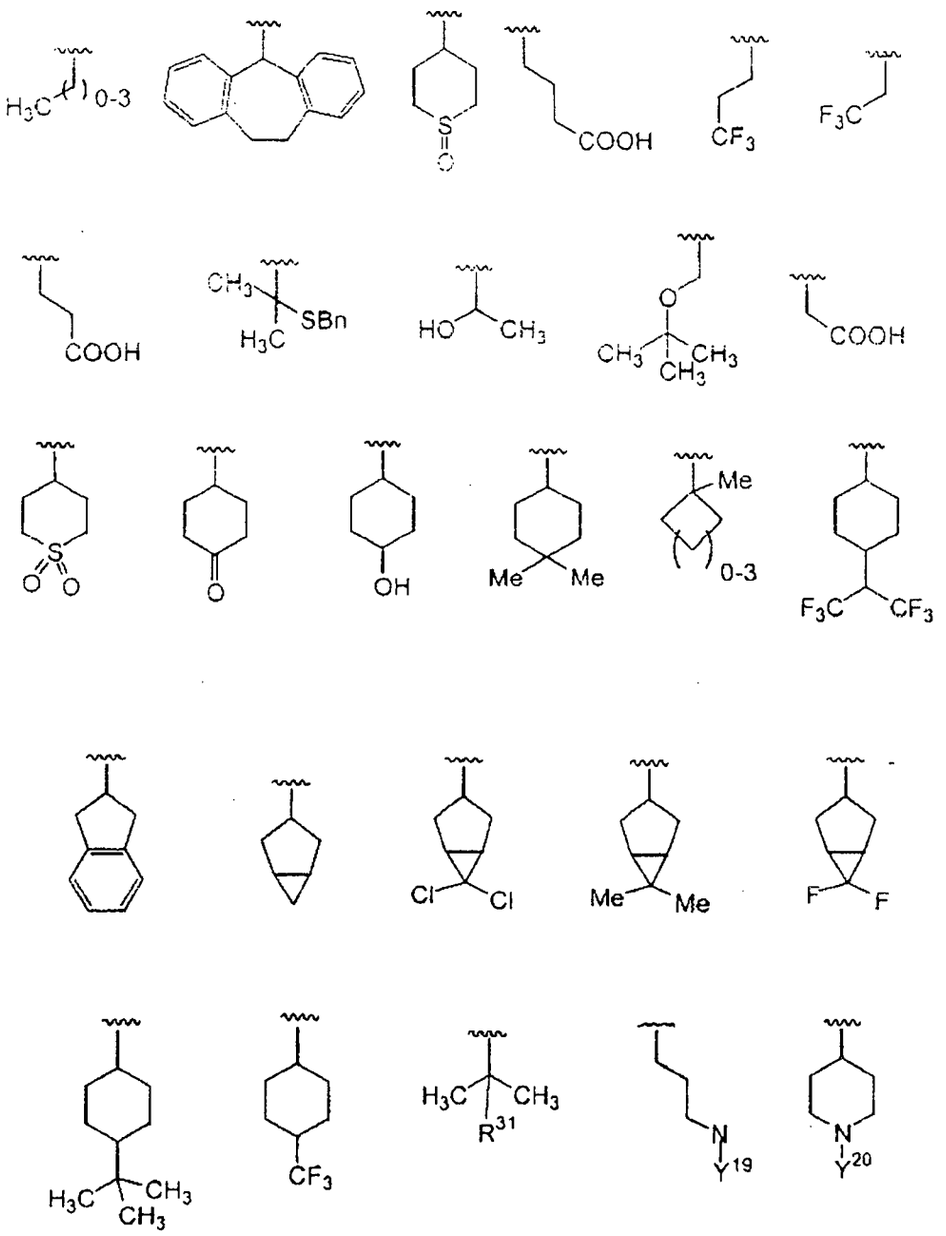
7. El compuesto de la reivindicación 2, en el cual R^2 se selecciona del grupo que consiste de los siguientes grupos funcionales:

000780


H
CH3
CH3
CH3
CH3
CH3
F
F
F
CH3
F3C
CF3
F
F
F
F
F
F
F
F
F3C
O
CH3
O
CH3
S(O)0-2
CH3
S(O)0-2
CH3
CH3
CH3
CH3
CH3
CH3
n = 0-3
F
F
n = 0-3
F
F
O
S
F
F
F
F
F

8. El compuesto de la reivindicación 7, en el cual R^3 se selecciona del grupo que consiste de:

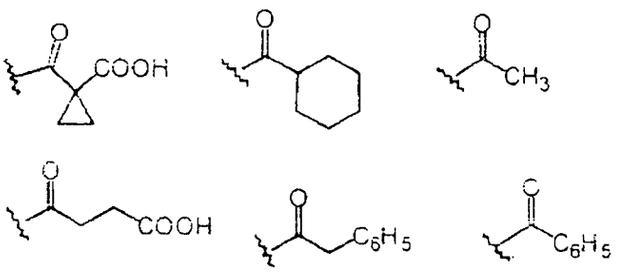




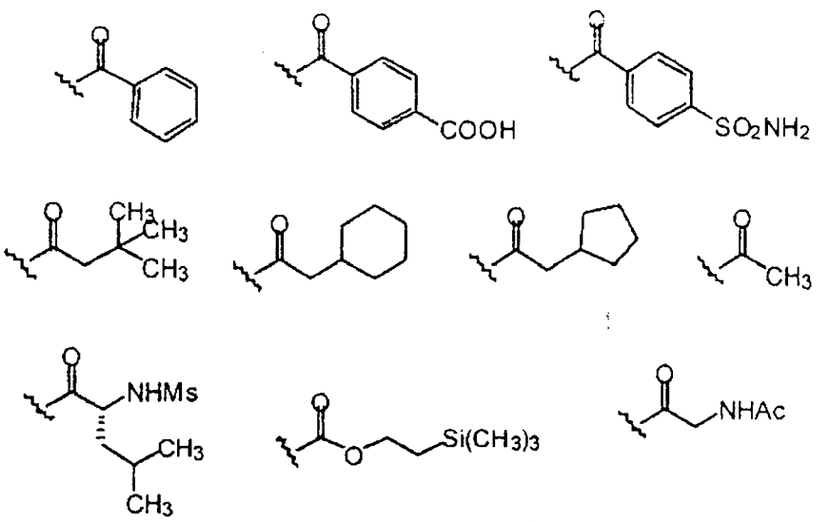
donde R^{31}= OH u O-alquilo;

Y^{19} se selecciona de los siguientes grupos funcionales:

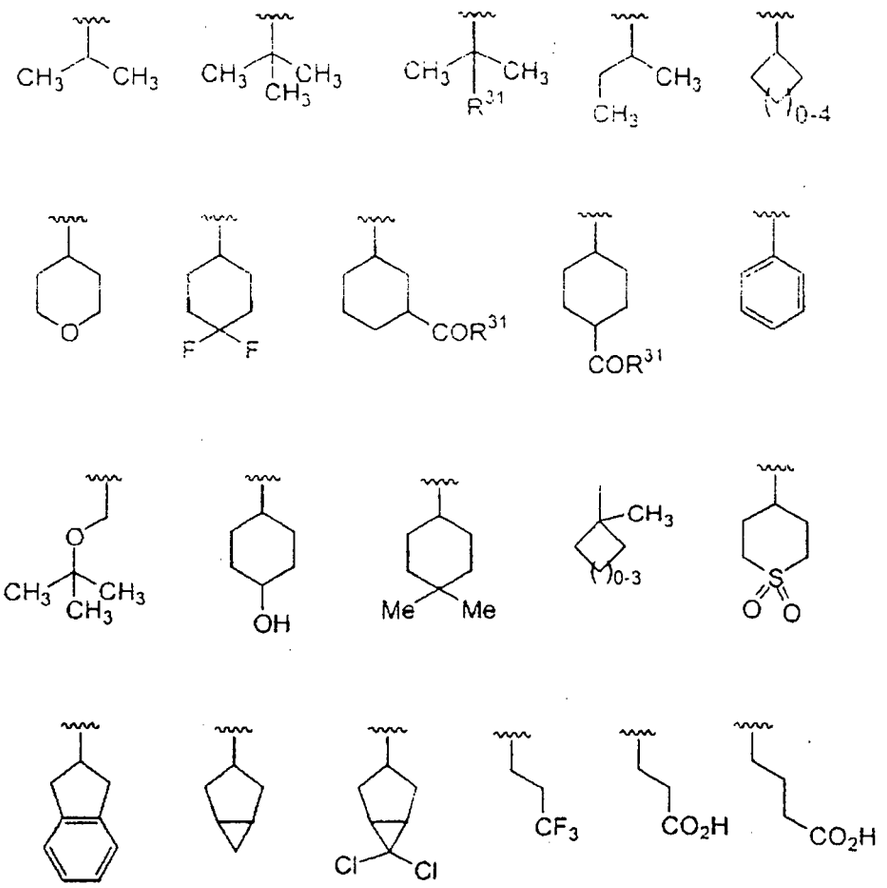
000783



e Y^{20} se selecciona de los siguientes grupos funcionales:



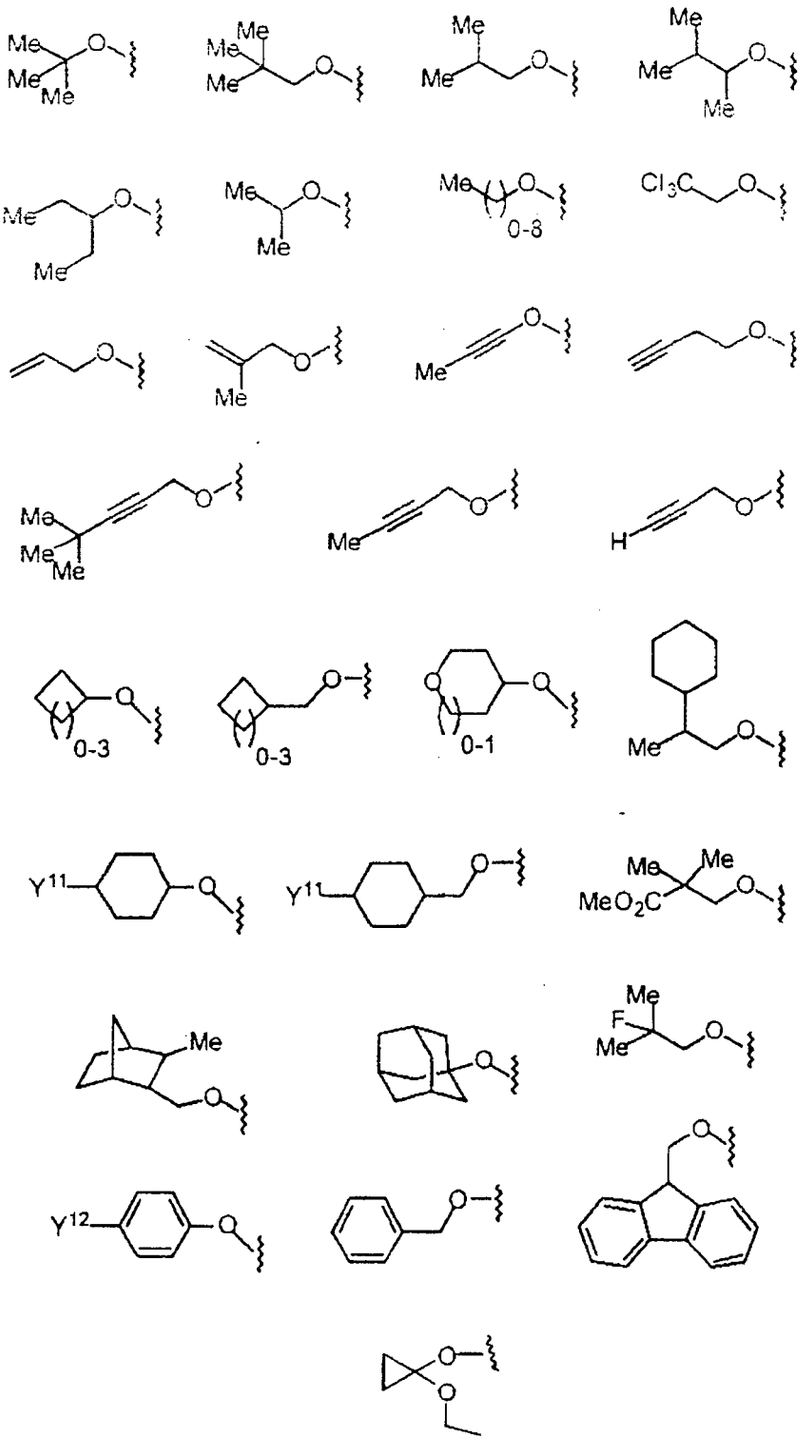
9. El compuesto de la reivindicación 8, en el cual R^3 se selecciona del grupo que consiste de los siguientes grupos funcionales:

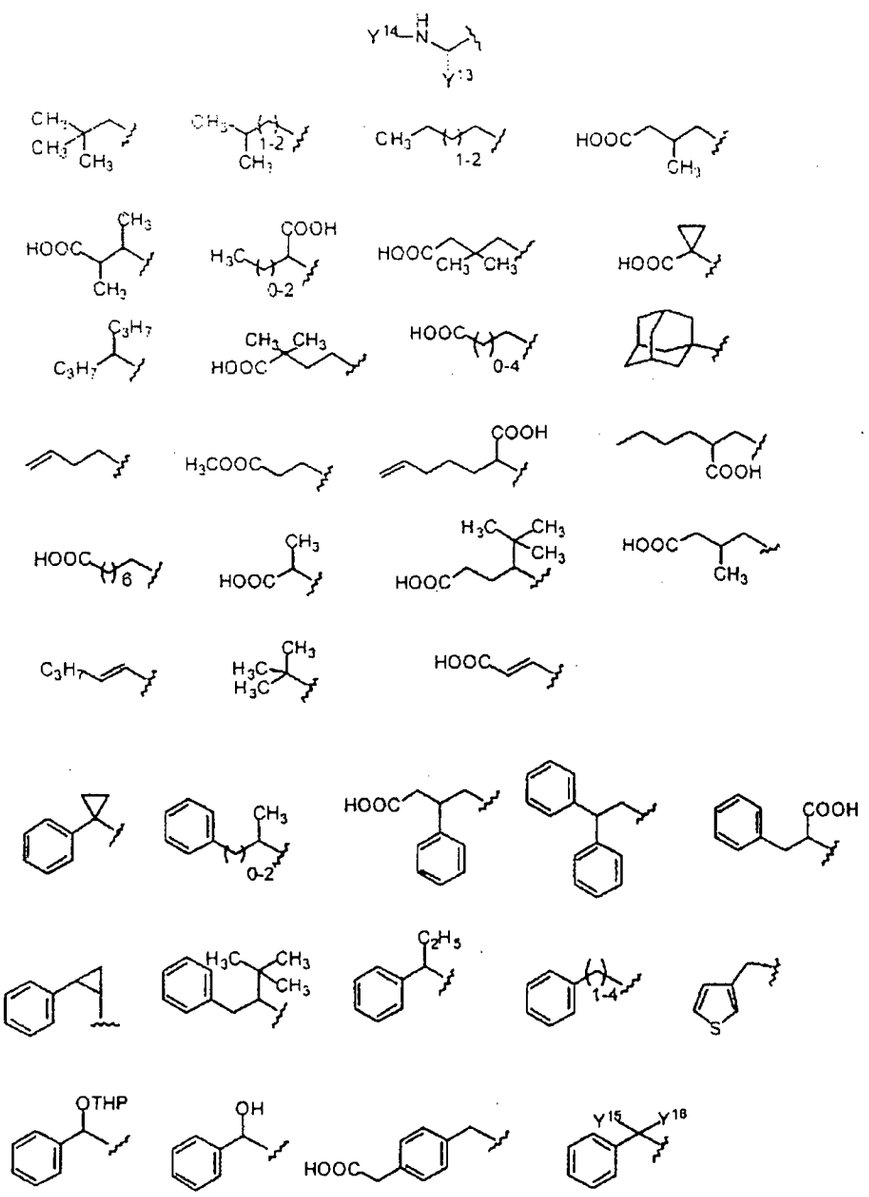


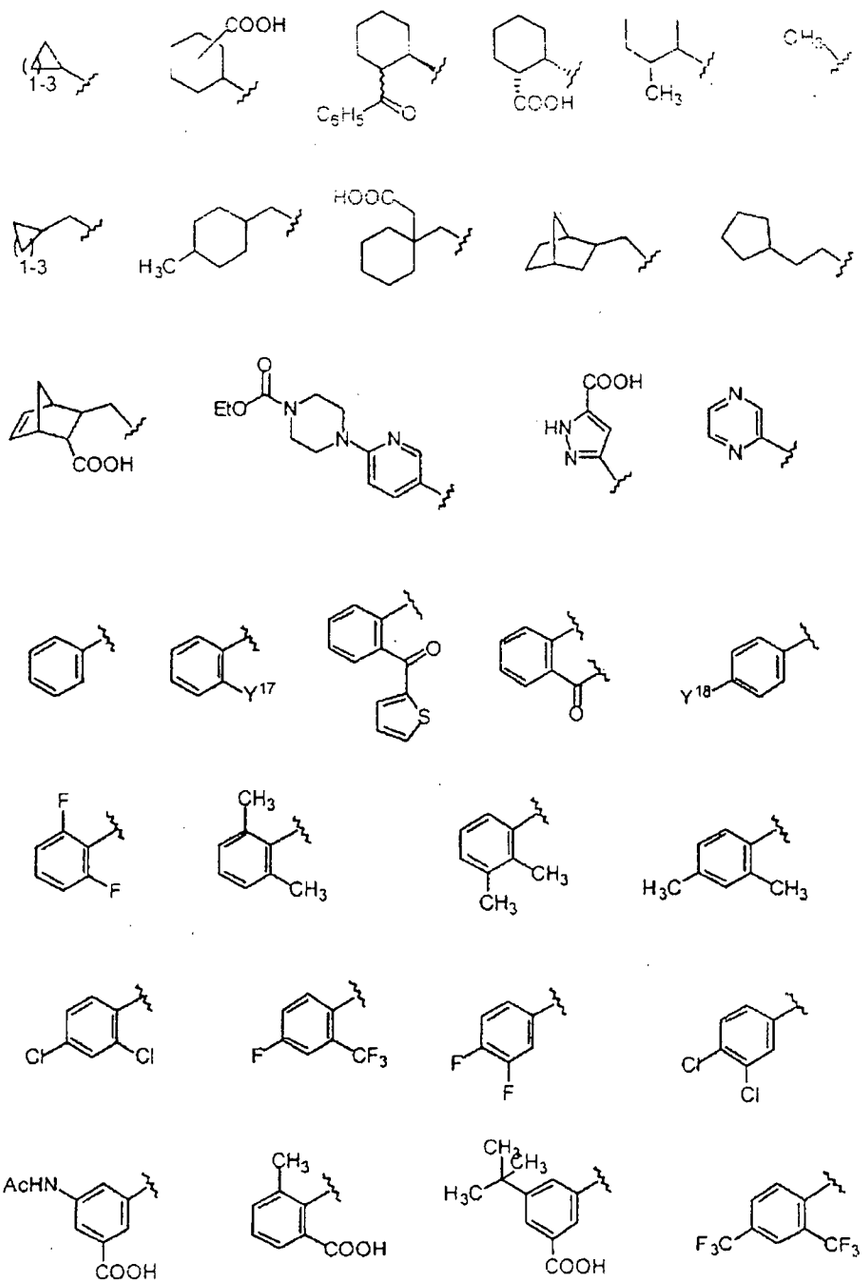
10. El compuesto de la reivindicación 9, en el cual Z es N y R^4 es H.

11. El compuesto de la reivindicación 10, en el cual W es C=O.

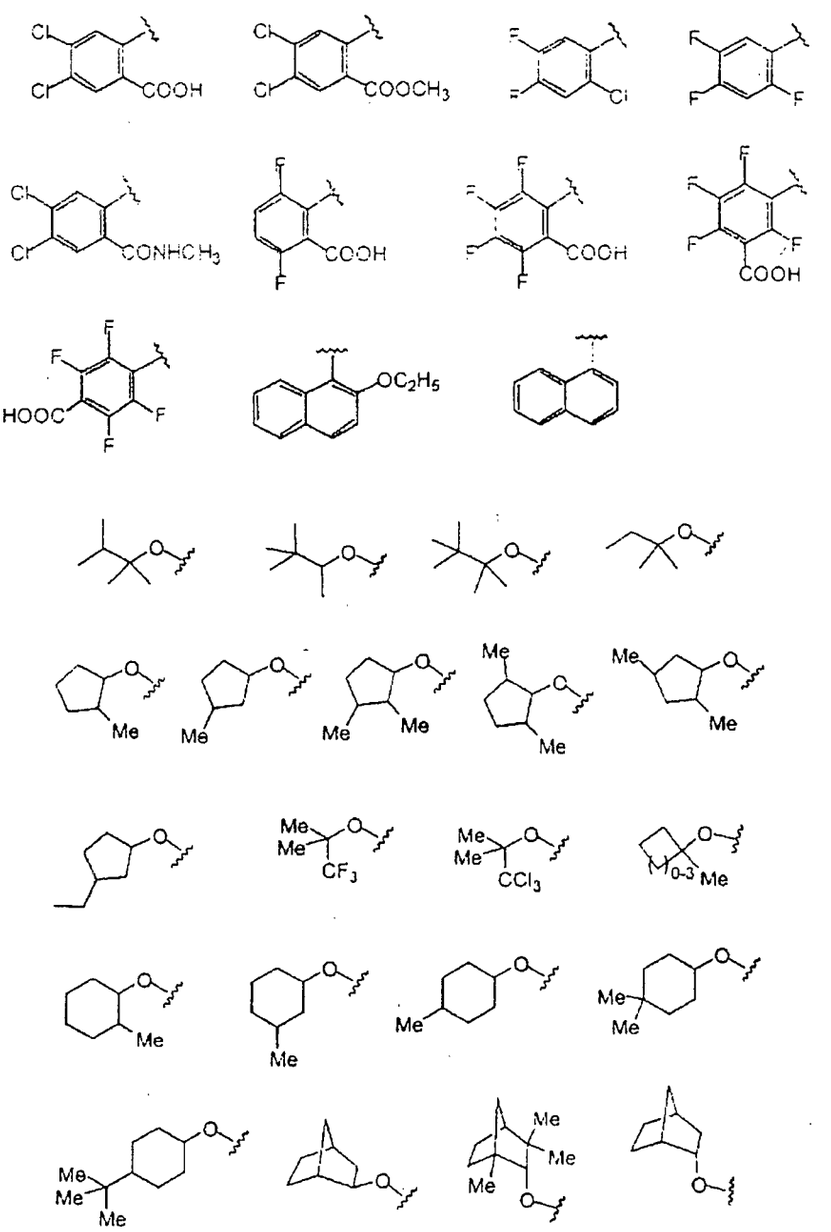
12. El compuesto de la reivindicación 11, en el cual Y se selecciona de los siguientes grupos funcionales:


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

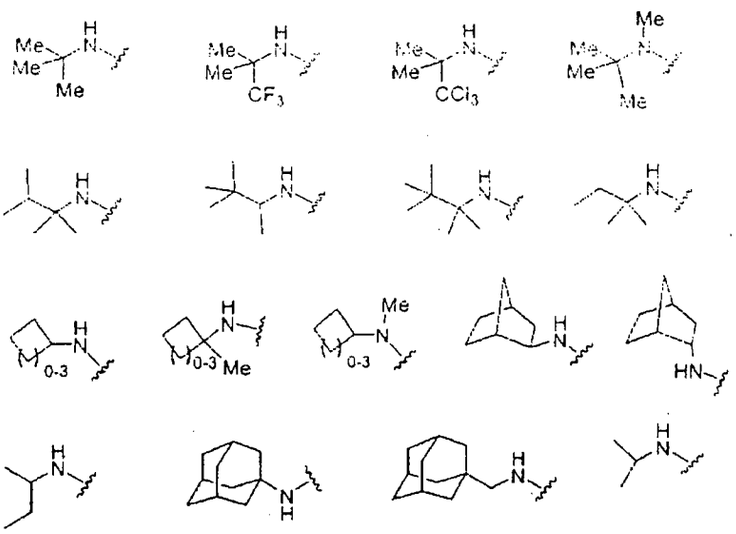

Y14
H
N
Y13
CH3
CH3
CH3
1-2
CH3
1-2
HOOC
CH3
HOOC
CH3
CH3
0-2
COOH
HOOC
CH3
CH3
HOOC
C3H7
C3H7
CH3
CH3
HOOC
HOOC
0-4
H3COOC
COOH
COOH
HOOC
6
HOOC
CH3
H3C
CH3
CH3
HOOC
HOOC
CH3
C3H7
H3C
H3C
CH3
HOOC
HOOC
0-2
COOH
C2H5
1-4
S
OTHP
OH
HOOC
Y15
Y16


1-3
COOH
C6H5
O
COOH
CH3
CH3
1-3
H3C
HOOC
COOH
EtO
O
N
N
N
COOH
HN
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
CH3
H3C
COOH
F3C
CF3

000788



000789



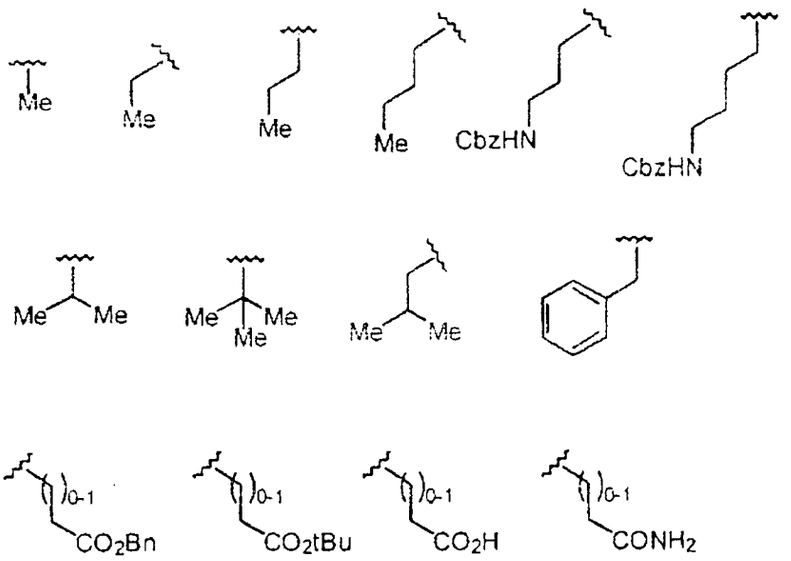
en los cuales:

R^{11} se seleccionan 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 grupos funcionales:

000790



Y^{14} se selecciona de $MeSO_2$, Ac, Boc, iBoc, Cbz, o Alloc;

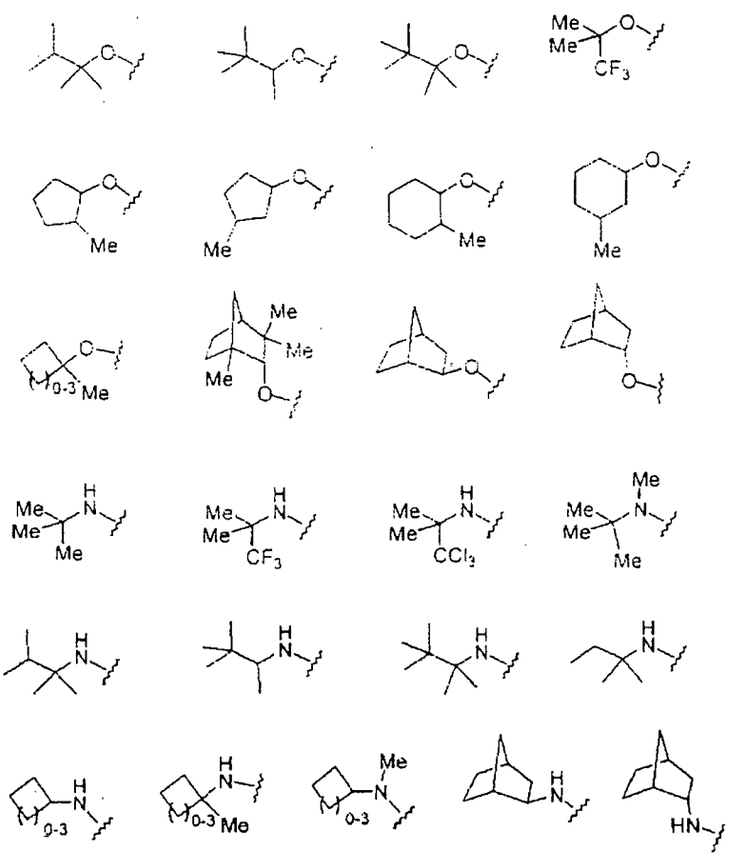
Y^{15} e Y^{16} se seleccionan en forma independiente de alquilo, arilo, heteroalquilo, y heteroarilo;

Y^{17} es CF_3, NO_2, $CONH_2$, OH, $COOCH_3$, OCH_3, OC_6H_5, C_6H_5, COC_6H_5, NH_2, o COOH; y

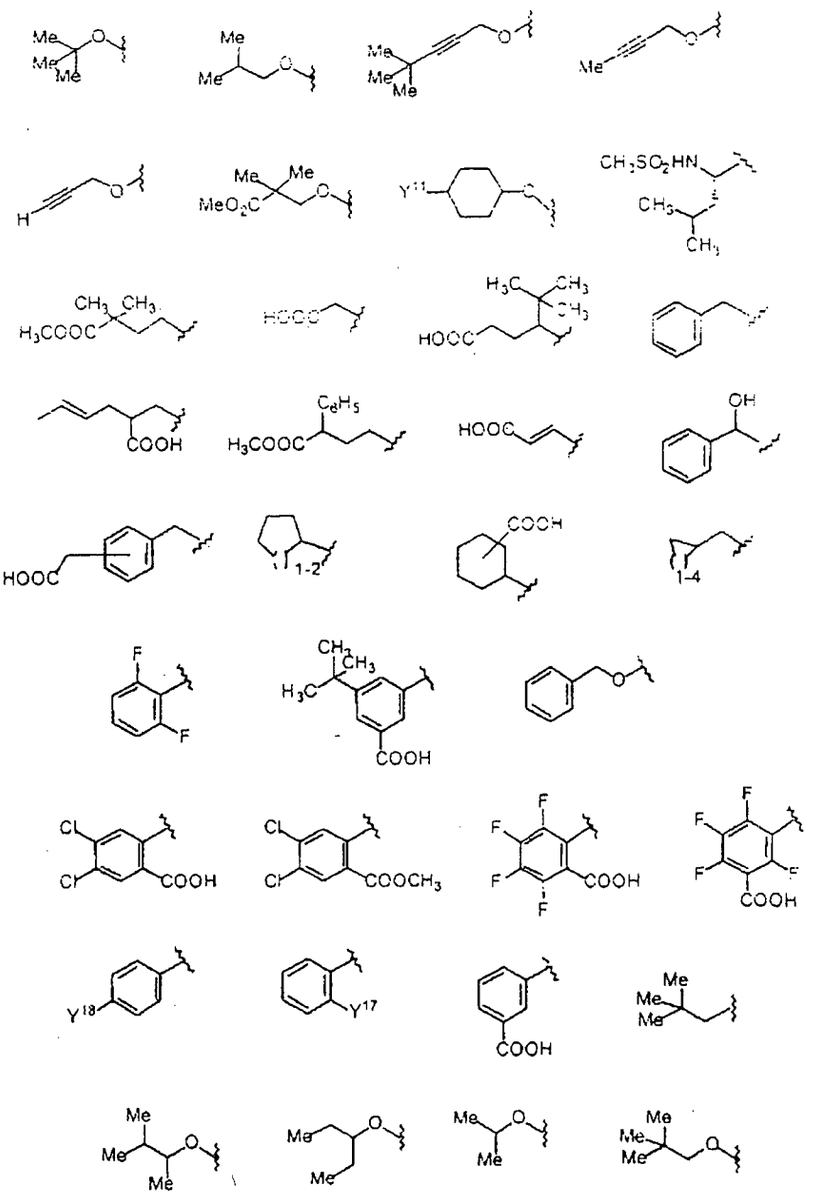
Y^{18} es $COOCH_3$, NO_2, $N(CH_3)_2$, F, OCH_3, CH_2COOH, COOH, SO_2NH_2, o $NHCOCH_3$.

13. El compuesto de la reivindicación 12, en el cual Y se selecciona del grupo que consiste de:

000791


Me
Me
CF3
Me
Me
Me
Me
0-3
Me
Me
Me
Me
O
H
N
Me
Me
Me
CF3
CCl3
0-3
0-3
Me
0-3
HN

000792



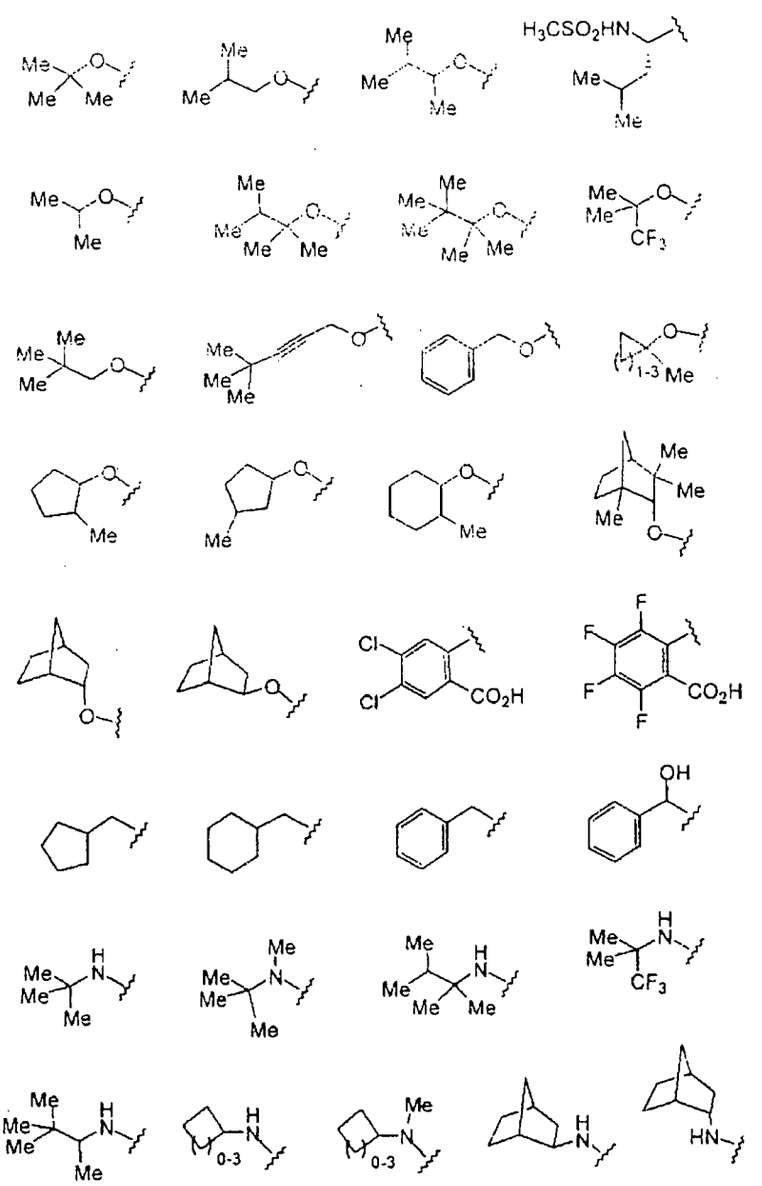
en los cuales:

Y^{17}= CF_3, NO_2, $CONH_2$, OH, NH_2, o COOH;

Y^{18}= F, COOH.

14. El compuesto de la reivindicación 13, en el cual Y se selecciona de los siguientes grupos funcionales:

030793

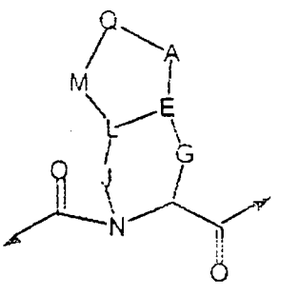


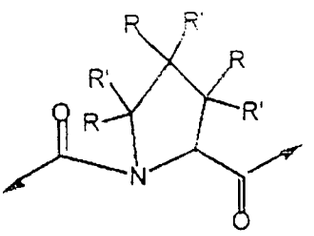
15. El compuesto de la reivindicación 14, en el cual L y M están ausentes, y J está enlazado directamente a E.

16. El compuesto de la reivindicación 14, en el cual L, J y M están ausentes, y E está enlazado directamente a N.

17. El compuesto de la reivindicación 14, en el cual G y M están ausentes.

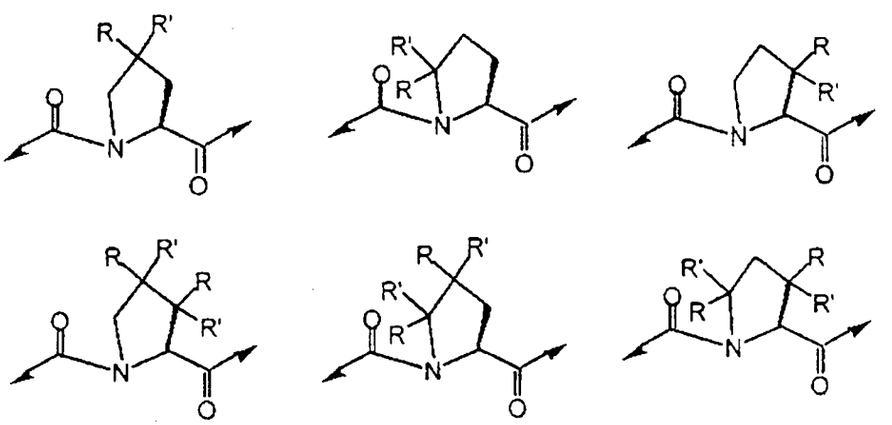
18. El compuesto de la reivindicación 14, en el cual el grupo funcional:





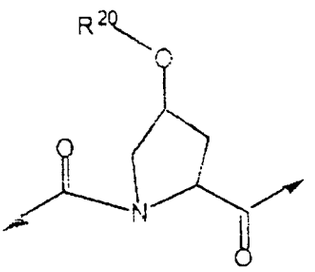
a

19. El compuesto de la reivindicación 18, en el cual la estructura a se selecciona de las siguientes estructuras:

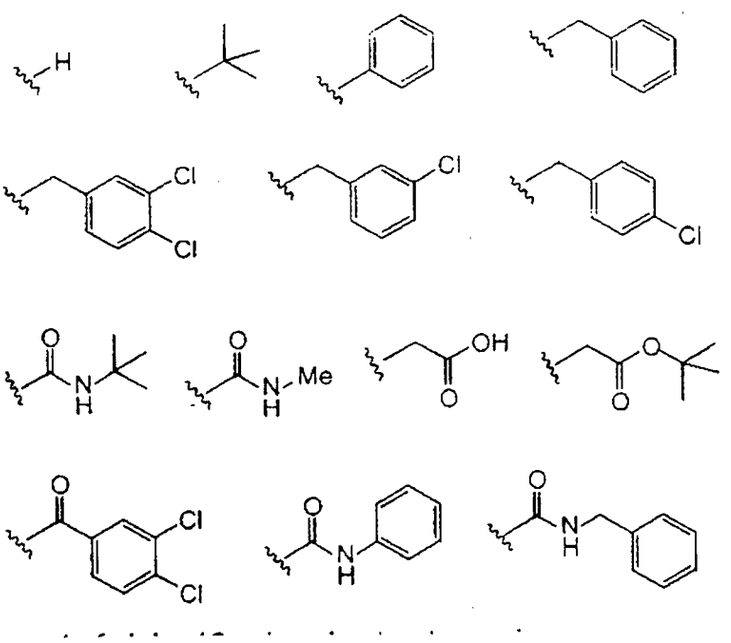


20. El compuesto de la reivindicación 18, en el cual la estructura a es:

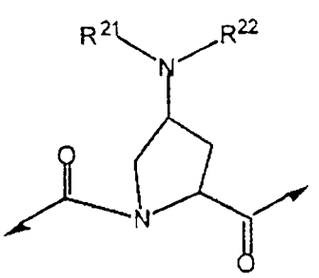
000795



en la cual R^{20} se selecciona de las siguientes estructuras:

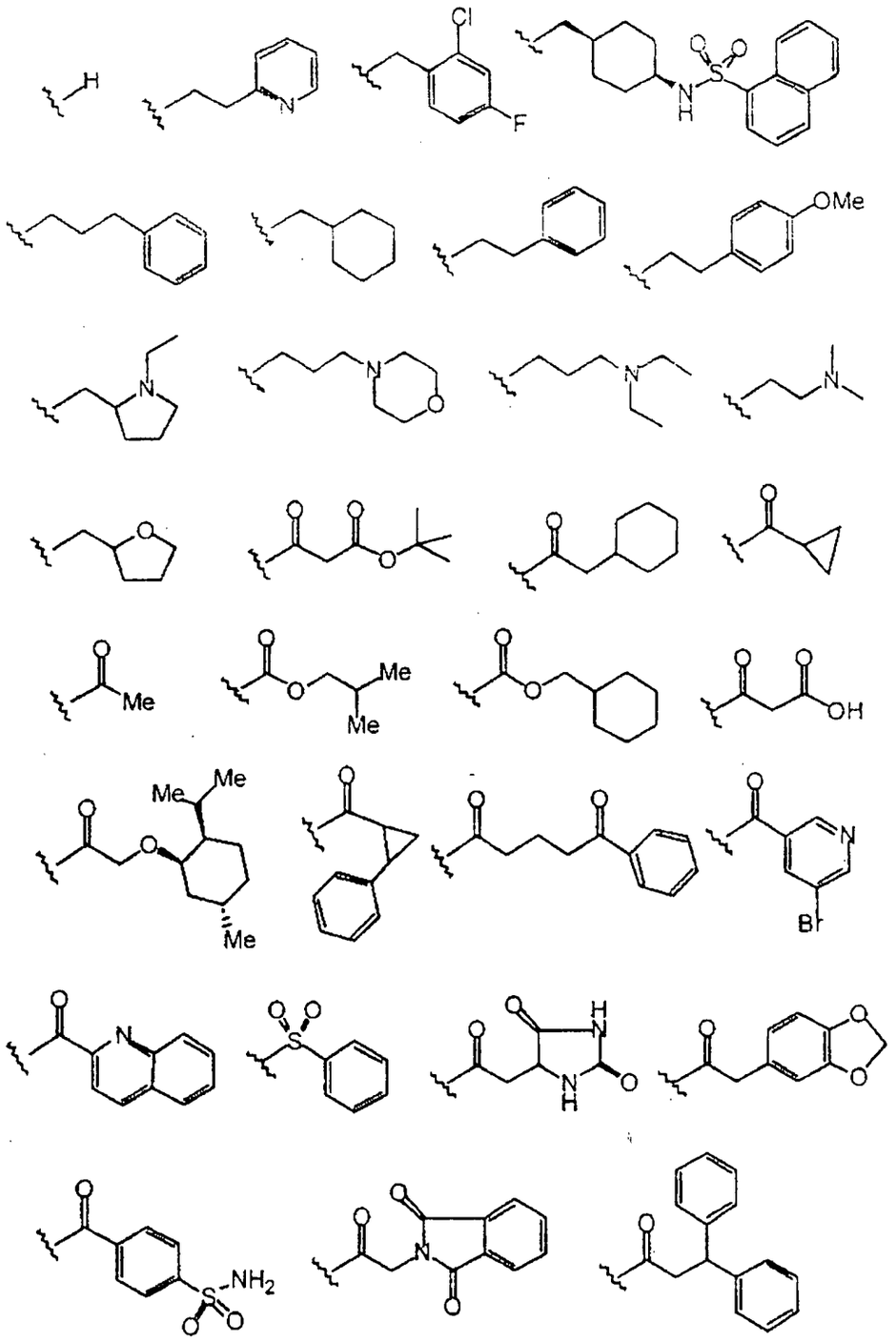


21. El compuesto de la reivindicación 18, en el cual la estructura a es:

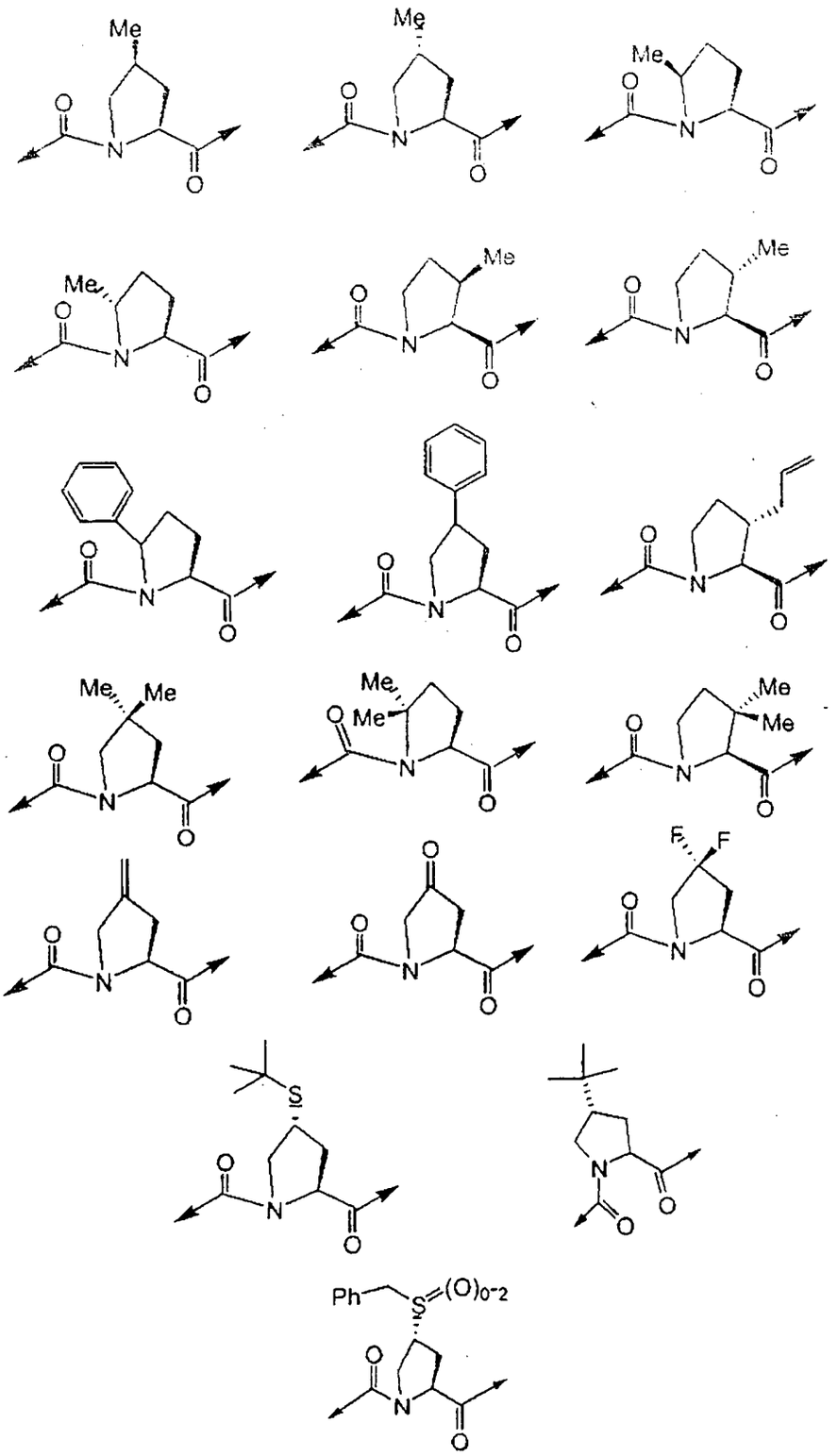


en la cual R^{21} y R^{22} pueden ser iguales o diferentes y se seleccionan en forma independiente de las siguientes estructuras:

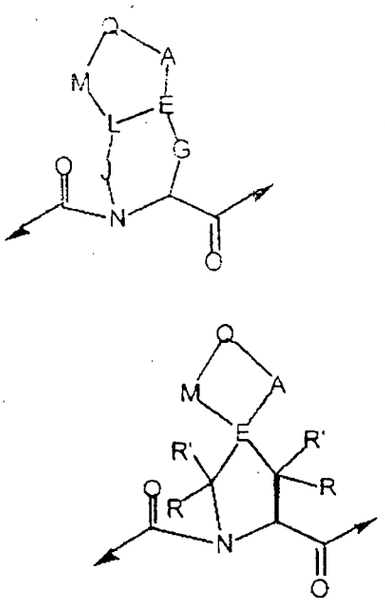
000796



22. El compuesto de la reivindicación 18, en el cual la estructura a se selecciona de las siguientes estructuras:


Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
Me
F
F
S
Ph
S
(O)0-2
N
O

23. El compuesto de la reivindicación 14, en el cual:

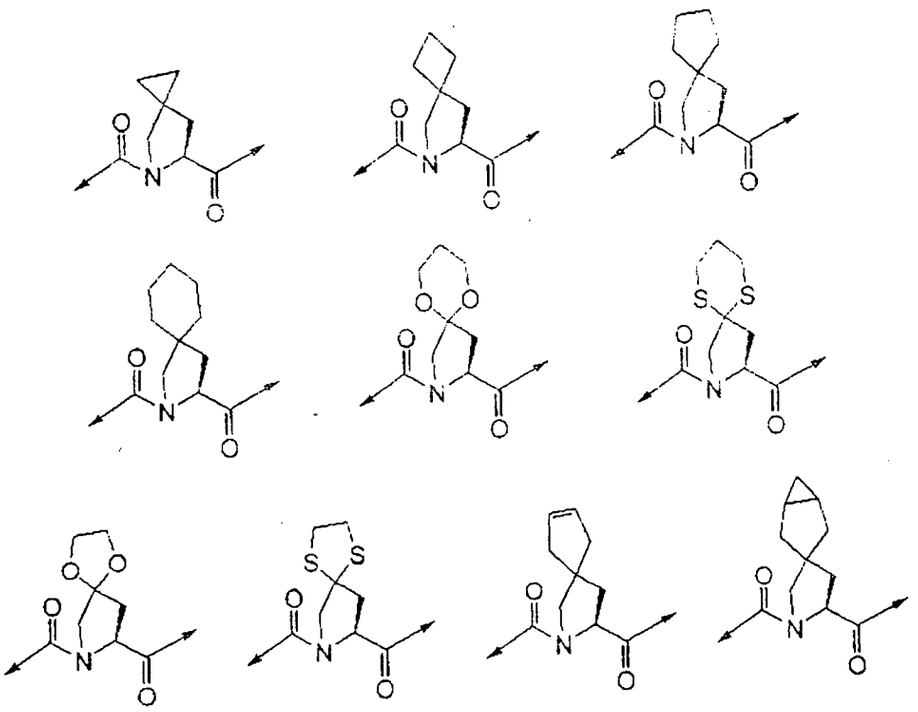


b

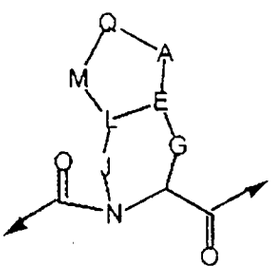
en el cual Q puede estar presente o ausente, y si Q está ausente, M está enlazado directamente a A.

24. El compuesto de la reivindicación 23, en el cual la estructura b se selecciona de las siguientes estructuras:

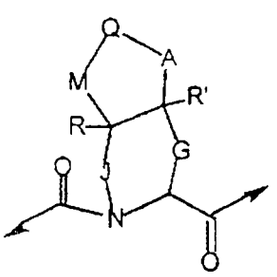
000799



25. El compuesto de la reivindicación 14, en el cual:



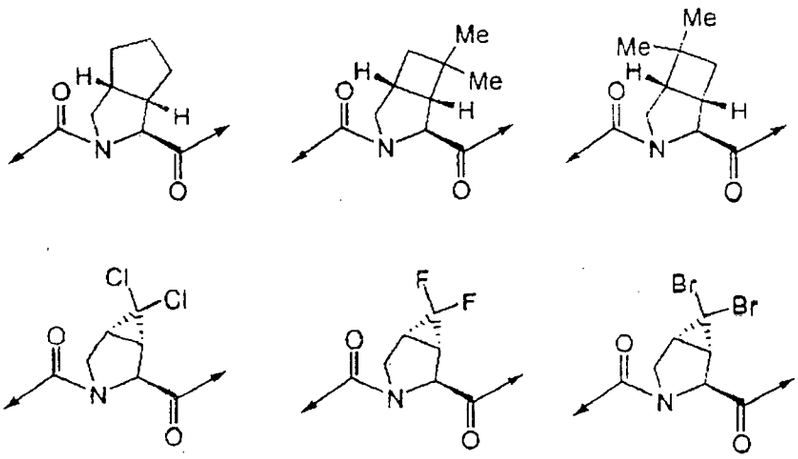
es



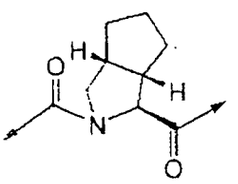
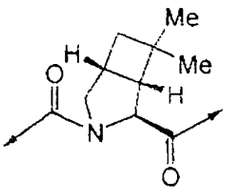
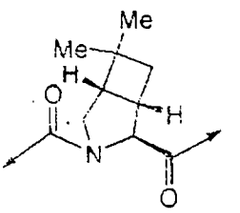
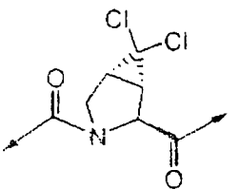
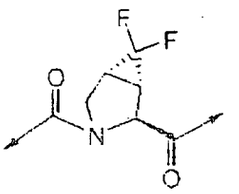
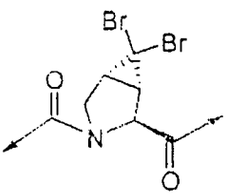
C

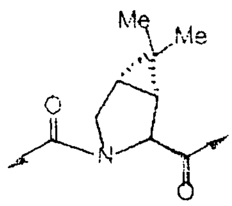
donde G y J se seleccionan en forma independiente del grupo que consiste de $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ y $(CRR')_p$; A y M se seleccionan en forma independiente del grupo que consiste de O, S, SO_2, NR, $(CH_2)_p$, $(CHR)_p$, $(CHR\text{-}CHR')_p$ y $(CRR')_p$; y Q es CH_2, CHR, CRR', NH, NR, O, S, SO_2, NR; $(CH_2)_p$, $(CHR)_p$, y $(CRR')_p$.

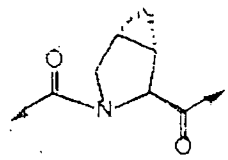
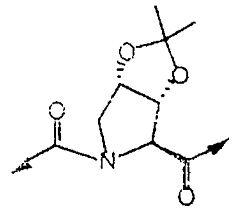
26. El compuesto de la reivindicación 25, en el cual la estructura c se selecciona de las siguientes estructuras:

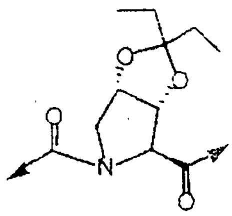
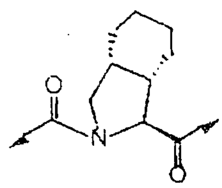
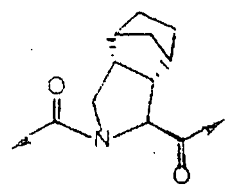


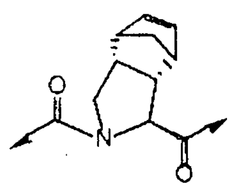
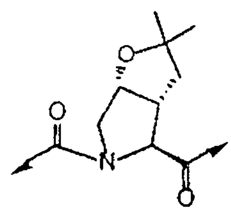
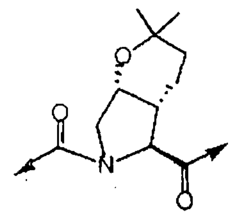
000801

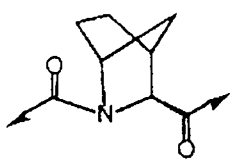
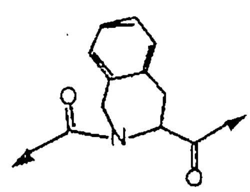
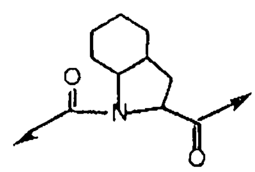







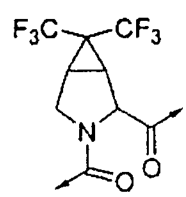


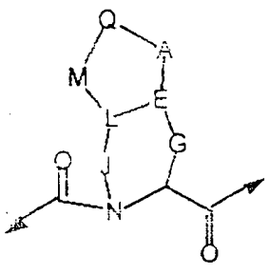




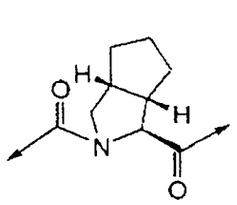
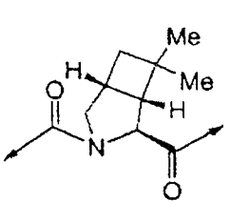
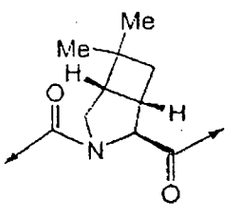
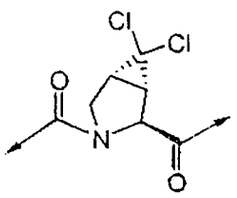
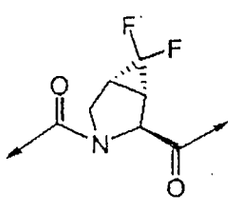
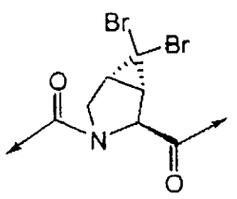
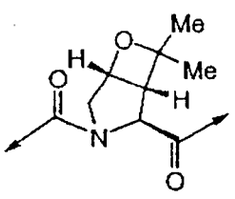
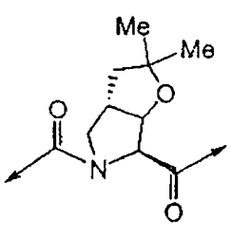
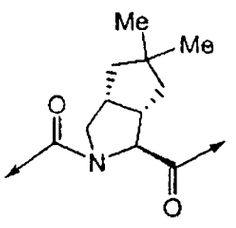
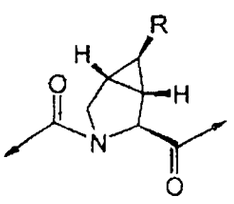
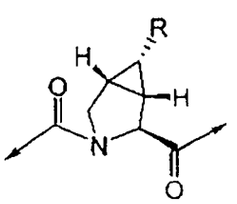
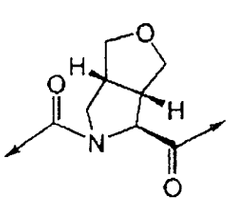
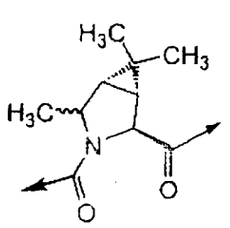


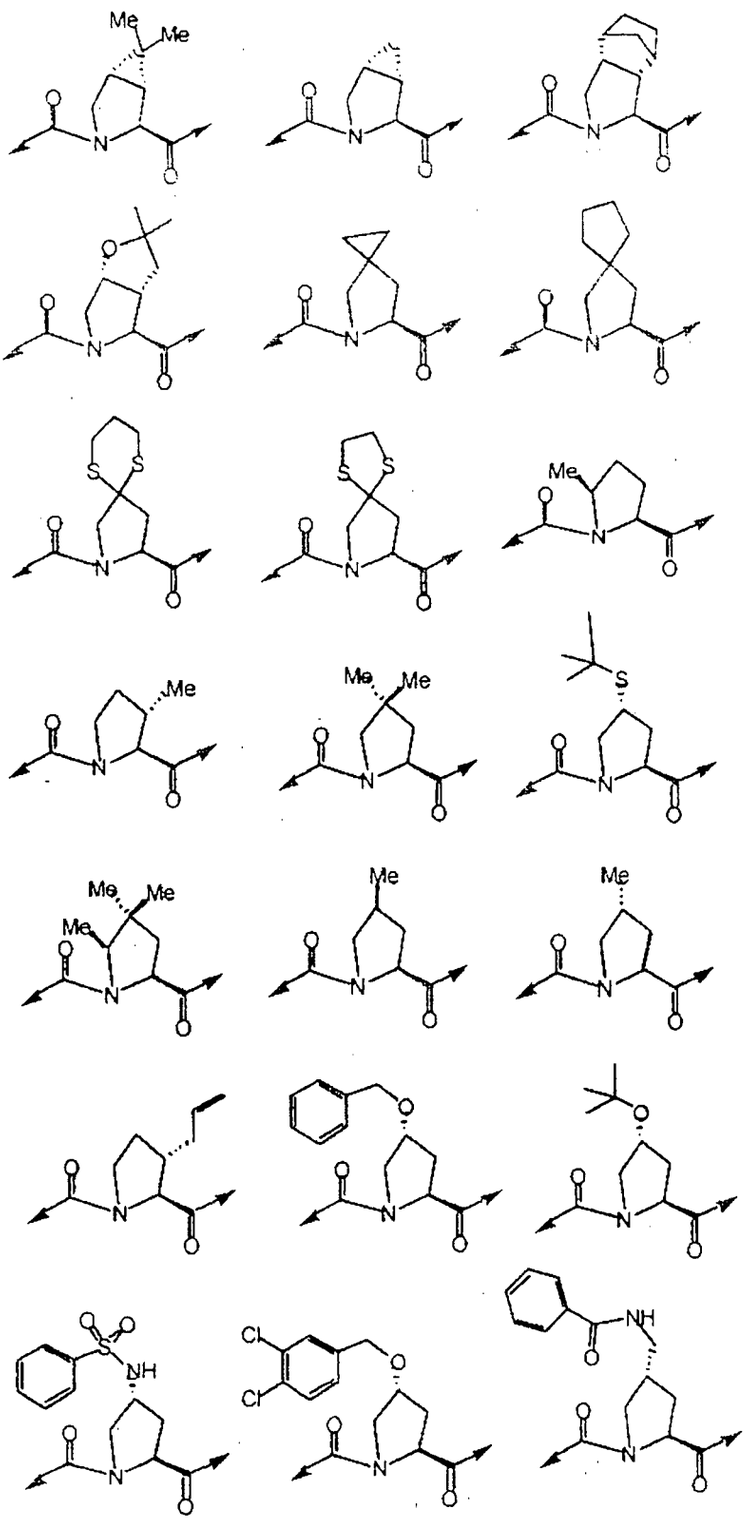
27. El compuesto de la reivindicación 14, en el cual:

030803

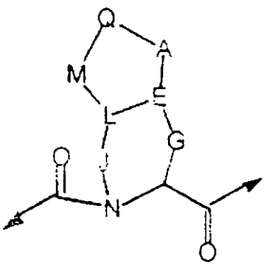


se selecciona de las siguientes estructuras:

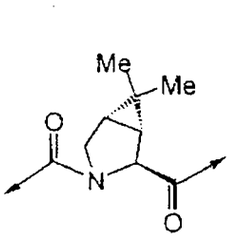
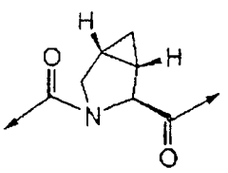
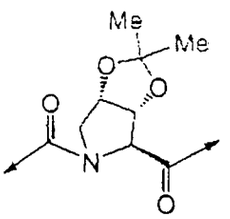
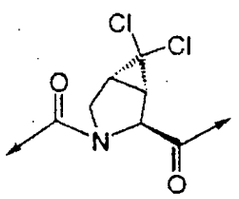
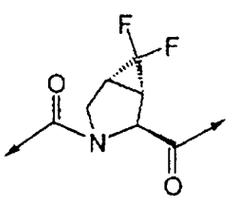
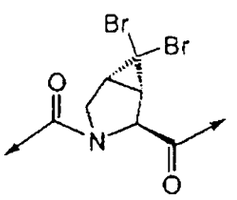
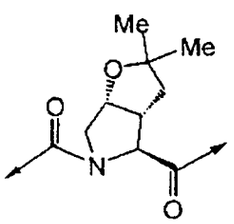
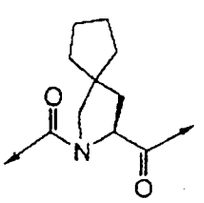
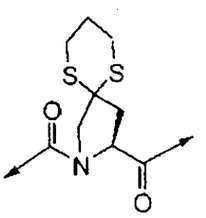
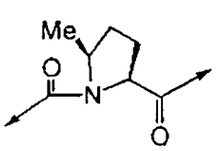
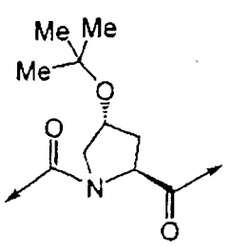
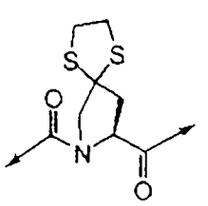
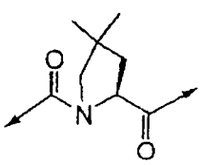
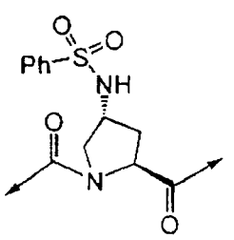
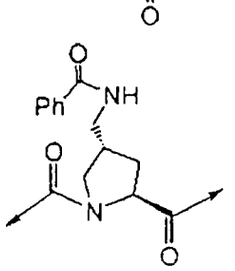
















28. El compuesto de la reivindicación 27, en el cual:



se selecciona de las siguientes estructuras:

29. Una composición farmacéutica que comprende, como ingrediente activo, un compuesto de la reivindicación 1.

30. La composición farmacéutica de la reivindicación 29 para usar en el tratamiento de trastornos asociados con el HCV.

31. La composición farmacéutica de la reivindicación 29 que comprende, además, un vehículo aceptable para uso farmacéutico.

32. La composición farmacéutica de la reivindicación 31, que comprende, además, un agente antiviral.

33. La composición farmacéutica de la reivindicación 32, que comprende, además, un interferon.

34. La composición farmacéutica de la reivindicación 33, en la cual dicho agente antiviral es ribavirina y dicho interferon es α-interferon o interferon pegilado.

35. Un método para el tratamiento de trastornos asociados con el HCV, dicho método comprende la administración a un paciente que lo necesita de una composición farmacéutica que comprende cantidades terapéuticamente efectivas de un compuesto de la reivindicación 1.

36. El método de la reivindicación 35, en el cual dicha administración es oral o subcutánea.

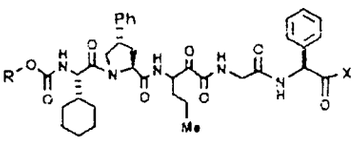
37. El uso de un compuesto de la reivindicación 1 para la fabricación de un medicamento para el tratamiento de trastornos asociados con el HCV.

38. Un método para preparar una composición farmacéutica para el tratamiento de trastornos asociados con el HCV, dicho método comprende llevar a contacto íntimo un compuesto de la reivindicación 1 y un vehículo aceptable para uso farmacéutico.

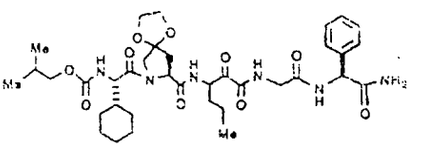
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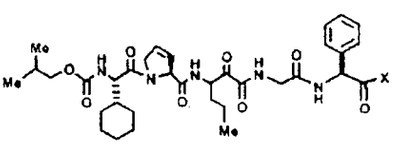
39. Un compuesto que exhibe actividad de inhibición de la proteasa de HCV, que incluye enantiómeros, estereoisómeros, rotámeros, tautómeros, racematos, y una prodroga de dicho compuesto, y sus sales aceptables para uso farmacéutico o solvatos de dicho compuesto, o de dicha prodroga, dicho compuesto se selecciona de las estructuras que aparecen a continuación:

000808

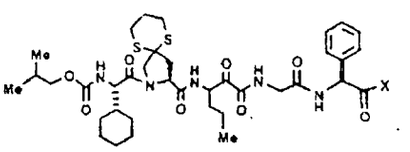


(R= t-butilo, X= NH_2)
(R= Isobutilo, X= NH_2)
(R= t-butilo, X=OH)
(R= Tricloroetilo, X=OH)

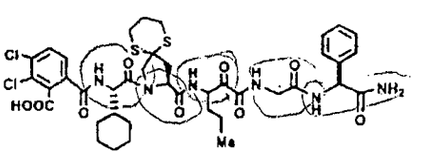


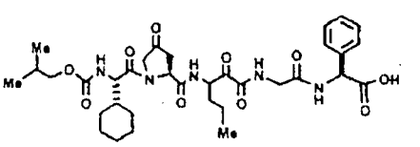


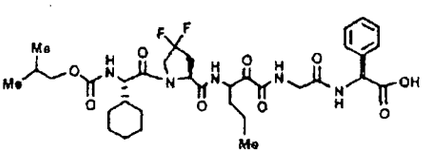
(X = O^{t}Bu)
(X = OH)

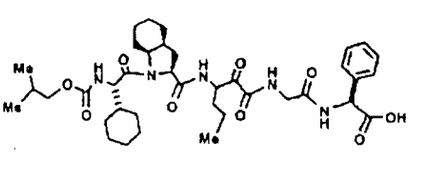


(X = OH)
(X = O^{t}Bu)
(X = NH_2)
(X = NHMe)
(X = NMe_2)

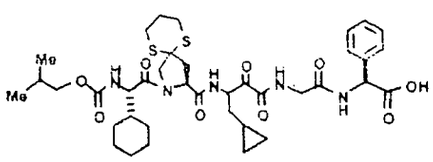


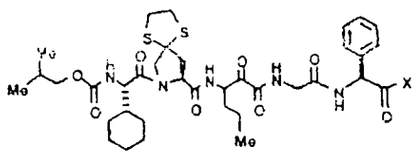




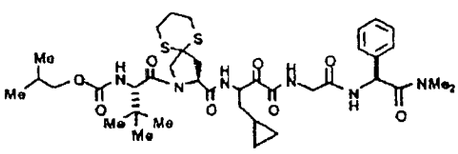


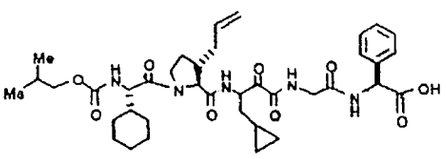
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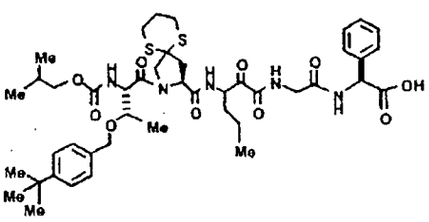


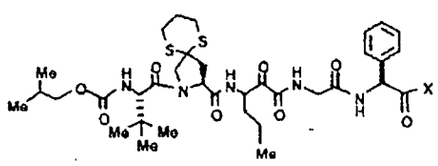


(X = NH_2)
(X = NMe_2)
(X = NHMe)
(X = OH)

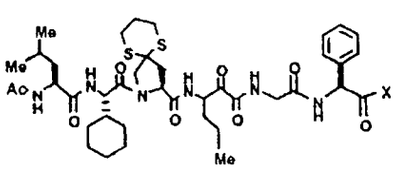


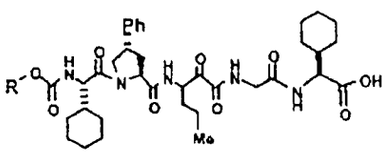






(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)

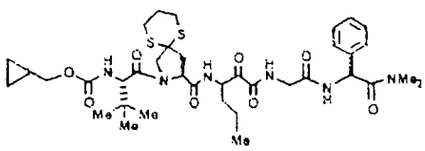


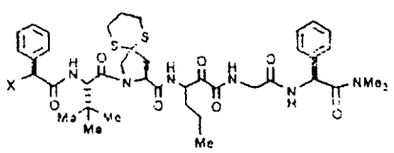


(X = O^{t}Bu)
(X = OH)
(X = NH_2)
(X = NMe_2)
(X = NMeOMe)

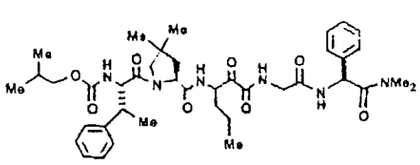
(R = t-butyl)
(R = Isobutyl)

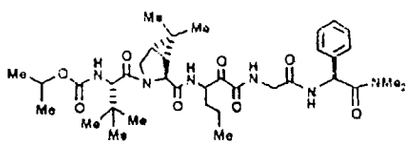
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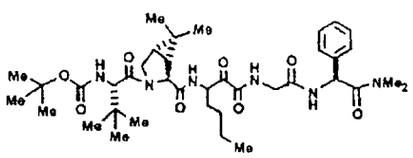


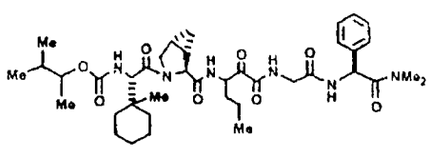


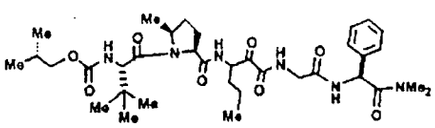
(X = Me, Y = CH_2Me)
(X = OAc, Y = Me)

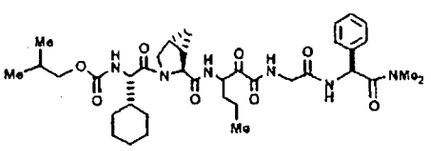


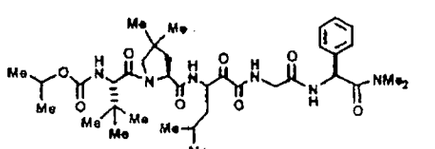


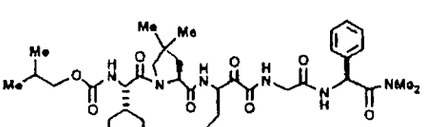


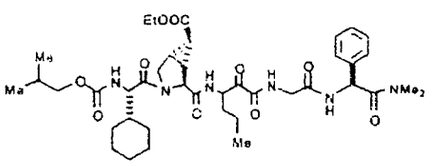


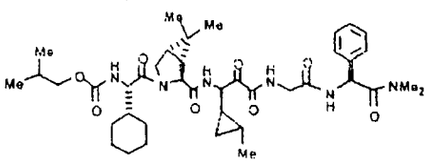


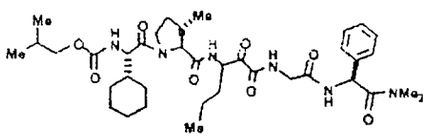


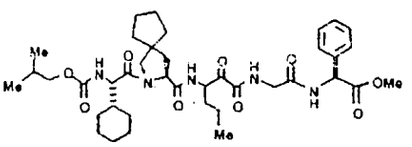


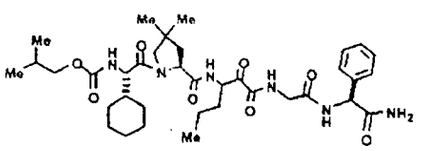


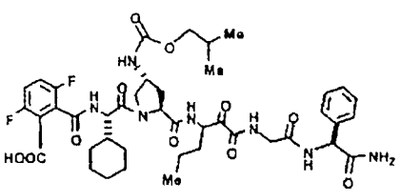


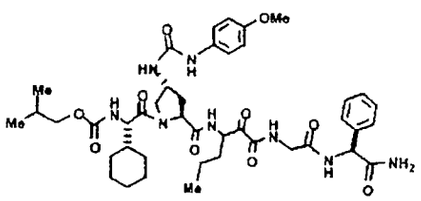


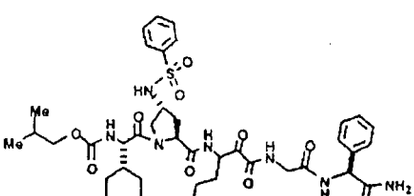


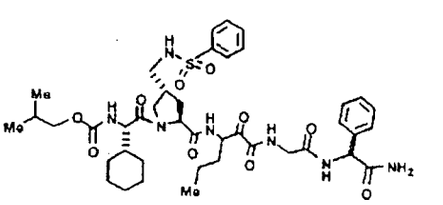




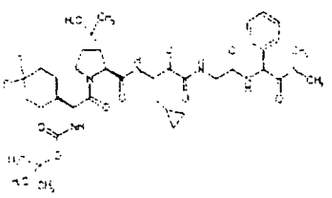


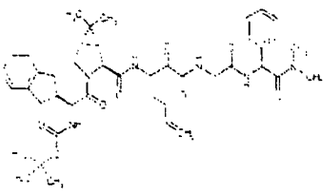


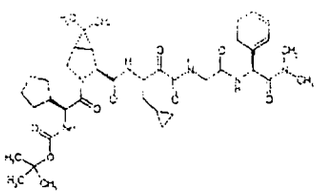


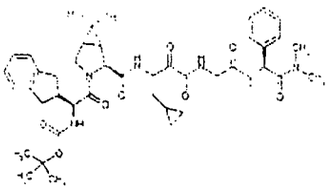


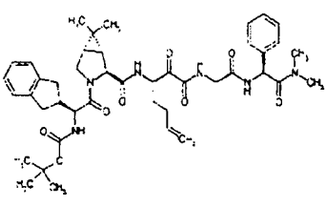
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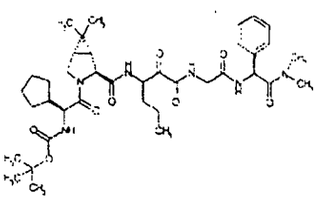


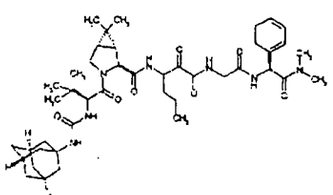


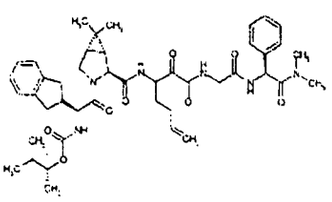


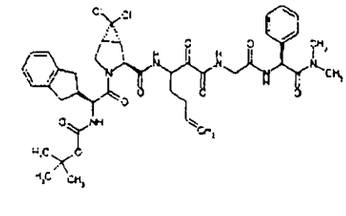


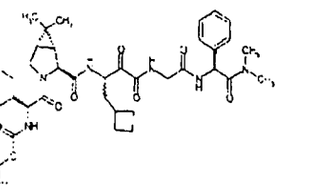


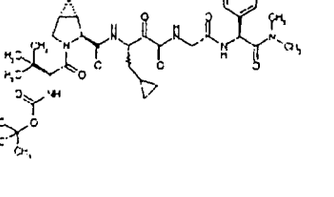


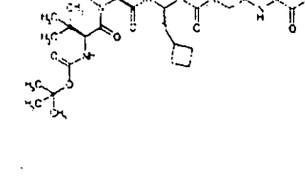




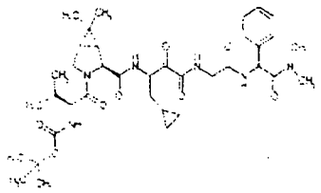
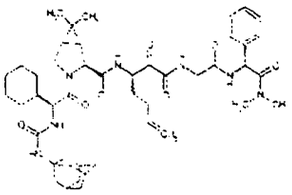
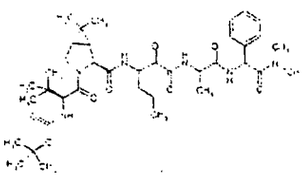
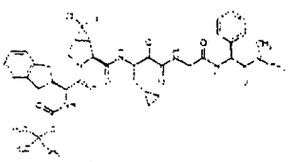
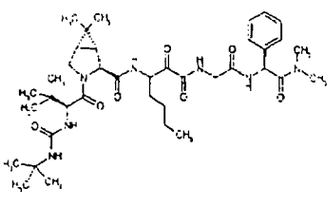
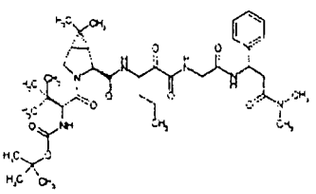
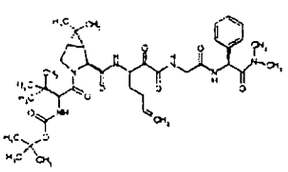
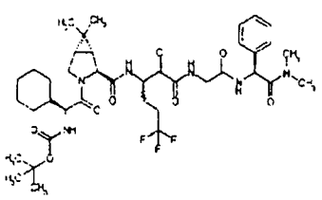
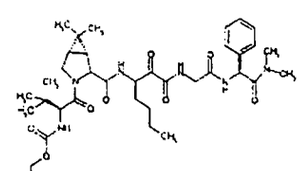
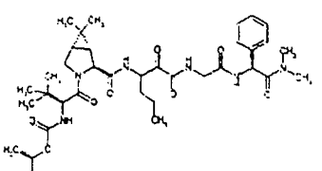
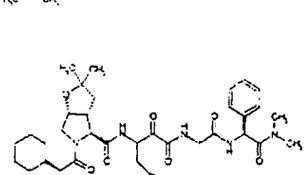
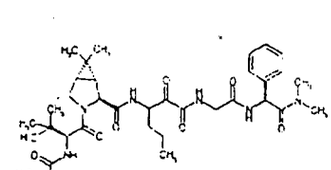






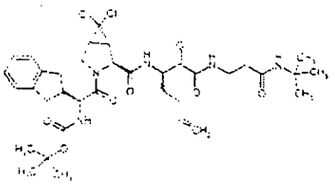


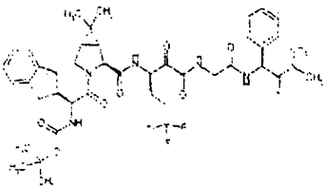
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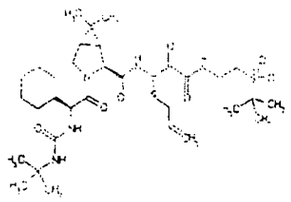













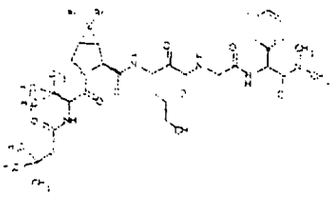


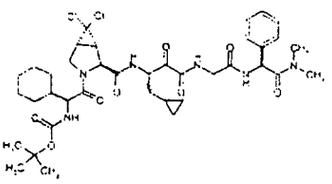
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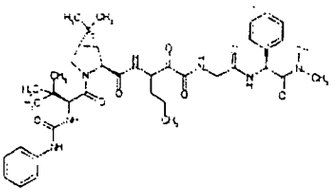


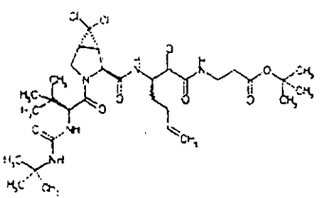


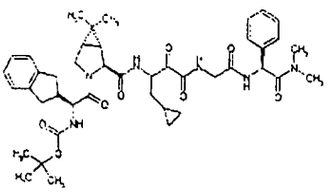


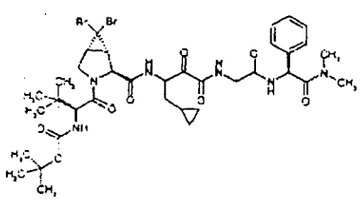


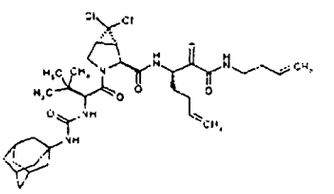


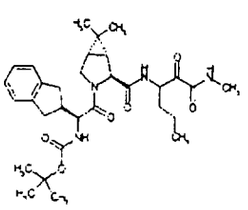


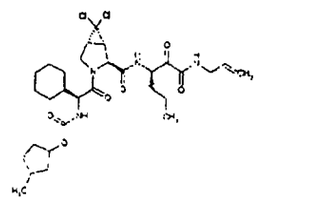




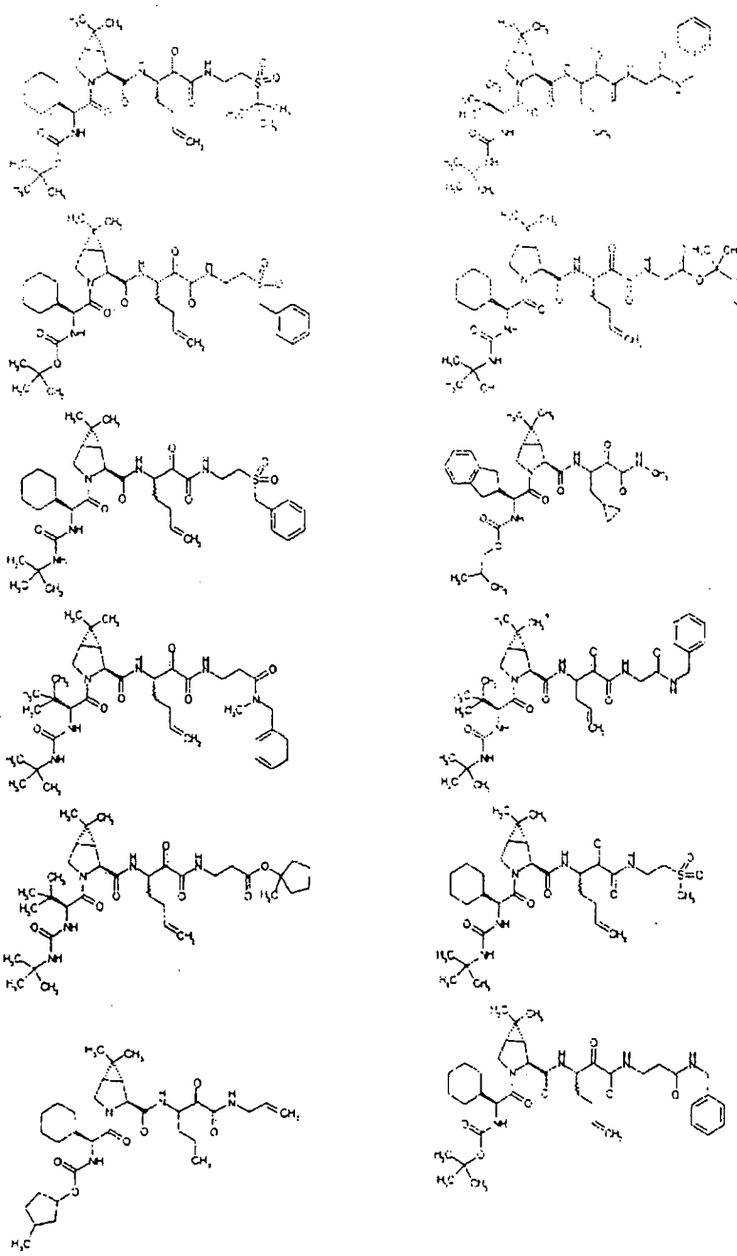


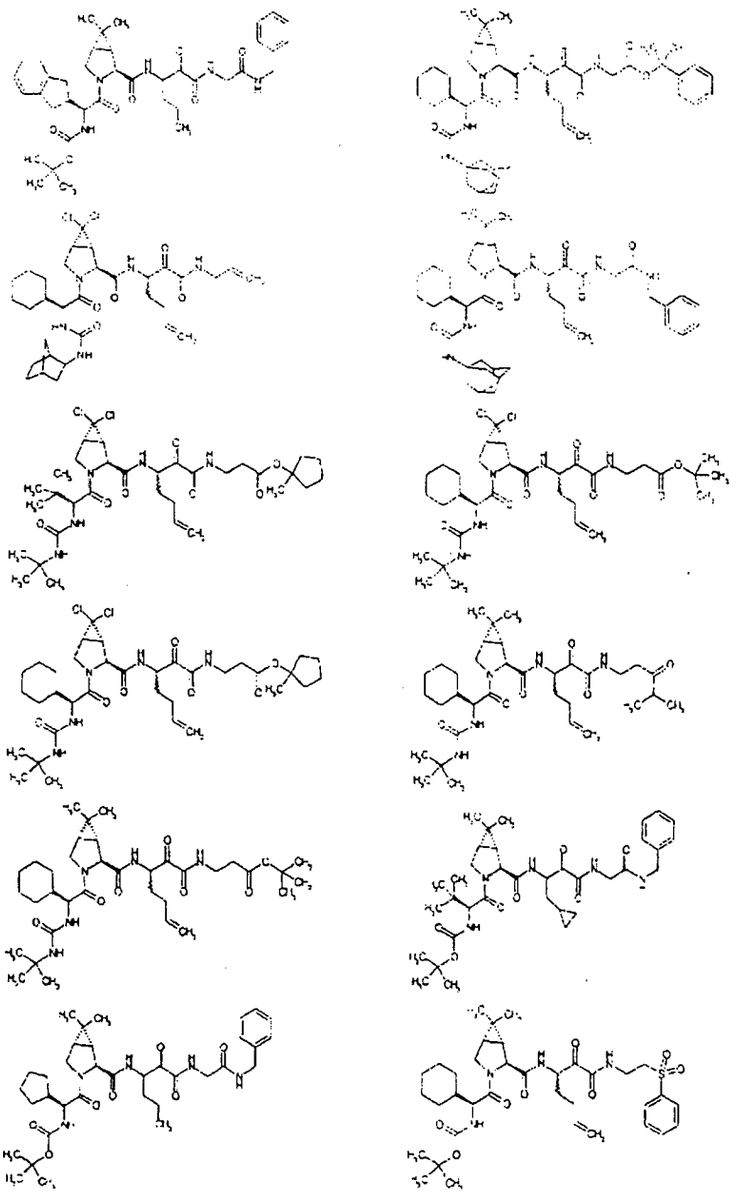




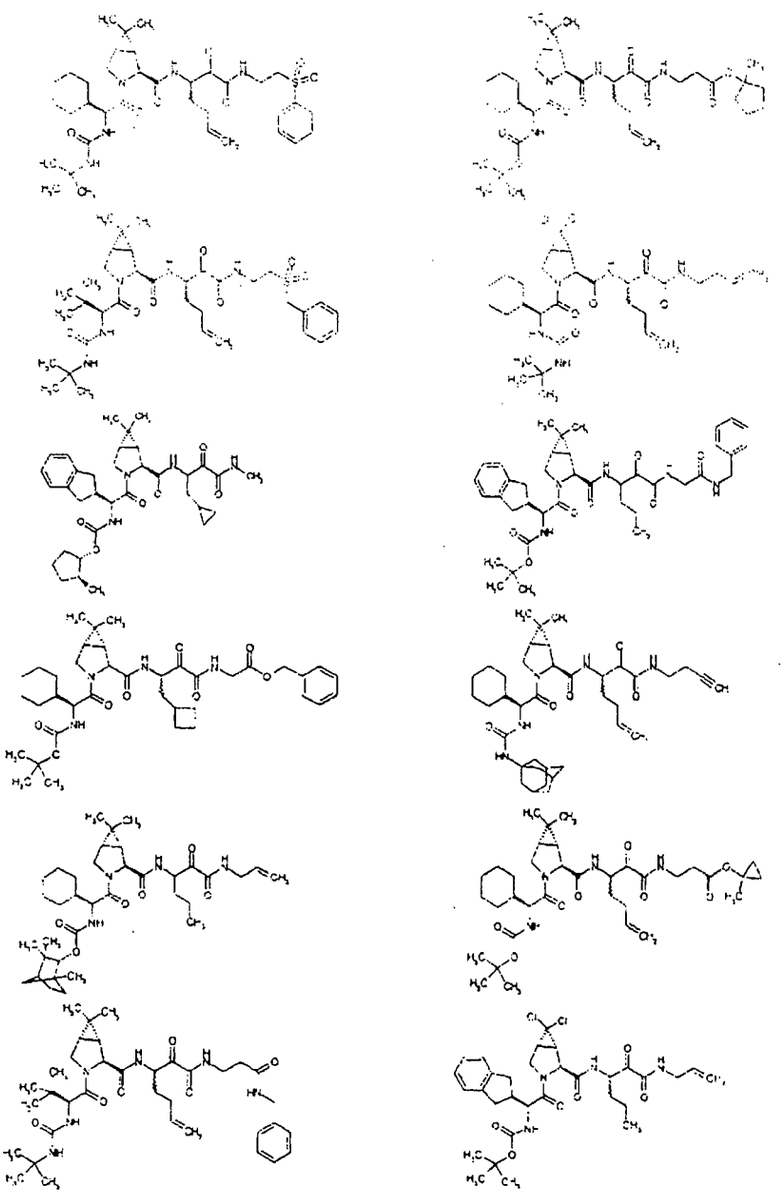


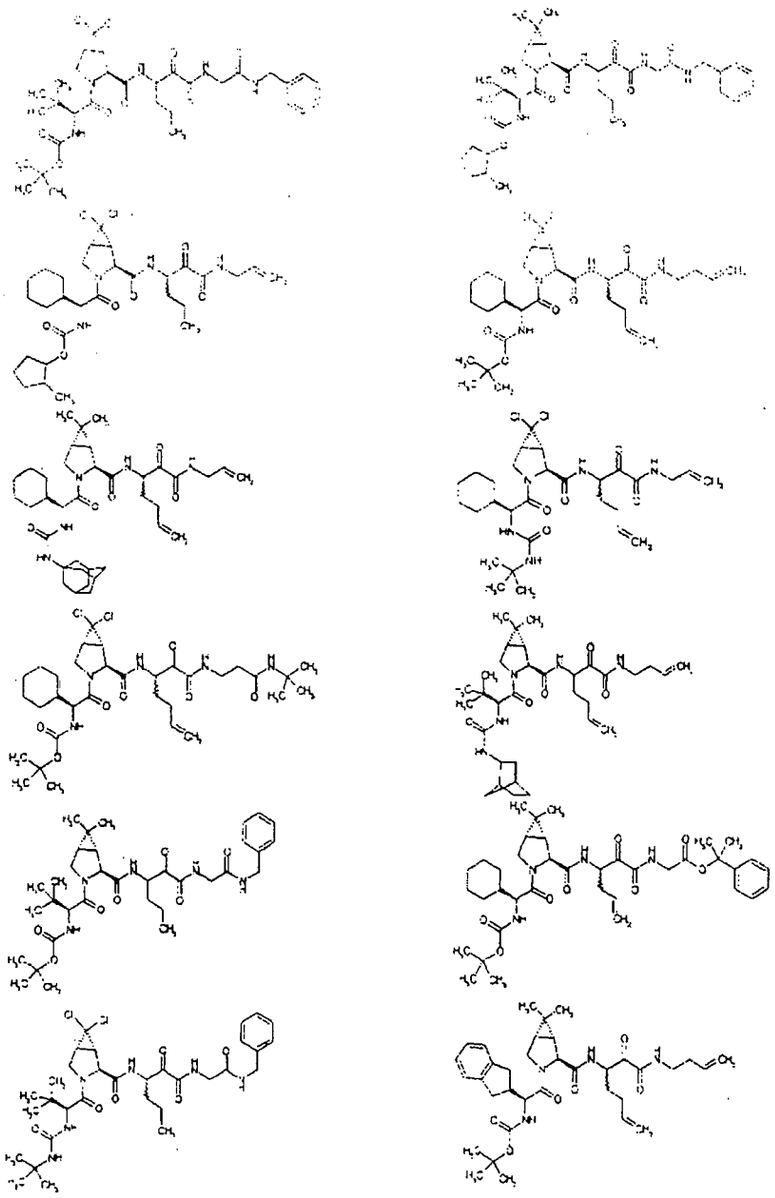
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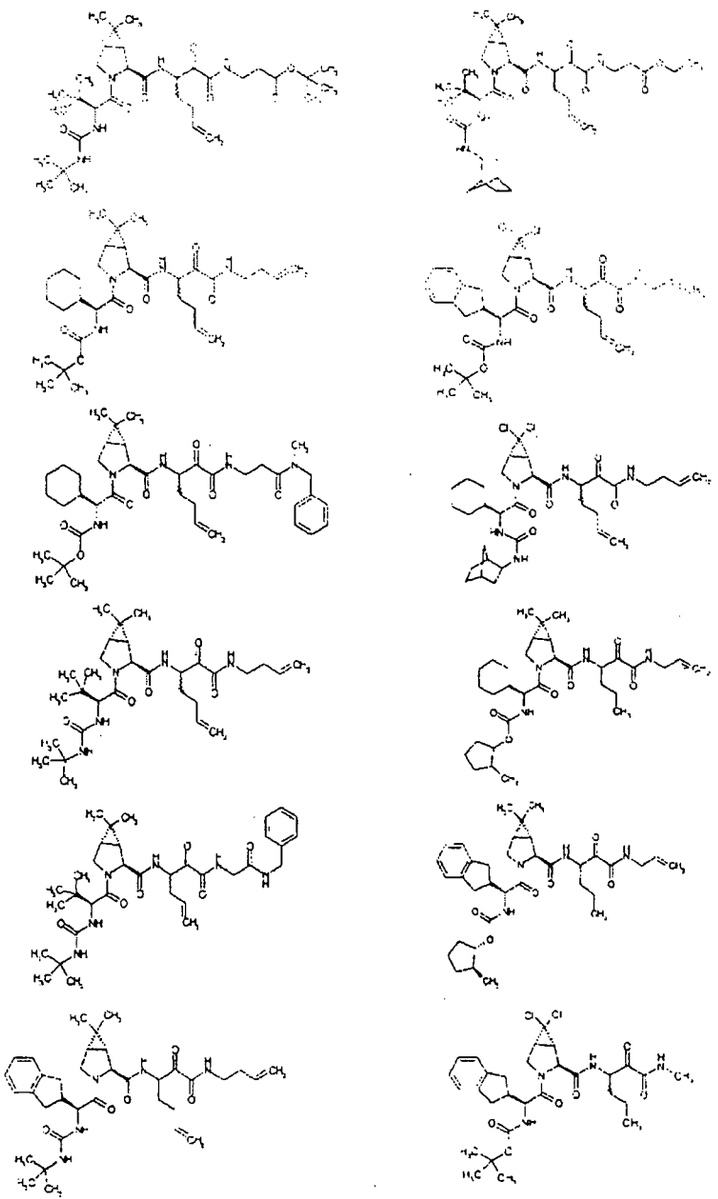




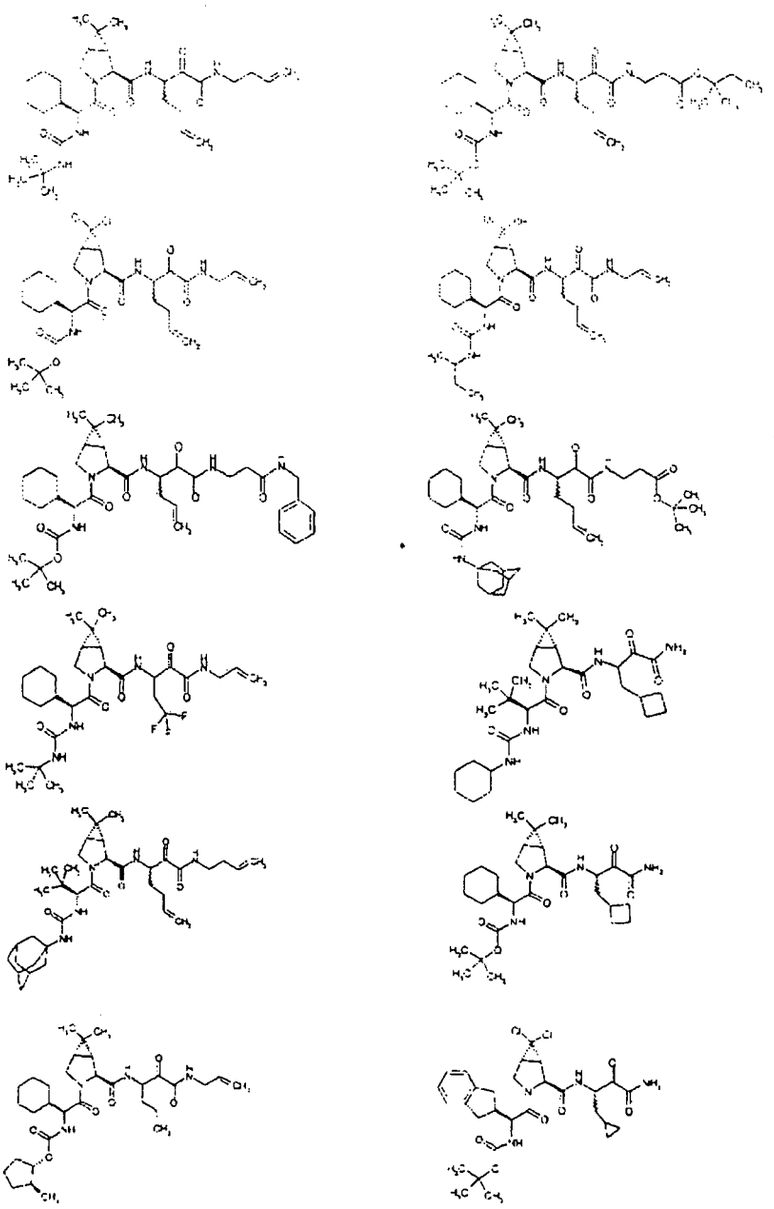
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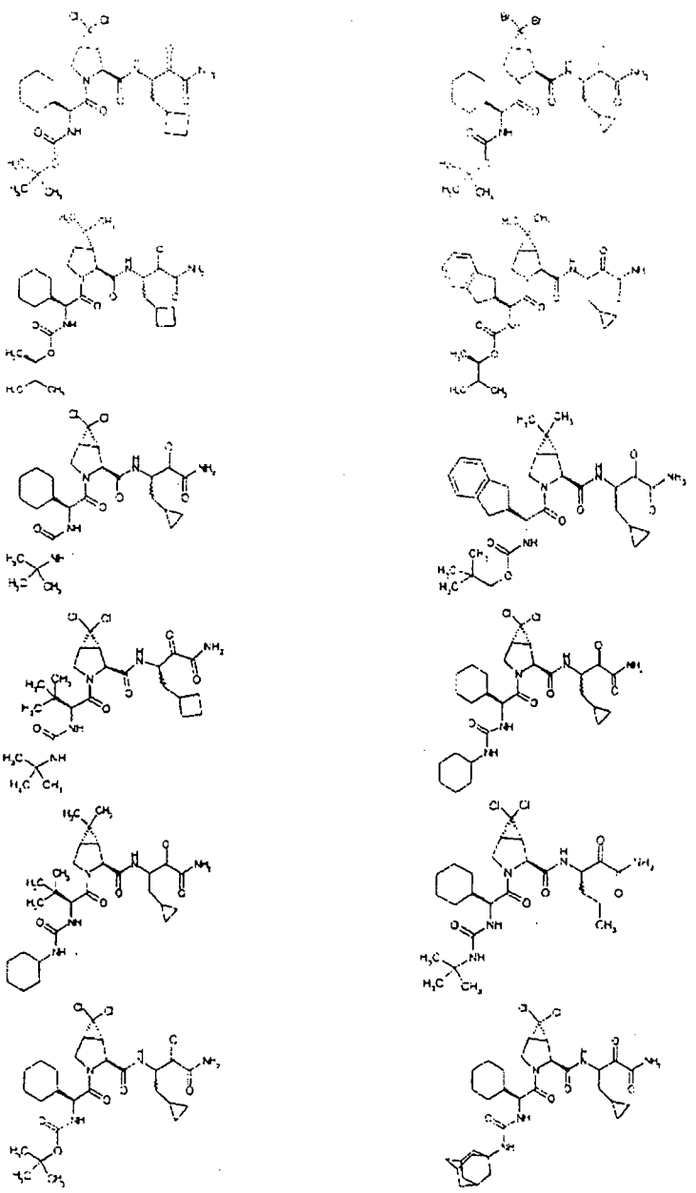




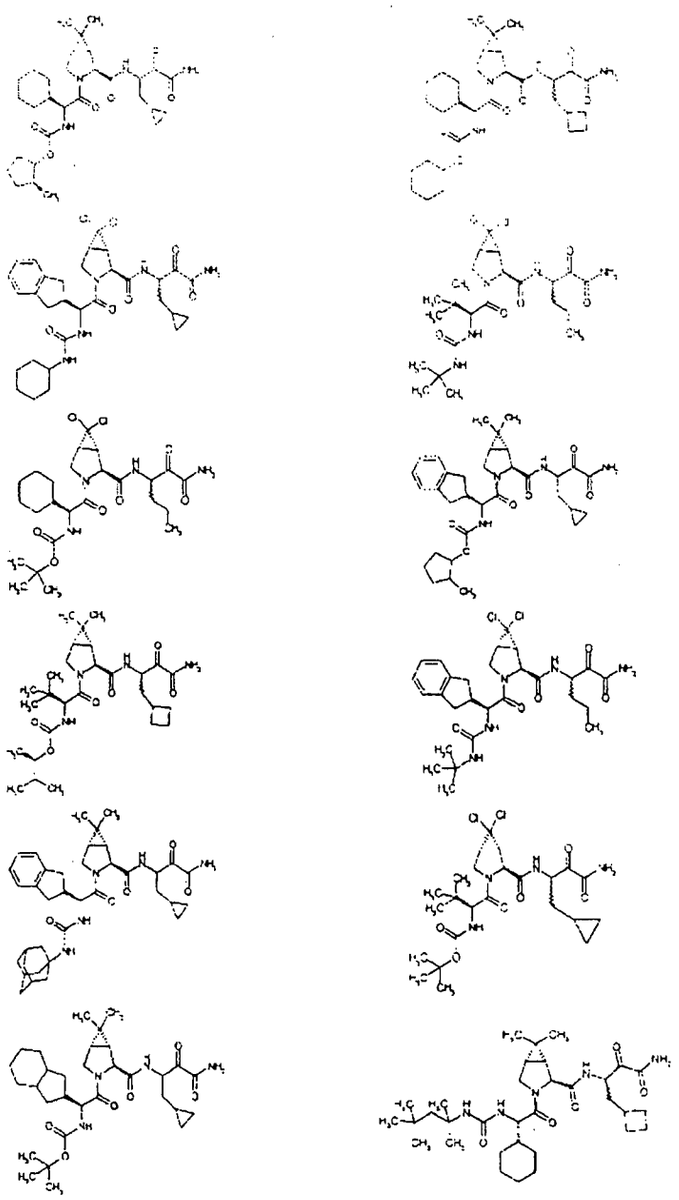
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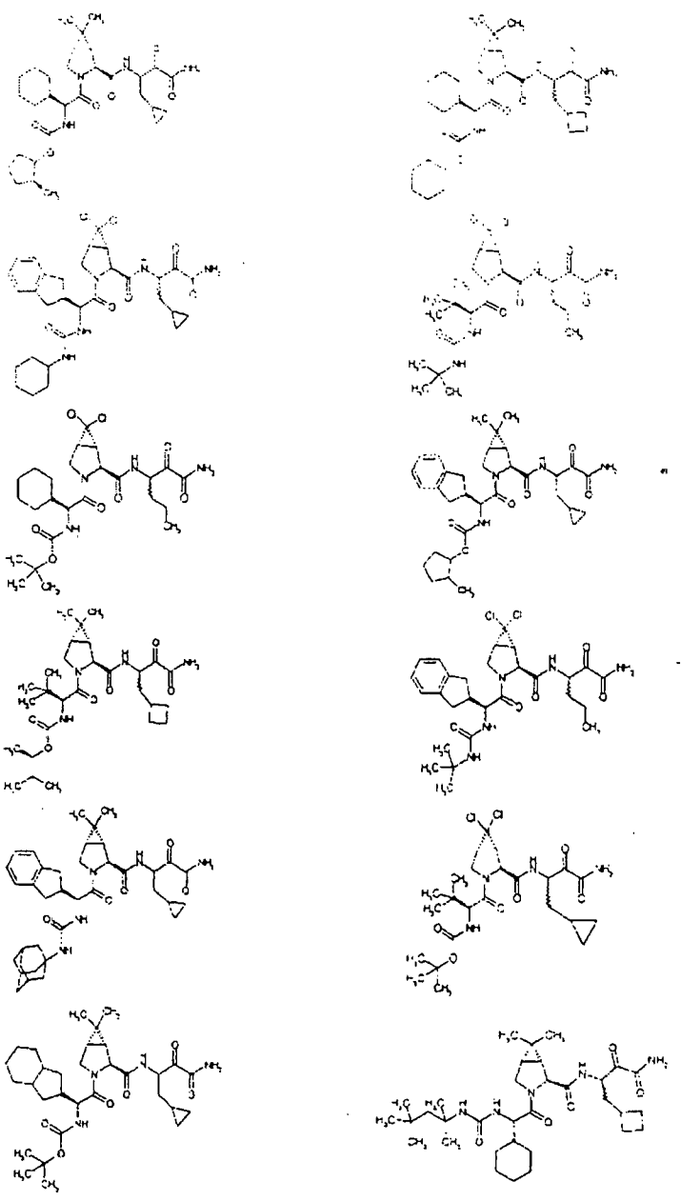


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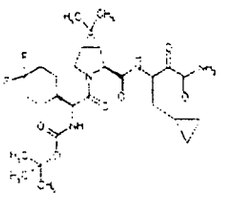


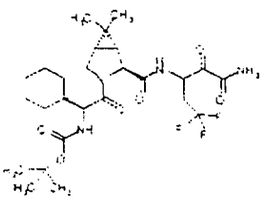
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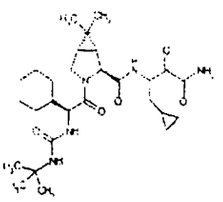


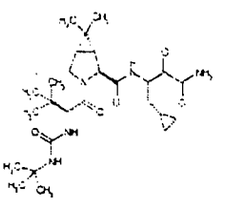


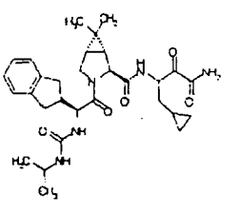
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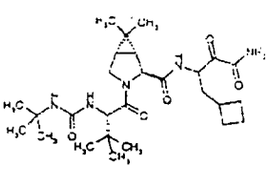


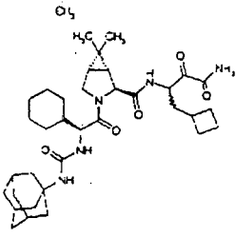


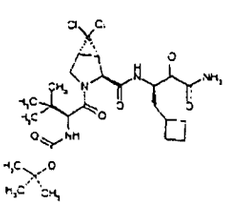


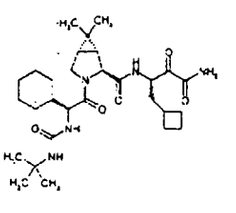


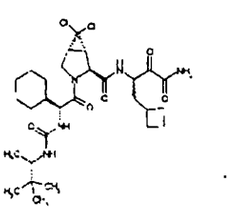




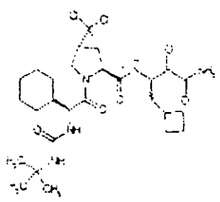


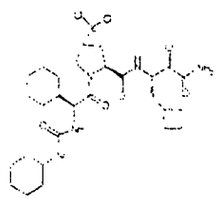


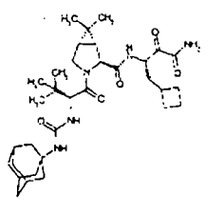


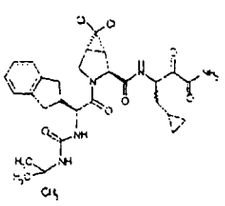


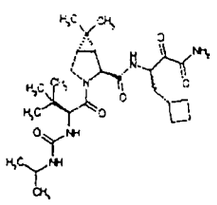
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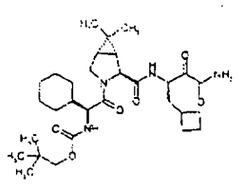


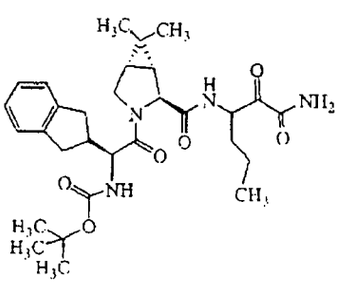




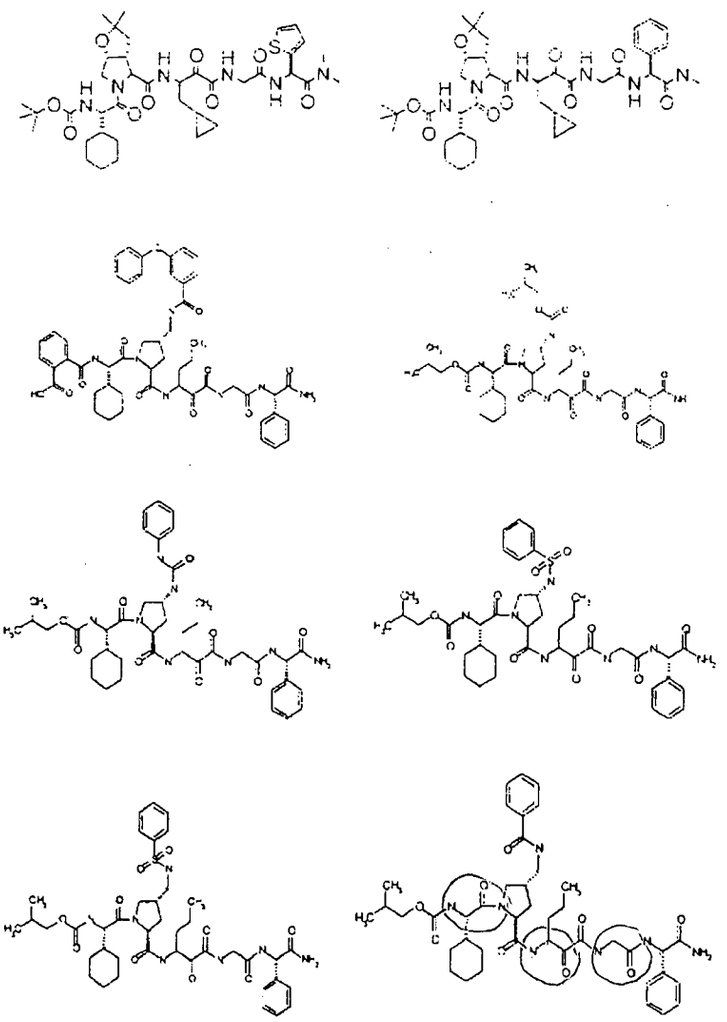




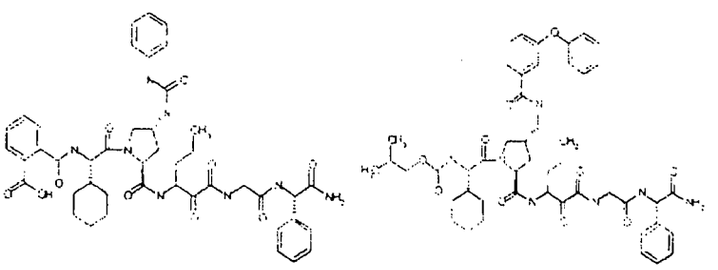


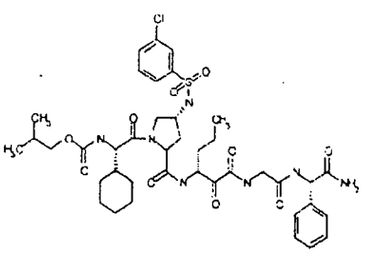


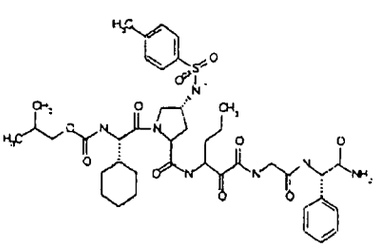
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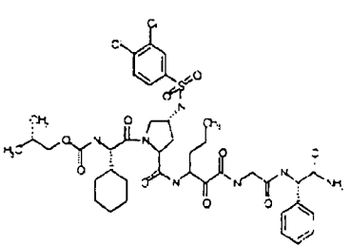


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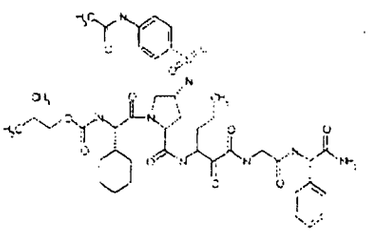


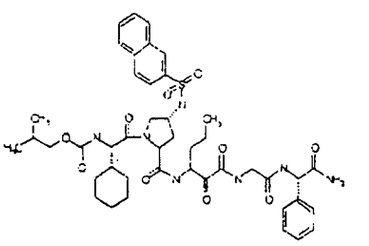


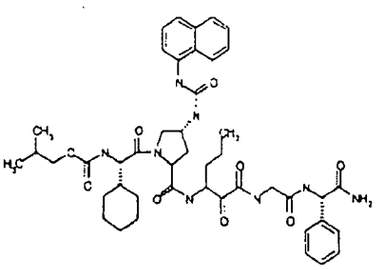




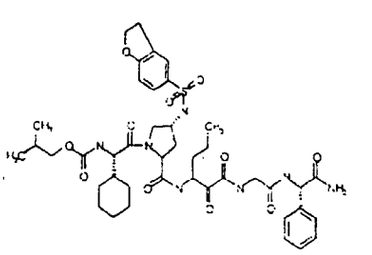
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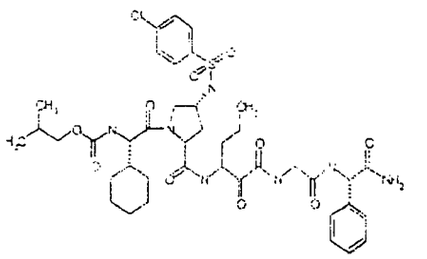


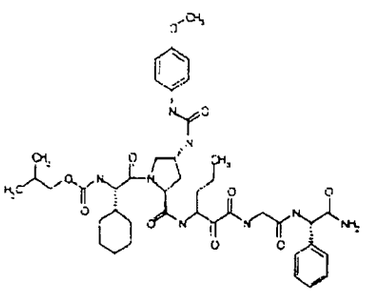


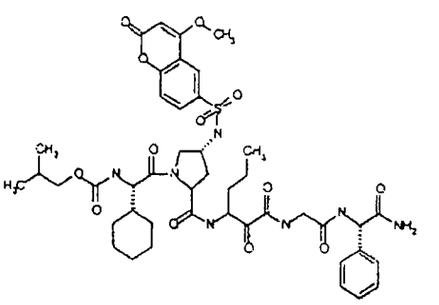
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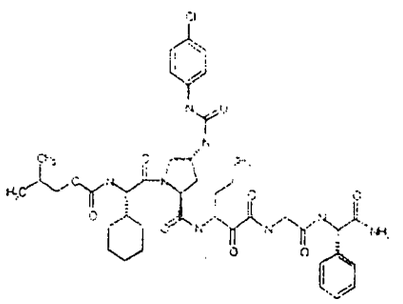
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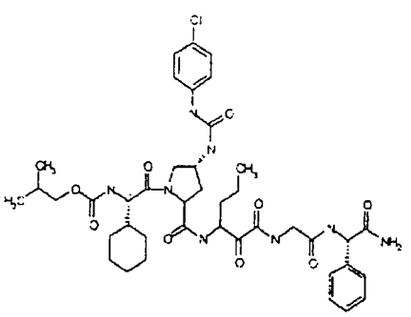


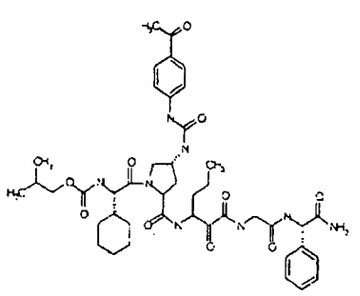




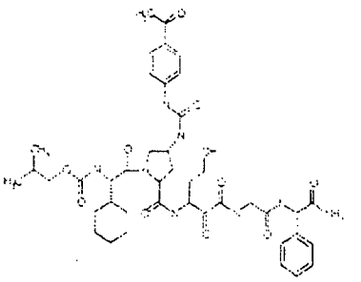
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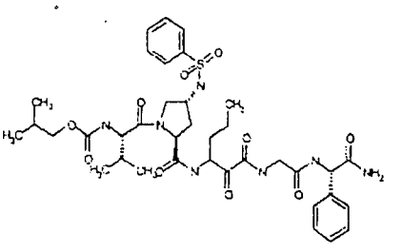


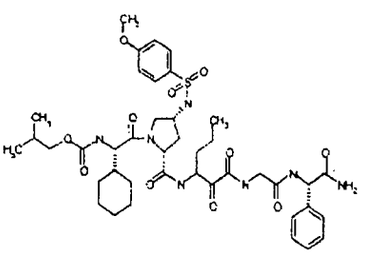


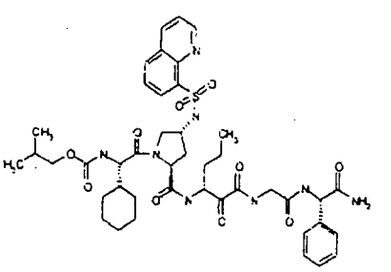


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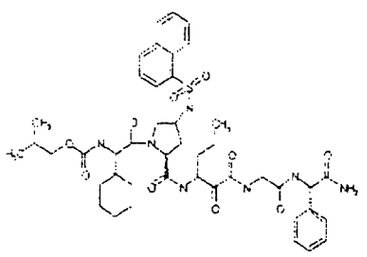


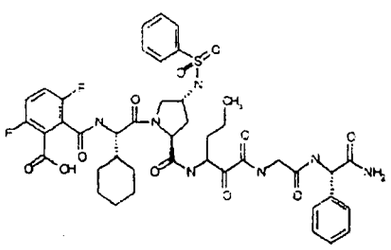


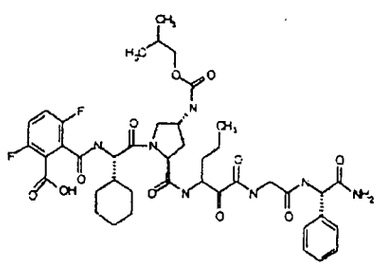




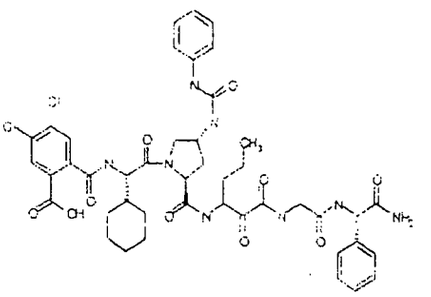
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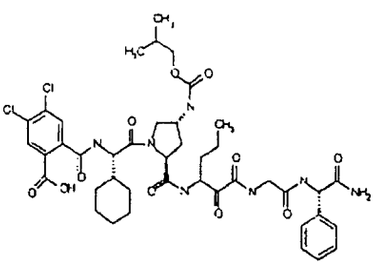


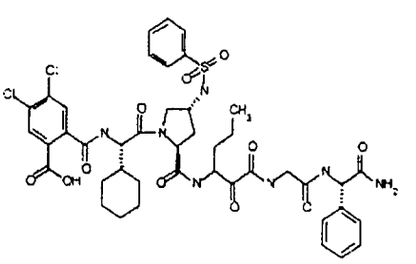


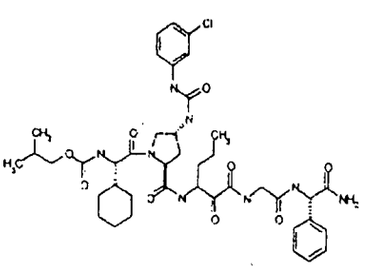


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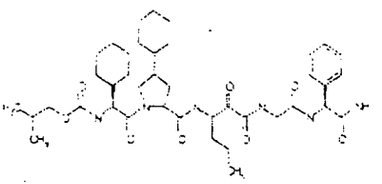


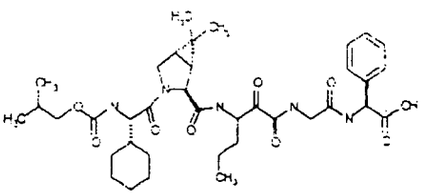


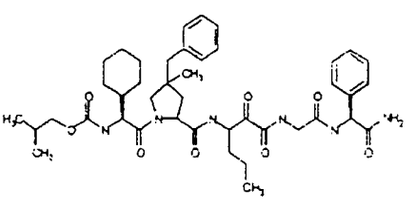


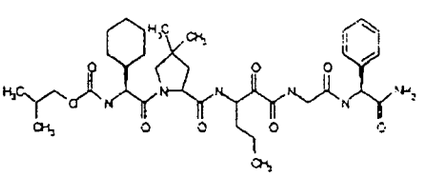


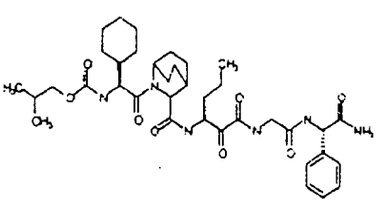
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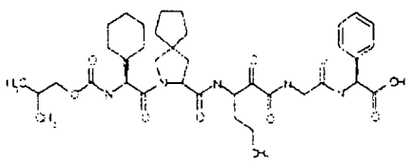


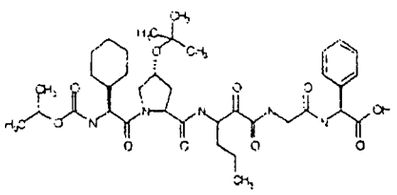


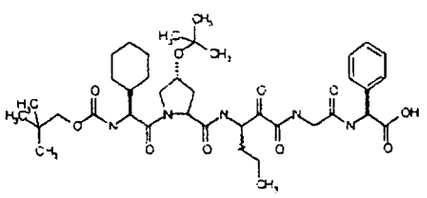


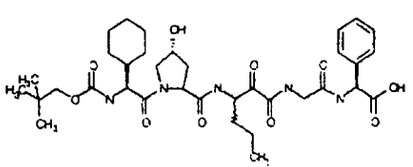


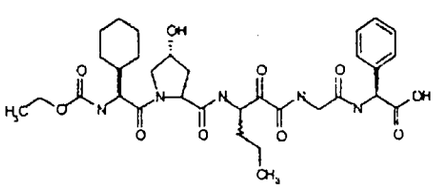
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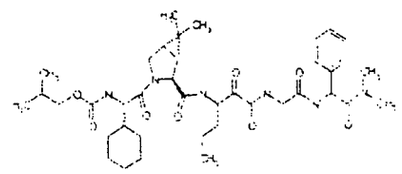


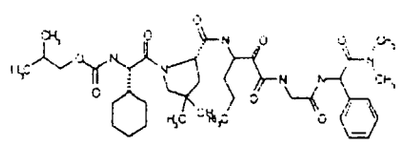


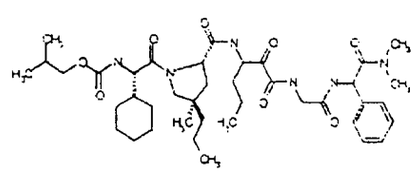


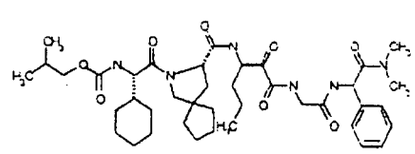


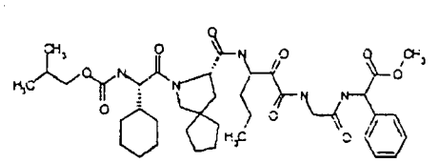
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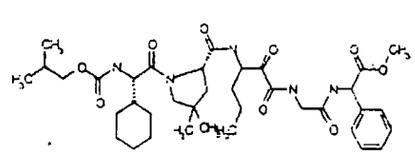


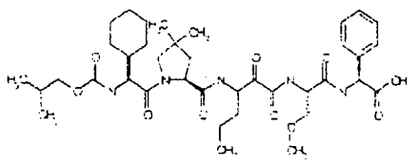


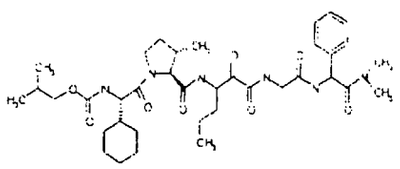


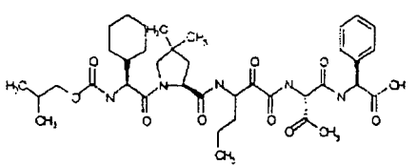


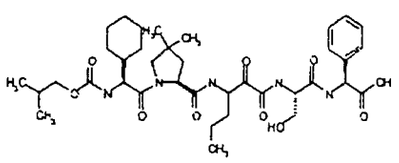


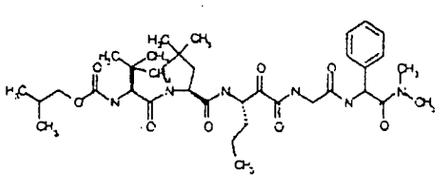


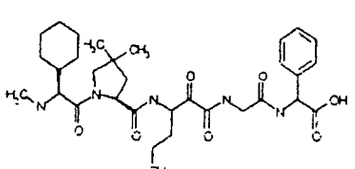




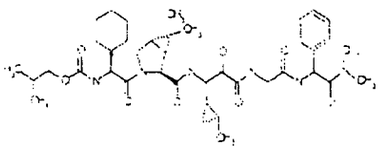


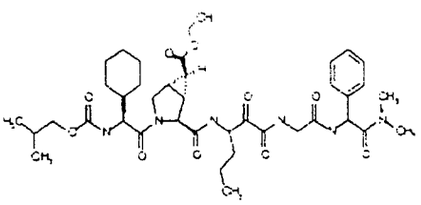


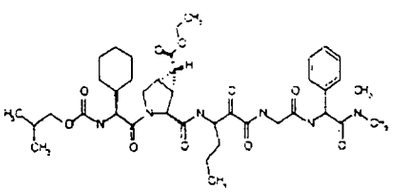


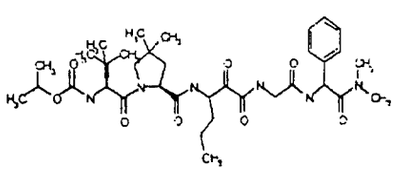


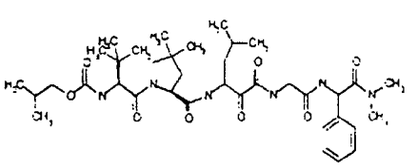
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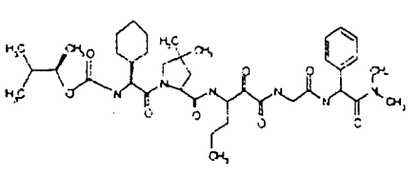




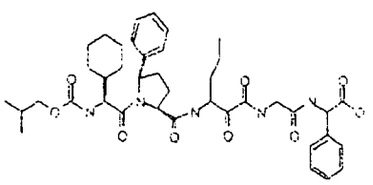


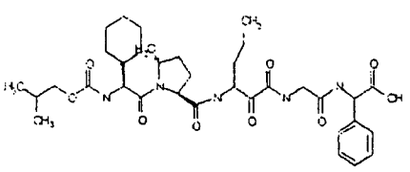


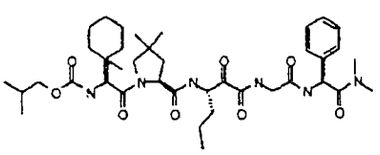


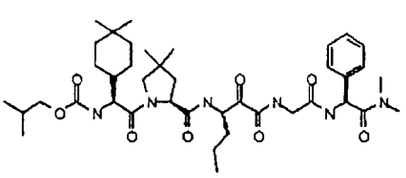


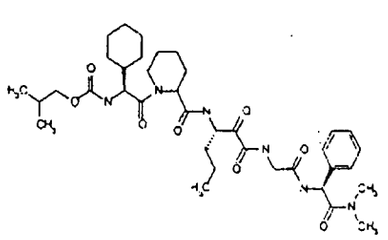
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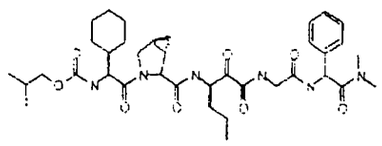


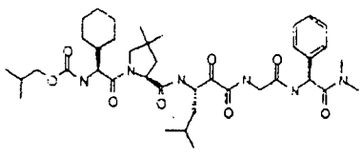


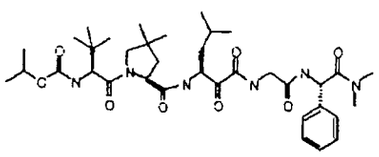


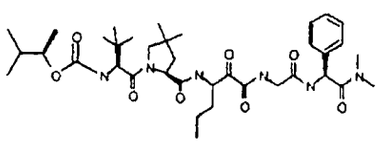


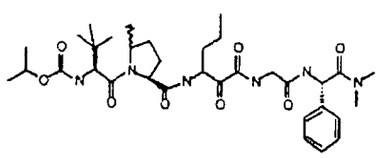
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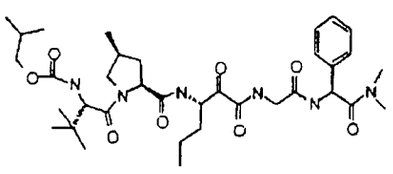




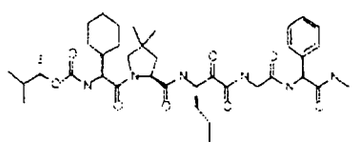


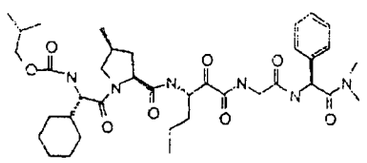


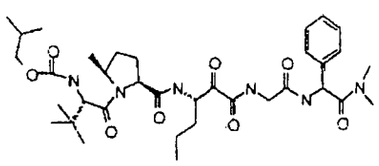


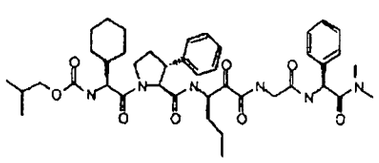


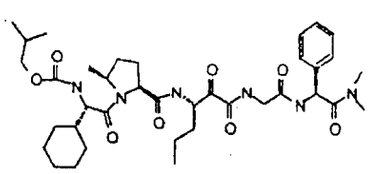
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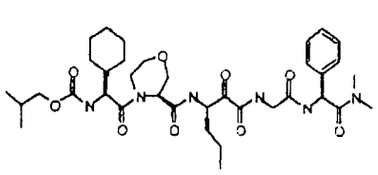




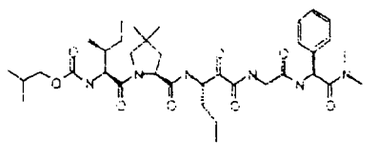


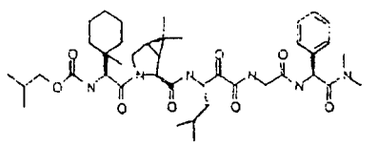


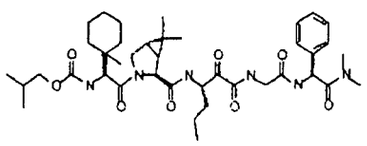


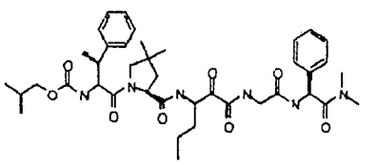


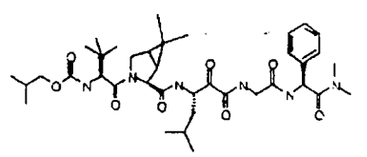
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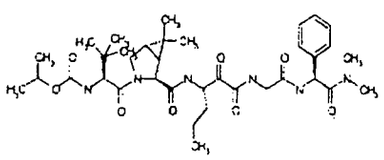




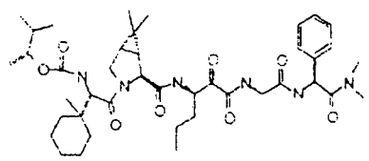


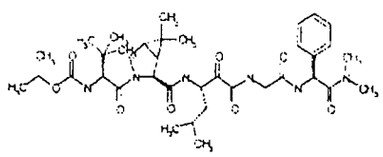


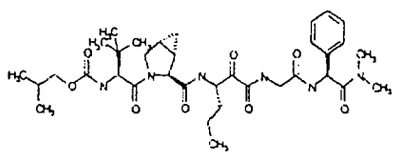


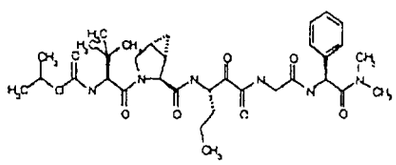


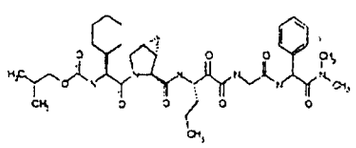
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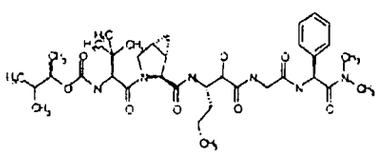




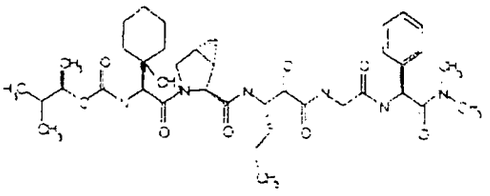








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40. Una composición farmacéutica para el tratamiento de trastornos asociados con el HCV, dicha composición comprende una cantidad terapéuticamente efectiva de uno o más compuestos de la reivindicación 39, y un vehículo aceptable para uso farmacéutico.

41. La composición farmacéutica de la reivindicación 40, que comprende, en forma adicional, un agente antiviral.

42. La composición farmacéutica de la reivindicación 41, que contiene, además, un interferon o un conjugado alfa del interferon PEG.

43. La composición farmacéutica de la reivindicación 42, en la cual dicho agente antiviral es ribavirina y dicho interferon es α-interferon.

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 de modulación de la actividad de la proteasa del virus de la hepatitis C (HCV), que comprende el contacto de la proteasa de HCV con uno o más compuestos de la reivindicación 39.

46. Un método para el tratamiento, la prevención o el alivio de uno o más 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 45, en el cual la proteasa de HCV es la proteasa NS3/NS4a.

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48. El método de la reivindicación 47, en el cual el compuesto o los compuestos inhiben la proteasa NS3/NS4a de HCV.

49. Un método para modular el procesamiento del polipéptido del virus de la hepatitis C (HCV), que comprende el contacto de una composición que contiene el polipéptido de HCV en condiciones en las cuales se procesa el polipéptido con uno o más compuestos de la reivindicación 39.

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Resumen de la invención

La presente invención describe nuevos compuestos que tienen actividad de inhibición de la proteasa de HCV como también métodos para preparar dichos compuestos. En otra realización, la invención describe composiciones farmacéuticas que comprenden dichos compuestos, como también métodos de uso para el tratamiento de trastornos asociados con la proteasa de HCV.

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PATENT DEPARTMENT
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To:

KALYANARMAN, P. S.
Schering-Plough Corporation
Patent Department K-6-1 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
ETATS-UNIS D'AMERIQUE

PCT 000847

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	15.11.2002
Applicant's or agent's file reference IN01159K	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US01/22678	19/07/2001	21/07/2000

Applicant
SCHERING CORPORATION et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d	Laakkonen, A

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
IN01159K		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US01/22678	19/07/2001	21/07/2000
International Patent Classification (IPC) or national classification and IPC C07K5/062		
Applicant SCHERING CORPORATION et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
08/02/2002	15.11.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d	Authorized officer Vogt, T

030843

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US01/22678

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-467 as originally filed

Claims, No.:

1-49 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination 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 readable 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.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US01/22678

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-38, 44-49.

because:

☒ the said international application, or the said claims Nos. 35, 36, 44-49 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-38.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	39-49
	No:	Claims	
Inventive step (IS)	Yes:	Claims	39-49
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	39-43

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US01/22678

No: Claims 44-49

2. Citations and explanations
see separate sheet

III No opinion.

The international search report (ISR) was not established for claims 1-38. The international preliminary examination report (IPER) will therefore not cover said claims (Rule 66(1)e PCT).

Hence, the IPER will only relate to the compounds disclosed in claim 39, the examples and closely related homologous compounds, and compositions and methods directed thereto.

Claims 35, 36 and 44-49 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

V Reasoned Statement.

Subject matter of the present application.

The provision of hepatitis C virus inhibitors of formula (I), compositions comprising the same and the medical use thereof.

Cited prior art documents (Rule 64(1) PCT).

D1: WO 01 74768 A.
D2: WO 01 40262 A.
D3: WO 00 52032 A.
D4: HAN ET AL. (04.2000) BIOORG. MED. CHEM. LETT. 10, 711-713.
D5: WO 99 07734 A.
D6: LLINAS-BRUNET ET AL. (1998) BIOORG. MED. CHEM. LETT. 8, 2719-2724.
D7: WO 98 17679 A.

D1, D2 and D3 are not prior art under Rule 64(1) PCT. The substantive examination does therefore not consider these documents.

Novelty (Art. 33(2) PCT).

D4 and D6 disclose HCV inhibitors that differ from the compounds of formula (I) of the present application in that the N-terminus contains P5 and P6 amino acids. D4 and D6

both disclose an alkyl or alkenyl group at the P1 position. In addition D4 discloses the use of di-ketones, -amides and -esters as the non-cleavable bond between the P1 and the P1' substituents.

D5 discloses HCV inhibitors, two of which appear to fall within the scope of the present claims. The compounds are designated numbers 109 and 116 (cf. Table 1). These compounds fall within the scope of present claim 1 with Y=cycloalkyl amide substituted with X12=carboxy to form the N-terminal group Ac-Chg. D5 further discloses the diketoamide non-cleavable bond and the alkyl at the P1-position (R2).
It follows that D5 is prejudicial to the novelty of the subject matter of present claims 1-11 (claims 4-6 are not restrictive on R14) and 29-38.

D7 discloses in tables 3-5 various HCV inhibitors falling within the scope of present claim 1, following the line of argumentation used for D5. In addition, in table 6 of D7 HCV inhibitors are disclosed that are prejudicial to the subject matter of present claims 1, 2, 7-11, 12 and 29-38 (see for instance compounds 149 and 178).
Consequently, D7 is prejudicial to the novelty of present claims 1-12 and 29-38.

To summarize: Although the search report was not completed for the subject matter of present claims 1-38, and as a result the IPER does not cover the subject matter of said claims, it appears that the subject matter of present claims 1-12 and 29-38 lacks novelty over the cited prior art.

Claims 39-49 contain features which alone or in combination with the claims to which they refer do not appear to have been disclosed in the cited prior art. The subject matter of said claims therefore appears to be novel (Art. 33(2) PCT). It is noted, however, that the compounds of claim 39 do not appear to share a single novel structural element or group of structural elements.

Inventive step (Art. 33(3) PCT).
The subject matter of claim 39 does not appear to be disclosed or suggested in the prior art. Moreover said compounds show high activity as HCV inhibitors.
Consequently the inventive step of the subject matter of said claim is acknowledged.

The inventive step of the subject matter of claims 40-49 is accordingly acknowledged.

Claims 39-49 appear to be inventive, because they contain features which alone or in combination with the claims to which they refer do not appear to have been suggested by any combination of the cited prior art documents.

Industrial applicability (Art. 33(4) PCT).

The subject matter of claims 1-34 and 37-43 meets the requirement of industrial applicability.

For the assessment of the present claims 35, 36 and 44-49 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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	USUARIO	RADICADOR
PATENTE DE INVENCIÓN **MODELO DE UTILIDAD**	( )	(X)
- Indicación de que se solicita la concesión de una patente.	( )	(X)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(X)
- Descripción de la invención.	( )	( )
- ujos de ser estos pertinentes.	( )	(X)
- Comprobante de Pago de las tasas establecidas.		
COMPLETA ( ) **INCOMPLETA**	(X)	( )
DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que 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	( )	( )

Edwar Navarro.
Firma Responsable:

20-01-2003
Fecha: