Libertad y Orden

REPÚBLICA DE COLOMBIA

DIVISIÓN DE PROPIEDAD INDUSTRIAL

PCT

PATENTE DE INVENCIÓN

Industria y Comercio
SUPERINTENDENCIA

06-82845

TITULO: NUEVOS COMPUESTOS COMO INHIBIDORES DE SERINA PROTEASA NS3 DEL VIRUS DEL A HEPATITIS C.

SOLICITANTE: SCHERING CORPORATION

DIRECCIÓN: 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, E.U.A.

APODERADO: J. IAN RAISBECK

BOGOTÁ, agosto 22 de 2006

P2006/000174

Nº reivind

SS

OLARTERAISBECK

061174.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-082845- -00000-0000
Fec: 2006-08-22 17:27:09 Dep. 2020 NUECREACIONES
Tra. 11 PATENTEIYII
Eve: 379 FASENACIONALII
Act 411 PRESENTACION Fólios: 367

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL 27/09/06

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) **S LICITANTE (71)**	**Nombre:** SCHERING CORPORATION **Dirección:** 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, E.U.A. **Nacionalidad o Domicilio:** ESTADOUNIDENSE **Lugar de Constitución:** ESTADOS UNIDOS DE AMERICA **Teléfono:** **Fax:** **E-mail:**	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual Número
REPRESENTANTE APODERADO	**Nombre:** J. IAN RAISBECK **Dirección:** World Trade Center, Torre A, Calle 100 No. 8ª-37 Piso 10. **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** C.C. [x] NIT [ ] C.E. [ ] Otro [ ] Cual Número 79.376.996 TP 135.799
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/US2005/005773 Fecha Febrero 24, 2005

Publicación Internacional No. WO 2005/087725 Fecha Septiembre 22, 2005

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

Clasificación Internacional (51) C07D 209/00.

A61P 31/12 1 3/16 ; A61K 38/55

Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 27, 2004	60/548,535

(9) **Comprobante de pago No.** 06-63.710 **Fecha** Agosto 22, 2006

(10) ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 06-057.472, sustitución
- [ ] 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).
- [x] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) FIGURA CARACTERÍSTICA:

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

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

LISTA DE INVENT RES PCT/US2005/005773

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54

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-082845- -00000-0000
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Act 411 PRESENTACION
Folios: 367

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 63,710
FECHA : AGOSTO 22 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEGR	CONSIGNACION	BANCO POPULAR	050-00110-6	52202107	10/08/2006	3,382,000.00

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	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

4
6

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Ref.: Nueva solicitud de Patente de Invención titulada : NUEVOS COMPUESTOS COMO INHIBIDORES DE SERINA PROTEASA NS3 DEL VIRUS DE LA HEPATITIS C. Solicitante : SCHERING CORPORATION

SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad, en el doctor **J. IAN RAISBECK LLINAS**, mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.376.996 de Bogotá y portador de la Tarjeta Profesional No. 135.799 del Consejo Superior de la Judicatura, para que sea él quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295 del C. S. de la J.

DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA.

NOTARIA

27

EL ANTERIOR ESCRITO DIRIGIDO A:

FUE PRESENTADO PERSONALMENTE
ANTE EL SUSCRITO NOTARIO VEINTISIETE
DE SANTAFE DE BOGOTA D.C.

C.C. [illegible] Y T.P.

Y ANTE LAS PRESENTES TESTIGOS DE TODO LO ANTERIOR
SE DEJA CONSTANCIA Y QUE LA FIRMA QUE LO
AUTORIZA ES IGUAL A LA QUE USA EN SUS

EL NOTARIO:



27 JUL. 2000 DELLA

MARIA EUGENIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

REPUBLICA DE COLOMBIA
27
Maria Eugenia Rojas
de Urueta
NOTARIA

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

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

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

CERTIFICADO

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

PODER DE REPRESENTACIÓN

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

CERTIFICADO NOTARIAL

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

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

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

Es traducción fiel del inglés, con copia archivo, para confrontación. Bogotá 5 septiembre, 2003.

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

8

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

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

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

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

CERTIFIED

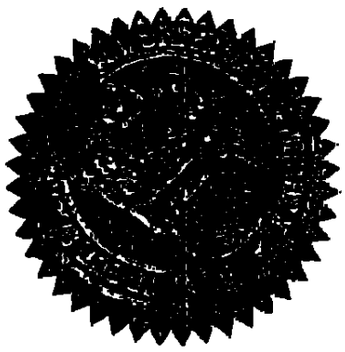
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

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

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
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TELEPHONE: +57-1 638-6200
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www.olarteraisbeck.com

Power of Attorney

The undersigned,
SCHERING CORPORATION

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

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

Poder

El suscrito,

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

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

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

Date/Fecha: August 7, 2003

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

AP
10

OLARTERAISBECK

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Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

of legal age and domiciled in 189 Greenwood Drive, Millburn, New Jersey 07041, U.S.A.
signed the foregoing document.

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

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

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

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

Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado
suscribió el documento que antecede.

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

4. Que
con sede principal ubicada en
está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

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

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

BLIC (Signature):

Marguerite LaCorte

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

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

(19) World Intellectual Property Organization
International Bureau

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22 September 2005 (22.09.2005)

PCT

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(51) International Patent Classification[7]: C07D 209/00

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(25) Filing Language: English

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(30) Priority Data:
60/548,535 27 February 2004 (27.02.2004) US

(71) Applicant *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ARASAPPAN, Ashok [IN/US]; 18 Larsen Court, Bridgewater, NJ 08807 (US). NJOROGE, F., George [US/US]; 11 Softwood Way, Warren, NJ 07059 (US). PADILLA-ACEVEDO, Angela, I. [CO/US]; 1003 Justin Lane, Apt. 2065, Austin, TX 78757 (US). CHEN, Kevin, X. [US/US]; 9 Gloria Avenue, Edison, NJ 08820 (US). BENNETT, Frank [GB/US]; 38 Keith Jeffries Avenue, Cranford, NJ 07016 (US). SANNIGRAHI, Mousumi [CA/US]; 2 New Providence Avenue, Summit, NJ 07901 (US). BOGEN, Stephane, L. [FR/US]; 13 Dahlia Road, Somerset, NJ 08873 (US). VENKATRAMAN, Srikanth [IN/US]; 35 Roanoke Street, Woodbridge, NJ 07095 (US). JAO, Edwin [US/US]; 15170 Sapling Ridge, Dayton, MD 21036 (US). SAKSENA, Anil, K. [US/US]; 53 Beverly Road, Upper Montclair, NJ 07043 (US). GIRIJAVALLABHAN, Viyyoor, M. [US/US]; 10 Maplewood Drive, Parsippany, NJ 07054 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

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

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

WO 2005/087725 A2

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

(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 COMPOUNDS AS INHIBITORS OF HEPATITIS C VIRUS NS3 SERINE PROTEASE

Field of the 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 additionally discloses novel compounds as inhibitors of the HCV NS3/NS4a serine protease. This application claims priority from U.S. provisional patent application, Serial Number 60/548,535 filed February 27, 2004.

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

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.

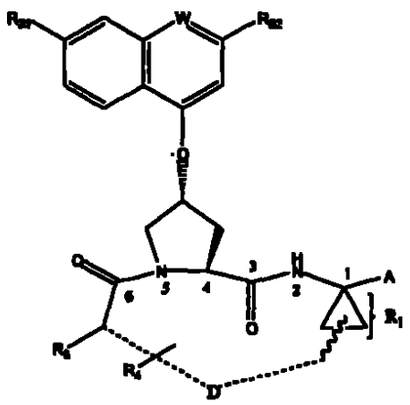
Inhibitors of HCV protease that have been reported include antioxidants (*see*, International Patent Application Publication No. WO 98/14181), certain peptides and peptide analogs (*see*, International Patent Application Publication No. WO 98/17679, Landro et al. (1997) Biochem. 36:9340-9348, Ingallinella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

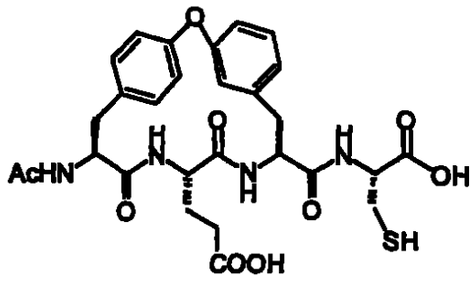
Reference is also made to the PCT Publications, No. WO 98/17679, published April 30, 1998 (Vertex Pharmaceuticals Incorporated); WO 98/22496, published May 28, 1998 (F. Hoffmann-La Roche AG); and WO 99/07734, published February 18, 1999 (Boehringer Ingelheim Canada Ltd.).

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 WO 00/59929 (US 6,608,027, Assignee: Boehringer Ingelheim (Canada) Ltd.; Published October 12, 2000) which discloses peptide derivatives of the formula:

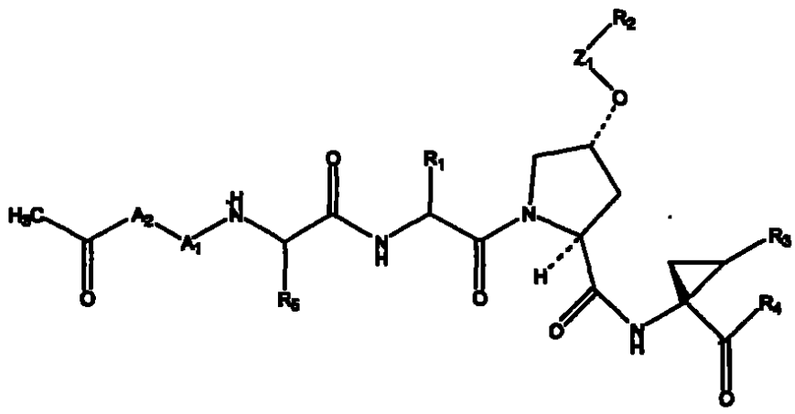


Reference is made to A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) describing the synthesis of bicylic analogs of an inhibitor of HCV NS3 protease. A compound disclosed therein has the formula:

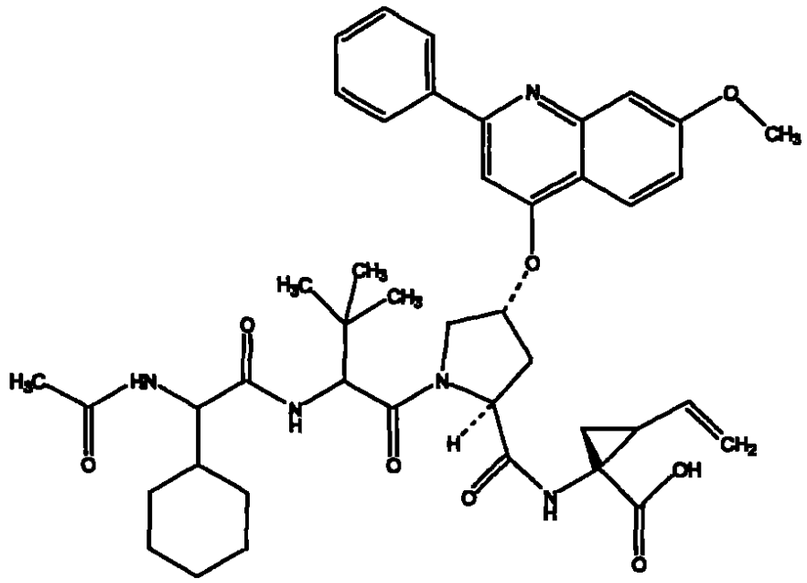


Reference is also made to W. Han *et al*, *Bioorganic & Medicinal Chem. Lett*, (2000) 10, 711-713, which describes the preparation of certain α-ketoamides, α-ketoesters and α-diketones containing allyl and ethyl functionalities.

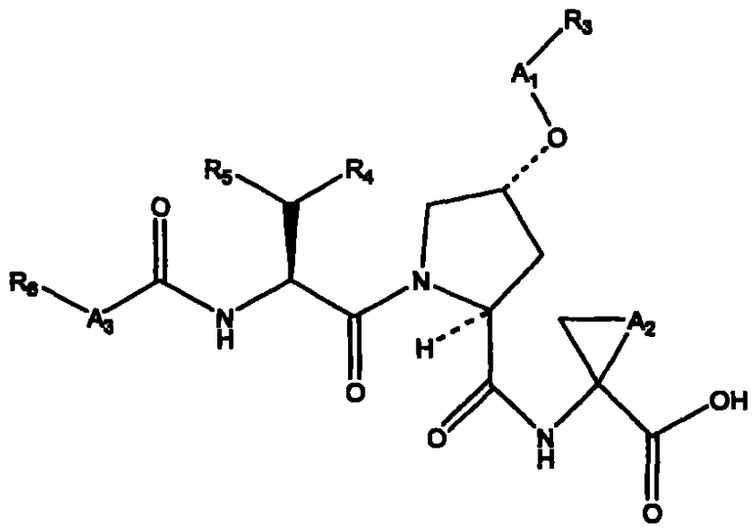
Reference is also made to WO 00/09558 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



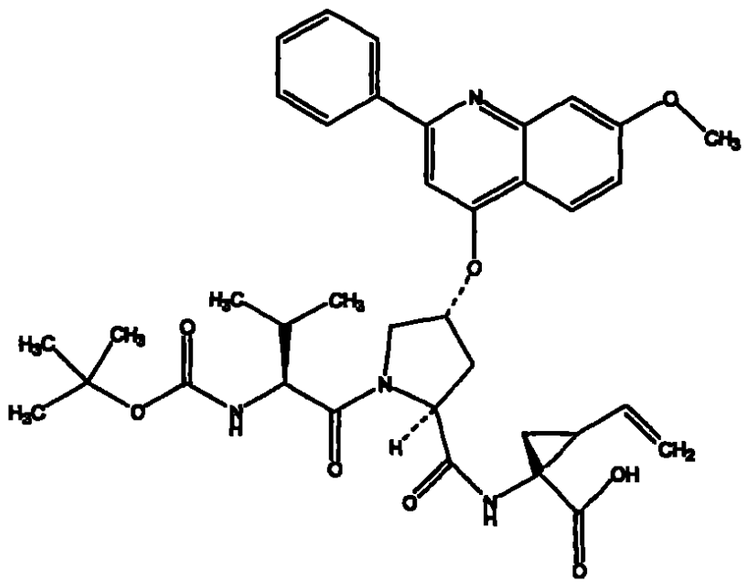
where the various elements are defined therein. An illustrative compound of that series is:



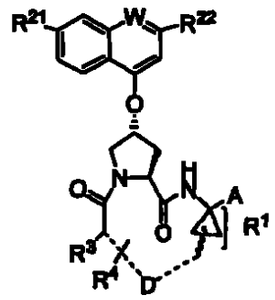
Reference is also made to WO 00/09543 (Assignee: Boehringer Ingelheim Limited; Published February 24, 2000) which discloses peptide derivatives of the formula:



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



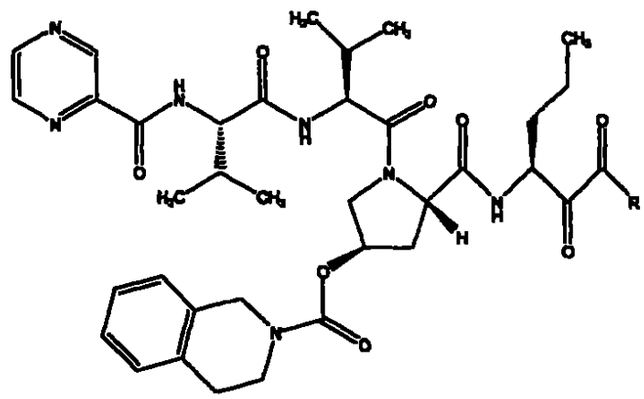
Reference is also made to U.S. 6,608,027 (Boehringer Ingelheim, Canada) which discloses NS3 protease inhibitors of the type:



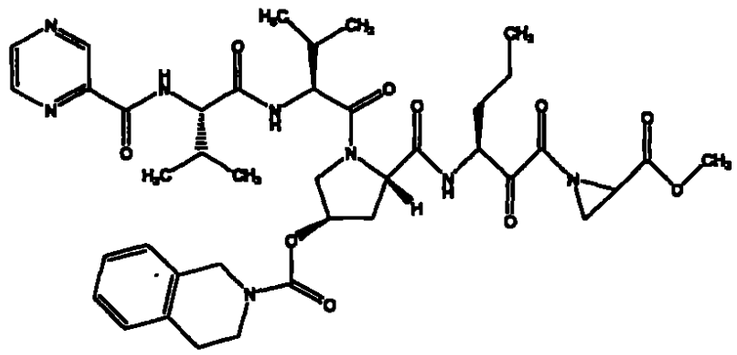
wherein the various moieties are defined therein.

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.

Reference is further made to WO 01/74768 (Assignee: Vertex Pharmaceuticals Inc) published October 11, 2001, which discloses certain compounds of the following general formula (R is defined therein) as NS3-serine protease inhibitors of Hepatitis C virus:



A specific compound disclosed in the afore-mentioned WO 01/74768 has the following formula:



PCT Publications WO 01/77113; WO 01/081325; WO 02/08198; WO 02/08256; WO 02/08187; WO 02/08244; WO 02/48172; WO 02/08251; and *pending U.S. patent application, Serial No. 10/052,386, filed January 18,* 2002, disclose various types of peptides and/or other compounds as NS-3 serine protease inhibitors of hepatitis C virus. The disclosures of those applications are incorporated herein by reference thereto.

There is a need for new treatments and therapies for HCV infection. There is a need for compounds useful in the treatment or prevention or amelioration of one or more symptoms of hepatitis C.

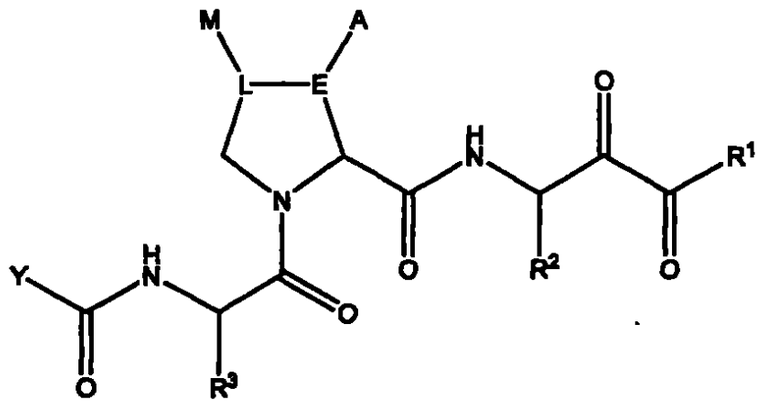
There is a need for methods of treatment or prevention or amelioration of one or more symptoms of hepatitis C.

There is a need for methods for modulating the activity of serine proteases, particularly the HCV NS3/NS4a serine protease, using the compounds provided herein.

There is a need for 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 or prevention of HCV or amelioration of one or more of the symptoms of hepatitis C using one or more such compounds or one or more such formulations. 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 invention discloses compounds, or enantiomers, stereoisomers, rotamers, tautomers, diastereomers or racemates of said compounds, or a pharmaceutically acceptable salt, solvate or ester of said compounds, said compounds having the general structure shown in structural Formula 1:

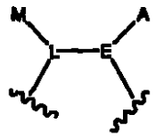


Formula I

wherein:

R^1 is H, OR^8, NR^9R^{10}, or CHR^9R^{10}, wherein R^8, R^9 and R^{10} can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, and heteroarylalkyl;

A and M can be the same or different, each being independently selected from R, OR, NHR, NRR', SR, SO_2R, and halo; or A and M are connected to each other such that the moiety:



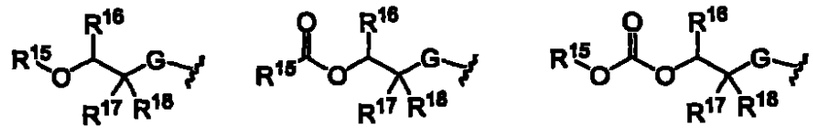
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

E is C(H) or C(R);

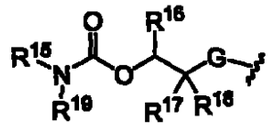
L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-, (cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R and R' in NRR' are connected to each other such that NRR' forms a four to eight-membered heterocyclyl;

and Y is selected from the following moieties:



or

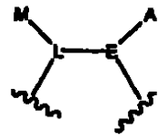


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, (i) either R^{15} and R^{16} are connected to each other to form a four to eight-membered cyclic structure, or R^{15} and R^{19} are connected to each other to form a four to eight-membered cyclic structure, and (ii) likewise, independently, R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

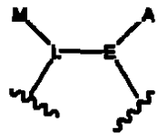
wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio,

alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, sulfonamido, alkylsulfonamido, arylsulfonamido, alkyl, aryl, heteroaryl, keto, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

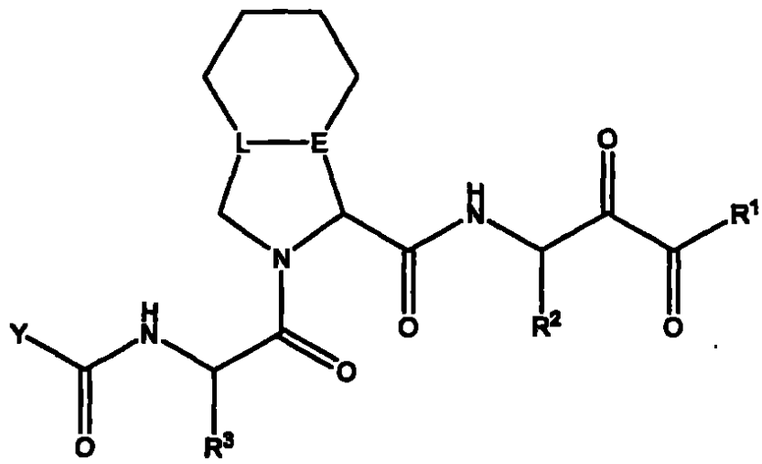
The above-noted statement "A and M are connected to each other such that the moiety:



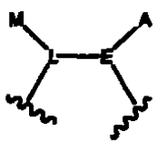
shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl" can be illustrated in a non-limiting matter as follows. Thus, for example, in the case where A and M are connected such that the moiety:



shown above in Formula I forms a six -membered cycloalkyl (cyclohexyl), Formula I can be depicted as:



One with ordinary skill in the art will appreciate that similar depictions for Formula I can be arrived at when A and M shown above in the moiety:



are connected to form a three, four, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl.

The statement above: "alternately, (i) either R^{15} and R^{16} are connected to each other to form a four to eight-membered cyclic structure, or R^{15} and R^{19} are connected to each other to form a four to eight-membered cyclic structure, and (ii) likewise, independently, R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl" means the following possibilities: (i) that R^{15} and R^{16} are connected to form a cyclic structure while R^{15} and R^{19} are not; (ii) that R^{15} and R^{19} are connected to form a cyclic structure while R^{15} and R^{16} are not; and that (iii) R^{17} and R^{18} are independently connected to form a cyclic structure, irrespective of whether the possibilities in (i) and (ii) exist or not.

In the above-noted definitions of R, R', R^2, and R^3 preferred alkyl is made of one to ten carbon atoms, preferred alkenyl or alkynyl is made of two to ten carbon atoms, preferred cycloalkyl is made of three to eight carbon atoms, and preferred heteroalkyl, heteroaryl or heterocycloalkyl has one to six oxygen, nitrogen, sulfur, or phosphorus atoms.

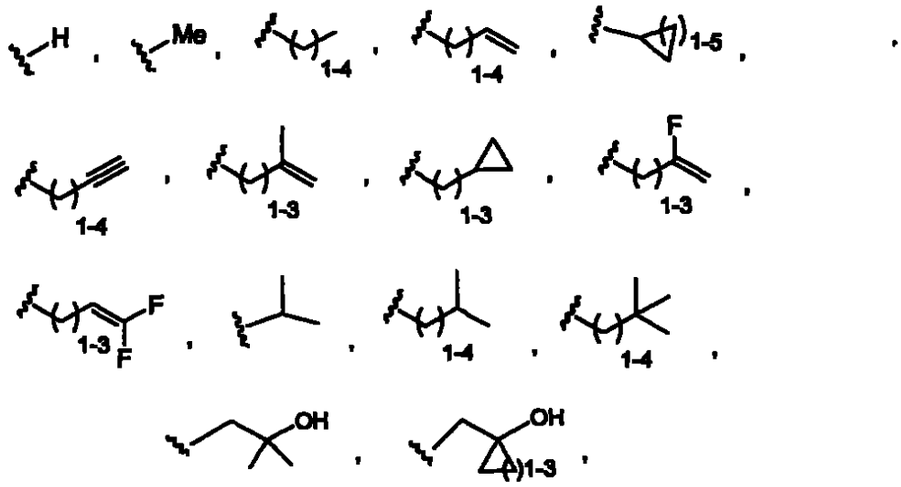
The compounds represented by Formula I, by themselves or in combination with one or more other suitable agents disclosed herein, can be useful for treating diseases such as, for example, HCV, HIV, AIDS (Acquired Immune Deficiency Syndrome), and related disorders, as well as for modulating the activity of hepatitis C virus (HCV) protease, preventing HCV, or ameliorating one or more symptoms of hepatitis C. Such modulation, treatment, prevention or amelioration can be done with the inventive compounds as well as with pharmaceutical compositions or formulations comprising such compounds. Without being limited to theory, it is believed that the HCV protease may be the NS3 or NS4a protease. The inventive compounds can inhibit such protease. They can also modulate the processing of hepatitis C virus (HCV) polypeptide.

Detailed Description

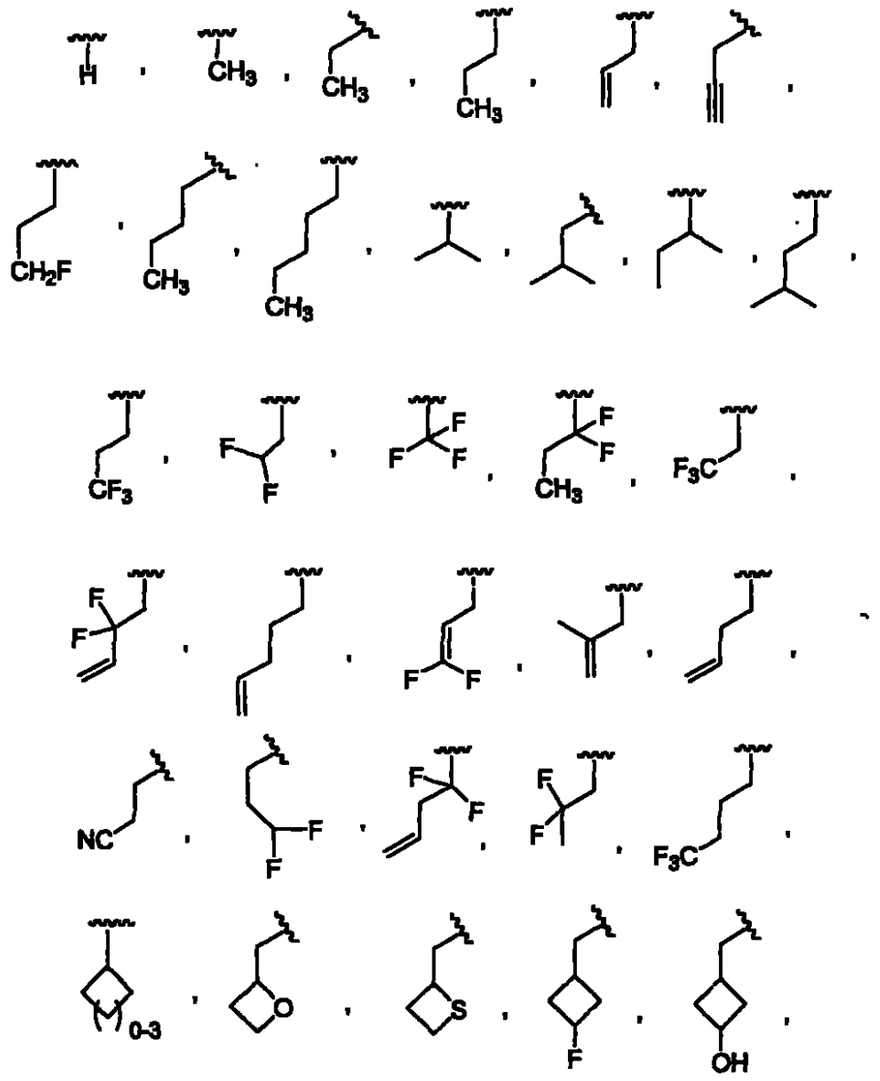
In an embodiment, the present invention discloses compounds which are represented by structural Formula 1 or a pharmaceutically acceptable salt, solvate or ester thereof, wherein the various moieties are as defined above.

In another embodiment, R^1 is NR^9R^{10}, and R^9 is H, R^{10} is H, or R^{14} wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaryl-alkyl.

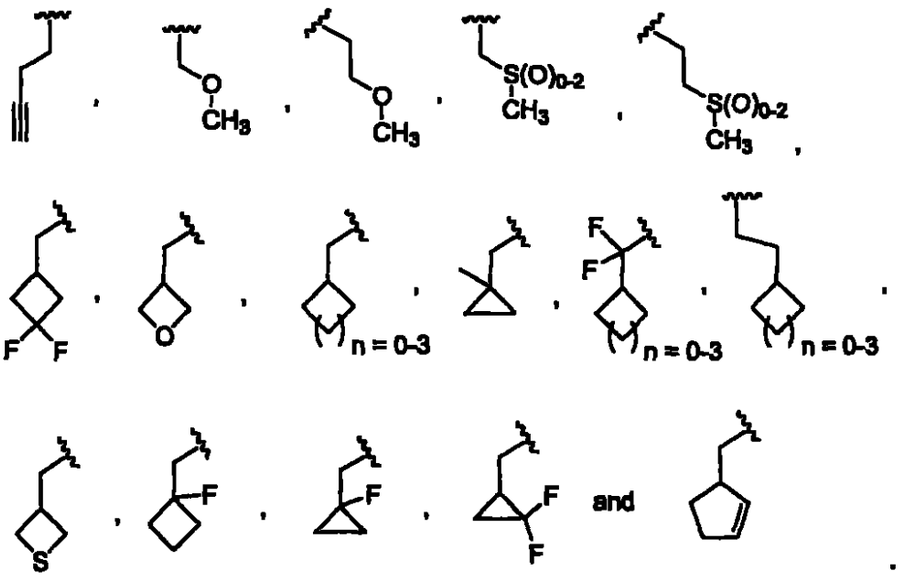
In another embodiment, R^{14} is selected from the group consisting of:



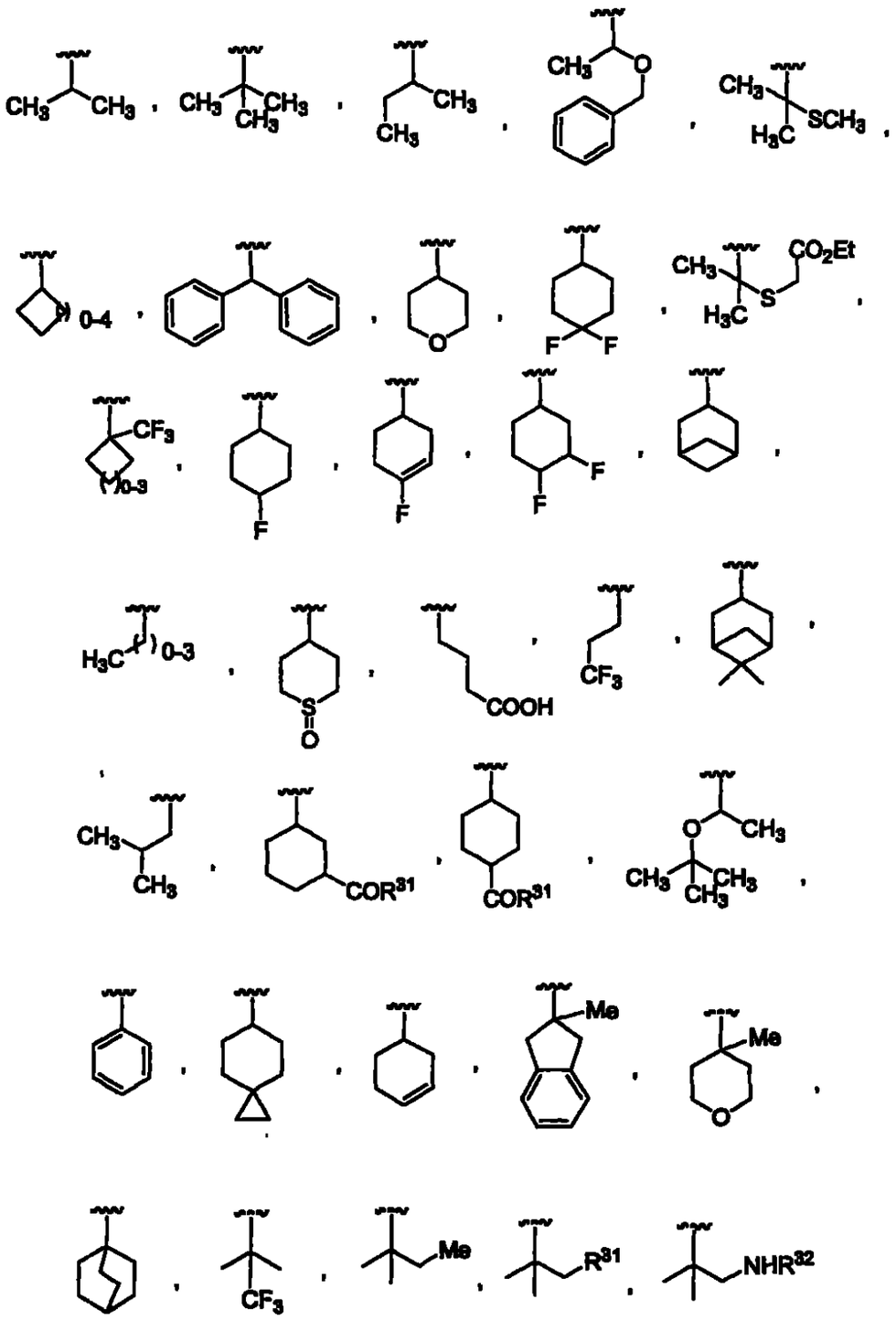
In another embodiment, R^2 is selected from the group consisting of the following moieties:

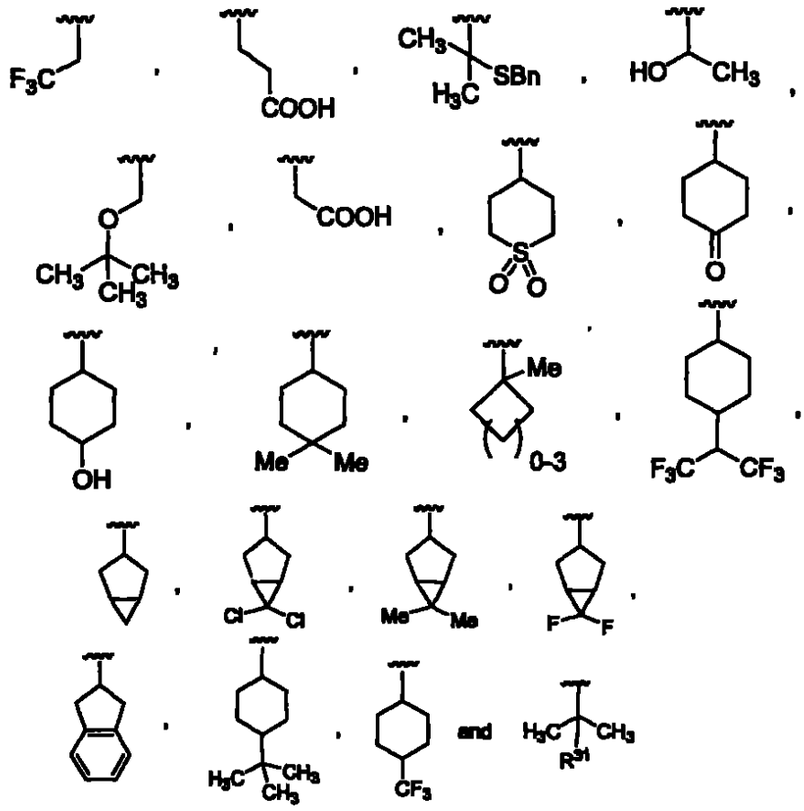

H
CH3
CH3
CH3
CH2F
CH3
CH3
CF3
F
F
F
F
F
CH3
F3C
F
F
F
F
NC
F
F
F
F
F
F3C
0-3
O
S
F
OH

5


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

In another embodiment, R^3 is selected from the group consisting of:

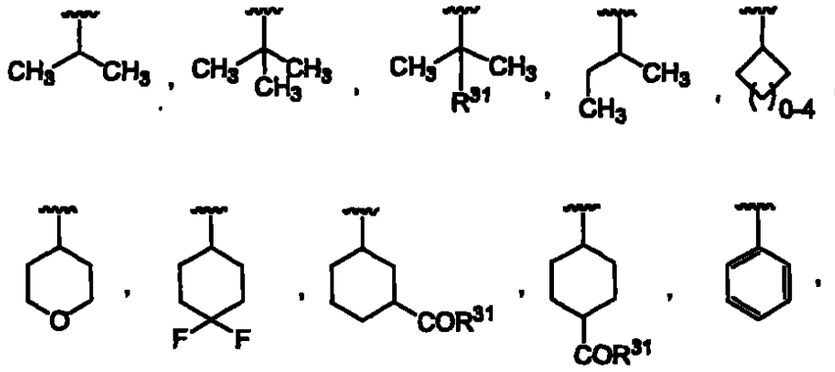


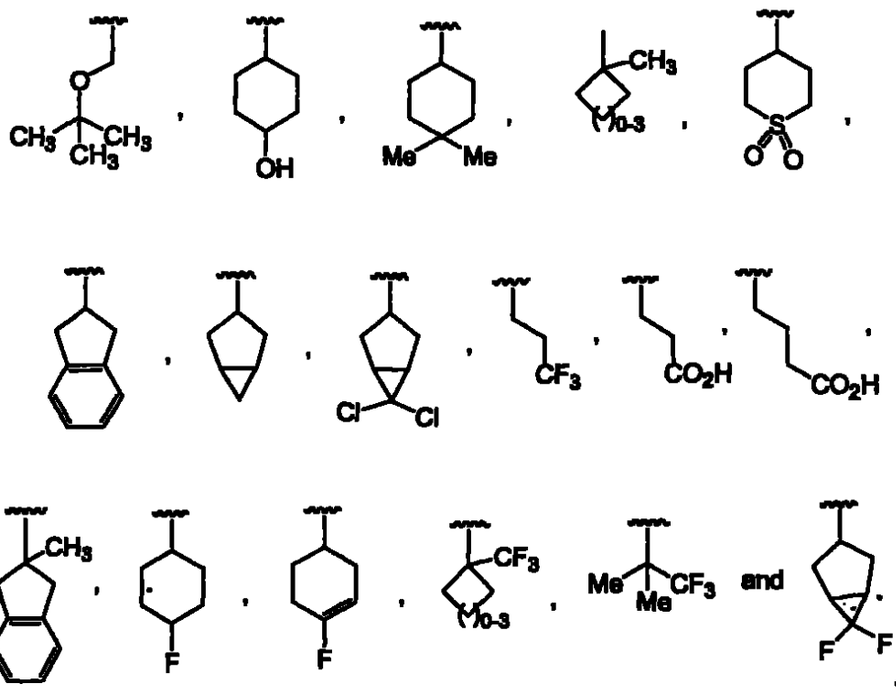


wherein R^{31} is OH or O-alkyl; and

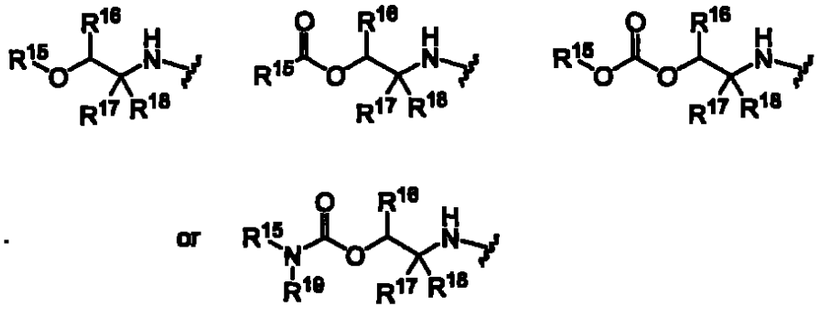
R^{32} is H, $C(O)CH_3$, C(O)OtBu or C(O)N(H)tBu.

In an additional embodiment, R^3 is selected from the group consisting of the following moieties:





In another embodiment, Y is selected from the following moieties:

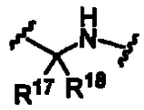


wherein R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or alternately, (i) either R^{15} and R^{16} are connected to form a four to eight-membered cyclic structure, or R^{15} and R^{19} are connected to form a four to eight-membered cyclic structure, and (ii) likewise, independently, R^{17} and R^{18} are connected to form a three to eight-membered cycloalkyl or heterocyclyl;

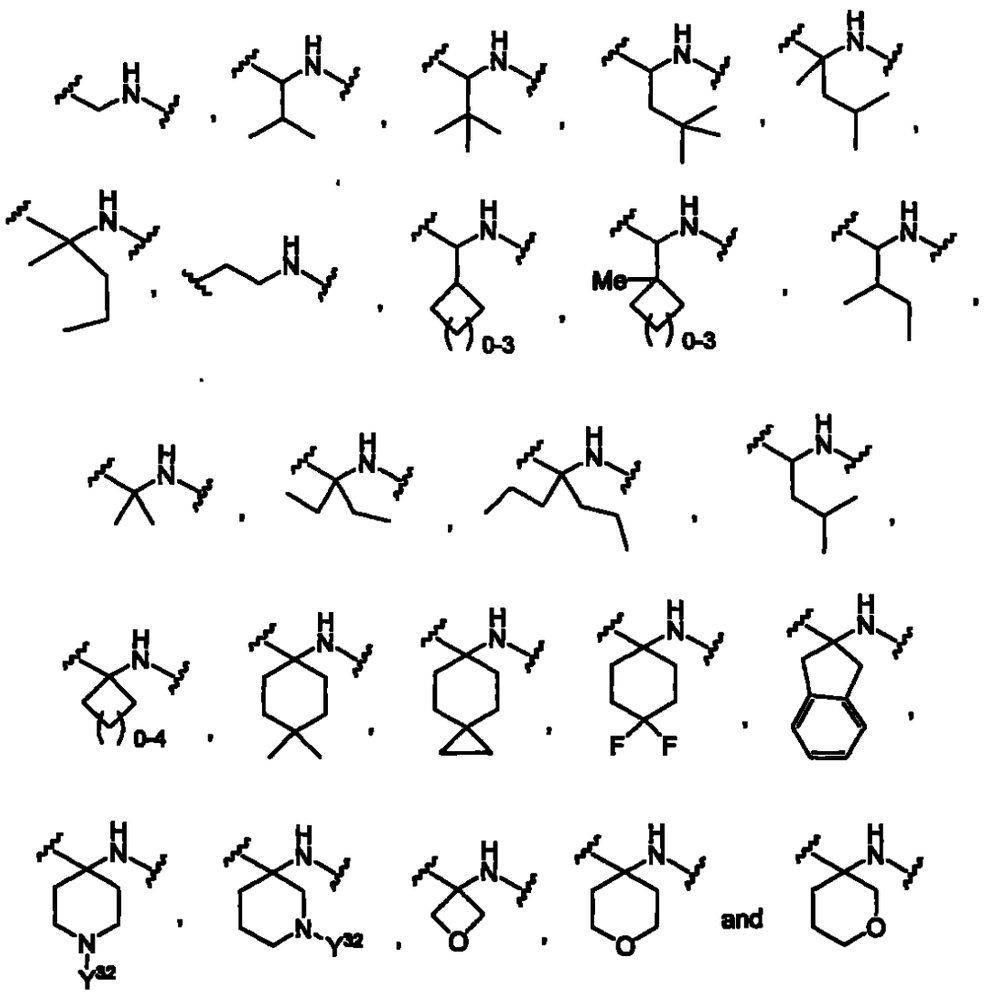
wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, sulfonamido, alkylsulfonamido, arylsulfonamido, keto, carboxy,

carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

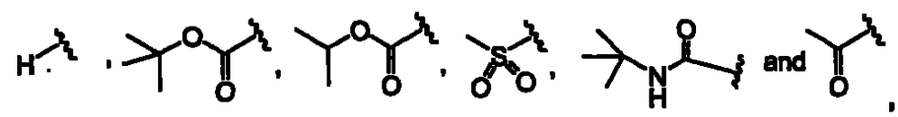
In an additional embodiment, the moiety:



is selected from the group consisting of:

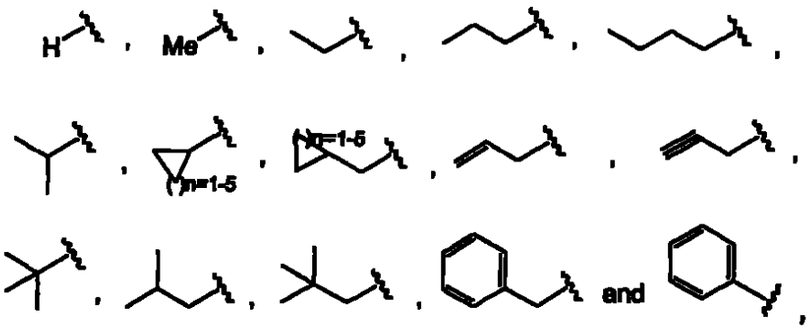


wherein Y^{32} is selected from the group consisting of:

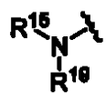


R^{16} is selected from H, methyl, phenyl, benzyl; and

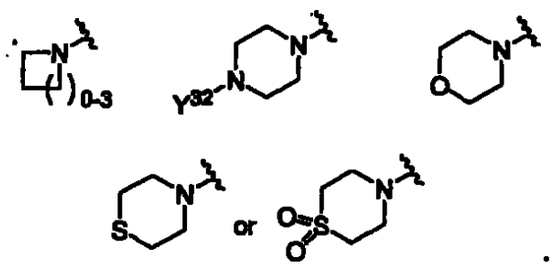
R^{15} and R^{19} maybe the same or different, each being independently selected from the following:



or alternately, the moiety:

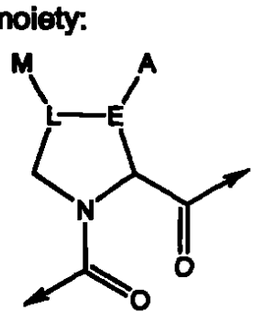


is selected from the following moieties:

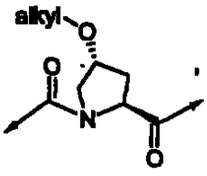


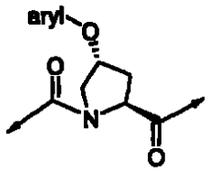
In an additional embodiment, R^{16} is H.

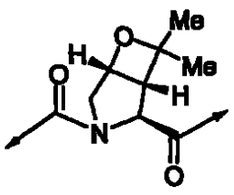
In another embodiment, the moiety:

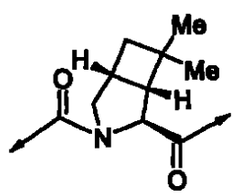


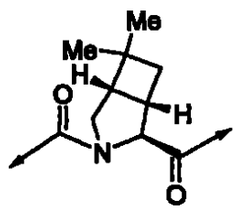
is selected from the following structures:

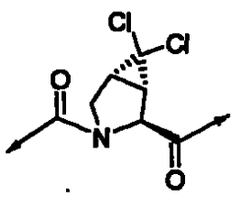

alkyl
O
O
N
O

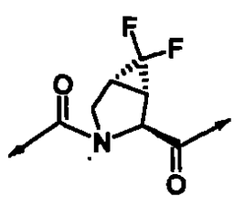

aryl
O
O
N
O

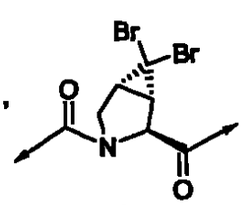

Me
O
H
Me
H
O
N
O

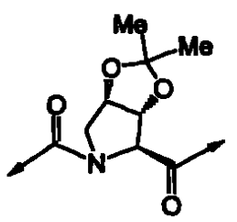

Me
H
Me
H
O
N
O

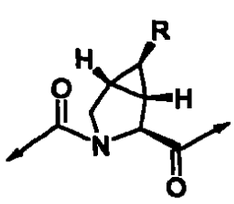

Me
Me
H
H
O
N
O

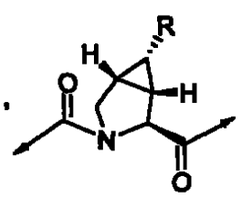

Cl
Cl
O
N
O

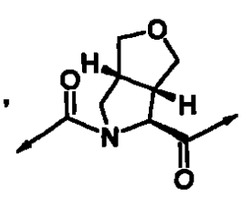

F
F
O
N
O

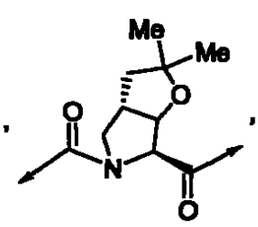

Br
Br
O
N
O

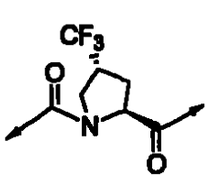

Me
Me
O
O
O
N
O

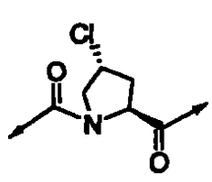

R
H
H
O
N
O

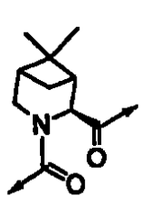

R
H
H
O
N
O

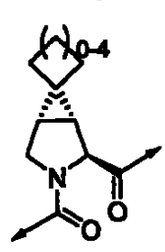

O
H
H
O
N
O

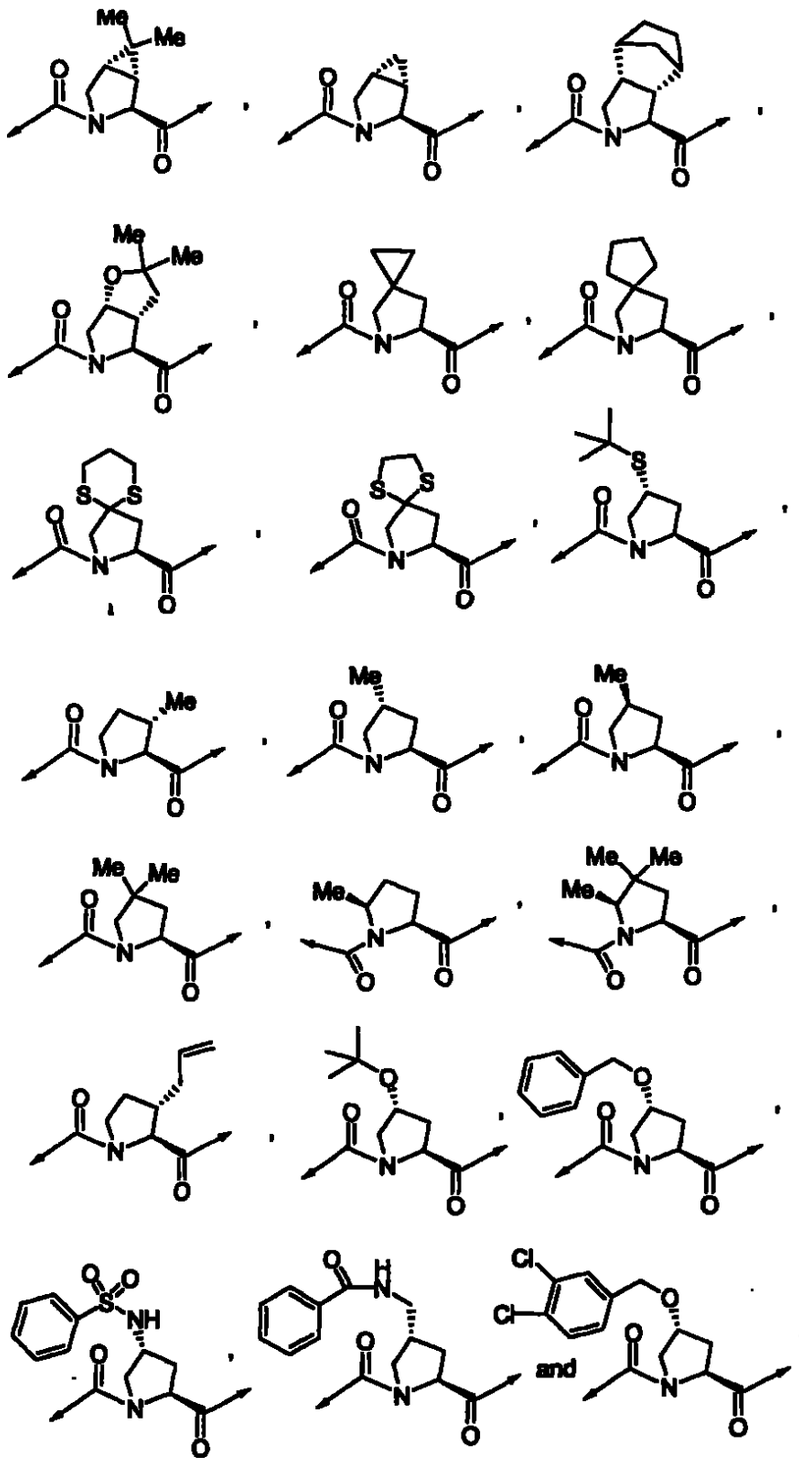

Me
Me
O
O
N
O


CF3
O
O
N
O

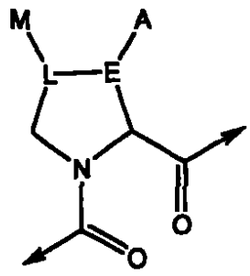

Cl
O
O
N
O


N
O
O

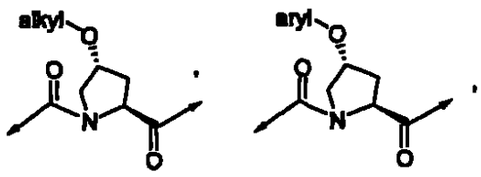

0-4
N
O
O

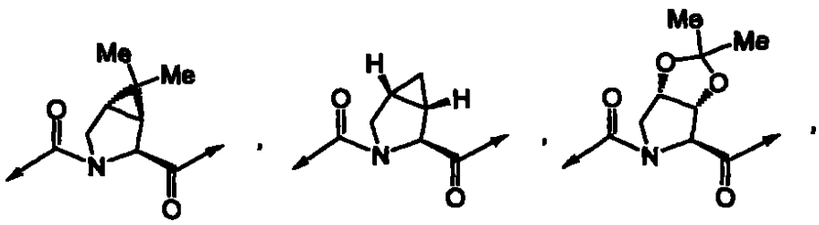


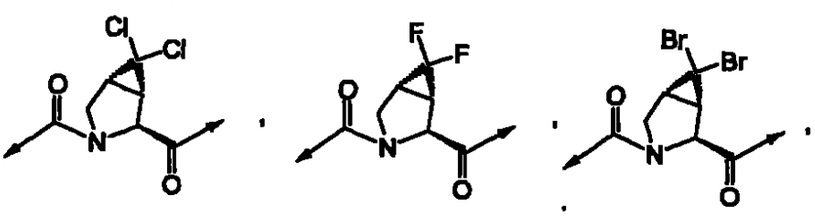
In an additional embodiment, the moiety:

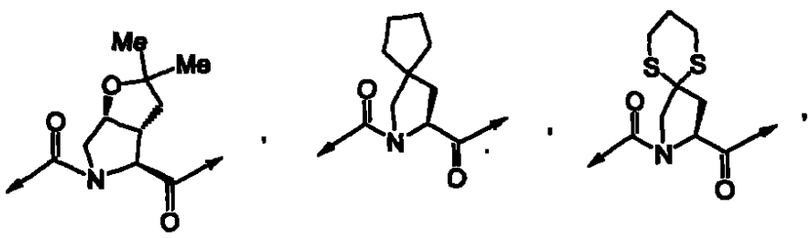


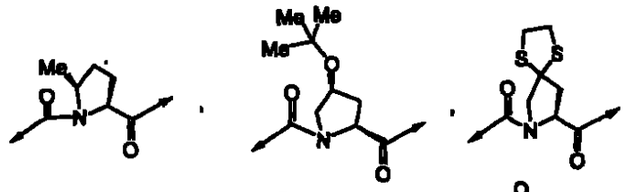
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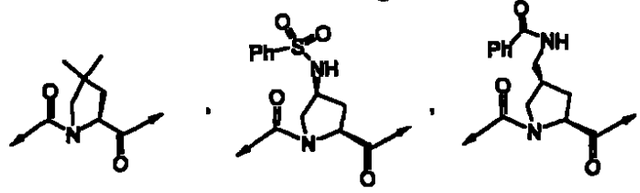




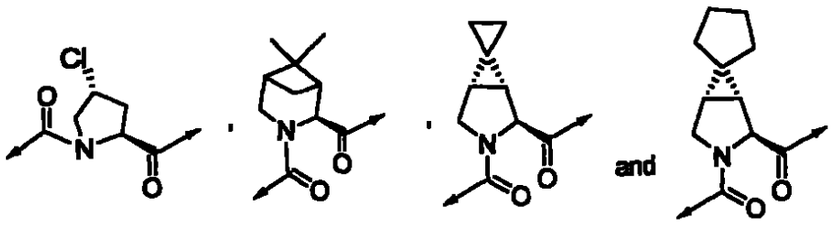




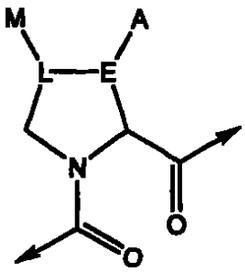




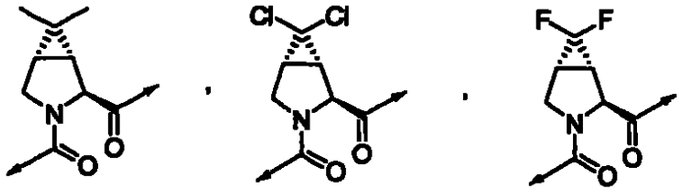
5

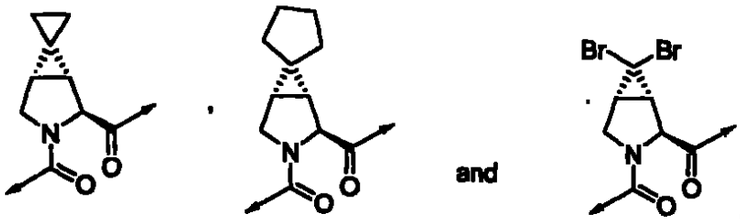


In a still additional embodiment, the moiety:

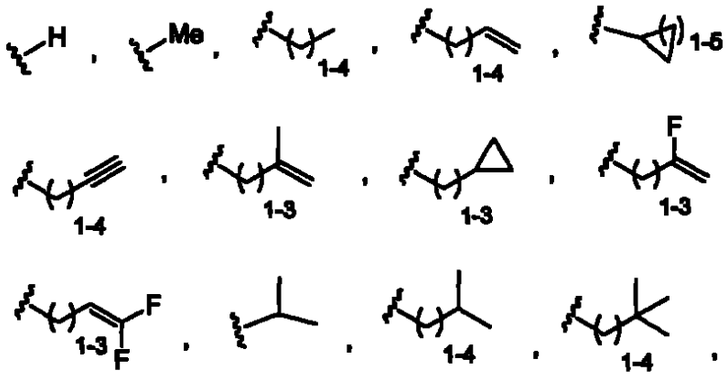


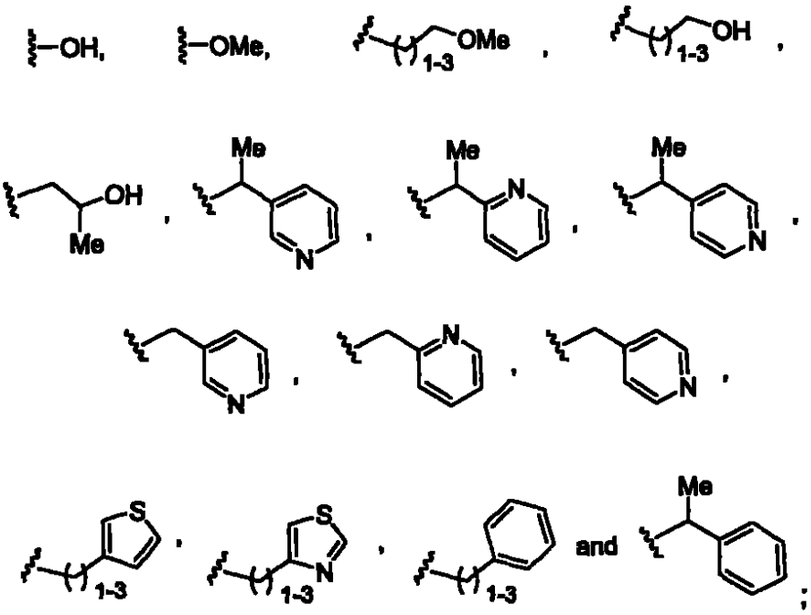
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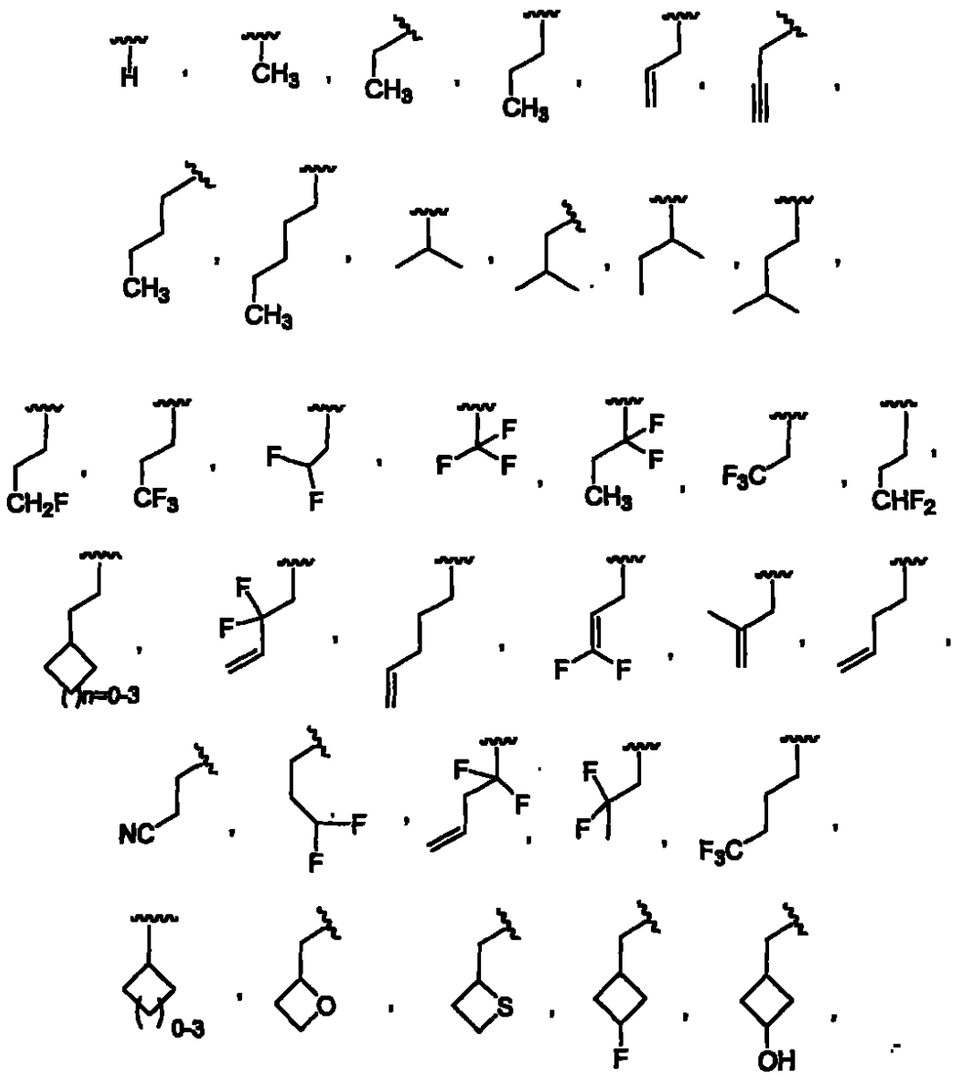


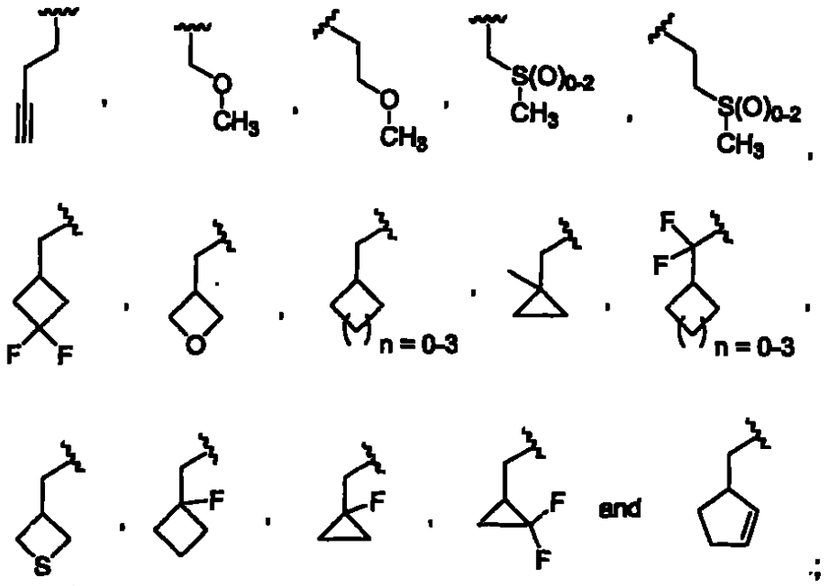
In a further additional embodiment, R^1 is NHR^{14}, where R^{14} is selected from the group consisting of:





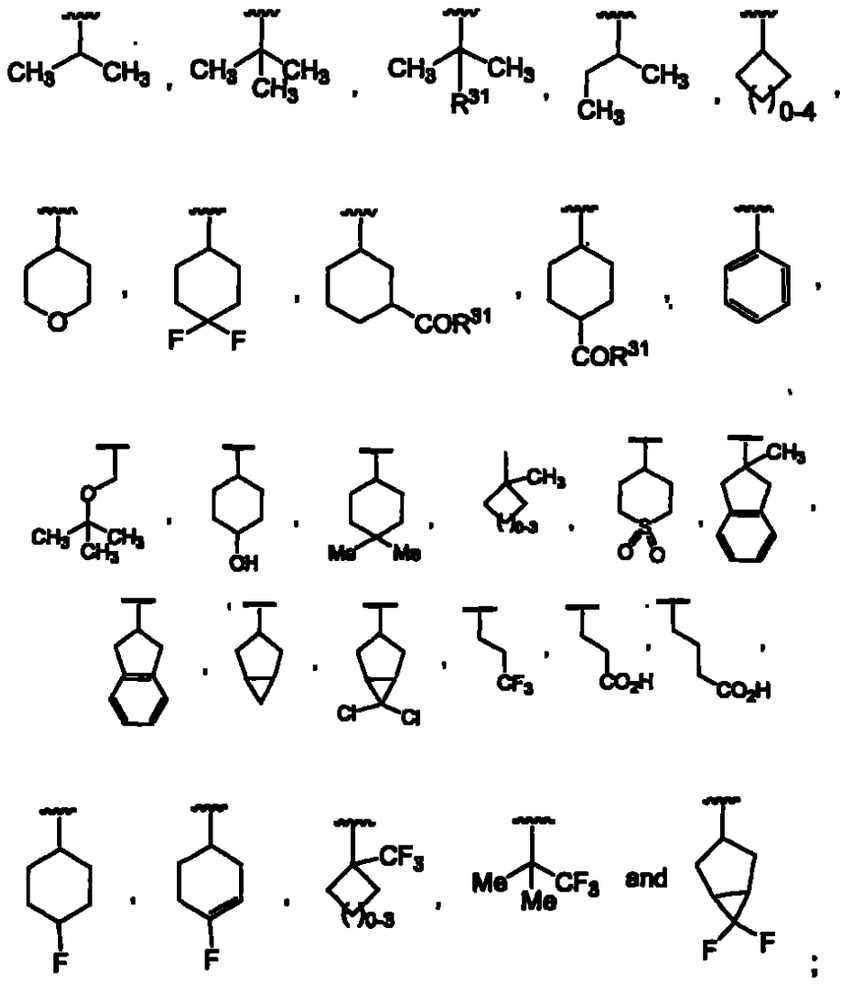
R^2 is selected from the group consisting of the following moieties:





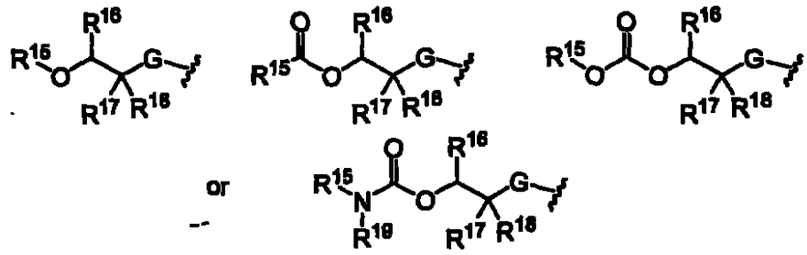
;

R^3 is selected from the group consisting of the following moieties:

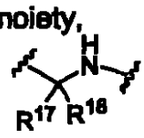


;

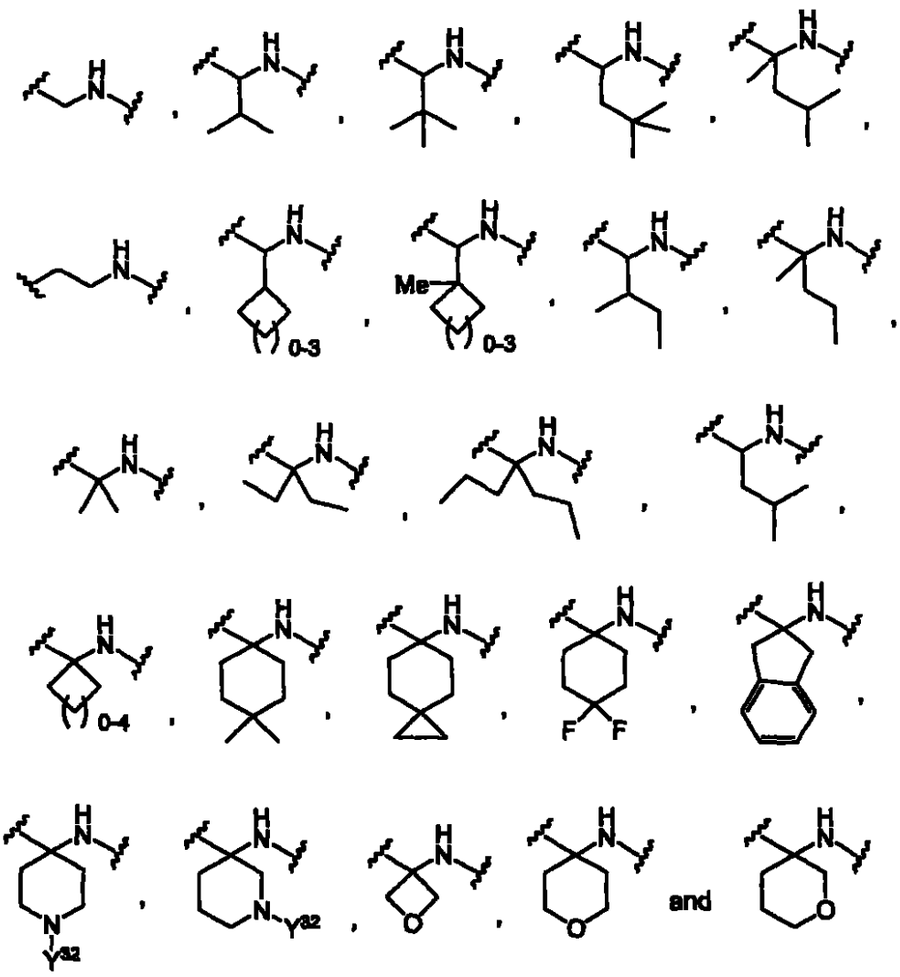
Y is selected from the group consisting of:



wherein G = NH, and the moiety,

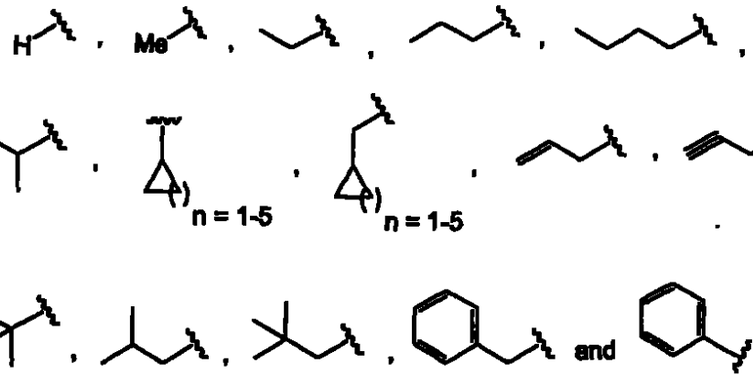


is selected from the group consisting of:

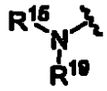


R^{16} = H, and

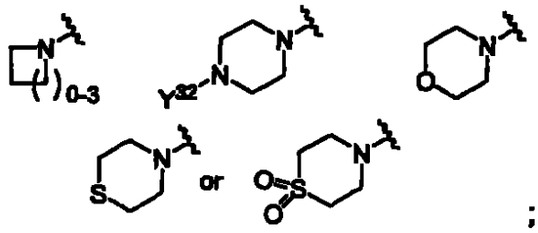
R^{15} and R^{19} can be the same or different, each being independently selected from the following:



or alternately, the moiety:

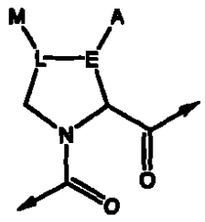


is represented by one of the following moieties,

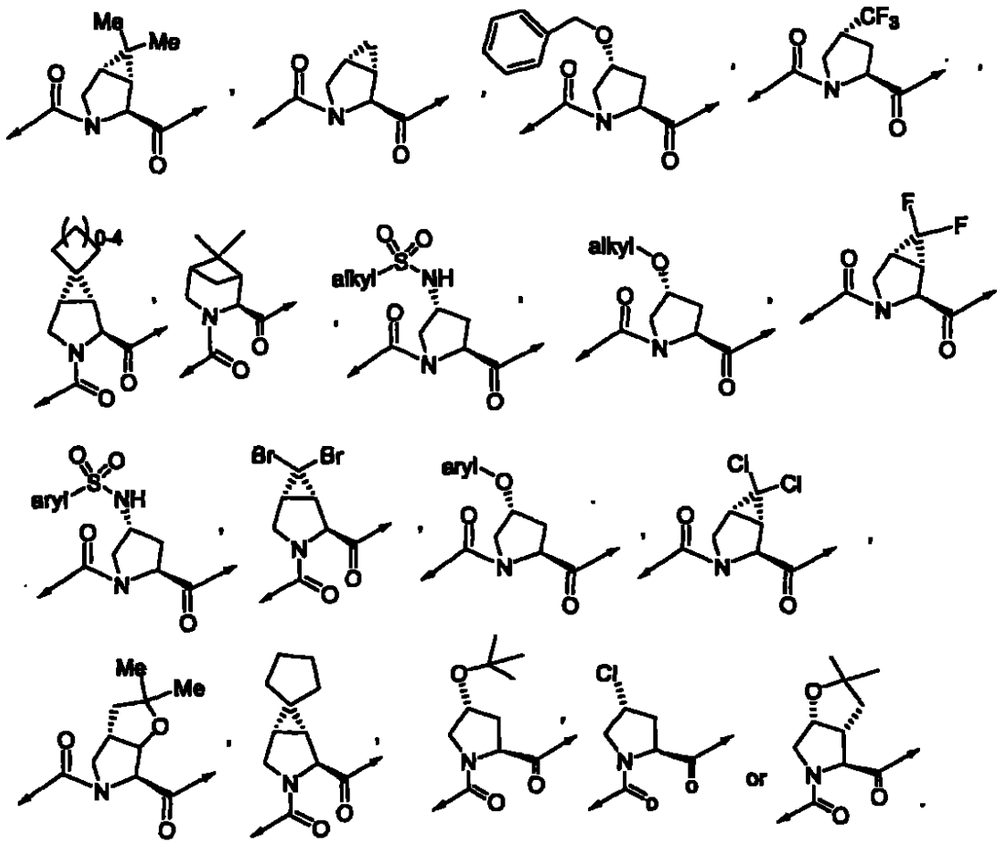


;

and the moiety:



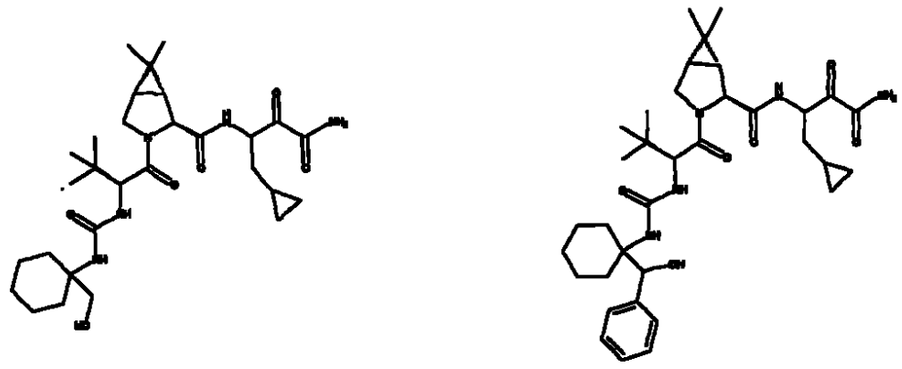
is:

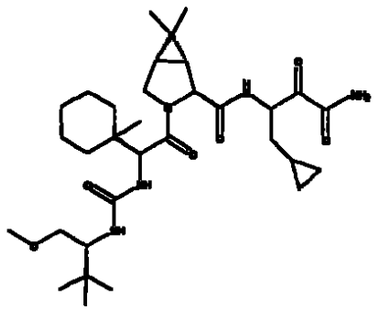


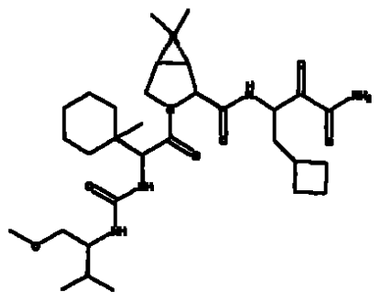
Yet another embodiment of the invention discloses compounds shown in **Table 1, Table 1A, Table 2** and **Table 3** later in this Description. Also shown in the **Tables** are the biological activities of several inventive compounds (as Ki* values).

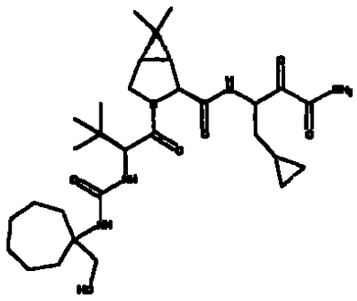
In an additional embodiment, this invention discloses the following compounds in **Table 4**:

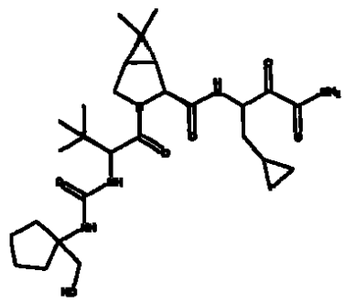
Table 4

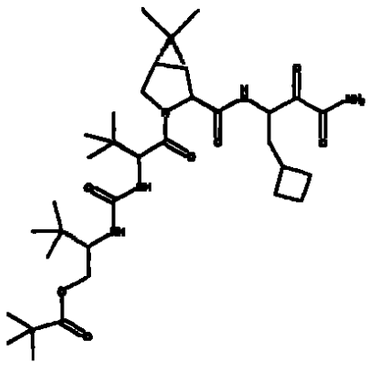


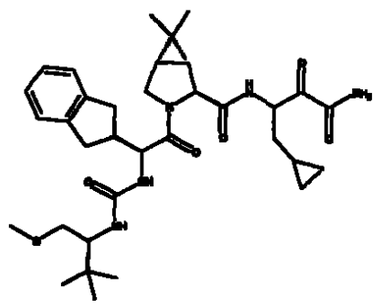


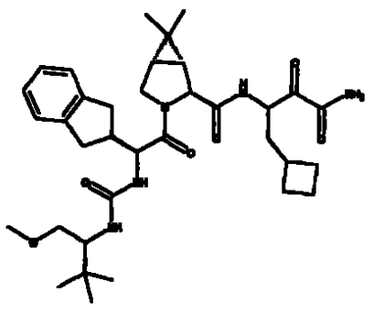


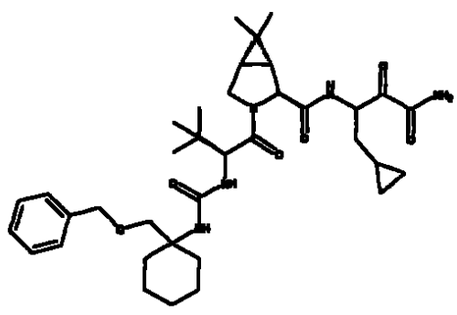


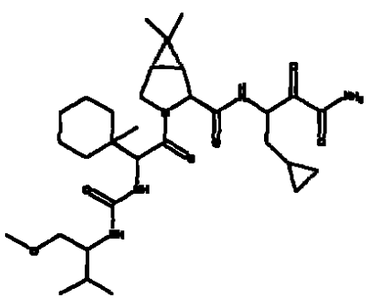


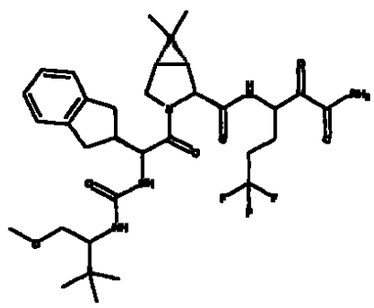


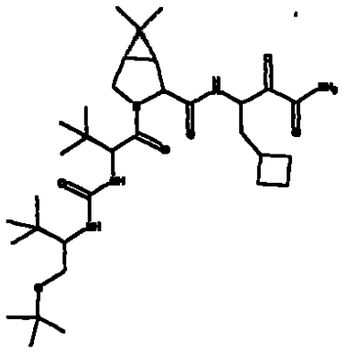


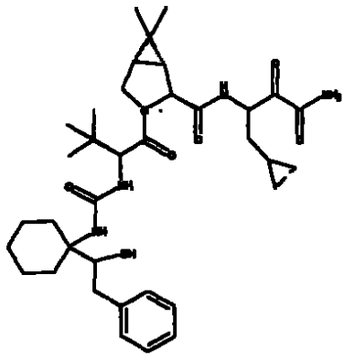


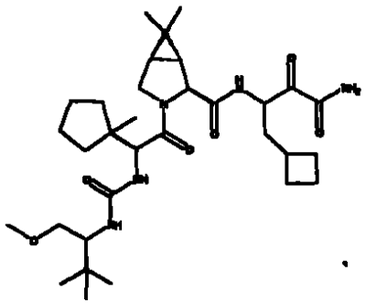


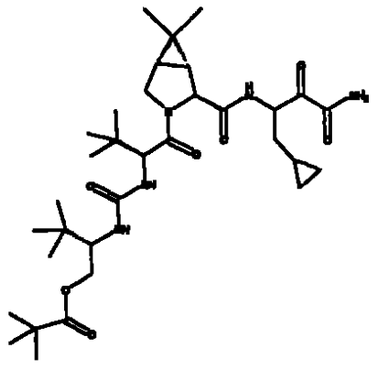


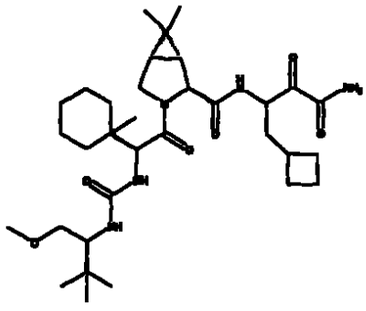


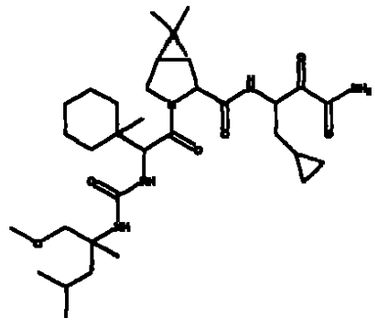


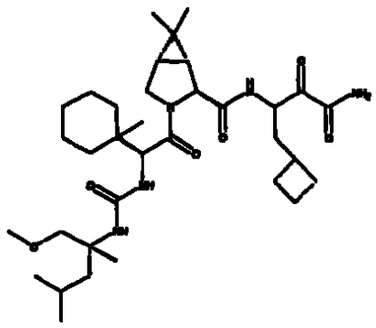


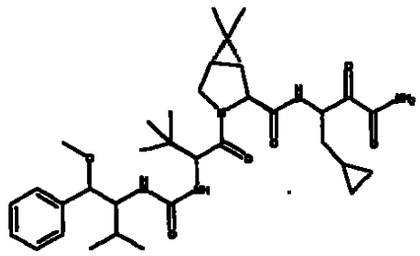


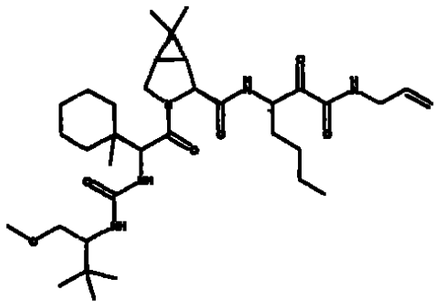


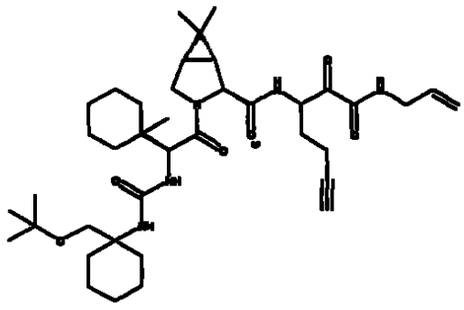


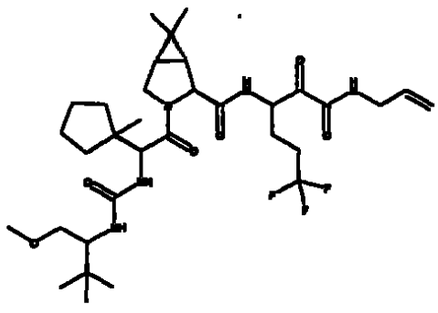


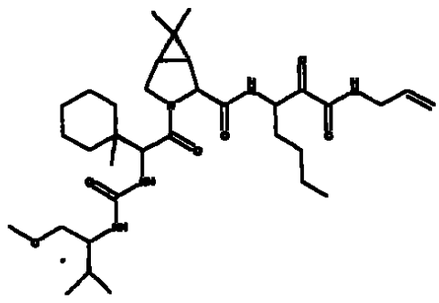


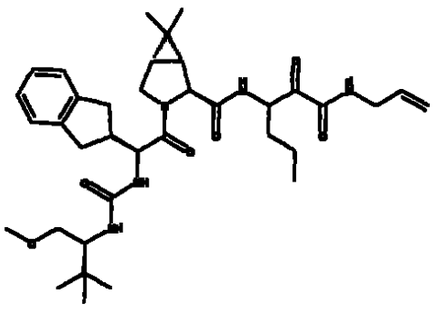


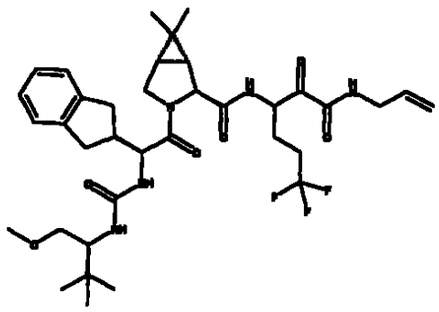


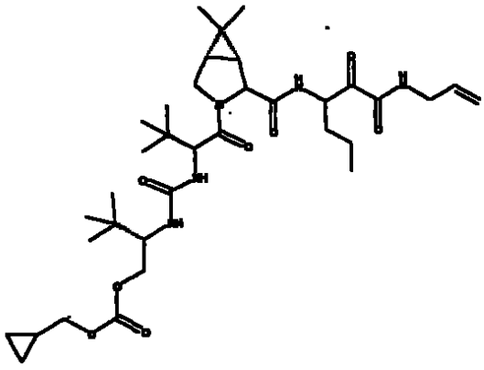


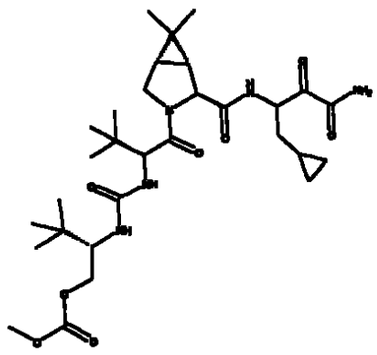


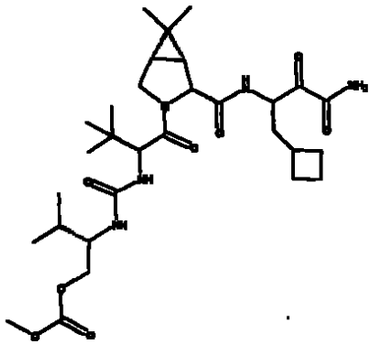


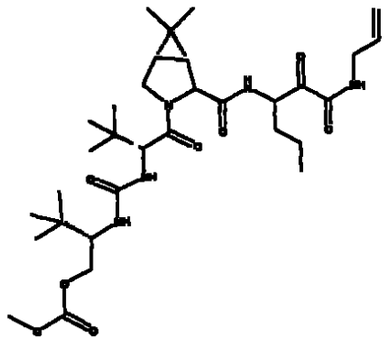


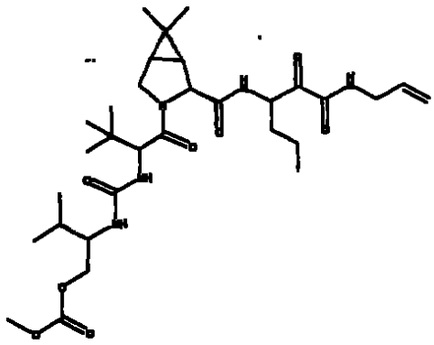


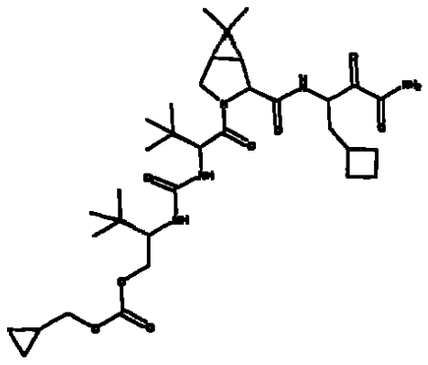


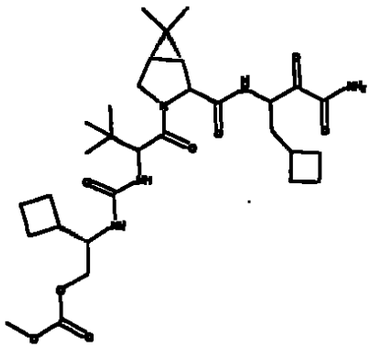


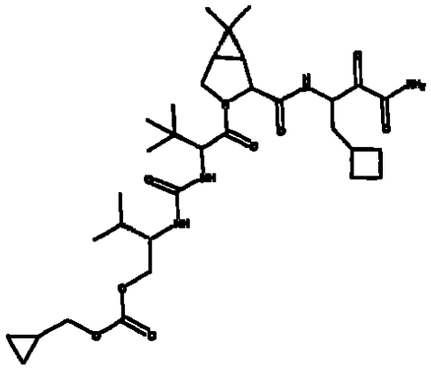


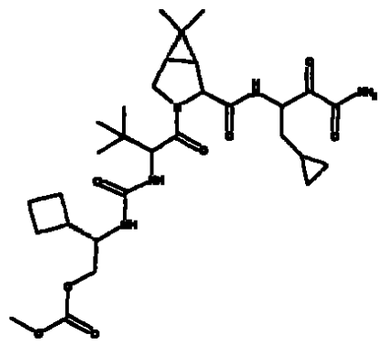


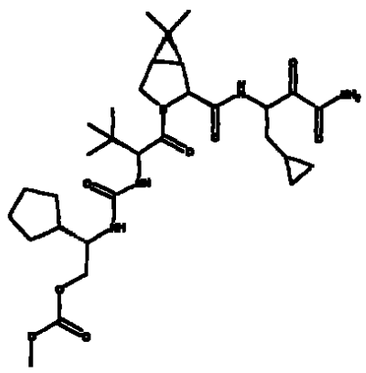


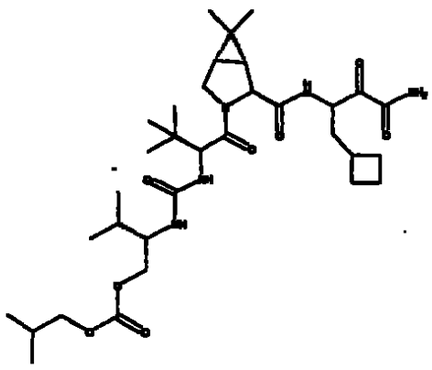


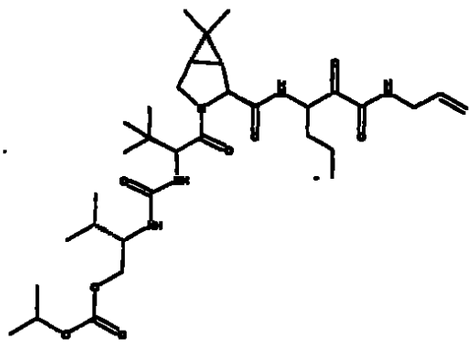


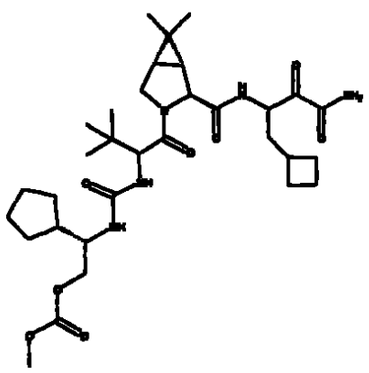


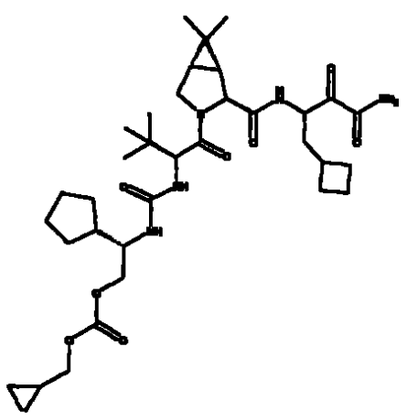


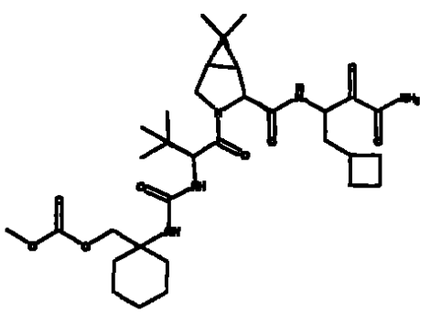


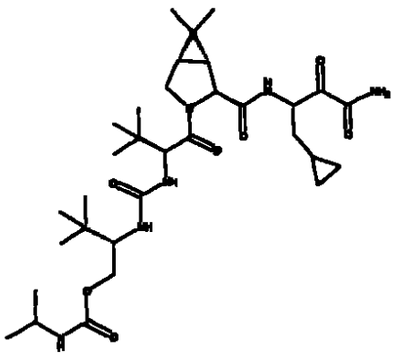


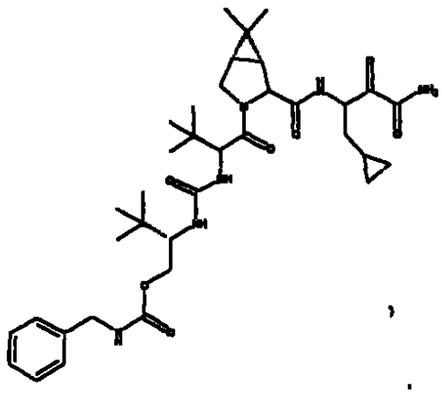


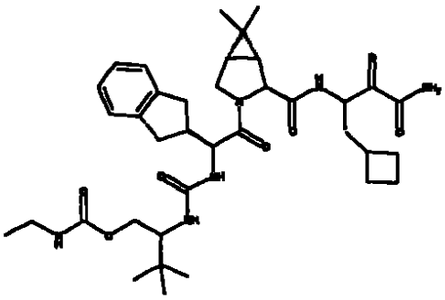


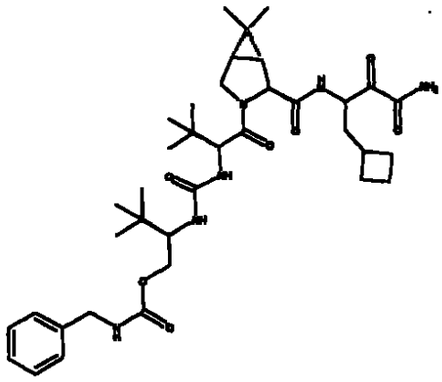


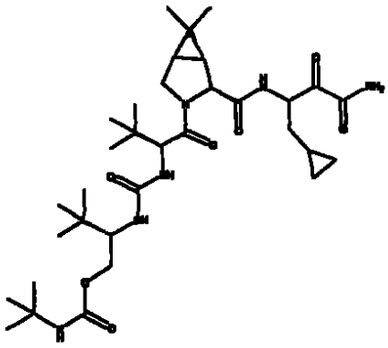


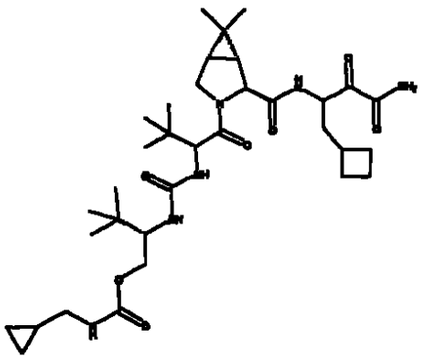


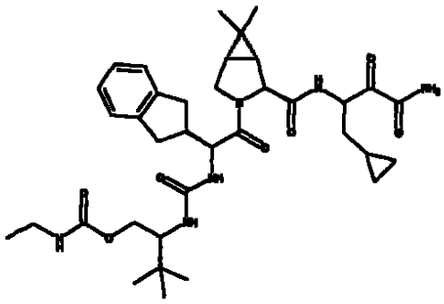


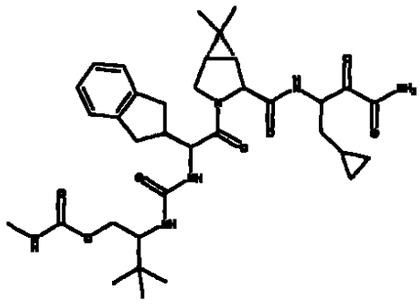


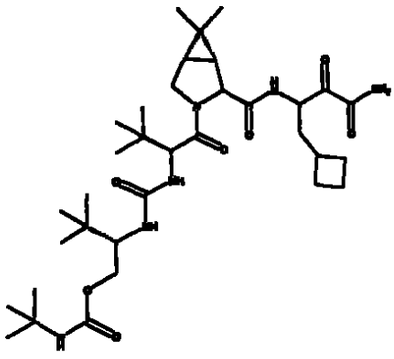


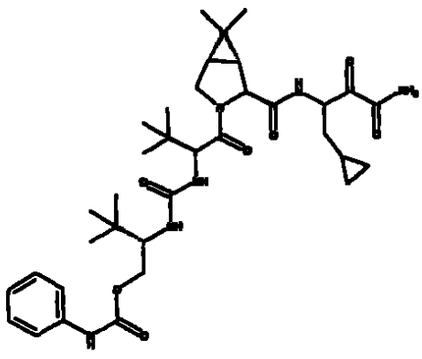


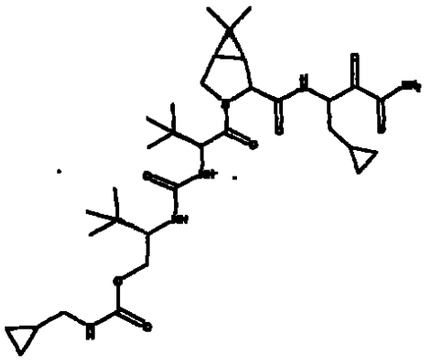


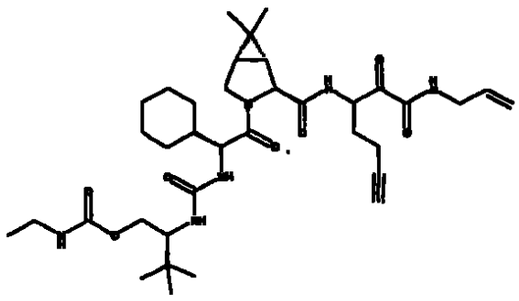


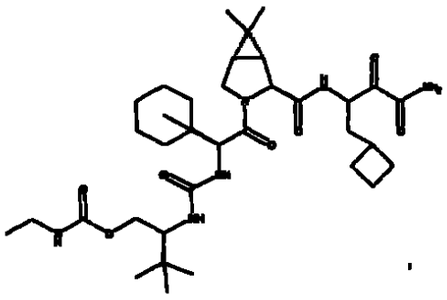


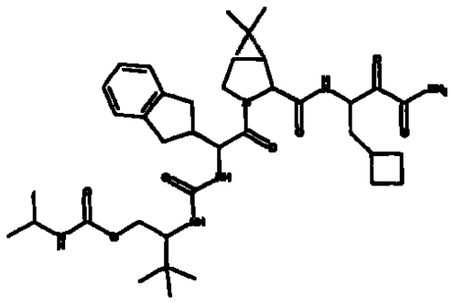


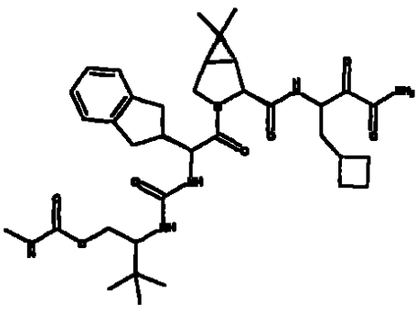


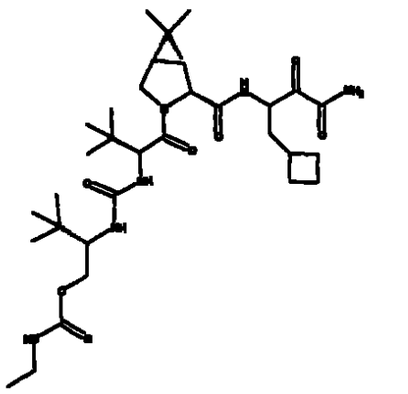


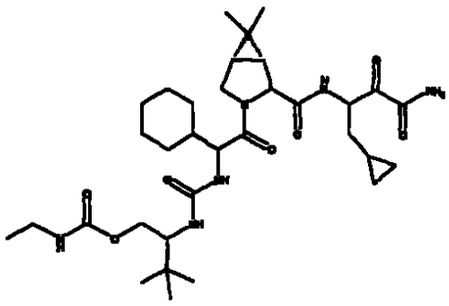


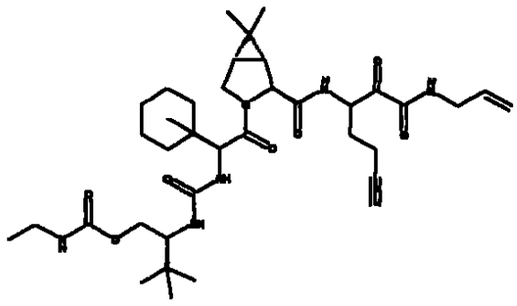


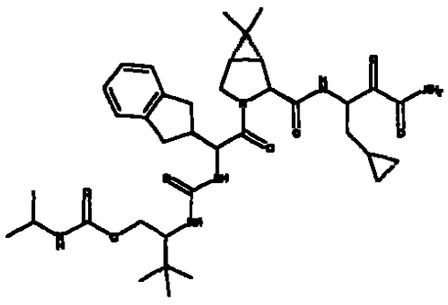


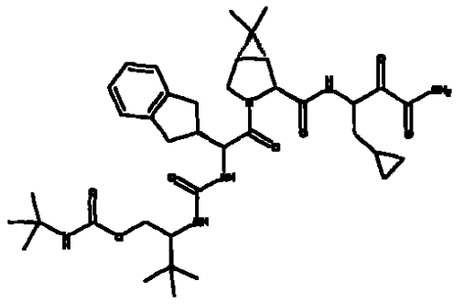


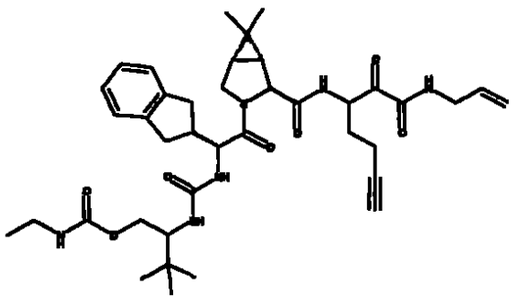


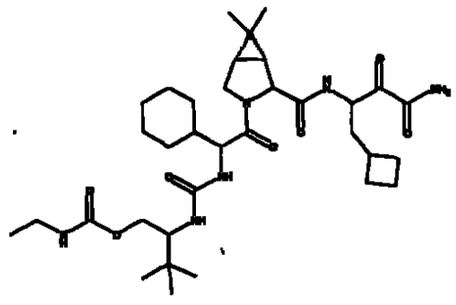


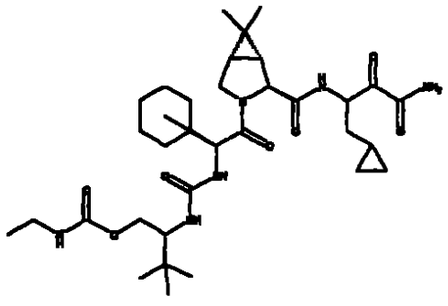


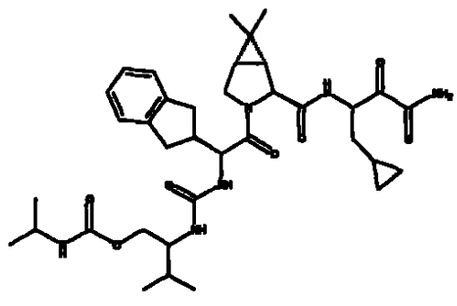


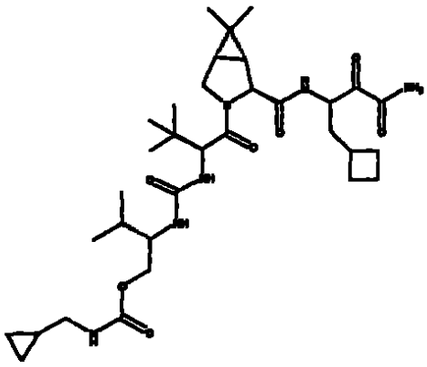


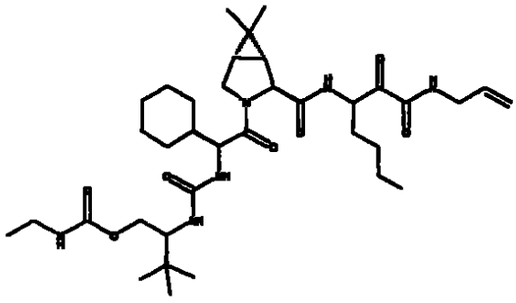


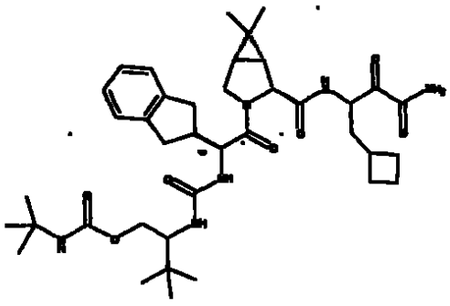


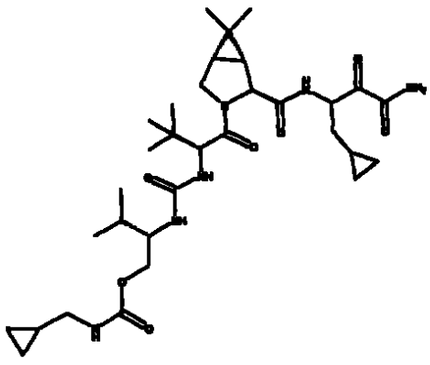


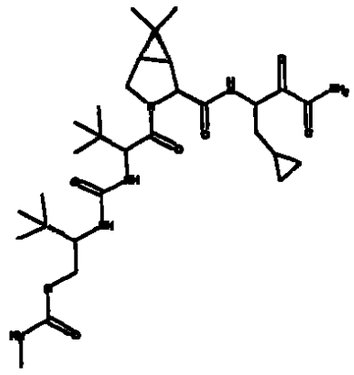


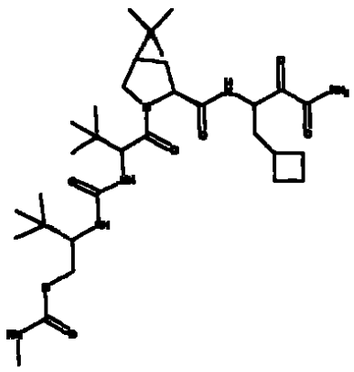


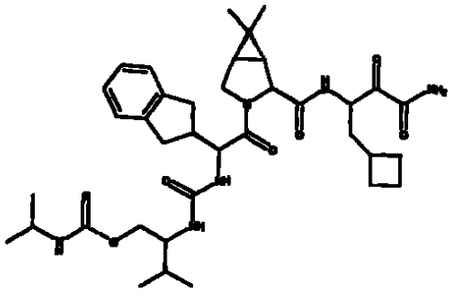


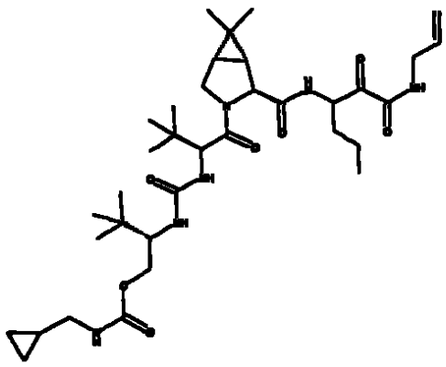


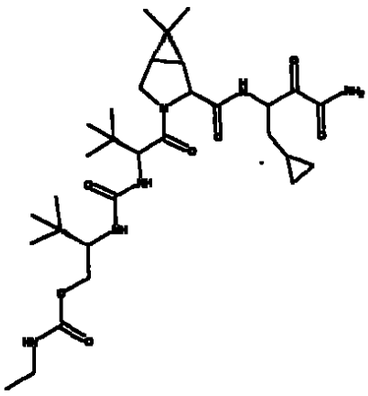


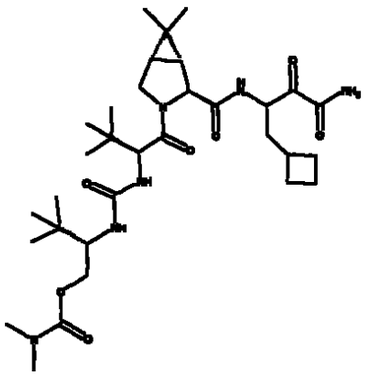


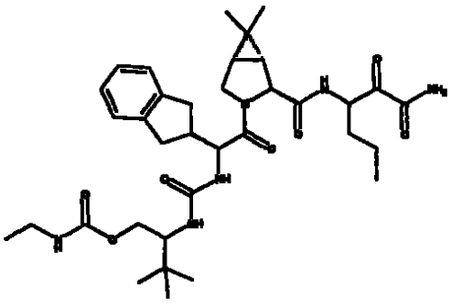


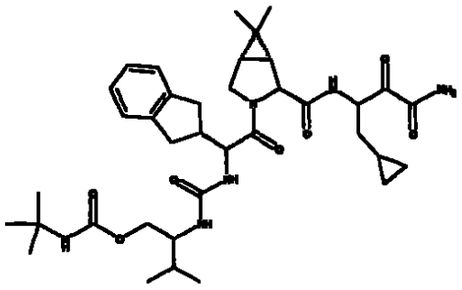


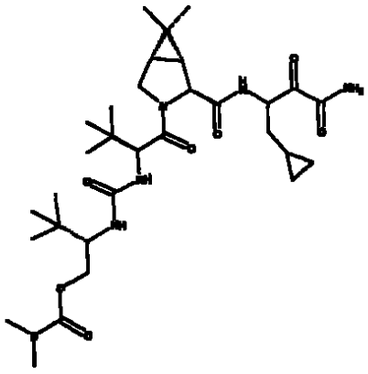


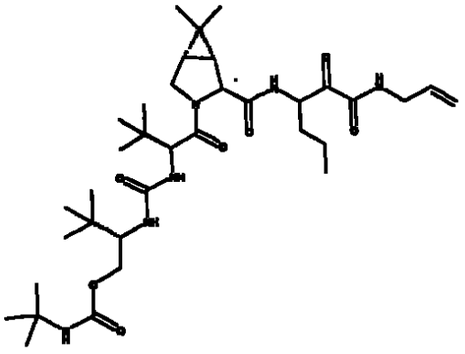


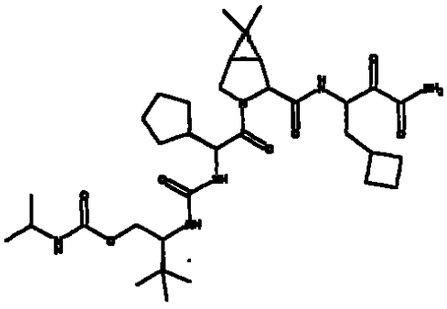


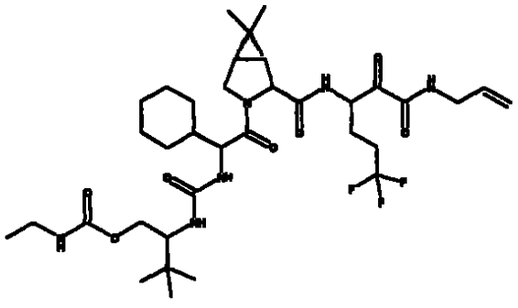


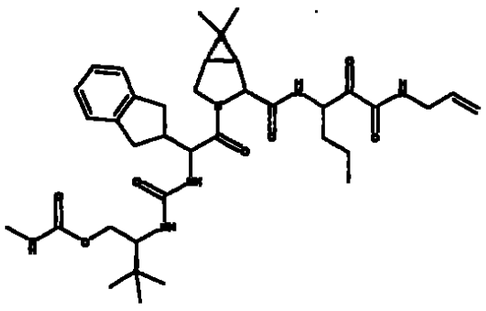


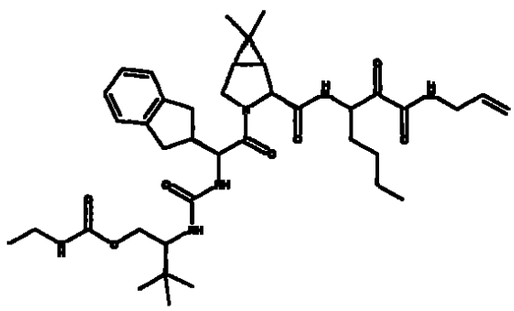


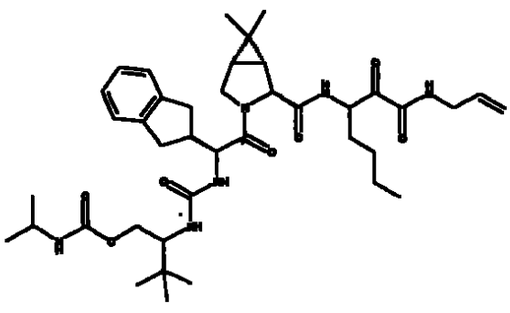


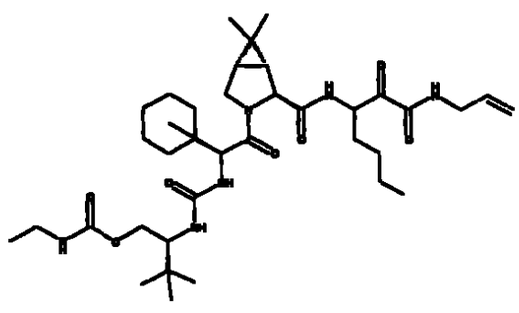


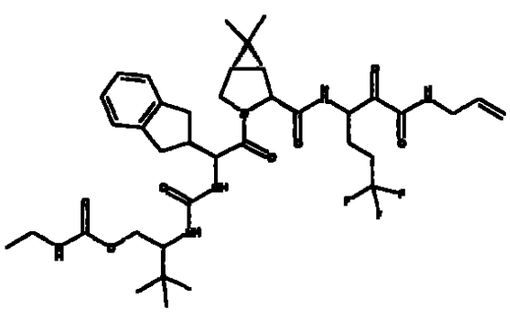


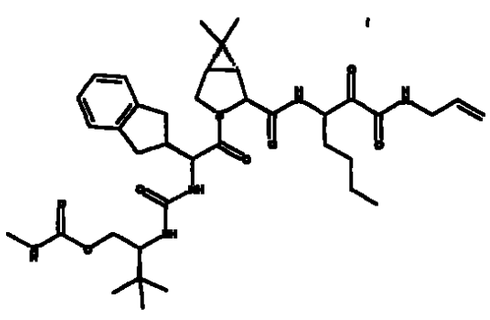


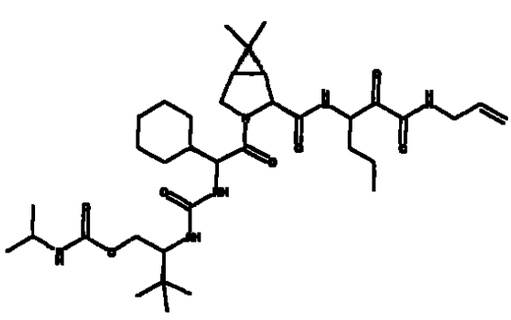


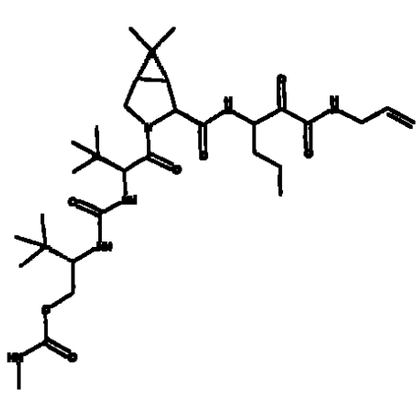


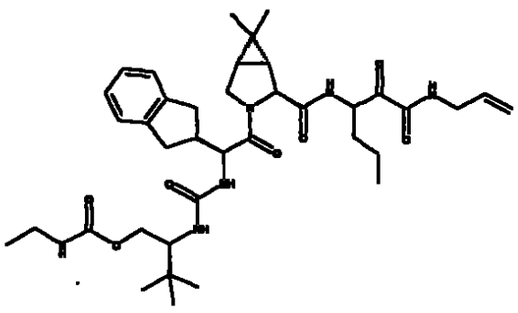


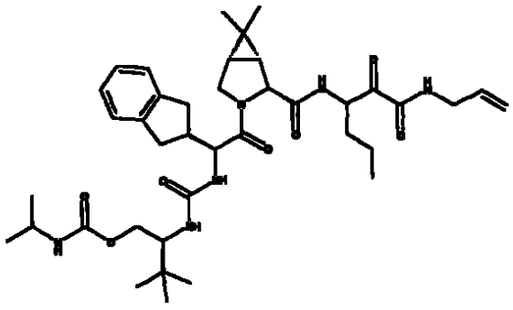


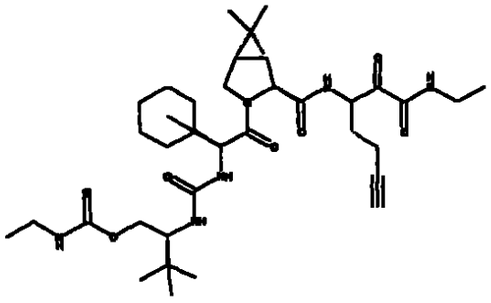


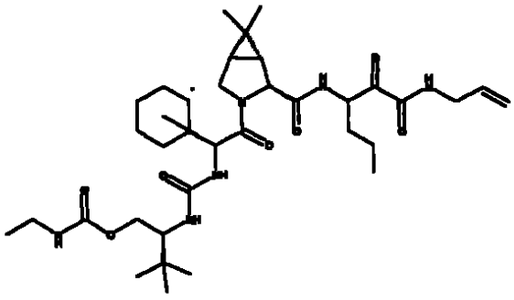


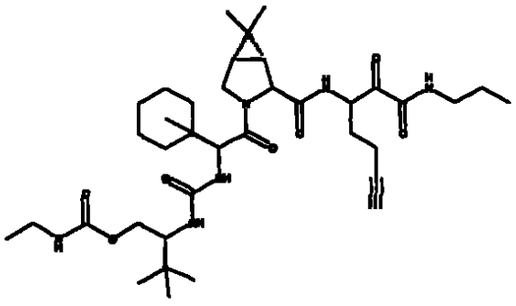


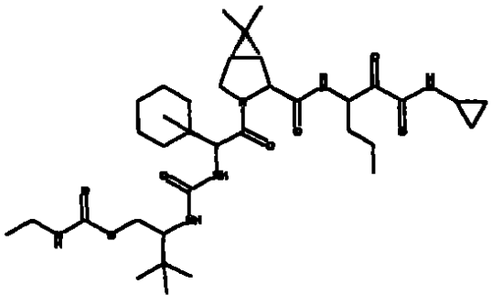


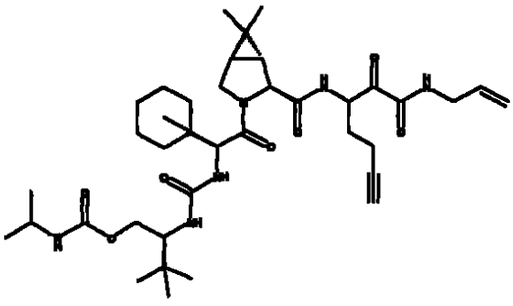


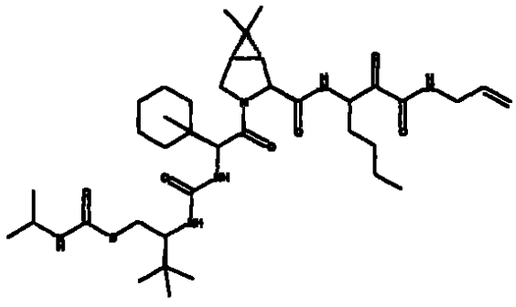


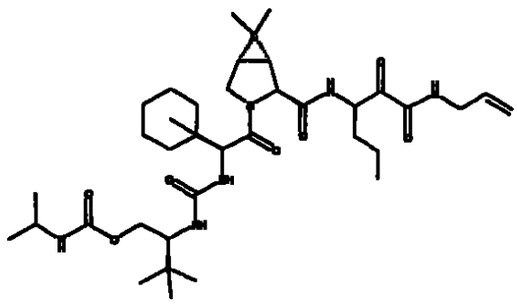


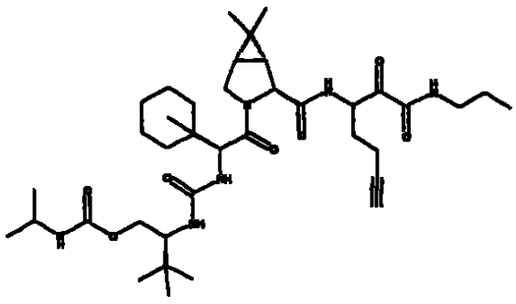


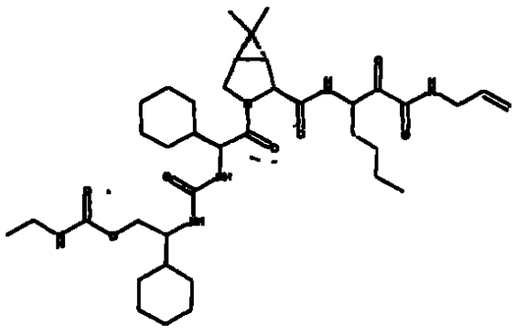


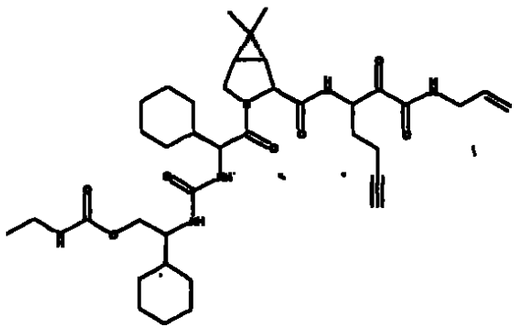


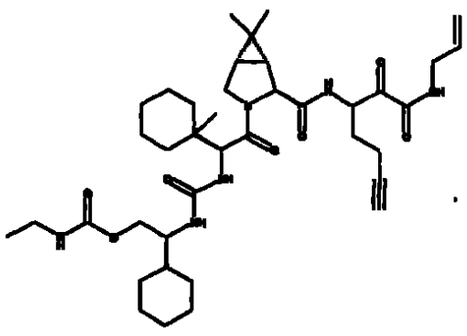


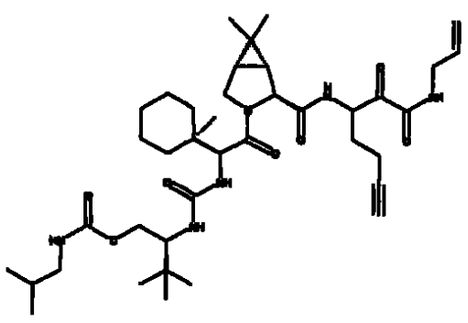


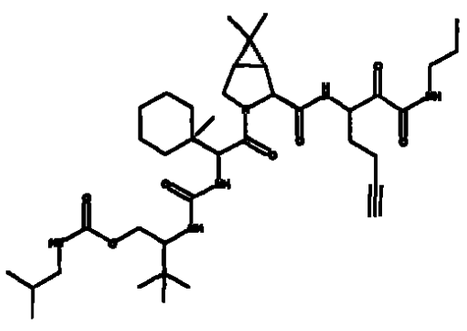


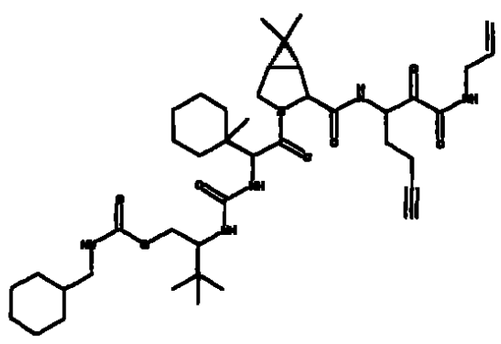


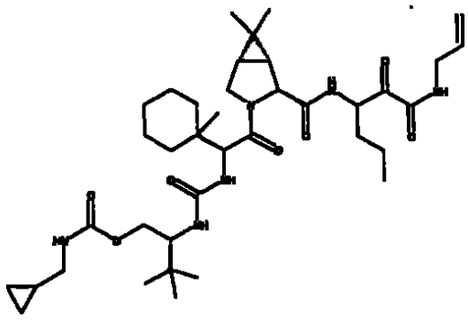
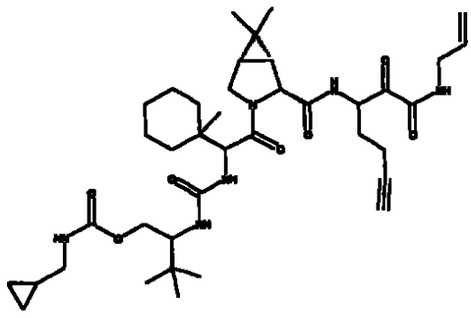
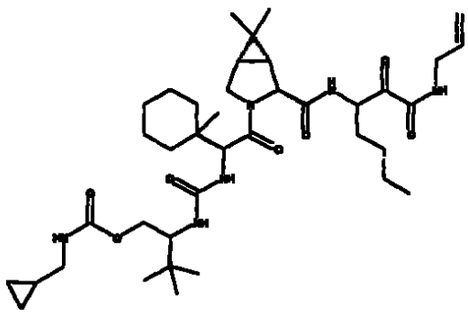
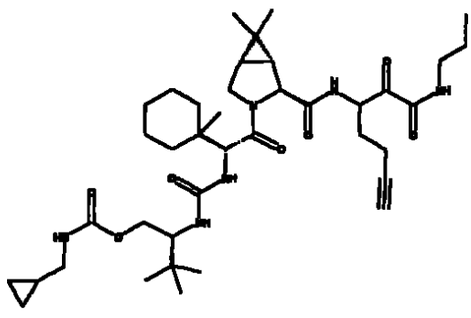
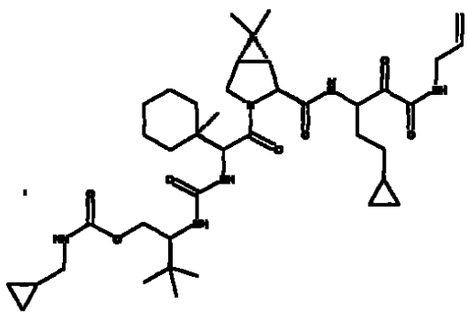
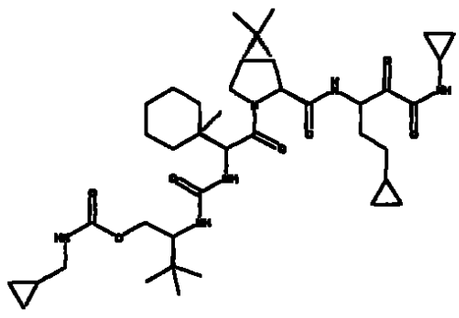






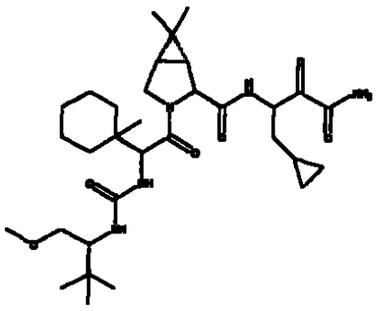


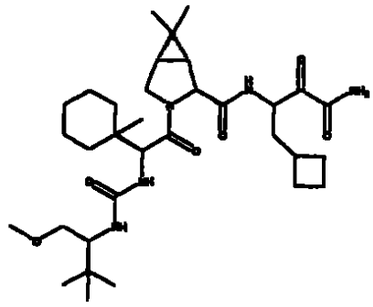


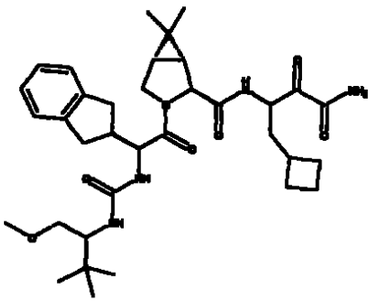







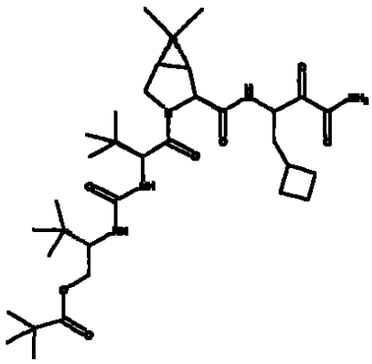
In an additional embodiment, the present invention discloses the following compounds in **Table 5**:

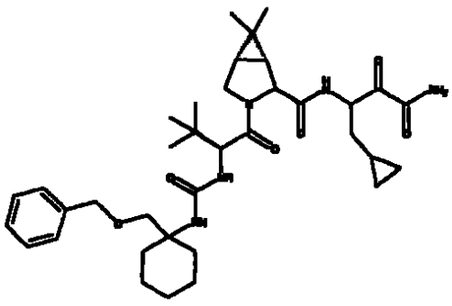
Table 5

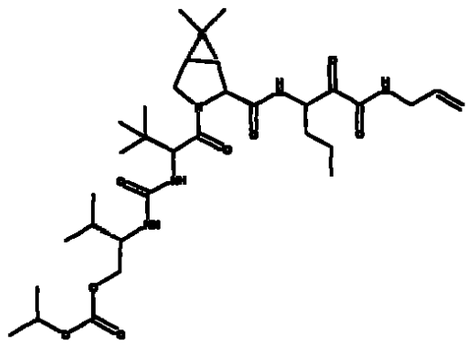


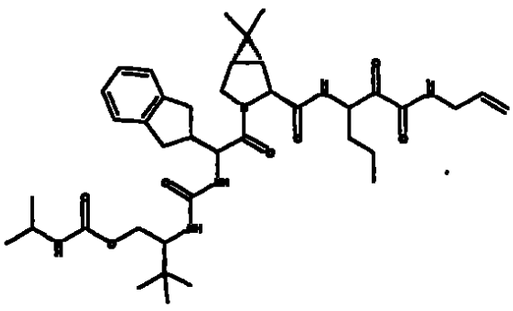


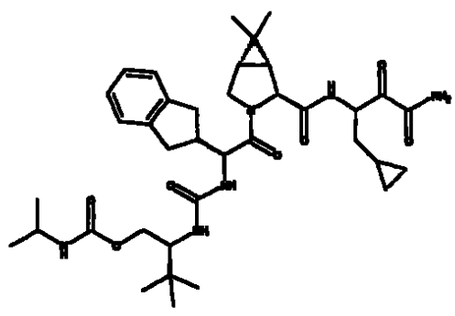


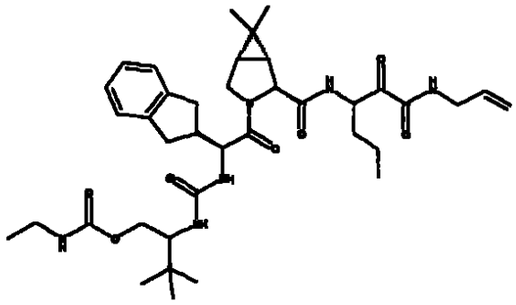


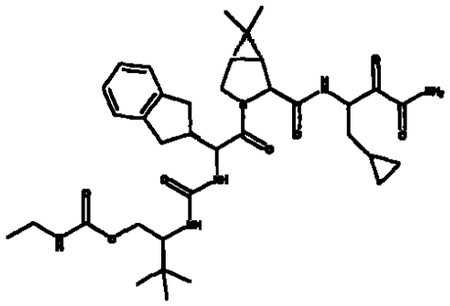


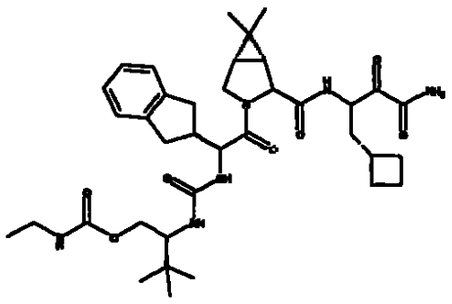


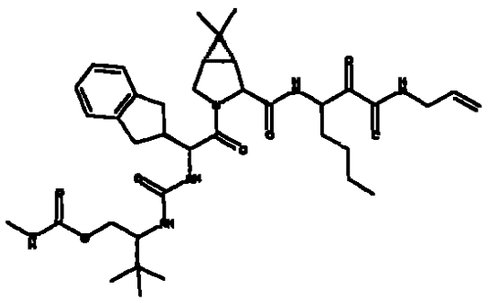


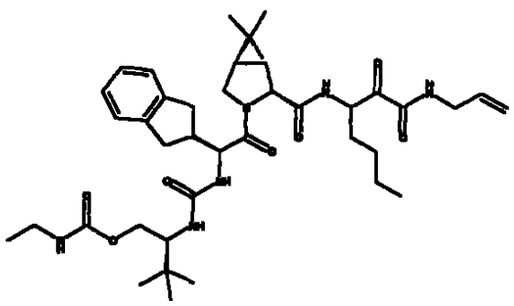


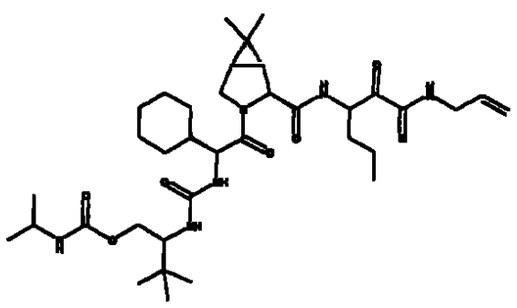


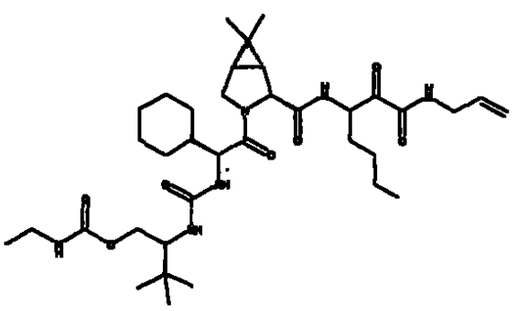


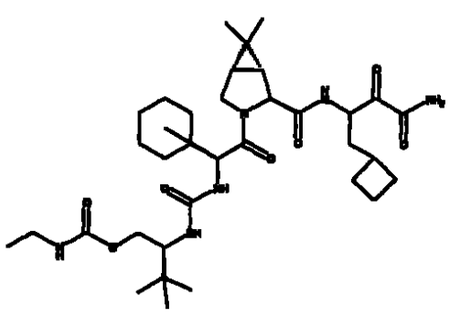


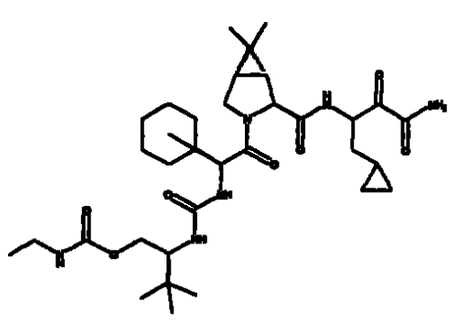


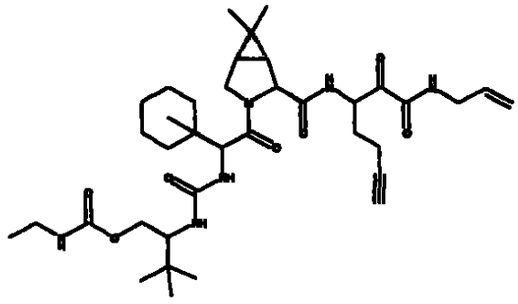




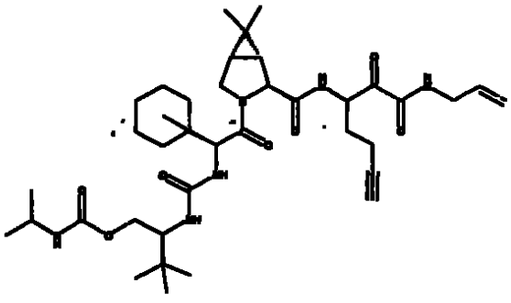


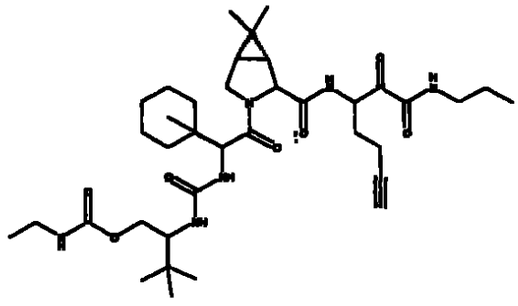


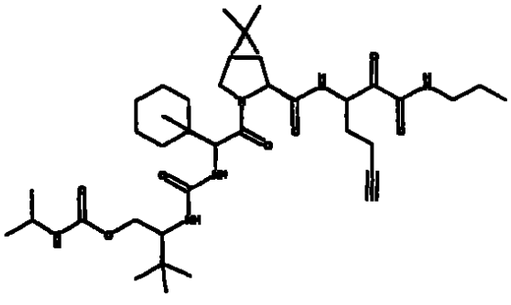


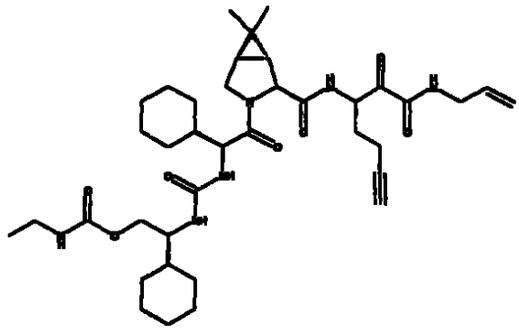


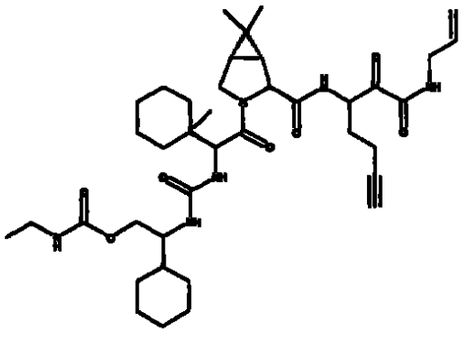
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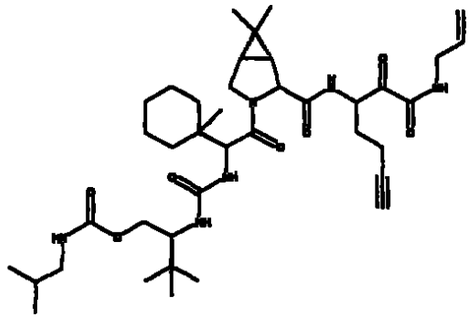


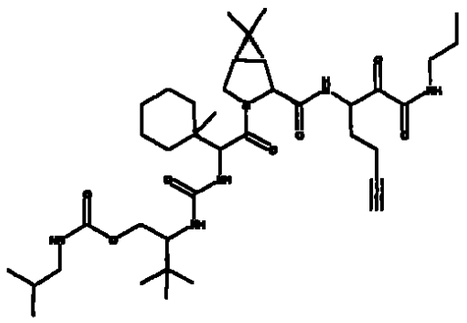


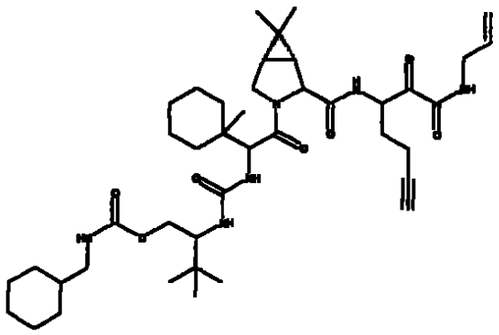


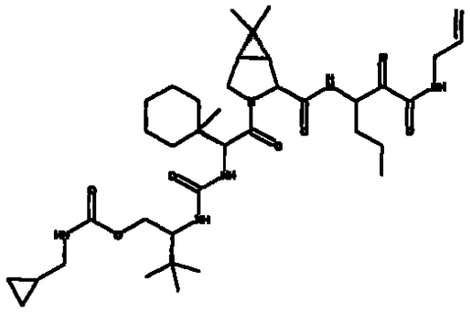


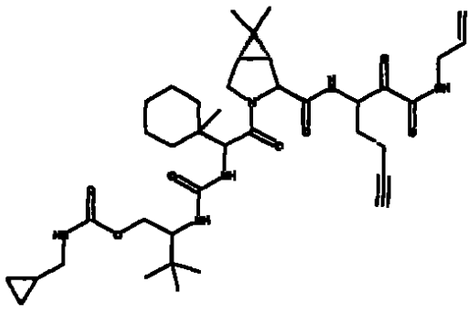


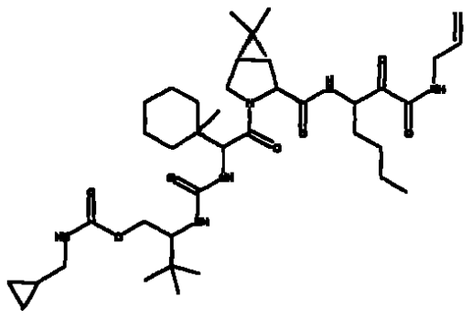


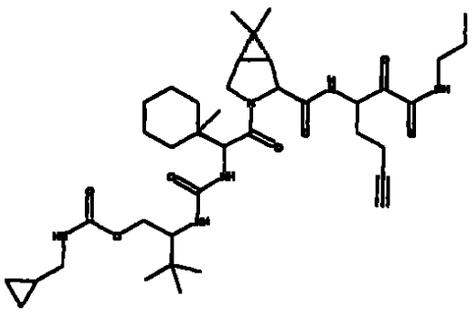


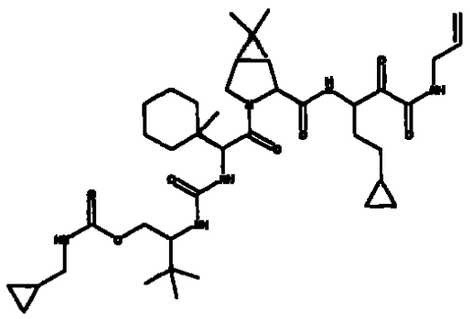


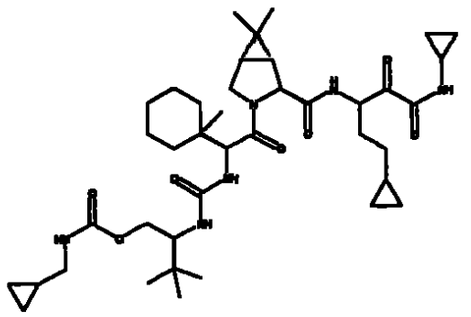












As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"Patient" includes both human and animals.

"Mammal" means humans and other mammalian animals.

"Alkyl" means an aliphatic hydrocarbon group which may be straight or branched and comprising about 1 to about 20 carbon atoms in the chain. Preferred alkyl groups contain about 1 to about 12 carbon atoms in the chain. More preferred alkyl groups contain about 1 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkyl chain. "Lower alkyl" means a group having about 1 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkyl" means that the alkyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl, aryl, cycloalkyl, cyano, hydroxy, alkoxy, alkylthio, amino, -NH(alkyl), -NH(cycloalkyl), $-N(alkyl)_2$, $-N(alkyl)_2$, carboxy and –C(O)O-alkyl. Non-limiting examples of suitable alkyl groups include methyl, ethyl, n-propyl, isopropyl and t-butyl.

"Alkenyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon double bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkenyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 6 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkenyl chain. "Lower alkenyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. The term "substituted alkenyl" means that the alkenyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of halo, alkyl. aryl, cycloalkyl, cyano, alkoxy and –S(alkyl). Non-limiting examples of suitable alkenyl groups include ethenyl, propenyl, n-butenyl, 3-methylbut-2-enyl, n-pentenyl, octenyl and decenyl.

"Alkynyl" means an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond and which may be straight or branched and comprising about 2 to about 15 carbon atoms in the chain. Preferred alkynyl groups have about 2 to about 12 carbon atoms in the chain; and more preferably about 2 to about 4 carbon atoms in the chain. Branched means that one or more lower alkyl groups such as methyl, ethyl or propyl, are attached to a linear alkynyl chain. "Lower alkynyl" means about 2 to about 6 carbon atoms in the chain which may be straight or branched. Non-limiting examples of suitable alkynyl groups include ethynyl, propynyl, 2-butynyl and 3-methylbutynyl. The term "substituted alkynyl" means that the alkynyl group may be substituted by one or more substituents which may be the same or different, each substituent being independently selected from the group consisting of alkyl, aryl and cycloalkyl.

"Aryl" means an aromatic monocyclic or multicyclic ring system comprising about 6 to about 14 carbon atoms, preferably about 6 to about 10 carbon atoms. The aryl group can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined herein. Non-limiting examples of suitable aryl groups include phenyl and naphthyl.

"Heteroaryl" means an aromatic monocyclic or multicyclic ring system comprising about 5 to about 14 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the ring atoms is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. Preferred heteroaryls contain about 5 to about 6 ring atoms. The "heteroaryl" can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The prefix aza, oxa or thia before the heteroaryl root name means that at least a nitrogen, oxygen or sulfur atom respectively, is present as a ring atom. A nitrogen atom of a heteroaryl can be optionally oxidized to the corresponding N-oxide. Non-limiting examples of suitable heteroaryls include pyridyl, pyrazinyl, furanyl, thienyl, pyrimidinyl, pyridone (including N-substituted pyridones), isoxazolyl, isothiazolyl, oxazolyl, thiazolyl, pyrazolyl, furazanyl, pyrrolyl, pyrazolyl, triazolyl, 1,2,4-thiadiazolyl, pyrazinyl, pyridazinyl, quinoxalinyl, phthalazinyl, oxindolyl, imidazo[1,2-a]pyridinyl, imidazo[2,1-b]thiazolyl, benzofurazanyl,

indolyl, azaindolyl, benzimidazolyl, benzothienyl, quinolinyl, imidazolyl, thienopyridyl, quinazolinyl, thienopyrimidyl, pyrrolopyridyl, imidazopyridyl, isoquinolinyl, benzoazaindolyl, 1,2,4-triazinyl, benzothiazolyl and the like. The term "heteroaryl" also refers to partially saturated heteroaryl moieties such as, for example, tetrahydroisoquinolyl, tetrahydroquinolyl and the like.

"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the alkyl.

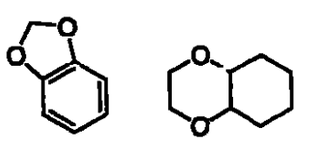
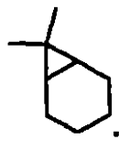
"Alkylaryl" means an alkyl-aryl- group in which the alkyl and aryl are as previously described. Preferred alkylaryls comprise a lower alkyl group. Non-limiting example of a suitable alkylaryl group is tolyl. The bond to the parent moiety is through the aryl.

"Cycloalkyl" means a non-aromatic mono- or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms. Preferred cycloalkyl rings contain about 5 to about 7 ring atoms. The cycloalkyl can be optionally substituted with one or more "ring system substituents" which may be the same or different, and are as defined above. Non-limiting examples of suitable monocyclic cycloalkyls include cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl and the like. Non-limiting examples of suitable multicyclic cycloalkyls include 1-decalinyl, norbornyl, adamantyl and the like, as well as partially saturated species such as, for example, indanyl, tetrahydronaphthyl and the like.

"Halogen" or "halo" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"Ring system substituent" means a substituent attached to an aromatic or non-aromatic ring system which, for example, replaces an available hydrogen on the ring system. Ring system substituents may be the same or different, each being independently selected from the group consisting of alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, alkylaryl, heteroaralkyl, heteroarylalkenyl, heteroarylalkynyl, alkylheteroaryl, hydroxy, hydroxyalkyl, alkoxy, aryloxy, aralkoxy, acyl, aroyl, halo, nitro, cyano, carboxy, alkoxycarbonyl, aryloxycarbonyl, aralkoxycarbonyl, alkylsulfonyl, arylsulfonyl,

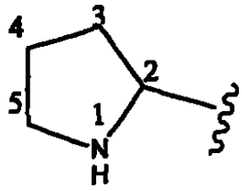
heteroarylsulfonyl, alkylthio, arylthio, heteroarylthio, aralkylthio, heteroaralkylthio, cycloalkyl, heterocyclyl, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), Y_1Y_2N-, Y_1Y_2N-alkyl-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- and -$SO_2NY_1Y_2$, wherein Y_1 and Y_2 can be the same or different and are independently selected from the group consisting of hydrogen, alkyl, aryl, cycloalkyl, and aralkyl. "Ring system substituent" may also mean a single moiety which simultaneously replaces two available hydrogens on two adjacent carbon atoms (one H on each carbon) on a ring system. Examples of such moiety are methylene dioxy, ethylenedioxy, -$C(CH_3)_2$- and the like which form moieties such as, for example:

 and  .

"Heterocyclyl" means a non-aromatic saturated monocyclic or multicyclic ring system comprising about 3 to about 10 ring atoms, preferably about 5 to about 10 ring atoms, in which one or more of the atoms in the ring system is an element other than carbon, for example nitrogen, oxygen or sulfur, alone or in combination. There are no adjacent oxygen and/or sulfur atoms present in the ring system. Preferred heterocyclyls contain about 5 to about 6 ring atoms. The prefix aza, oxa or thia before the heterocyclyl root name means that at least a nitrogen, oxygen or sulfur atom respectively is present as a ring atom. Any –NH in a heterocyclyl ring may exist protected such as, for example, as an -N(Boc), -N(CBz), -N(Tos) group and the like; such protections are also considered part of this invention. The heterocyclyl can be optionally substituted by one or more "ring system substituents" which may be the same or different, and are as defined herein. The nitrogen or sulfur atom of the heterocyclyl can be optionally oxidized to the corresponding N-oxide, S-oxide or S,S-dioxide. Non-limiting examples of suitable monocyclic heterocyclyl rings include piperidyl, pyrrolidinyl, piperazinyl, morpholinyl, thiomorpholinyl, thiazolidinyl, 1,4-dioxanyl, tetrahydrofuranyl, tetrahydrothiophenyl, lactam, lactone, and the like.

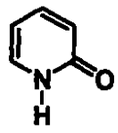
It should be noted that in hetero-atom containing ring systems of this invention, there are no hydroxyl groups on carbon atoms adjacent to a N, O or

S, as well as there are no N or S groups on carbon adjacent to another heteroatom. Thus, for example, in the ring:

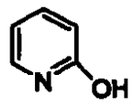


there is no -OH attached directly to carbons marked 2 and 5.

It should also be noted that tautomeric forms such as, for example, the moieties:



and



are considered equivalent in certain embodiments of this invention.

"Alkynylalkyl" means an alkynyl-alkyl- group in which the alkynyl and alkyl are as previously described. Preferred alkynylalkyls contain a lower alkynyl and a lower alkyl group. The bond to the parent moiety is through the alkyl. Non-limiting examples of suitable alkynylalkyl groups include propargylmethyl.

"Heteroaralkyl" means a heteroaryl-alkyl- group in which the heteroaryl and alkyl are as previously described. Preferred heteroaralkyls contain a lower alkyl group. Non-limiting examples of suitable aralkyl groups include pyridylmethyl, and quinolin-3-ylmethyl. The bond to the parent moiety is through the alkyl.

"Hydroxyalkyl" means a HO-alkyl- group in which alkyl is as previously defined. Preferred hydroxyalkyls contain lower alkyl. Non-limiting examples of suitable hydroxyalkyl groups include hydroxymethyl and 2-hydroxyethyl.

"Acyl" means an H-C(O)-, alkyl-C(O)- or cycloalkyl-C(O)-, group in which the various groups are as previously described. The bond to the parent moiety is through the carbonyl. Preferred acyls contain a lower alkyl. Non-limiting examples of suitable acyl groups include formyl, acetyl and propanoyl.

"Aroyl" means an aryl-C(O)- group in which the aryl group is as previously described. The bond to the parent moiety is through the carbonyl. Non-limiting examples of suitable groups include benzoyl and 1- naphthoyl.

"Alkoxy" means an alkyl-O- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy and n-butoxy. The bond to the parent moiety is through the ether oxygen.

"Aryloxy" means an aryl-O- group in which the aryl group is as previously described. Non-limiting examples of suitable aryloxy groups include phenoxy and naphthoxy. The bond to the parent moiety is through the ether oxygen.

"Aralkyloxy" means an aralkyl-O- group in which the aralkyl group is as previously described. Non-limiting examples of suitable aralkyloxy groups include benzyloxy and 1- or 2-naphthalenemethoxy. The bond to the parent moiety is through the ether oxygen.

"Alkylthio" means an alkyl-S- group in which the alkyl group is as previously described. Non-limiting examples of suitable alkylthio groups include methylthio and ethylthio. The bond to the parent moiety is through the sulfur.

"Arylthio" means an aryl-S- group in which the aryl group is as previously described. Non-limiting examples of suitable arylthio groups include phenylthio and naphthylthio. The bond to the parent moiety is through the sulfur.

"Aralkylthio" means an aralkyl-S- group in which the aralkyl group is as previously described. Non-limiting example of a suitable aralkylthio group is benzylthio. The bond to the parent moiety is through the sulfur.

"Alkoxycarbonyl" means an alkyl-O-CO- group. Non-limiting examples of suitable alkoxycarbonyl groups include methoxycarbonyl and ethoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aryloxycarbonyl" means an aryl-O-C(O)- group. Non-limiting examples of suitable aryloxycarbonyl groups include phenoxycarbonyl and naphthoxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Aralkoxycarbonyl" means an aralkyl-O-C(O)- group. Non-limiting example of a suitable aralkoxycarbonyl group is benzyloxycarbonyl. The bond to the parent moiety is through the carbonyl.

"Alkylsulfonyl" means an alkyl-$S(O_2)$- group. Preferred groups are those in which the alkyl group is lower alkyl. The bond to the parent moiety is through the sulfonyl.

"Arylsulfonyl" means an aryl-$S(O_2)$- group. The bond to the parent moiety is through the sulfonyl.

The term "substituted" means that one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency under the existing circumstances is not exceeded, and that the substitution results in a stable compound. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound' or "stable structure" is meant a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

The term "one or more" or "at least one", when indicating the number of substituents, compounds, combination agents and the like, refers to at least one, and up to the maximum number of chemically and physically permissible, substituents, compounds, combination agents and the like, that are present or added, depending on the context. Such techniques and knowledge are well known within the skills of the concerned artisan.

The term "optionally substituted" means optional substitution with the specified groups, radicals or moieties.

The term "isolated" or "in isolated form" for a compound refers to the physical state of said compound after being isolated from a synthetic process or natural source or combination thereof. The term "purified" or "in purified form" for a compound refers to the physical state of said compound after being obtained from a purification process or processes described herein or well known to the skilled artisan, in sufficient purity to be characterizable by standard analytical techniques described herein or well known to the skilled artisan.

It should also be noted that any heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the hydrogen atom(s) to satisfy the valences.

When a functional group in a compound is termed "protected", this means that the group is in modified form to preclude undesired side reactions at the protected site when the compound is subjected to a reaction. Suitable protecting groups will be recognized by those with ordinary skill in the art as well as by reference to standard textbooks such as, for example, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

When any variable (e.g., aryl, heterocycle, R^2, etc.) occurs more than one time in any constituent or in Formula 1, its definition on each occurrence is independent of its definition at every other occurrence.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula 1 or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are *incorporated herein by reference thereto.*

"Solvate" means a physical association of a compound of this invention with one or more solvent molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates, and the like. "Hydrate" is a solvate wherein the solvent molecule is H_2O.

"Effective amount" or "therapeutically effective amount" is meant to describe an amount of compound or a composition of the present invention effective in inhibiting the CDK(s) and thus producing the desired therapeutic, ameliorative, inhibitory or preventative effect.

The compounds of Formula 1 can form salts which are also within the scope of this invention. Reference to a compound of Formula 1 herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula 1 contains both a basic moiety, such as, but not limited to a pyridine or imidazole, and an acidic moiety, such as, but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also useful. Salts of the compounds of the Formula 1 may be formed, for example, by reacting a compound of Formula 1 with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

Exemplary acid addition salts include acetates, ascorbates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, fumarates, hydrochlorides, hydrobromides, hydroiodides, lactates, maleates, methanesulfonates, naphthalenesulfonates, nitrates, oxalates, phosphates, propionates, salicylates, succinates, sulfates, tartarates, thiocyanates, toluenesulfonates (also known as tosylates,) and the like. Additionally, acids which are generally considered suitable for the formation of pharmaceutically useful salts from basic pharmaceutical compounds are discussed, for example, by P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration,

Washington, D.C. on their website). These disclosures are incorporated herein by reference thereto.

Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium, and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as dicyclohexylamines, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quarternized with agents such as lower alkyl halides (e.g. methyl, ethyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, and dibutyl sulfates), long chain halides (e.g. decyl, lauryl, and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

All such acid salts and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

Pharmaceutically acceptable esters of the present compounds include the following groups: (1) carboxylic acid esters obtained by esterification of the hydroxy groups, in which the non-carbonyl moiety of the carboxylic acid portion of the ester grouping is selected from straight or branched chain alkyl (for example, acetyl, n-propyl, t-butyl, or n-butyl), alkoxyalkyl (for example, methoxymethyl), aralkyl (for example, benzyl), aryloxyalkyl (for example, phenoxymethyl), aryl (for example, phenyl optionally substituted with, for example, halogen, C_{1-4}alkyl, or C_{1-4}alkoxy or amino); (2) sulfonate esters, such as alkyl- or aralkylsulfonyl (for example, methanesulfonyl); (3) amino acid esters (for example, L-valyl or L-isoleucyl); (4) phosphonate esters and (5) mono-, di- or triphosphate esters. The phosphate esters may be further esterified by, for example, a C_{1-20} alcohol or reactive derivative thereof, or by a 2,3-di (C_{6-24})acyl glycerol.

Compounds of Formula 1, and salts, solvates, esters and prodrugs thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers (for example, geometric isomers, optical isomers, and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs), such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

Polymorphic forms of the compounds of Formula I, and of the salts, solvates, esters and prodrugs of the compounds of Formula I, are intended to be included in the present invention.

It is to be understood that the utility of the compounds of Formula 1 for the therapeutic applications discussed herein is applicable to each compound by itself or to the combination or combinations of one or more compounds of Formula 1 as illustrated, for example, in the next immediate paragraph. The same understanding also applies to pharmaceutical composition(s) comprising such compound or compounds and method(s) of treatment involving such compound or compounds.

The compounds according to the invention can have pharmacological properties; in particular, the compounds of Formula 1 can be inhibitors of HCV protease, each compound by itself or one or more compounds of Formula 1 can be combined with one or more compounds selected from within Formula 1. The compound(s) can be useful for treating diseases such as, for example, HCV, HIV, (AIDS, Acquired Immune Deficiency Syndrome), and related disorders, as well as for modulating the activity of hepatitis C virus (HCV)

protease, preventing HCV, or ameliorating one or more symptoms of hepatitis C.

The compounds of Formula 1 may be used for the manufacture of a medicament to treat disorders associated with the HCV protease, for example, the method comprising bringing into intimate contact a compound of Formula 1 and a pharmaceutically acceptable carrier.

In another embodiment, this invention provides pharmaceutical compositions comprising the inventive compound or compounds as an active ingredient. The pharmaceutical compositions generally additionally comprise at least one 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.

The compounds of the invention may also be administered orally, intravenously, intranasally or subcutaneously.

The compounds of the invention may also comprise preparations which are 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 molety 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 inventive compounds or 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 compound or 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. Illustrative procedures are outlined in the following reaction schemes. The illustrations should not be construed to limit the scope of the invention which is defined in the appended claims. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

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.

For the procedures described below, the following abbreviations are used:

Abbreviations

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(3H)-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: Isoprppyl
^{t}Bu or Bu^{t}: tert-Butyl
Boc: tert-Butyloxycarbonyl
Cbz: Benzyloxycarbonyl
Cp: Cylcopentyldienyl
Ts: p-toluenesulfonyl
Me: Methyl
HATU: O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
DMAP: 4-N,N-Dimethylaminopyridine
BOP: Benzotriazol-1-yl-oxy-tris(dimethylamino)hexafluorophosphate
PCC: Pyridiniumchlorochromate

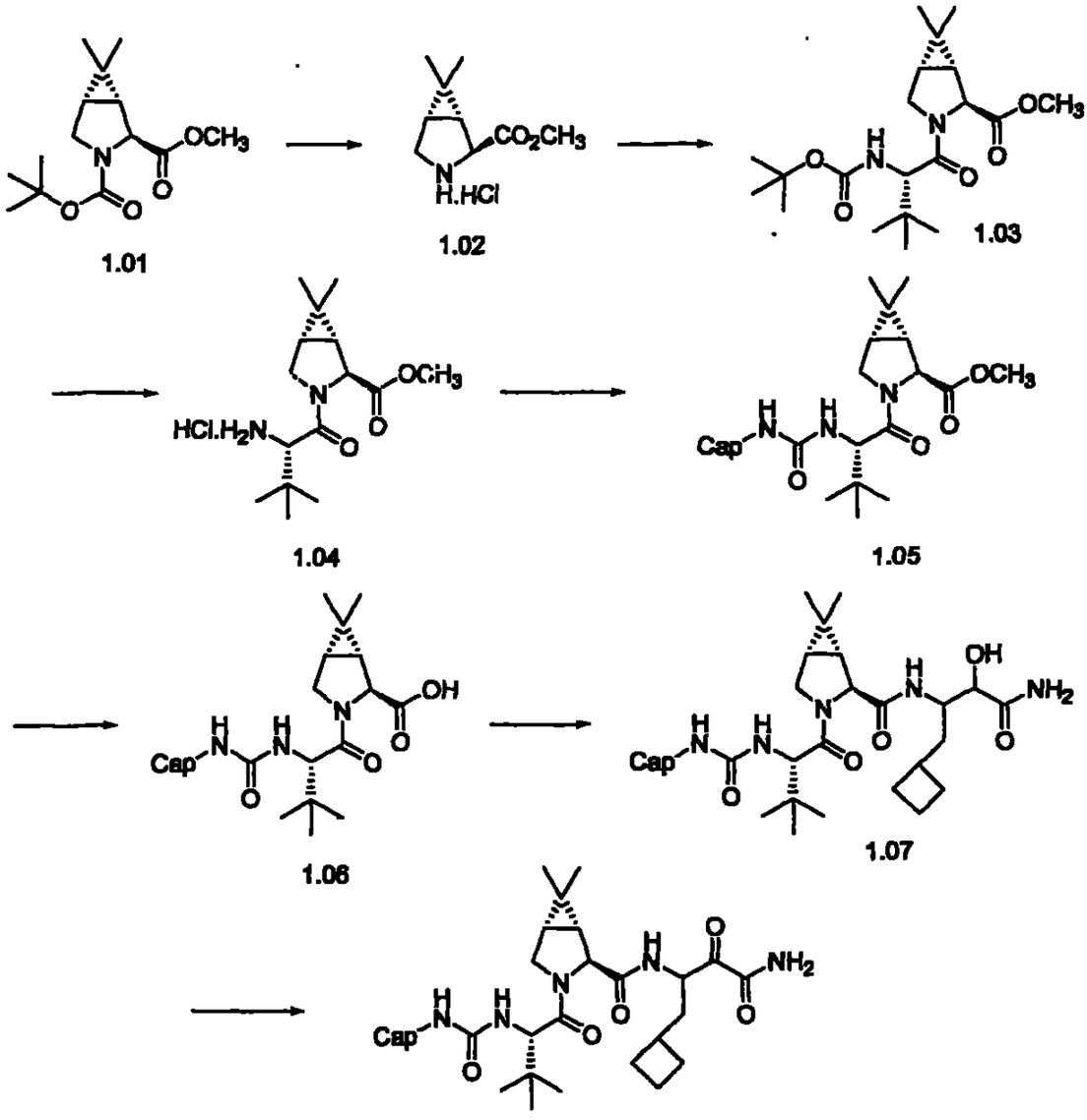
General Schemes for Preparation of Target Compounds

Compounds of the present invention were synthesized using the general schemes (Methods A-E) described below.

Method A:

Deprotection of the N-Boc functionality of 1.01 under acidic conditions provided the hydrochloride salt 1.02 which was subsequently coupled with N-Boc-tert-leucine under peptide coupling methodology to afford 1.03. N-Boc deprotection followed by treatment with appropriate isocyanate gave the urea 1.05. Hydrolysis of the methyl ester provided the acid 1.06. Peptide coupling

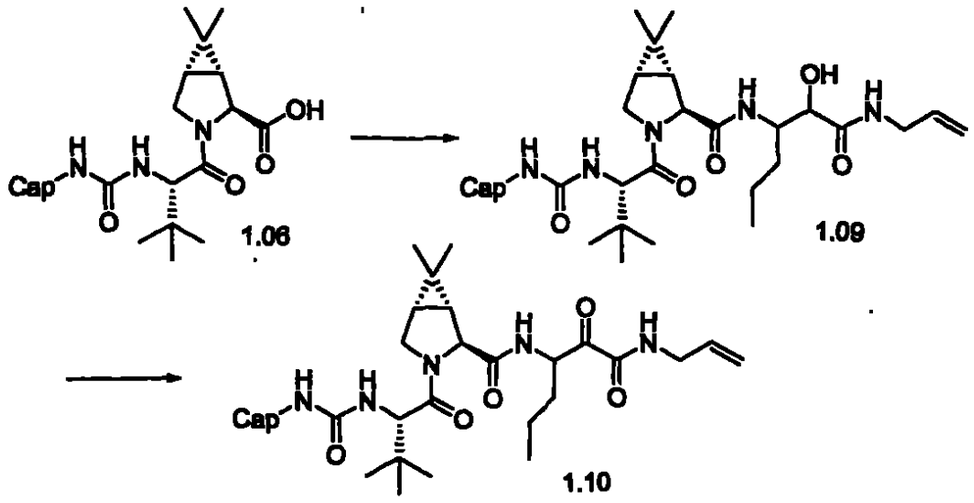
of the acid 1.06 with the appropriate P_1-P' primary amide moiety afforded the hydroxyl amide 1.07. Oxidation (Moffatt or related process - T.T.Tidwell, *Synthesis*, **1990**, 857; or Dess-Martin's – *J. Org. Chem.*, **1983**, *48*, 4155) resulted in the target compound 1.08.



1.01 1.02 1.03 1.04 1.05 1.06 1.07 1.08

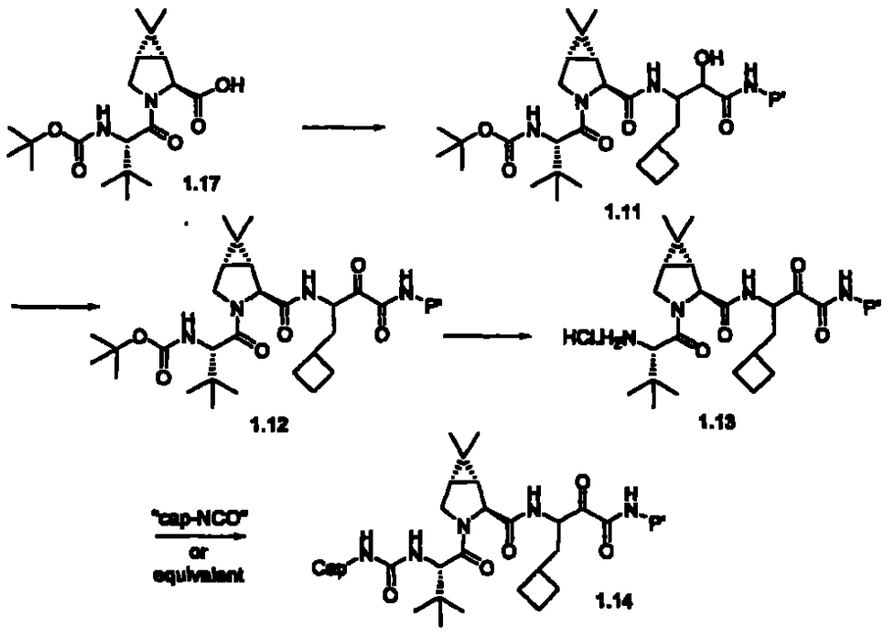
Method B

Peptide coupling of the acid 1.06 with the appropriate P_1-P' secondary amide moiety afforded the hydroxyl amide 1.09. Oxidation (Moffatt or Dess-Martin's) resulted in the target compound 1.10.



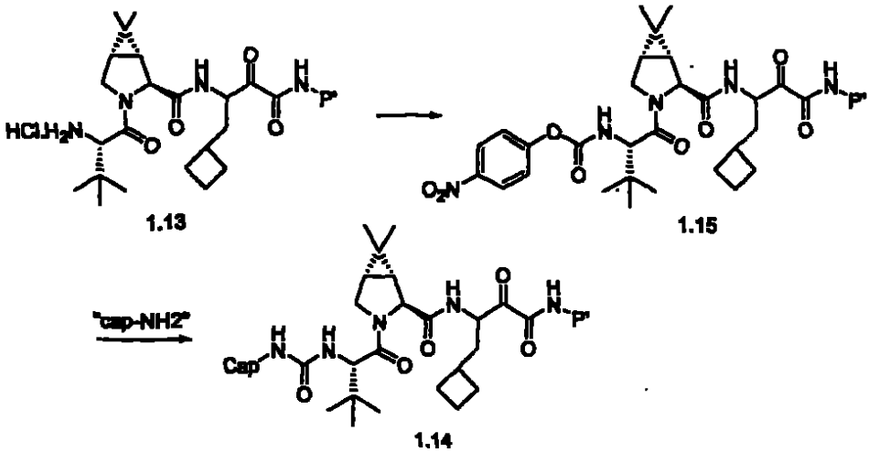
Method C

In another variation, peptide coupling of the N-Boc-P_2-P_3-acid 1.17 with the appropriate P_1-P' amide moiety afforded the hydroxyl amide 1.11. Oxidation (Moffatt or Dess-Martin's) resulted in the keto amide 1.12. Deprotection of the N-Boc functionality gave the hydrochloride salt 1.13. Treatment with a suitable isocyanate (or isocyanate equivalent) resulted in the target compound 1.14.



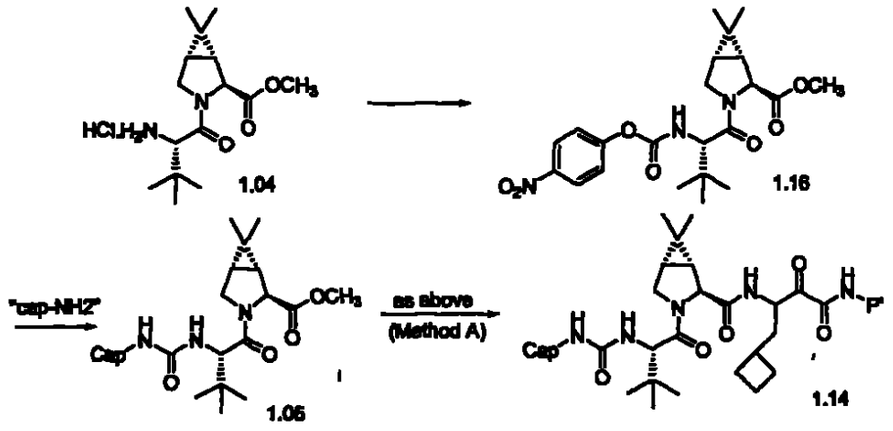
Method D

In yet another variation, the hydrochloride salt 1.13 was converted to the 4-nitrophenyl carbamate 1.15 by reaction with 4-nitrophenyl chloroformate. Subsequent treatment with an amin (or amine hydrochloride salt) of choice provided the target compound 1.14.



Method E

In yet another variation, the dipeptide hydrochloride salt 1.03 was converted to the 4-nitrophenyl carbamate as described above. Treatment with an amine (or amine hydrochloride salt) of choice provided the urea derivative 1.05. Hydrolysis and further elaboration as described in Methods A/B provided the target compounds 1.14.

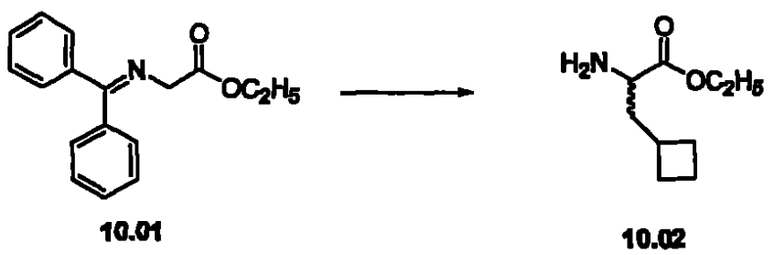


Preparation of Intermediates:

Preparation of P_1-P' moieties:

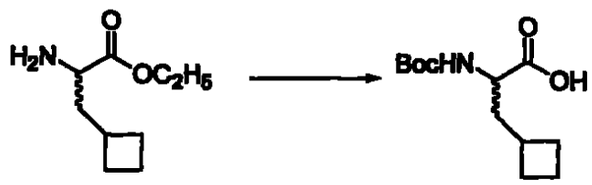
Preparation of Intermediates 10.11 and 10.12:

Step 1:



A stirred solution of ketimine 10.01 (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 the pure amine (10.02, 18 g) as a colorless oil.

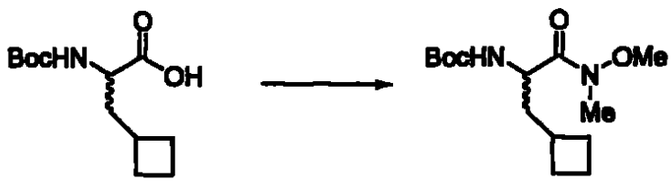
Step 2



10.02 10.03

A solution of the amine 10.02 (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 10.03 as a colorless viscous oil which was used for the next step without any further purification.

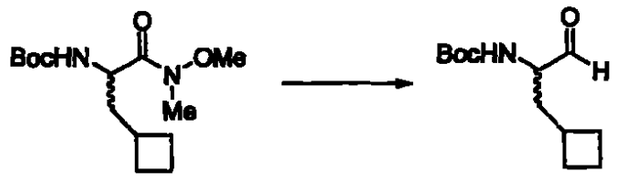
Step 3



10.03 10.04

A solution of the acid 10.03 (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 10.04 (15.0 g) as a colorless solid.

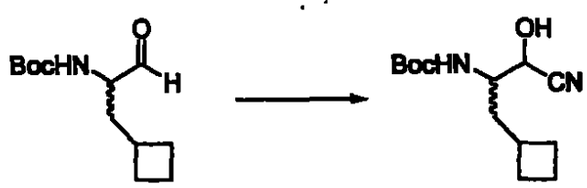
Step 4



10.04 10.05

A solution of the amide 10.04 (15 g, 52.1 mmol) in dry THF (200 mL) was treated dropwise 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 10.05 as a viscous colorless oil (14 g).

Step 5

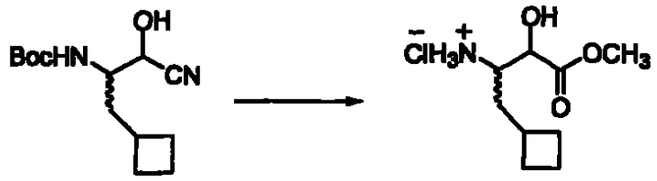


10.05 10.06

A solution of the aldehyde 10.05 (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 **10.06** (10.3 g) as a colorless liquid

Step 6

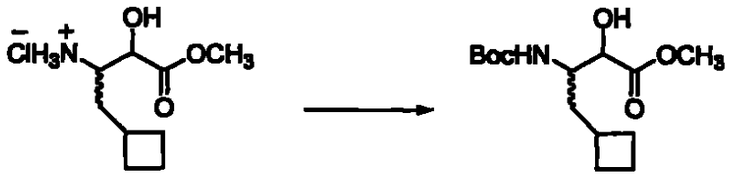


10.06 **10.07**

Methanol saturated with HCl*, prepared by bubbling HCl gas through CH_3OH (700 ml) at 0 °C, was treated with the cyanohydrin **10.06** and heated to reflux for 24 h. The reaction was concentrated *in vacuo* to yield **10.07**, which was used in the next step without purification.

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

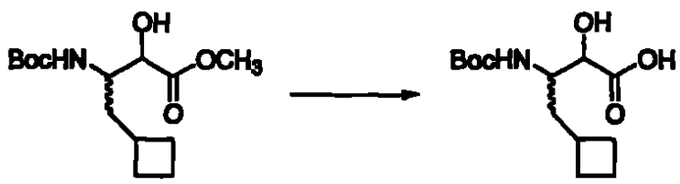
Step 7



10.07 **10.08**

A solution of the amine hydrochloride **10.07** 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 **10.08**.

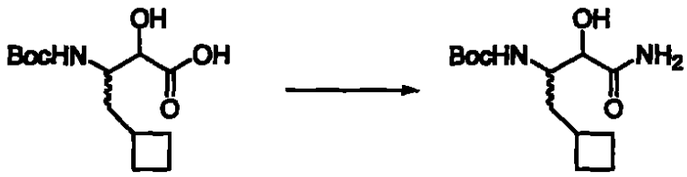
Step 8.



10.08 **10.09**

A solution of methyl ester **10.08** (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 acidified with aq HCl (1 M, 15 mL) and concentrated *in vacuo*. The residue was dried in vacuum to afford **10.09** in quantitative yield.

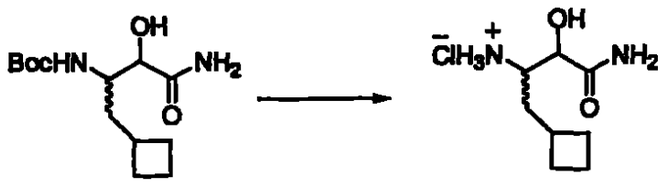
Step 9



10.09 **10.10**

A solution of the acid **10.09** (from above) 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 **10.10**, which was used as it was in the following steps. (Alternatively **10.10** can also be obtained directly by the reaction of **10.06** (4.5 g, 17.7 mmol) with aq. H_2O_2 (10 mL), LiOH•H_2O (820 mg, 20.8 mmol) at 0 °C in 50 mL of CH_3OH for 0.5 h.)

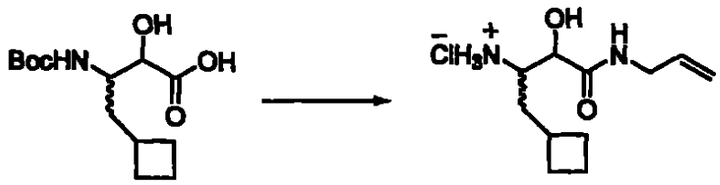
Step 10



10.10 **10.11**

A solution of **10.10** 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 the intermediate **10.11** as a solid, which was used without further purification.

Step 11

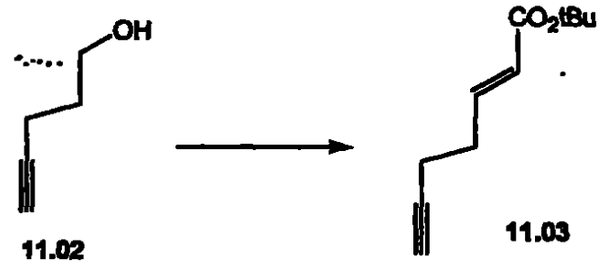


10.09 10.12

The required intermediate **10.12** was obtained from compound **10.09** using essentially the procedures described above in Steps 9, 10 with appropriate reagents.

Preparation of Intermediate 11.01

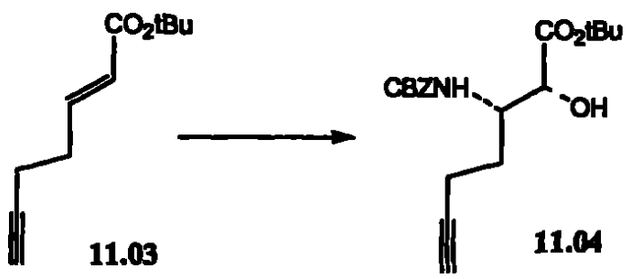
Step 1



11.02 11.03

To a solution of 4-pentyn-1-ol, **11.02** (4.15g; Aldrich) was added Dess-Martin Periodinane (30.25g; Aldrich) and the resulting mixture was stirred for 45min. before the addition of (tert-Butoxycarbonylmethylene)triphenylphosphorane (26.75g; Aldrich). The resulting dark reaction was stirred overnight, diluted with EtOAc), washed with aq. sodium sulfite. sat. aq. NaHCO3, water, brine and dried. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using 1% EtOAc in hexanes as eluent to give the desired compound, **11.03** (3.92g). Some impure fractions were also obtained but set aside at this time.

Step 2

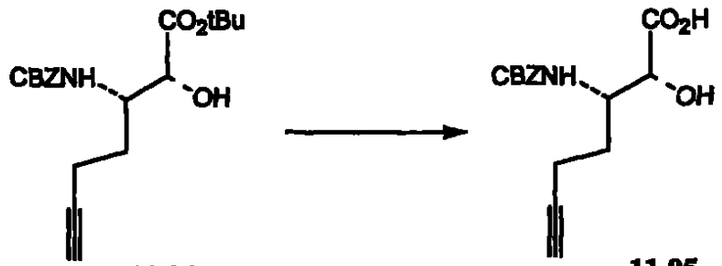


11.03 11.04

Using the alkene **11.03** (1.9g) in n-propanol (20ml; Aldrich)), benzyl carbamate (4.95g; Aldrich) in n-propanol (40ml), NaOH (1.29g) in water (79ml), tert-butyl hypochlorite (3.7ml), (DHQ)2PHAL (0.423g; Aldrich)) in n-

propanol (37.5ml), and potassium osmate:dehydrate (0.1544g; Aldrich) and the procedure set forth in Angew. Chem. Int. Ed. Engl (1998), 35, (23/24), pp. 2813-7.gave a crude product which was purified by silica gel column chromatography using EtOAc:Hexanes (1:5) to give the desired amino alcohol 11.04 (1.37g, 37%) as a white solid.

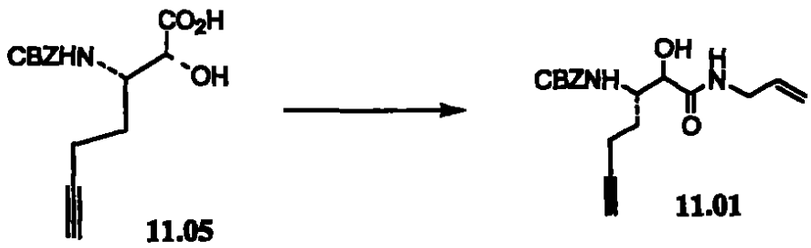
Step 3



11.04 11.05

To the ester 11.04 (0.700g) was added 4M HCl in dioxane (20ml; Aldrich) and the resulting mixture was allowed to stand at room temperature overnight. The volatiles were removed under reduced pressure to give the acid 11.05 (0.621g) as a white solid.

Step 4



11.05 11.01

BOP reagent (3.65g; Sigma) followed by triethylamine (3.45ml) were added to a dichloromethane (20ml) solution of the carboxylic acid 11.05 (2.00g) and allyl amine (0.616ml) at room temperature and the resulting mixture was stirred overnight. The reaction mixture was partitioned between EtOAc and 10% aq. HCl. The organic phase was separated, washed with sat. aq. sodium bicarbonate, water, dried (magnesium sulfate). The crude reaction product was purified by silica gel column chromatography using (EtOAc:Hexanes; 70:30) as eluent to provide the desired amide 11.01 (1.73g) as a viscous yellow oil.

Preparation of Intermediates 12.03 and 12.04

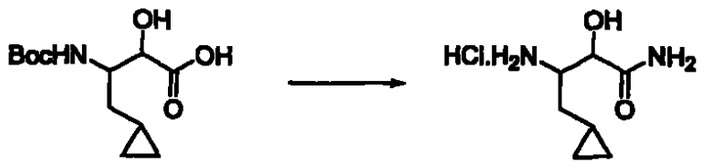
Step 1



12.01 12.02

Compound **12.01** was converted to the required material **12.02** using essentially the procedures described for Intermediate **10.11**, Steps 3-8.

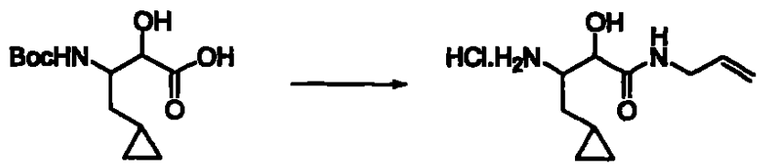
Step 2



12.02 12.03

Compound **12.02** was converted to the required Intermediate **12.03** using essentially the procedures described for Intermediate **10.11**, Steps 9, 10..

Step 3



12.02 12.04

Compound **12.02** was converted to the required intermediate **12.03** using essentially the procedures described for Intermediate **10.12**, Step 11.

Preparation of Intermediate **13.01**

Step 1



13.02 13.03

To a stirred solution of 1-nitrobutane, **13.02** (16.5 g, 0.16 mol) and glyoxylic acid in H_2O (28.1 g, 0.305 mol) and MeOH (122 mL) at 0°C-5°C, was added dropwise triethylamine (93 mL, 0.667 mol) over 2 hrs. The solution was warmed to room temperature, stirred overnight and concentrated to dryness to give an oil. The oil was then dissolved in H_2O and acidified to pH =1 with 10% HCl, followed by extraction with EtOAc. The combined organic

solution was washed with brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the product **13.03** (28.1 g, 99% yield).

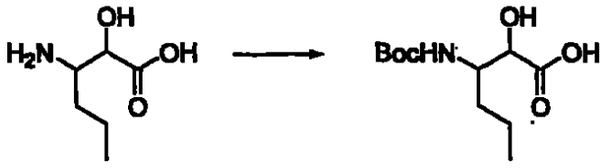
Step 2



13.03 **13.04**

To a stirred solution of compound **13.03** (240 g, 1.35 mol) in acetic acid (1.25 L) was added 10% Pd/C (37 g). The resulting solution was hydrogenated at 59 psi for 3 hrs and then at 60 psi overnight. The acetic acid was then evaporated and azeotroped 3 times with toluene, then triturated with MeOH and ether. The solution was then filtered and azeotroped twice with toluene to afford **13.04** as an off white solid (131 g, 0.891 mol, 66%).

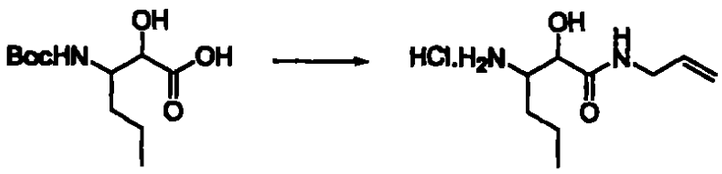
Step 3



13.04 **13.05**

To a stirred solution of the amino acid **13.04** (2.0 g, 13.6 mmol) in dioxane (10 mL) and H_2O (5mL) at 0°C, was added 1N NaOH solution (4.3 mL, 14.0 mmol). The resulting solution was stirred for 10 minutes, followed by addition of di-*t*-butyldicarbonate (0.110 g, 14.0 mmol) and stirred at 0^0C for 15 minutes. The solution was then warmed to room temperature, stirred for 45 minutes and kept at refrigerator overnight and concentrated to dryness to give a crude material. To the solution of this crude material in EtOAc (100 mL) and ice, was added $KHSO_4$ (3.36 g) and H_2O (32 mL) and stirred for 4-6 minutes. The organic layer was then separated and the aqueous layer was extracted twice with EtOAc and the combined organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated to dryness to give the product **13.05** as a clear gum (3.0 g, 89% yield).

Step 4

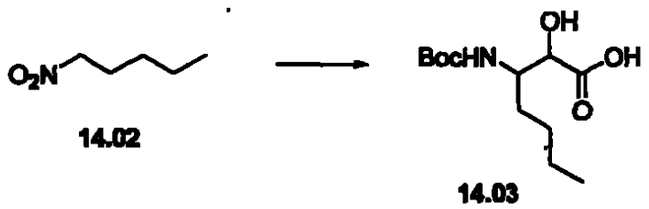


13.05 13.01

Compound 13.05 was converted to the required intermediate 13.01 using essentially the procedures described for Intermediate 10.12, Step 11.

Preparation of Intermediate 14.01

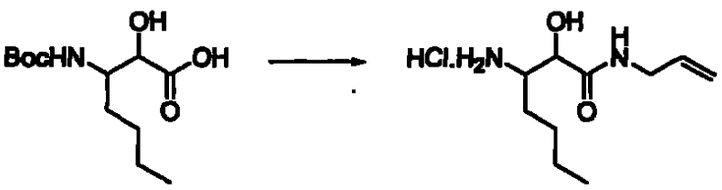
Step 1



14.02 14.03

Compound 14.02 was converted to the required material 14.03 using essentially the procedures described for Intermediate 13.01, Steps 1-3.

Step 2

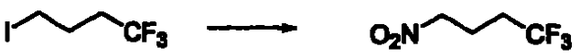


14.03 14.01

Compound 14.03 was converted to the required intermediate 14.01 using essentially the procedures described for Intermediate 10.12, Step 11.

Preparation of Intermediate 15.01

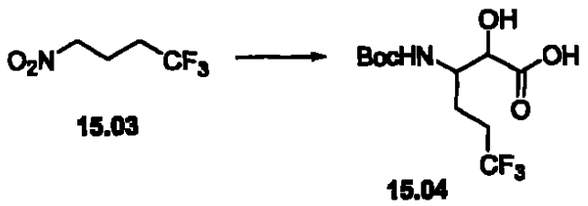
Step 1



15.02 15.03

To a suspension of silver nitrite (9 g, 58.5 mmol) in diethyl ether (25 mL) at 0°C was added a solution of 4-iodo-1,1,1-trifluorobutane, 15.02 (10 g, 42.0 mmol) in diethyl ether (25 mL) slowly through an addition funnel (approx. 15 min). The resulting mixture was vigorously stirred at 0°C and warmed to rt. After 50 h, the solid material was filtered off through a celite pad. The resulting diethyl ether solution was concentrated *in vacuo* to give 15.03 as colorless oil, which was used without further purification.

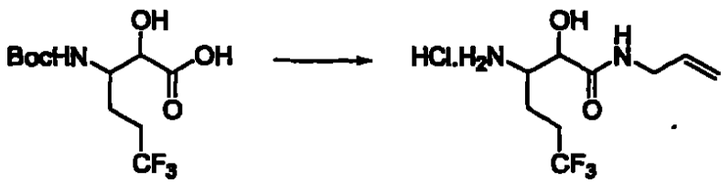
Step 2



15.03 15.04

Compound **15.03** was converted to the required material **15.04** using essentially the procedures described for Intermediate **13.01**, Steps 1-3.

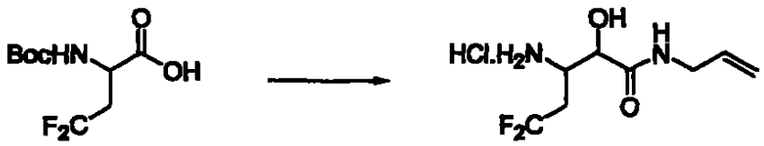
Step 3



15.04 15.01

Compound **15.04** was converted to the required intermediate **15.01** using essentially the procedures described for Intermediate **10.12**, Step 11.

Preparation of Intermediate **16.01**

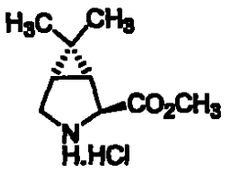


16.02 16.01

The acid **16.02** (Winkler, D.; Burger, K., *Synthesis*, **1996**, 1419) is processed as described above (preparation of Intermediate **10.12**) to give the expected intermediate **16.01**.

PREPARATION OF P_2 / P_3-P_2 MOIETIES

Preparation of Intermediate **20.01**



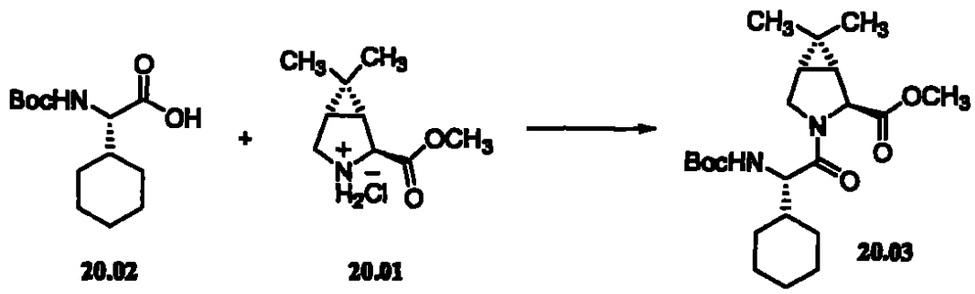
20.01

The amino ester **20.01** was prepared following the method of R. Zhang and J. S. Madalengoitia (*J. Org. Chem.* **1999**, *64*, 330), with the exception that the Boc group was cleaved by the reaction of the Boc-protected amino acid with methanolic HCl (4M HCl in dioxane was also employed for the deprotection).

(Note: In a variation of the reported synthesis, the sulfonium ylide was replaced with the corresponding phosphonium ylide)

Preparation of Intermediate 20.04

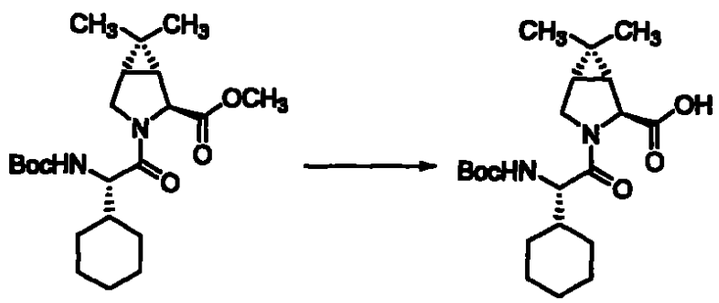
Step 1



20.02 20.01 20.03

A solution of commercial amino acid Boc-Chg-OH, **20.02** (Senn chemicals, 6.64 g, 24.1 mmol) and amine hydrochloride **20.01** (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 **20.03** (6.0 g) as a colorless solid.

Step 2

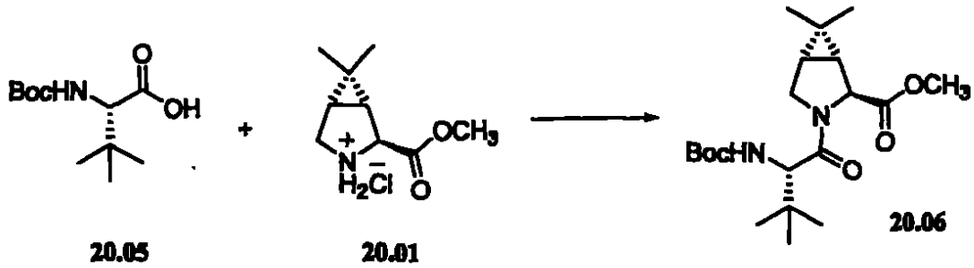


20.03 20.04

A solution of methyl ester **20.03** (4.0 g, 9.79 mmol) in THF/H_2O (1:1) was treated with $LiOH \cdot H_2O$ (401 mg, 9.79 mmol) and stirred at rt. for 3 h. The reaction mixture was acidified with aq. HCl and concentrated in *vacuo* to obtain the required intermediate, free acid **20.04**.

Preparation of Intermediate 20.08

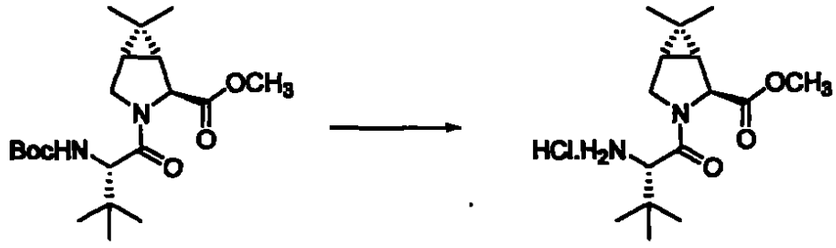
Step 1



20.05 20.01 20.06

A solution of Boc-tert-Leu **20.05** (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 salt **20.01** (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 **20.06** as a colorless solid.

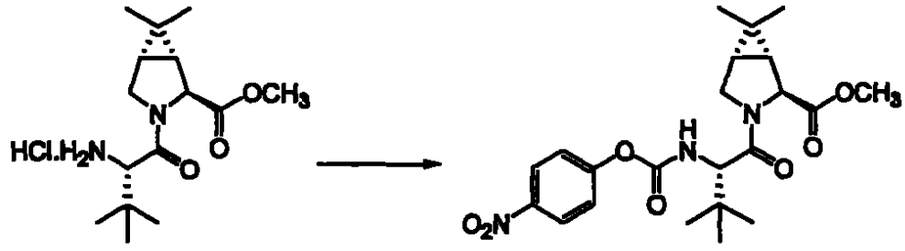
Step 2



20.06 20.07

A solution of methyl ester **20.06** (4.0 g, 10.46 mmol) was dissolved in 4M HCl in dioxane and stirred at rt. for 3 h. The reaction mixture was concentrated in *vacuo* to obtain the amine hydrochloride salt, **20.07** which was used without purification.

Step 3



20.07 20.08

A solution of the amine salt **20.07** (840 mg, 2.64 mmol) in THF (14 mL)/acetonitrile (2 mL) was cooled to 0°C. 4-Nitrophenylchloroformate (800

mg, 3.96 mmol) was added followed by pyridine (0.64 mL, 7.92 mmol). The reaction was slowly warmed to room temperature over 3 hrs when TLC indicated reaction completion. Diethyl ether (50 mL) was added and the resulting precipitate was filtered off. The filtrate was washed with saturated ammonium chloride solution (1 x), brine (1 x), dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography using 20/80 EtOAc/hexanes which afforded 1.15 g of the required intermediate **20.08**.

Preparation of Intermediate **21.01**

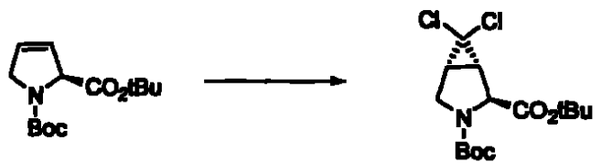
Step 1



21.02 **21.03**

To a stirred solution of *N*-Boc-3,4-dehydroproline **21.02** (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 **21.03** as a pale yellow oil (5.29 g, 84%).

Step 2

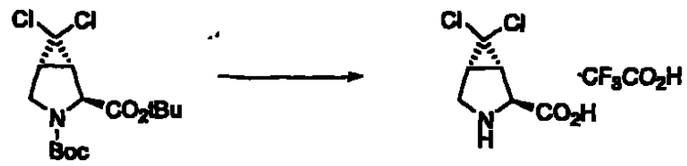


21.03 **21.04**

To a stirred solution of the dehydroproline derivative **21.03** (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 dark 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 **21.04** as an off-white solid.

Step 3



21.04 **21.05**

The solution of **21.04** (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, **21.05** which was used in Step 4 without further purification.

Step 4

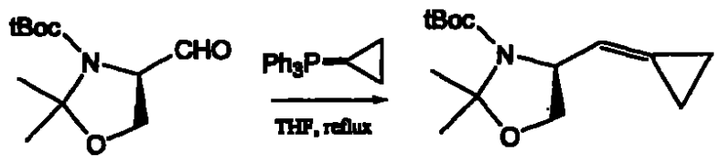


21.05 **21.01**

Concentrated hydrochloric acid (4.5 mL) was added to a solution of the residue **21.05** 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 **21.01**, which was used further without purification.

Preparation of Intermediate 22.01

Step 1

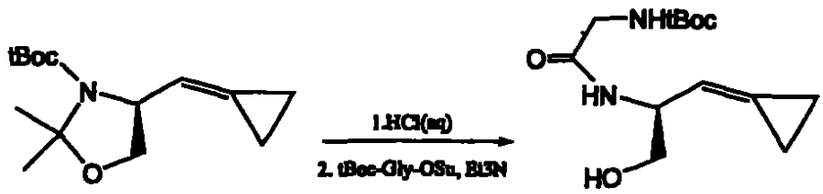


22.02 **22.03**

Potassium bis(trimethylsilyl)amide (158ml of a 0.5M solution in toluene; 79mmol) was added to a stirred suspension of cyclopropyltriphenylphosphonium bromide (33.12g; 86.4mmol) in anhydrous tetrahydrofuran (130ml) and the resulting orange mixture was stirred under an atmosphere of nitrogen at room temperature for a period of 1h., before the addition of the aldehyde **22.02** (9.68g; 42.2mmol) in THF (8ml). The reaction

was then refluxed under an atmosphere of nitrogen for a period of 2h. After cooling, methanol, diethyl ether and Rochelles salt were added. The organic phase was separated, washed with brine, dried and concentrated under reduced pressure. The crude reaction product was purified by silica gel column chromatography using EtOAc-hexane (1:99) to EtOAc-hexane (5:95) to provide the alkene **22.03** (8.47g) as a yellow oil.

Step 2



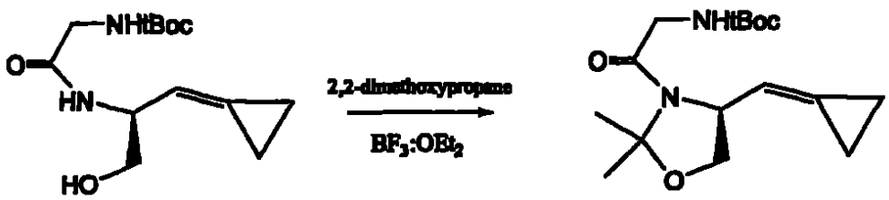
22.03 **22.04**

A solution of 1M HCl in MeOH/MeOAc was prepared by adding 14.2ml of acetyl chloride dropwise into cold methanol and diluting the resulting solution to 200ml at room temperature.

The carbamate **22.03** (9.49g; 37.5mmol) was dissolved in methanol (12ml) and added to 1M HCl in MeOH/MeOAc (150ml) while cooled in an ice bath. The resulting mixture was maintained at this temperature for 1h., then the ice bath was removed and stirring continued overnight at room temperature. The volatiles were removed under reduced pressure to yield a yellow oil which was used in the next step without purification.

The yellow oil was dissolved in a mixture of THF (30ml) and MeOH (20ml) and treated with triethylamine (15ml; 108mmol) until the solution was pH=9-10. After placing in an ice bath, the mixture was treated with N-Boc-Gly-OSu (11.22g; 41mmol). The ice bath was withdrawn and the reaction stirred at room temp. for 1h. The volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography using methanol (1-3%) in dichloromethane providing the desired amide **22.04** (9.09g).

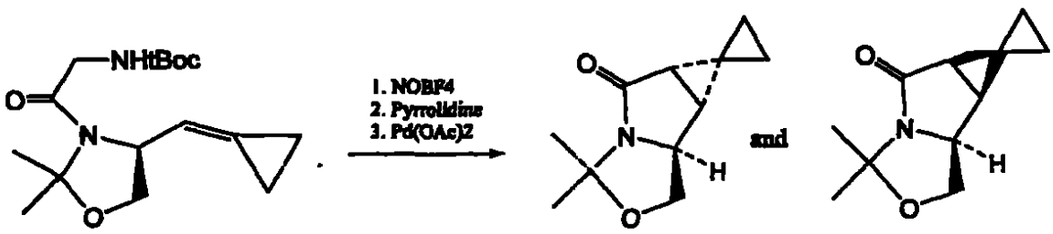
Step 3



22.04 **22.05**

The alcohol **22.04** (9.09g; 33.6mmol) was dissolved in acetone (118.5ml) and treated with 2,2-dimethoxypropane (37.4ml;304mmol) and BF_3:Et_2O (0.32ml; 2.6mmol) and the resulting mixture was stirred at room temperature for a period of 5.5h The reaction solution was treated with a few drops of triethylamine and the volatiles were removed under reduced pressure. The residue was purified by silica gel column chromatography using 5-25% EtOAc in hexanes to provide the N,O-acetal **22.05** (8.85g).

Step 4

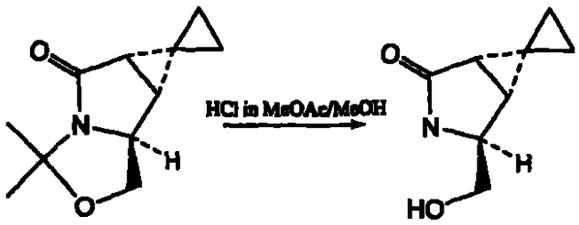


22.05 **22.06** **22.07**

The carbamate **22.05** (8.81g; 28.4mmol) was dissolved in acetonitrile (45ml) and the solution was cooled to –40°C under an atmosphere of nitrogen. Pyridine (6.9ml; 85.3mmol) followed by nitrosium tetrafluoroborate (6.63g; 56.8mmol) were added and the resulting reaction mixture maintained below 0°C until TLC indicated that no starting material remained (approx. 2.25h.). Pyrrolidine (20ml; 240mmol) was added and the cooling bath was withdrawn and stirring was continued at room temperature for 1h. and then the volatiles were removed under reduced pressure. The residue was quickly passed through a pad of silica gel to provide a yellow oil.

The yellow oil was dissolved in anhydrous benzene (220ml) and palladium acetate (0.317g; 1.41mmol) was added before heating the resulting mixture to reflux, under an atmosphere of nitrogen for a period of 1.5h. After cooling, the volatiles were removed under reduced pressure and the dark residue was purified by silica gel column chromatography using EtOAc-hexane (1:4) to provide the I) the trans- pyrrolidinone **22.06** (1.94g) followed by ii) the cis- pyrrolidinone **22.07** (1.97g).

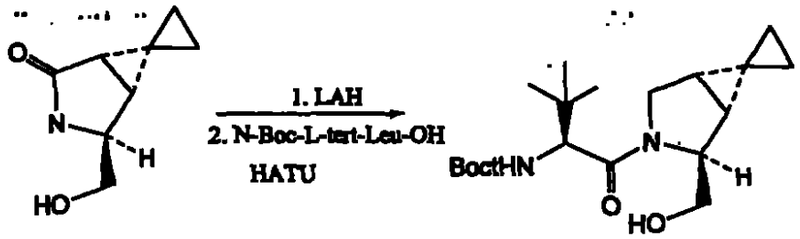
Step 5



22.06 22.08

Freshly prepared 1M HCl in MeOAc/MeOH (10ml; as described above) was added to the N,O-acetal **22.06** and stirred at room temperature for 1h. The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using 0-4%MeOH in dichloromethane as eluent to provide the desired alcohol **22.08** (1.42g), a yellow oil.

Step 6



22.08 22.09

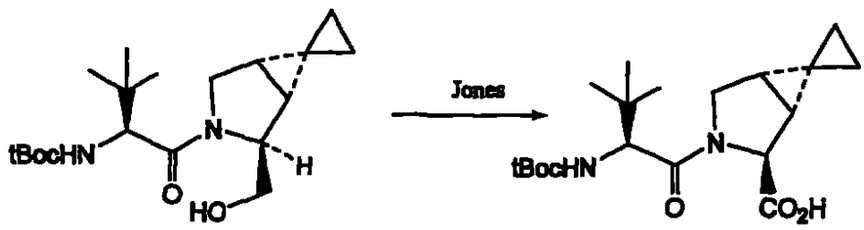
To a solution of the lactam **22.08** (1.29g; 8.44mmol) in anhydrous tetrahydrofuran (55ml) was added lithium aluminum hydride (2.40g; 63.2mmol) and the resulting mixture was refluxed for 8h. After cooling, water, followed by 15% aq. NaOH were added and the resulting mixture was filtered through celite and the solid was washed thoroughly with THF and MeOH. The solvent was removed under reduced pressure and the residue redissolved in dichloromethane, dried and concentrated under reduced pressure to provide the pyrrolidine, used without purification.

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

54
54

silica gel column chromatography using EtOAc:hexanes (1:3) to give the desired amide **22.09** (2.00g).

Step 7

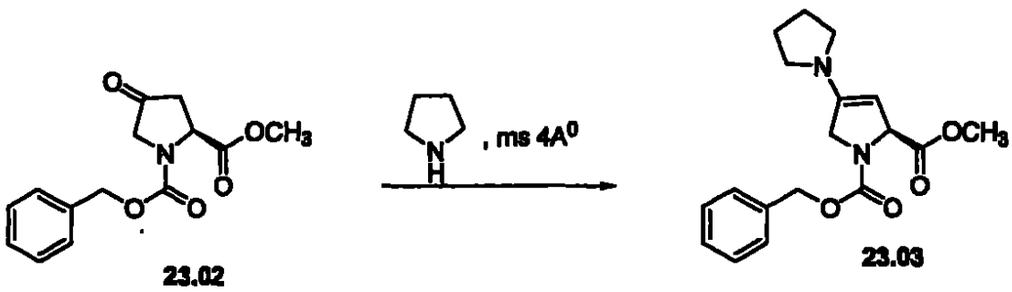


22.09 **22.01**

The alcohol **22.09** (2.00g; 5.67mmol) was dissolved in acetone (116ml) and cooled in an ice bath for 10min. This solution was then added to a cooled Jones reagent (14.2ml; approx 2mmol/ml) and the resulting mixture was stirred at 5C for 0.5h and the cooling bath was removed. The reaction was stirred for a further 2h. at room temp., before adding to sodium sulfate (28.54g), celite (15g) in EtOAc (100ml). Isopropanol (15ml) was added after 1min and then stirred for a further 10min. and filtered. The filtrate was concentrated under reduced pressure, providing a brown oil which was dissolved in EtOAc. This solution was washed with water, 3% aq. citric acid, brine, dried and concentrated to provide the desired carboxylic acid **22.01** (1.64g) as a white solid.

Preparation of Intermediate **23.01**

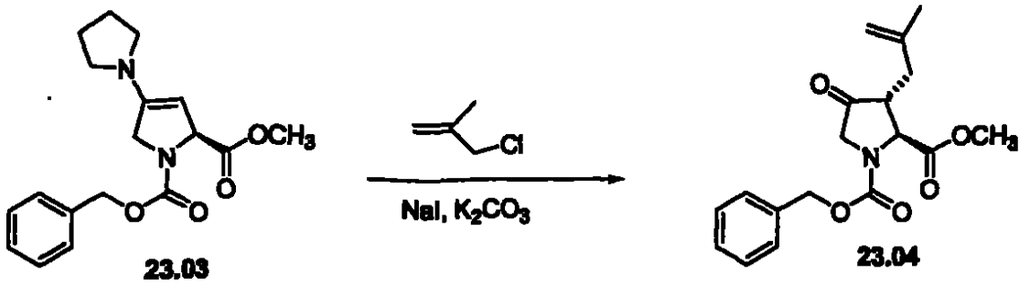
Step 1



23.02 **23.03**

To the mixture of ester **23.02** (6.0g) and molecular sieve (5.2g) in anhydrous methylene chloride (35 mL) was added 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, **23.03**.

Step 2



23.03 23.04

To a solution of the product **23.03** 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, **23.04**.

Step 3



23.04 23.05

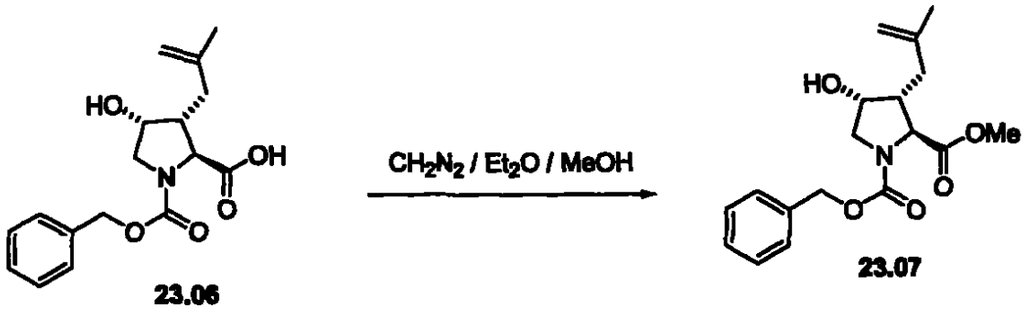
The product **23.04** from the preceding step (2.7 g, 8.16 mmoL) was dissolved in dioxane (20 mL) and treated with freshly prepared 1N LiOH (9 mL). The reaction mixture was stirred at ambient temperature under N_2 for 20 h. The reaction mixture was taken in EtOAc and washed with H_2O. The combined aqueous phase was cooled to 0^0C and acidified 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 $MgSO_4$, and concentrated to give the desired acid, **23.05** (3.40 g).

Step 4



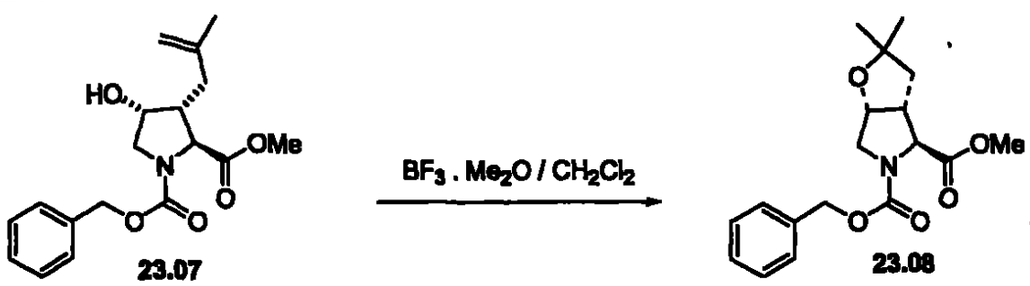
To a suspension of $NaBH(OAc)_3$ (3.93g, 18.5 mmoL) in CH_2Cl_2 (55 mL) was added a solution of product **23.05** from preceding step in anhydrous CH_2Cl_2 (20 mL) and acetic acid (2 mL). The slurry was stirred at ambient temperature for 20 h . Ice cold water (100 mL) was added to the slurry and stirred for 1/2 hr. Organic layer was separated, filtered, dried and evaporated to yield the desired product, **23.06**.

Step 5



To a solution of the product **23.06** 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, **23.07**.

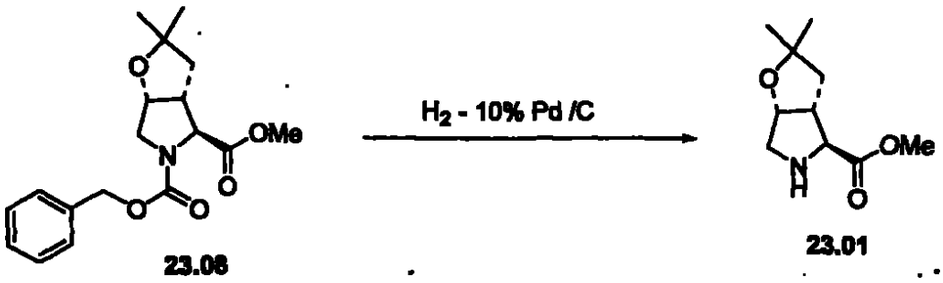
Step 6



To a solution of product **23.07** 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 chromatographed on silica gel eluting with a gradient of EtOAc / hexane to afford 0.88 g of the desired compound, **23.08**.

Step 7



23.08 **23.01**

To a solution of the product **23.08** (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 yield the desired compound, **23.01**.

PREPARATION OF P_3 MOIETIES

Preparation of Intermediate **50.01**

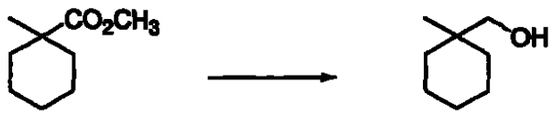
Step 1



50.02 **50.03**

To a solution of **50.02** (15 g) in MeOH (150 mL) was added conc HCl (3-4 mL) and the mixture was refluxed for 16 h. The reaction mixture was cooled to room temperature and concentrated. The residue was taken in diethyl ether (250 mL) and washed with cold saturated sodium bicarbonate solution, and brine. The organic layer was dried (Na_2SO_4) and concentrated to afford the methyl ester **50.03** (12.98 g) which was carried forward without further purification.

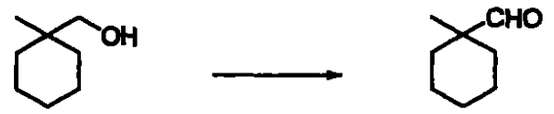
Step 2



50.03 50.04

The methyl ester 50.03 from above was dissolved in methylene chloride (100 mL) and cooled to -78°C, under nitrogen atmosphere. DIBAL (1.0 M solution in methylene chloride, 200 mL) was added dropwise over 2 h period. The reaction mixture was warmed to room temperature over 16 h. The reaction mixture was cooled to 0°C and MeOH (5-8 mL) was added dropwise. A solution of aqueous 10% sodium potassium tartarate (200 mL) was slowly added with stirring. Diluted with methylene chloride (100 mL) and separated the organic layer (along with some white precipitate). The organic layer was washed with 1 N HCl (250 mL), brine (200 mL), dried (Na_2SO_4) and concentrated to provide the alcohol 50.04 (11.00 g) as a clear oil.

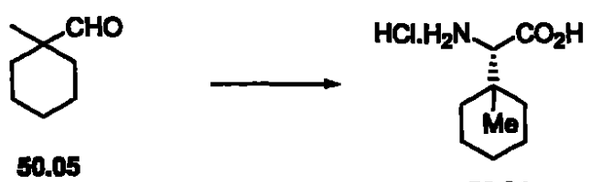
Step 3



50.04 50.05

The alcohol 50.04from above was dissolved in methylene chloride (400 mL) and cooled to 0°C under nitrogen atmosphere. PCC (22.2 g) was added in portions and the reaction mixture was slowly warmed to room temperature over 16 h. The reaction mixture was diluted with diethyl ether (500 mL) and filtered through a pad of celite. The filtrate was concentrated and the residue was taken in diethyl ether (500 mL). This was passed through a pad of silica gel and the filtrate was concentrated to provide the aldehyde 50.05 which was carried forward without further purification.

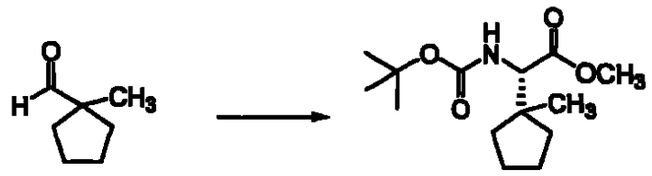
Step 4



50.05 50.01

The aldehyde 50.05 from above was converted to the desired material 50.01 using essentially the method of Chakraborty *et. al* (Tetrahedron, 1995, 51(33), 9179-90).

Preparation of Intermediate 51.01

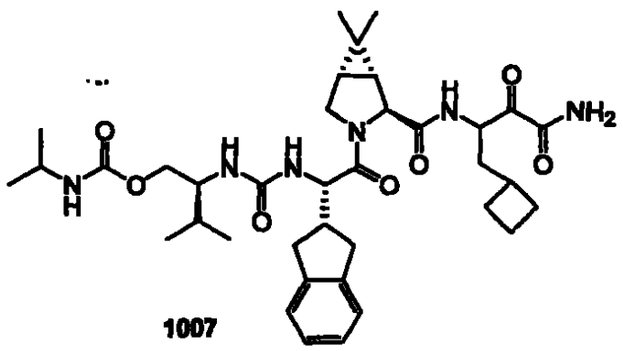


51.02 51.01

The required intermediate 51.01 was obtained from the aldehyde 51.02 using the literature described procedure (T. K. Chakraborty et al., *Tetrahedron*, 1995, 51 (33), 9179-90).

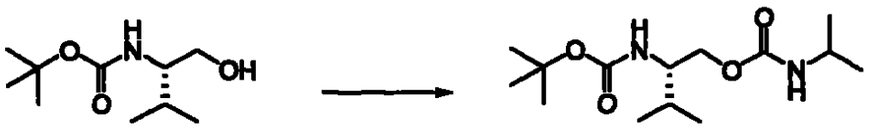
PREPARATION OF SPECIFIC EXAMPLES

Preparation of Example 1007



1007

Step 1



1007a 1007b

Commercially available compound 1007a (Aldrich Chemical Co., Milwaukee, Wisconsin, USA) was converted to 1007b according to the literature procedure (M. E. Duggan, J. S. Imagire *Synthesis* 1989, 131-2) in 90% yield. LC-MS: 289 (M+H).

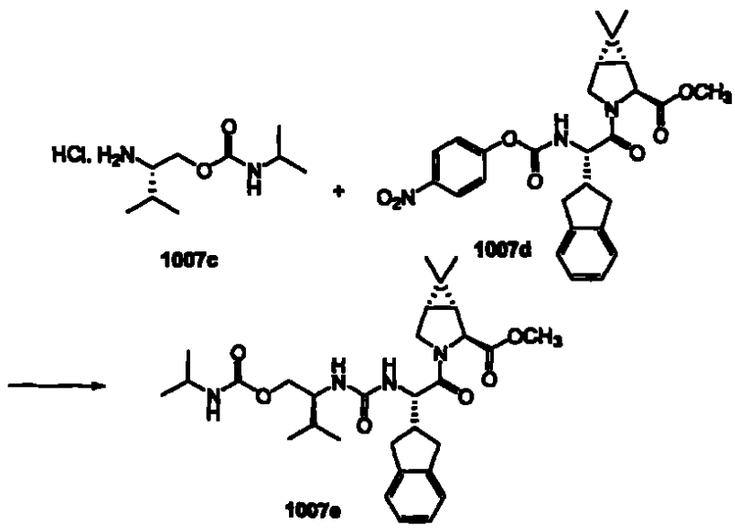
Step 2



1007b 1007c

Deprotection of 1007b using 4M HCl in dioxane at room temperature for 3 hrs provided 1007c in quantitative yield. This material was used without further purification.

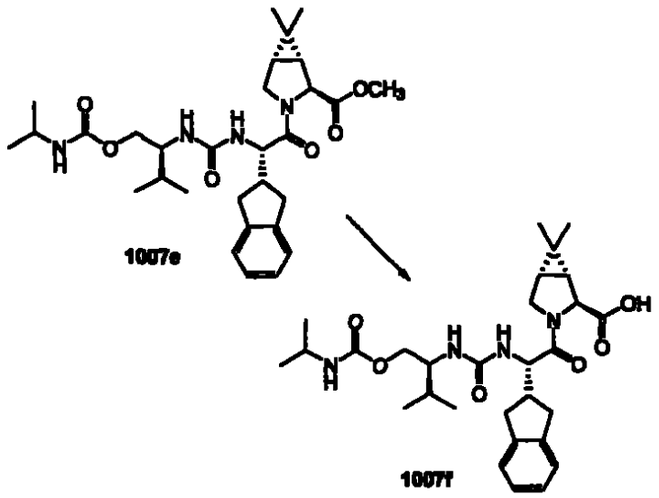
Step 3



Compound **1007d** was obtained from appropriate starting materials/reagents using the previously described procedures (See preparation of Intermediate **20.08**).

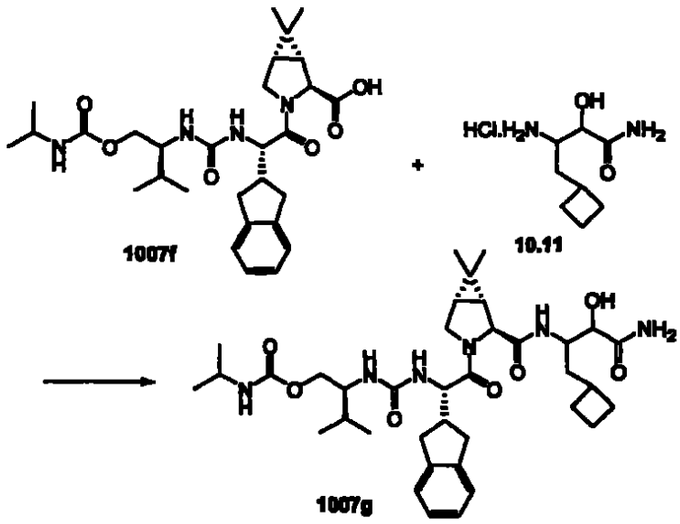
To a solution of **1007d** (200 mg, 0.394 mmol) in dichloromethane (10 mL) at 0°C, under nitrogen atmosphere, was added **1007c** (115 mg, 0.512 mmol) followed by DIPEA (0.22 mL, 1.182 mmol). The reaction was maintained at that temperature for 30 min and stored in the freezer (-20°C) for 48 hrs. The reaction mixture was quenched with saturated ammonium chloride solution and the product was extracted into dichloromethane (3 x). The combine organic layers was washed with brine (1 x), dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography using 30/70 acetone/hexanes which provided the required compound **1007e** in 69% yield. LC-MS: 557 (M+H).

Step 4



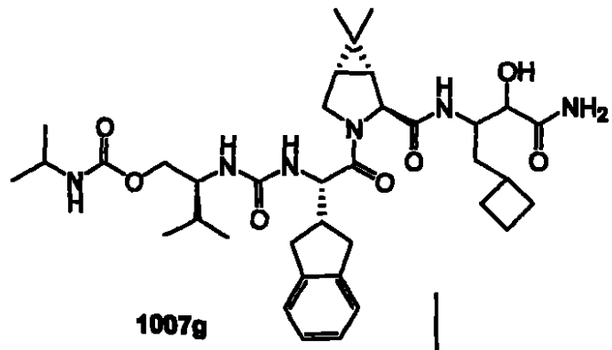
Hydrolysis of the methyl ester of 1007e to provide the required acid 1007f was carried out as described before (see preparation of Intermediate 20.04, Step 2) with appropriate modifications.

Step 5

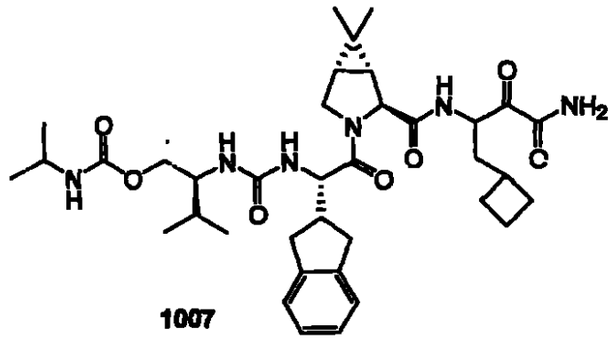


Coupling reaction of the acid 1007f (0.125 mmol) with the amine salt 10.11 was carried out as described before (see preparation of Intermediate 20.08, Step 1) with modifications (HATU instead of BOP, DIPEA instead of NMM; the reaction was carried out at 0°C for 15 min and warmed to 10°C over 24 hrs) and appropriate amounts of the reagents. The crude material obtained after workup, 1007g was carried forward without purification. LC-MS: 697.2 (M+H).

Step 6



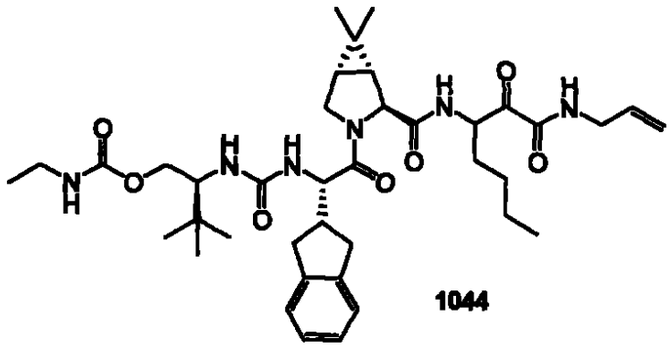
1007g



1007

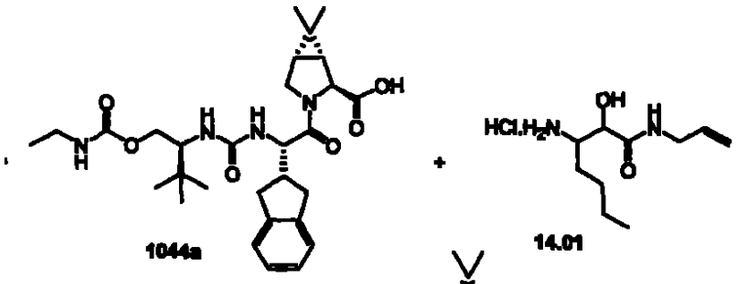
To a cold (0°C) solution of the material from above, **1007g** (0.125 mmol) in DMSO/toluene (3 mL each) was added EDCI (240 mg, 1.25 mmol) followed by dichloroacetic acid (0.052 mL, 0.625 mmol). After 15 min, the cold bath was removed and the reaction mixture was warmed to room temperature over 16 hr. The reaction mixture was diluted with EtOAc (20 mL) and washed with aqueous 1N $NaHSO_4$ (20 mL). The aqueous layer was separated and extracted with EtOAc (20 mL). The combined organic layers was washed with aqueous 1N $NaHSO_4$ (20 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography using 40/60 acetone/hexanes to provide the required target compound **1007** (57 mg, 0.082 mmol, 66% yield). LC-MS: 695.2 (M+H).

Preparation of Example 1044



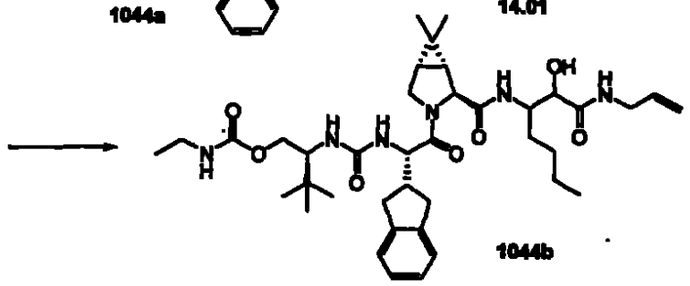
1044

Step 1



1044a

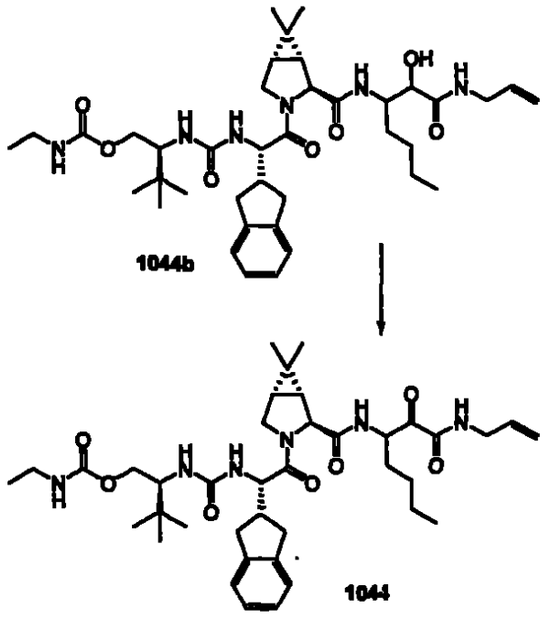
14.01



1044b

Coupling reaction of the acid **1044a**, obtained in a similar manner as described for **1007f** (see preparation of Example **1007**), with the amine salt **14.01** was carried out as described before (see preparation of Example **1007**, Step 5). The crude material obtained after workup, **1044b** was carried forward without purification. LC-MS: 725.2 (M+H).

Step 2:



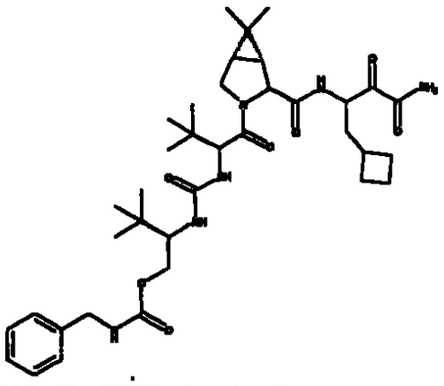
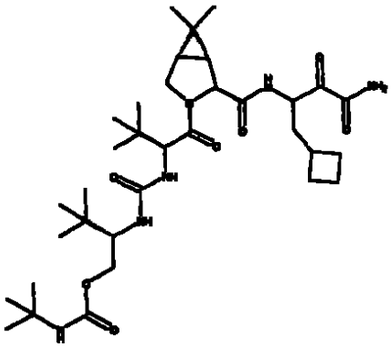
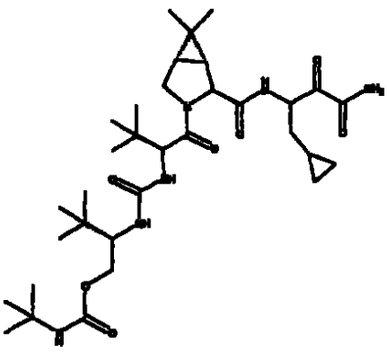
1044b

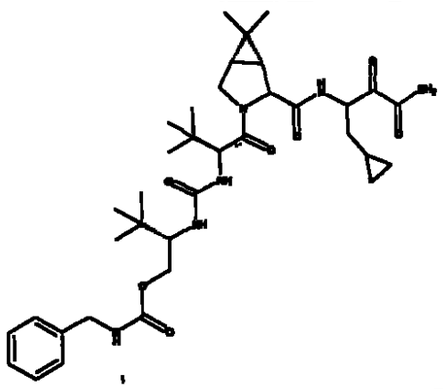
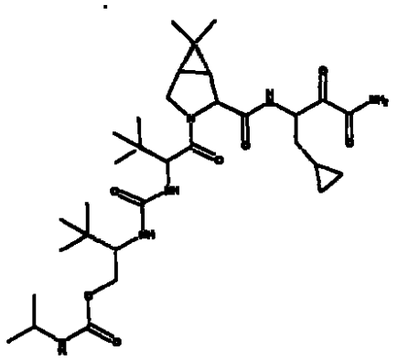
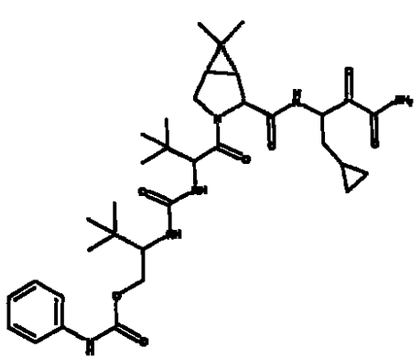
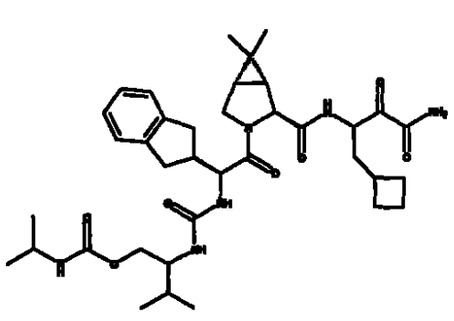
1044

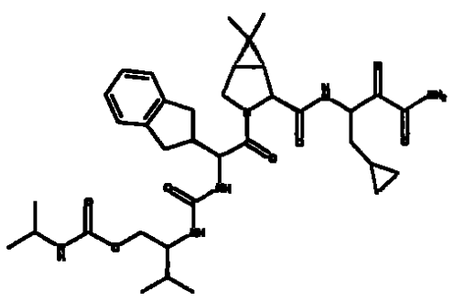
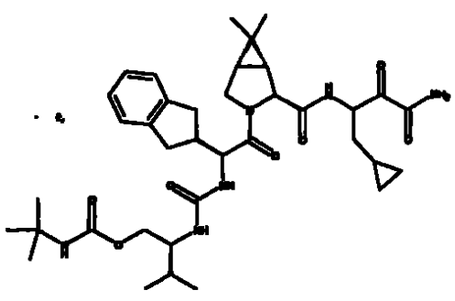
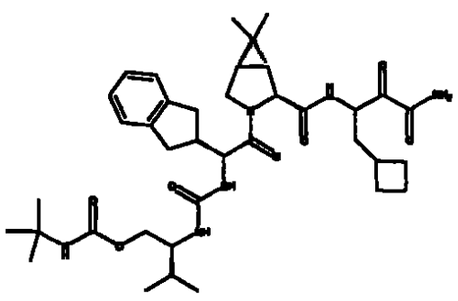
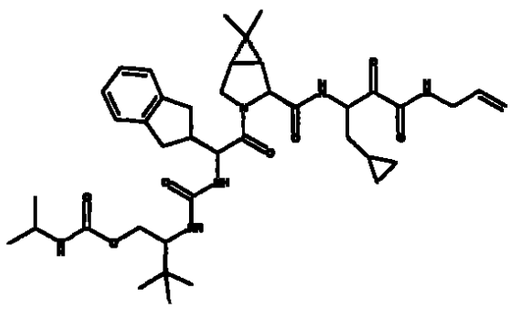
To a solution of the material from above, **1044b** (0.054 mmol) in dichloromethane (5 mL) was added Dess-Martin's periodinane (68 mg, 0.16 mmol). The reaction mixture was stirred at room temperature, under nitrogen atmosphere, for 4.5 hrs. The reaction mixture was diluted with dichloromethane (10 mL) and washed with aqueous 10% $Na_2S_2O_3$ (30 mL), saturated $NaHCO_3$ (30 mL), brine (30 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography using 35/65 acetone/hexanes to provide the required target compound **1044** (23 mg, 0.032 mmol, 59% yield). LC-MS: 723.2 (M+H).

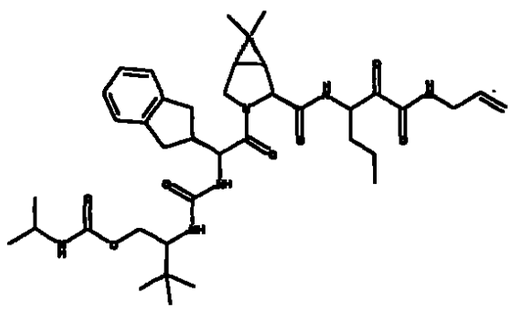
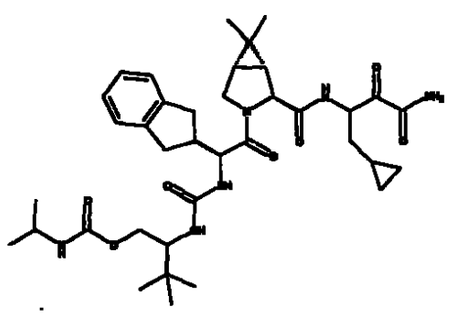
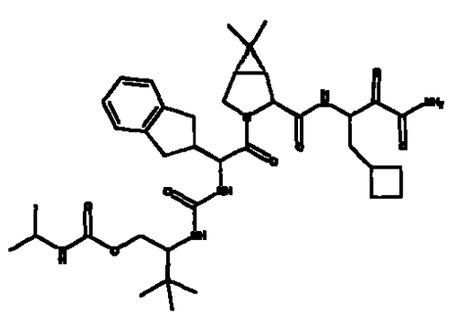
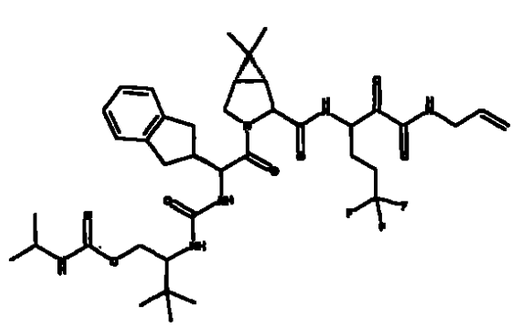
Compounds in the following **Table 1** and **Table 1A** were essentially prepared using the above-described procedures (Preparation of Examples **1007** and **1044**) with appropriate reagents and modifications as described in the General Schemes for Preparation of Target Compounds, Methods A-E.

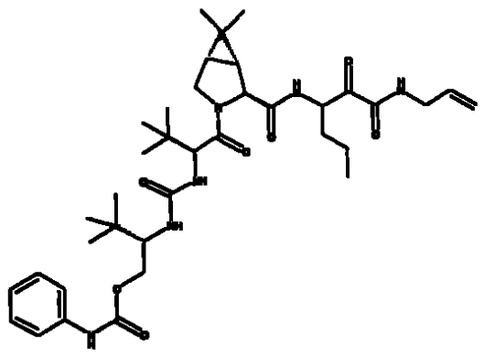
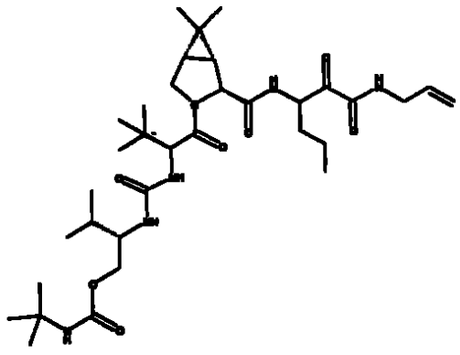
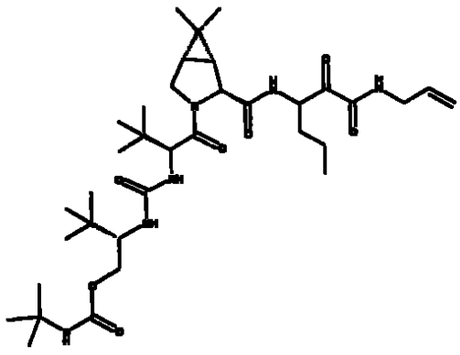
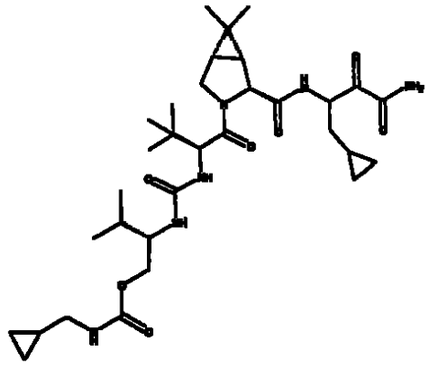
Table 1

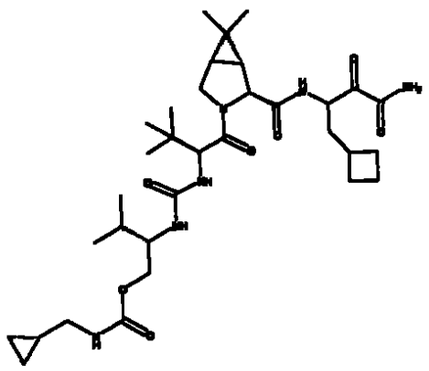
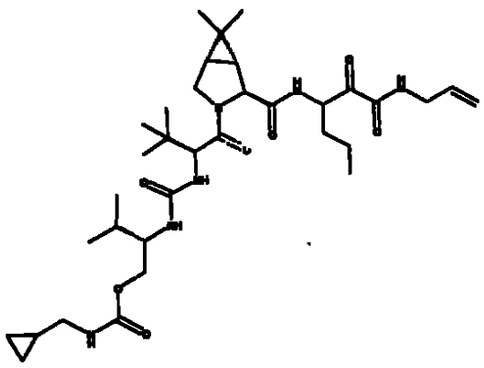
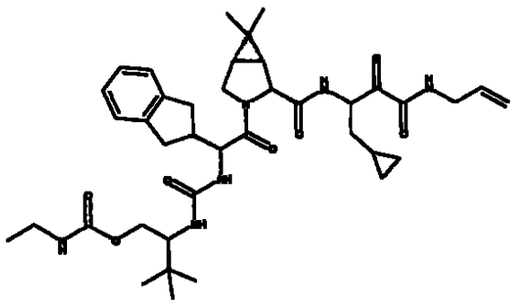
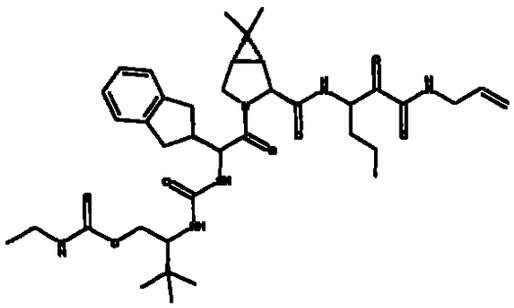
Example #	Structure	Ki* (nM)	Mol Weight
1001		A	696.885
1002		A	662.868
1003		A	648.841

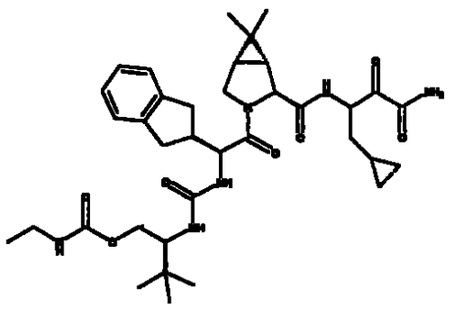
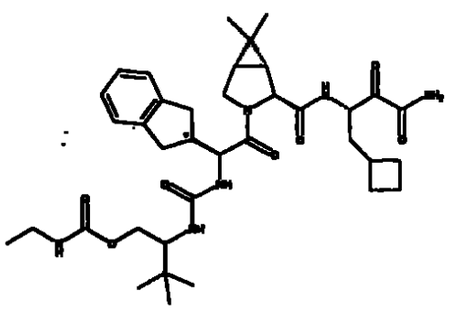
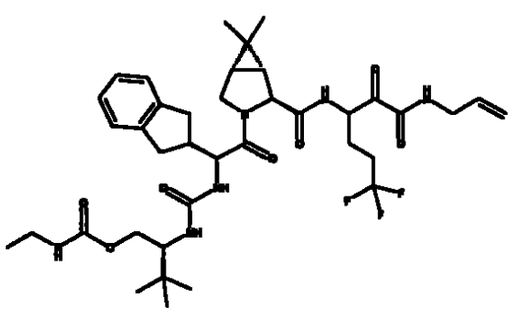
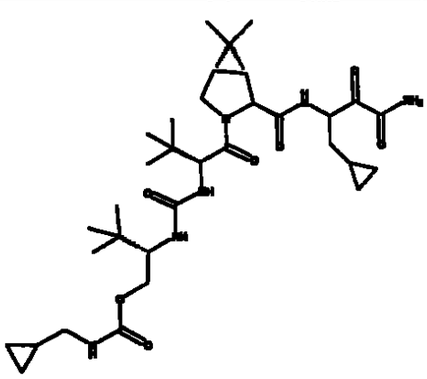
1004		A	682.859
1005		A	634.815
1006		A	668.832
1007		A	694.87

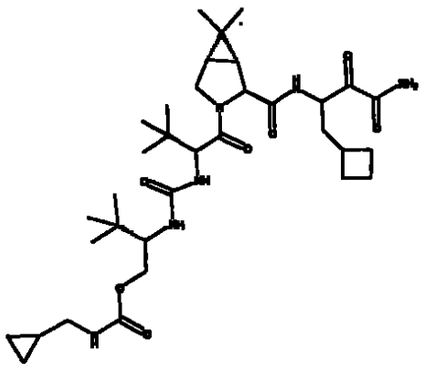
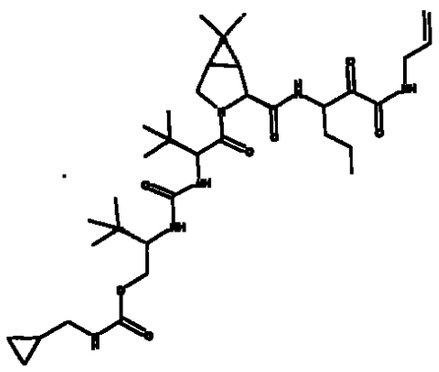
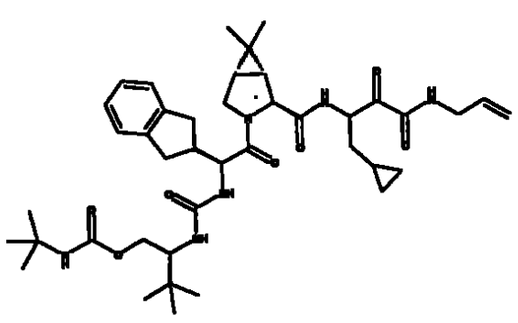
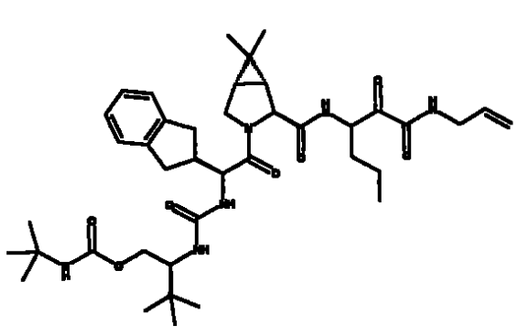
1008		A	680.843
1009		A	694.87
1010		A	708.896
1011		A	734.934

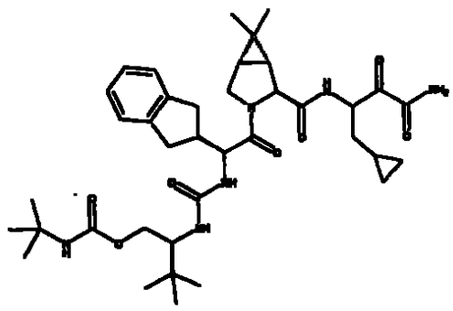
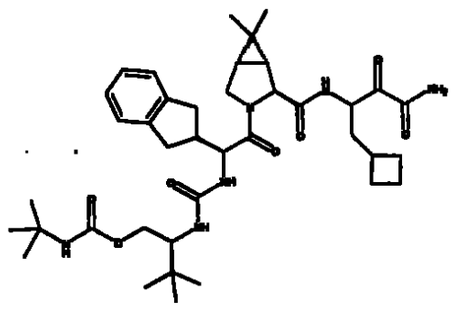
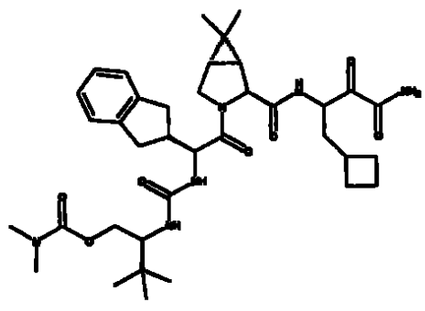
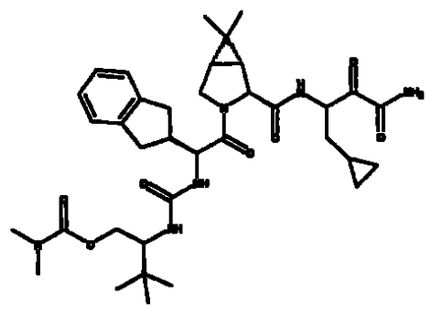
1012		A	722.923
1013		A	694.87
1014		A	708.896
1015		A	776.895

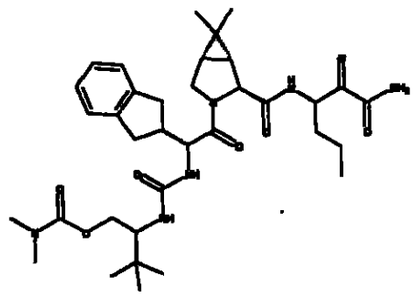
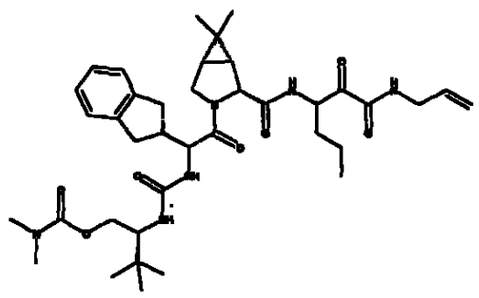
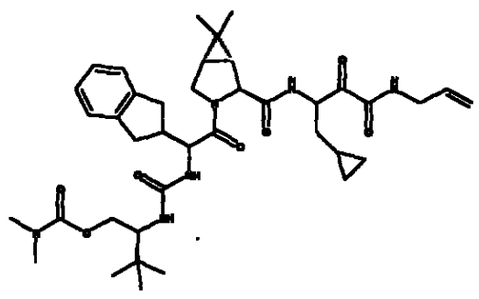
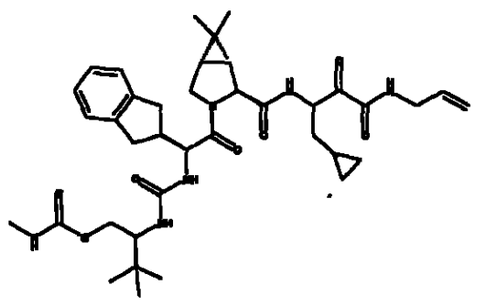
1016		A	696.885
1017		A	662.868
1018		A	676.895
1019		A	632.799

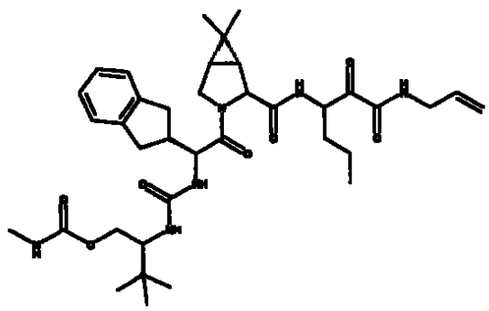
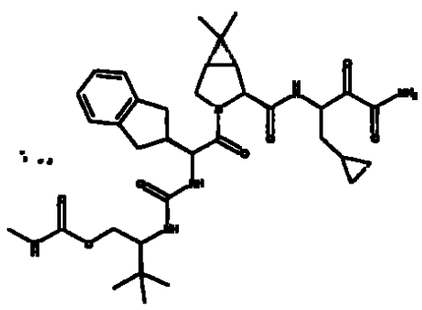
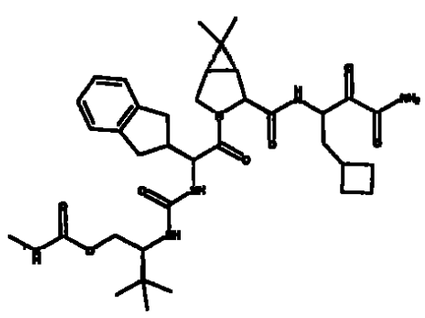
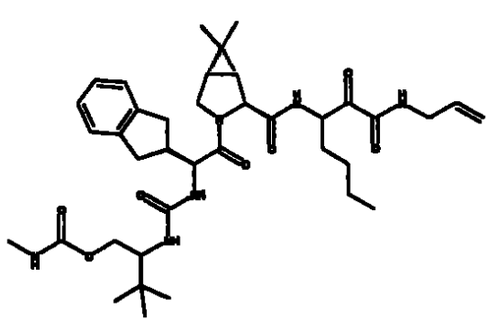
1020		A	646.826
1021		A	660.852
1022		A	720.907
1023		A	708.896

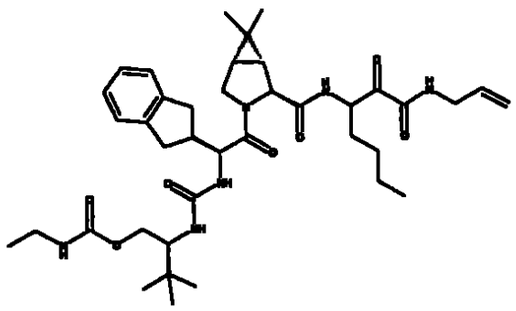
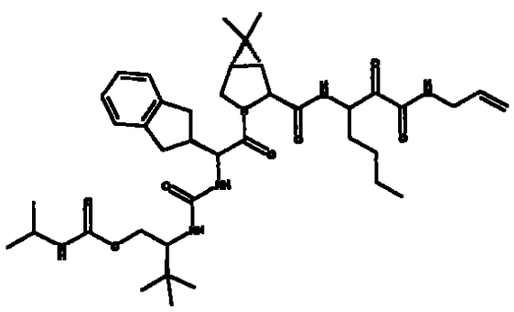
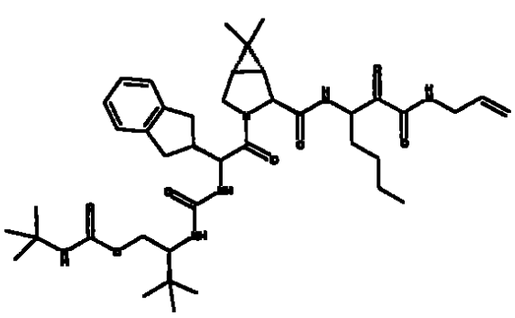
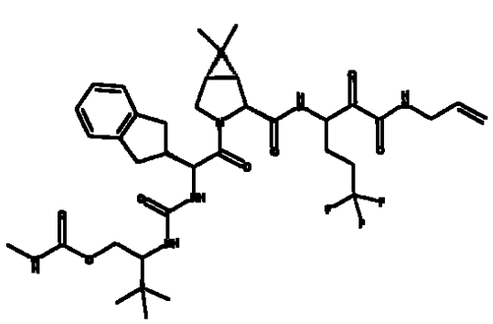
1024		A	680.843
1025		A	694.87
1026		A	762.868
1027		A	646.826

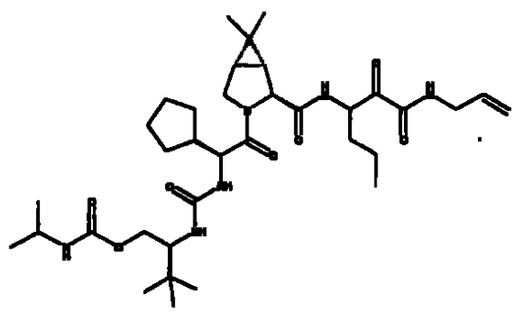
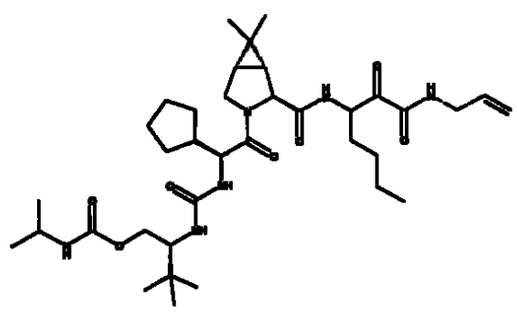
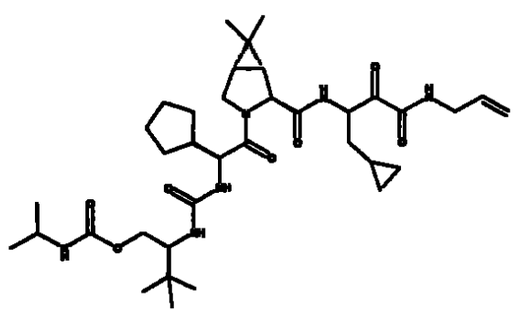
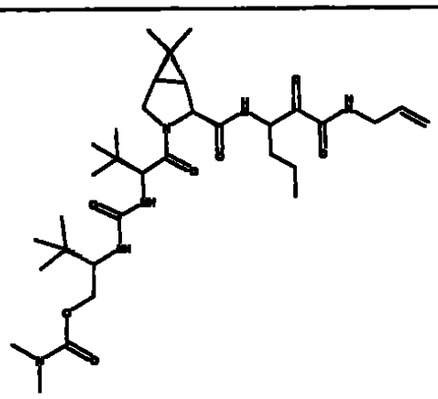
1028		A	660.852
1029		A	674.879
1030		A	748.961
1031		A	736.95

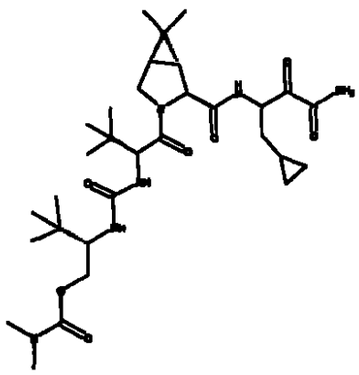
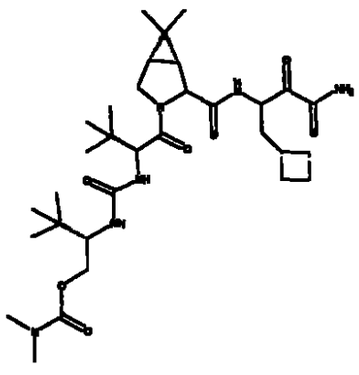
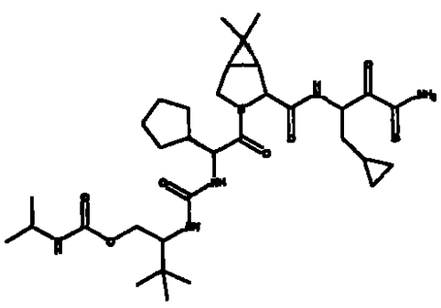
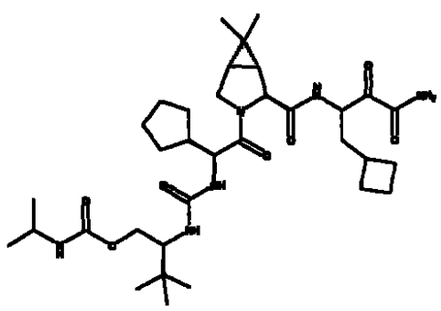
1032		A	708.896
1033		A	722.923
1034		A	694.87
1035		A	680.843

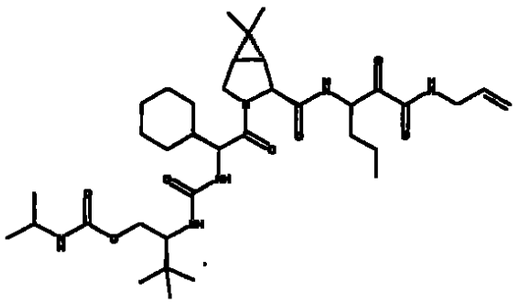
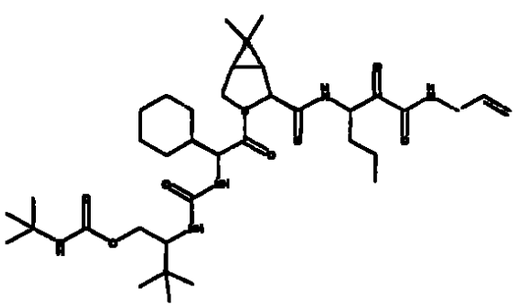
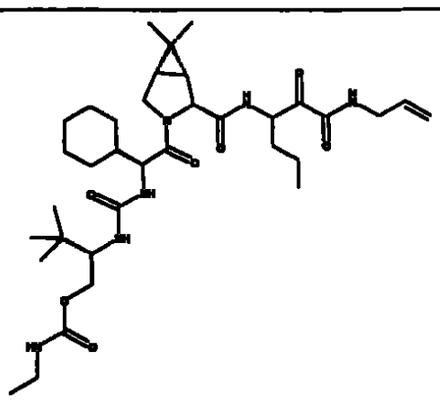
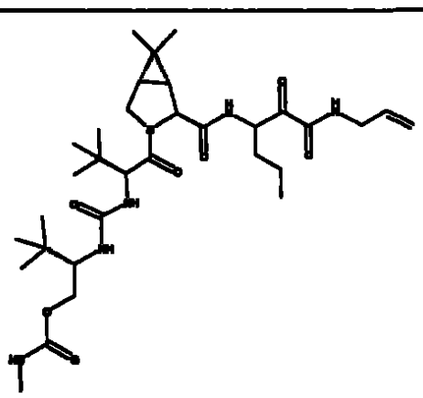
1036		A	666.832
1037		B	708.896
1038		B	720.907
1039		A	706.881

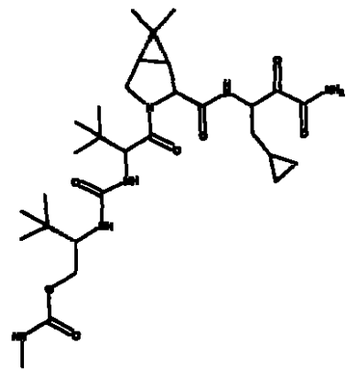
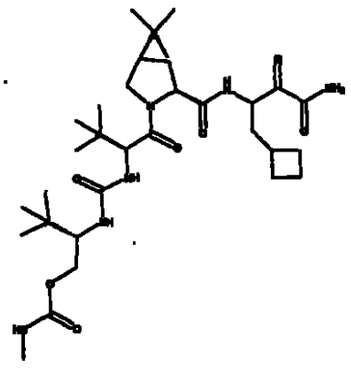
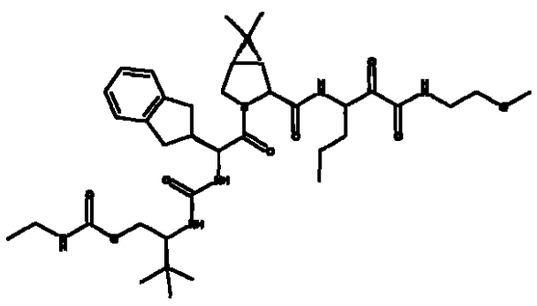
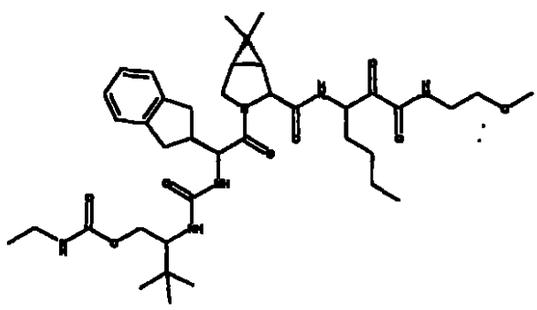
1040		A	694.87
1041		A	666.816
1042		A	680.843
1043		A	708.896

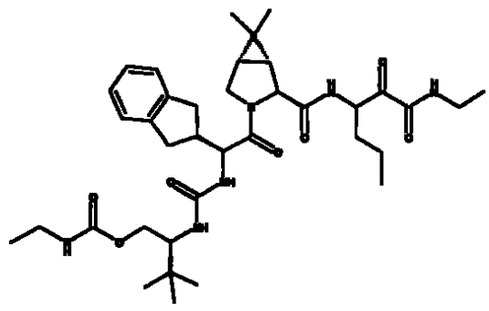
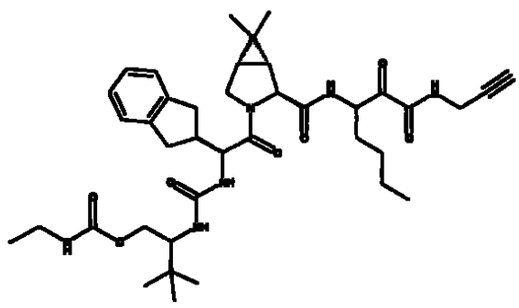
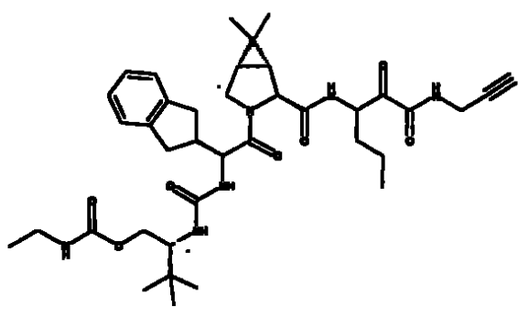
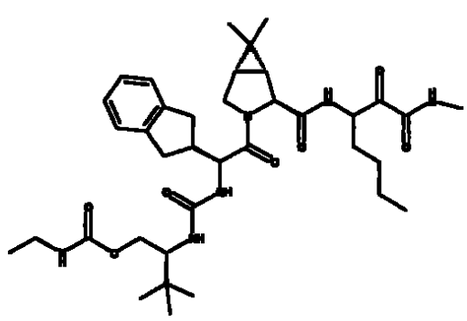
1044		A	722.923
1045		A	736.95
1046		A	750.977
1047		A	748.841

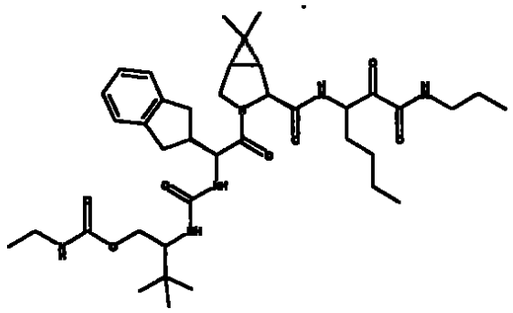
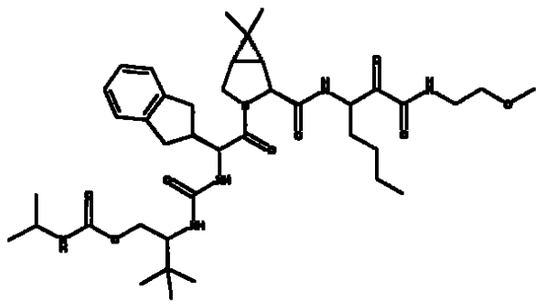
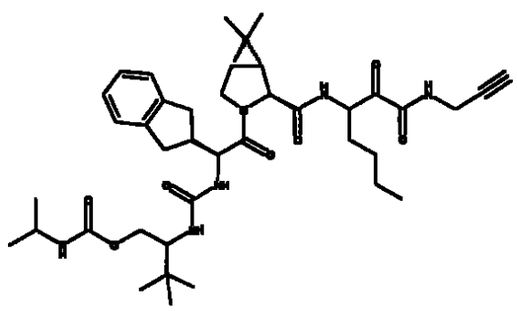
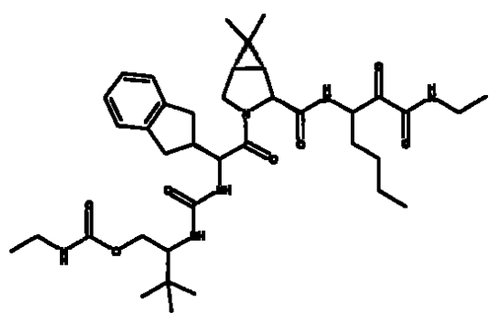
1048		A	674.879
1049		A	688.906
1050		B	686.89
1051		A	648.841

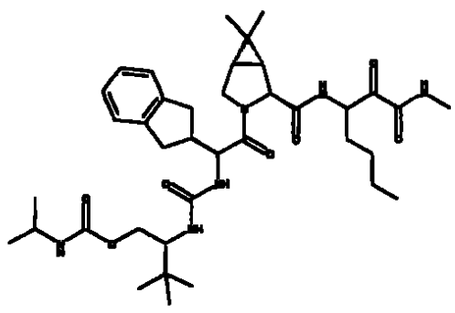
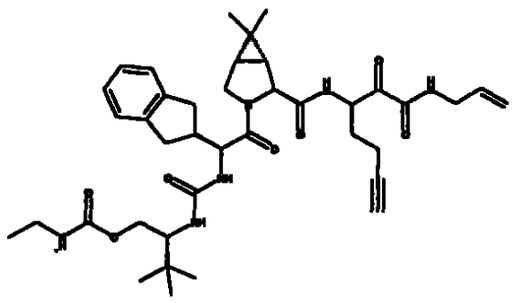
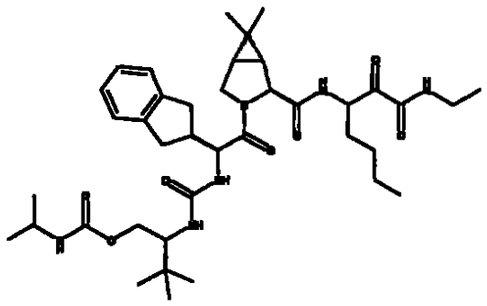
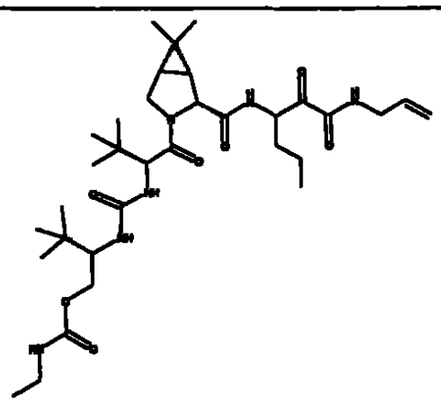
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1053		A	634.815
1054		A	646.826
1055		A	660.852

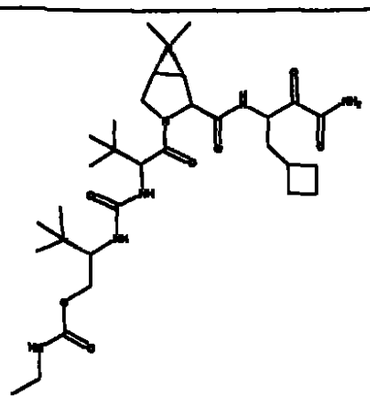
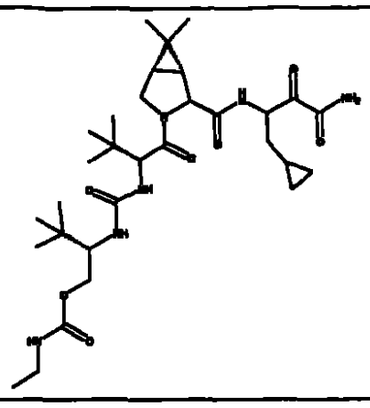
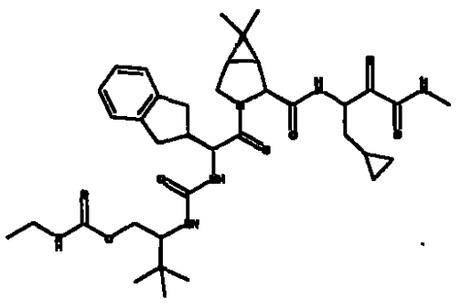
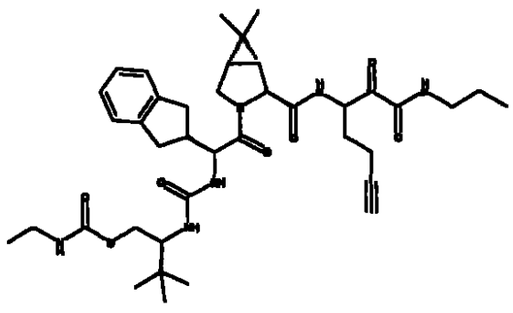
1056		A	688.906
1057		A	702.933
1058		A	674.879
1059		A	634.815

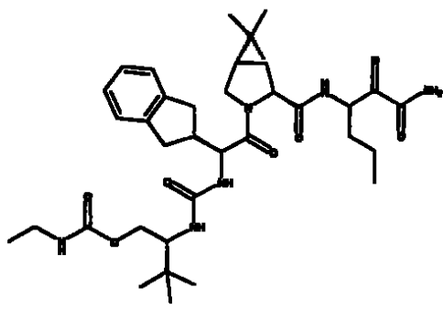
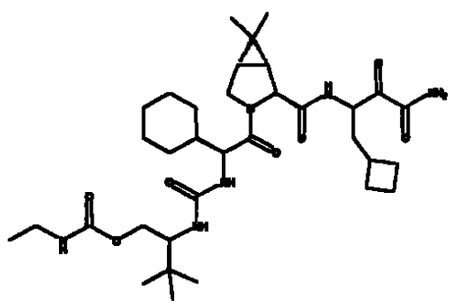
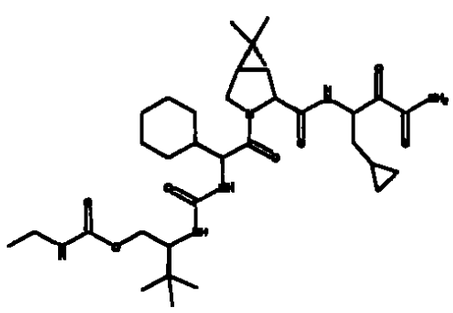
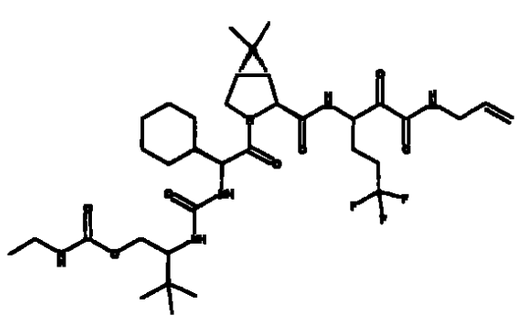
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1061		A	620.788
1062		B	726.912
1063		B	740.938

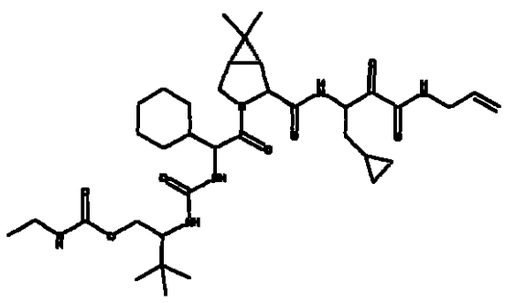
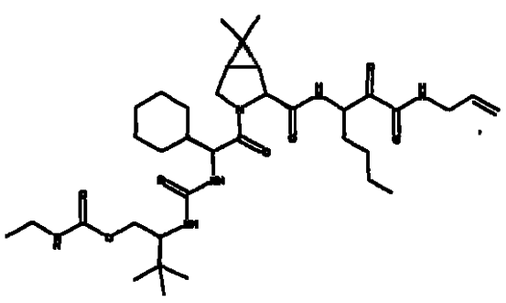
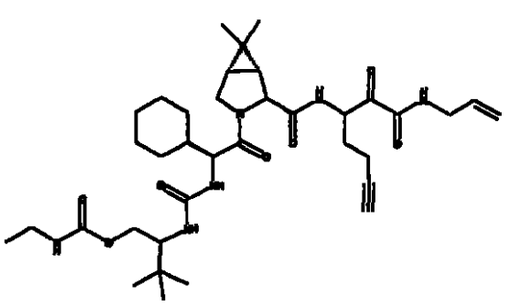
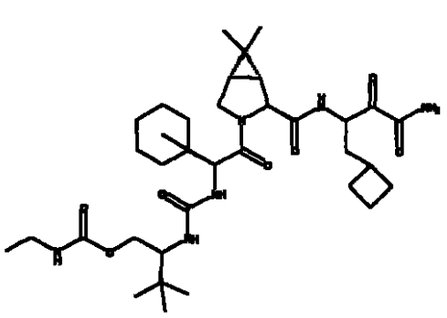
1064		B	696.885
1065		A	720.907
1066		A	706.881
1067		A	696.885

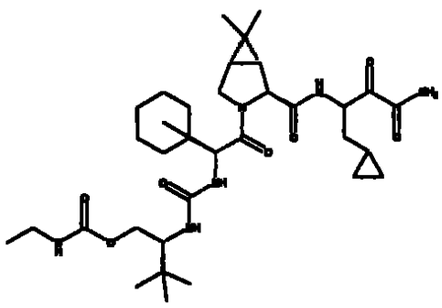
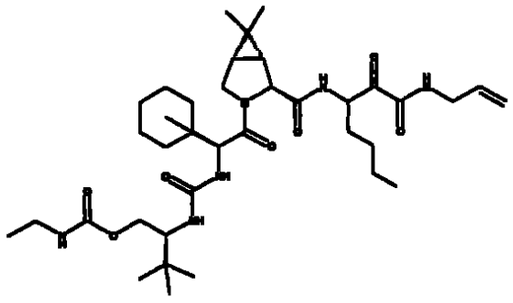
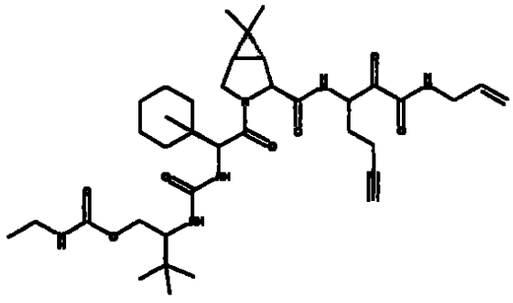
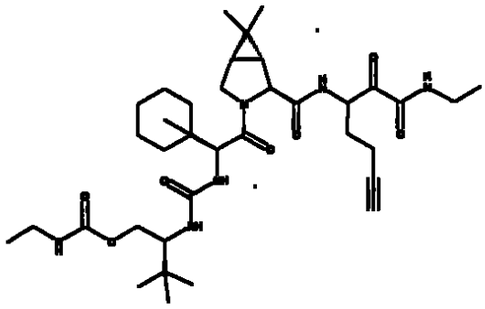
1068		B	724.939
1069		B	754.965
1070		A	734.934
1071		A	710.912

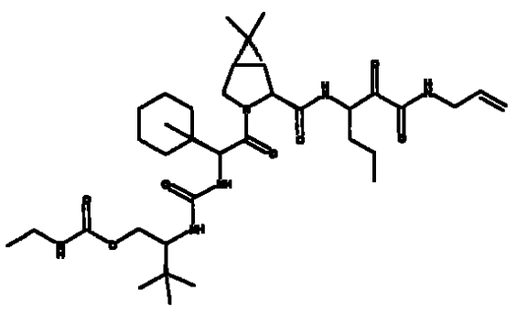
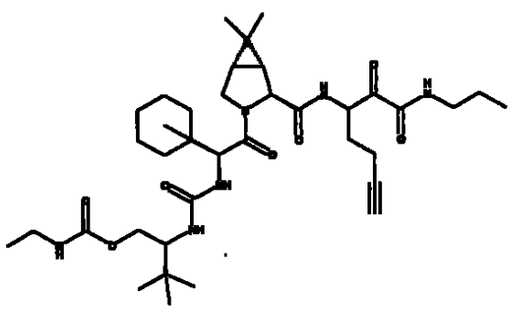
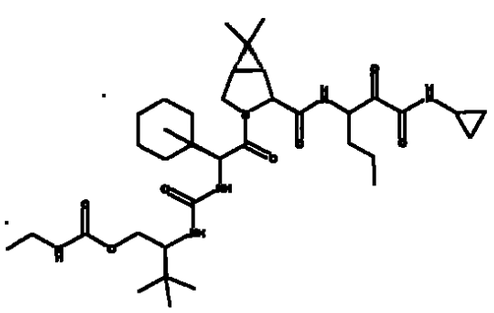
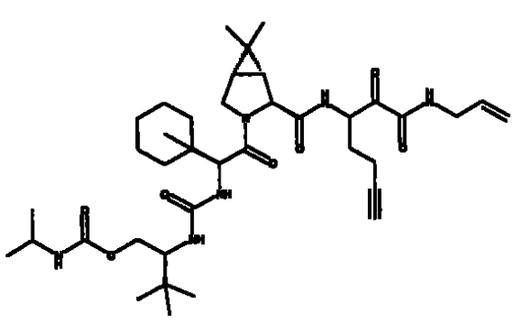
1072		A	710.912
1073		A	718.892
1074		B	724.939
1075		A	648.841

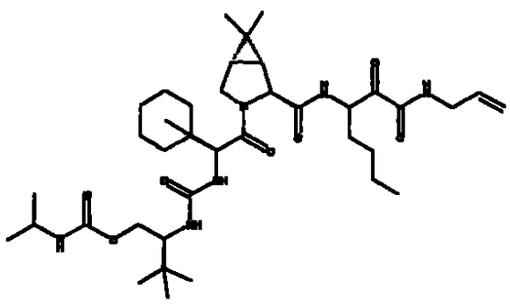
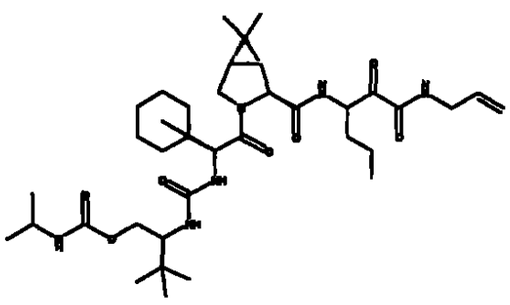
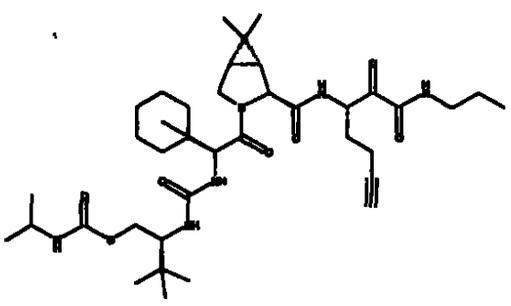
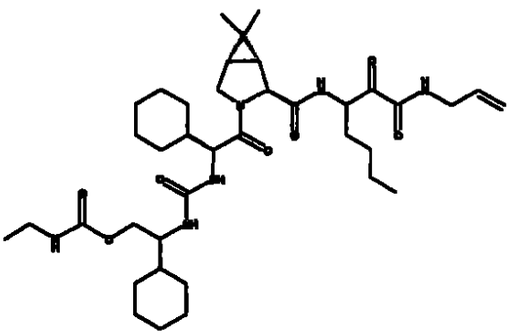
1076		A	634.815
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1078		B	694.87
1079		A	720.907

1080		A	668.832
1081		A	660.852
1082		A	646.826
1083		A	728.851

1084		A	686.89
1085		A	688.906
1086		A	684.874
1087		A	674.871

1088		A	660.844
1089		A	702.924
1090		A	698.892
1091		A	686.882

1092		A	688.898
1093		A	700.908
1094		A	688.898
1095		A	712.919

1096		A	716.951
1097		A	702.924
1098		A	714.935
1099		A	714.935

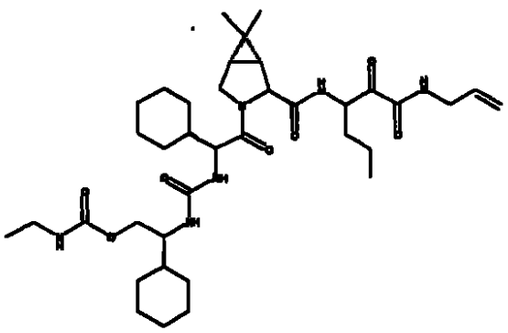
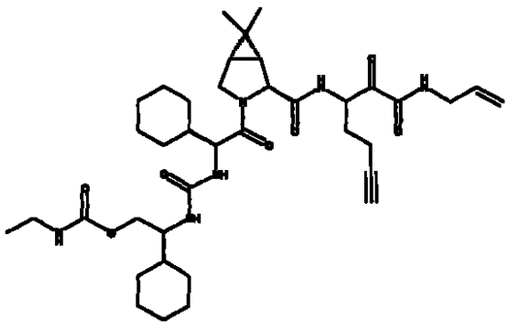
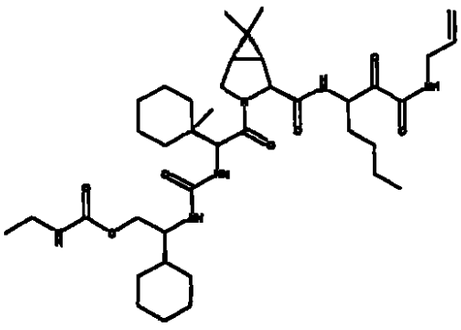
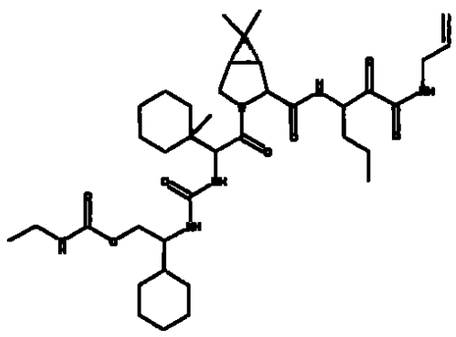
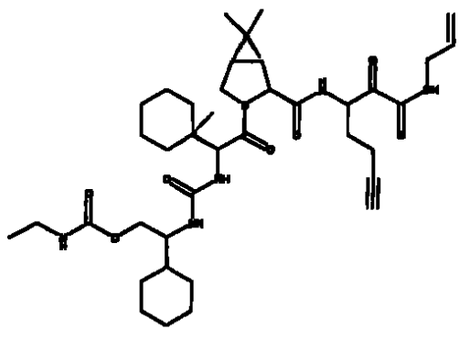
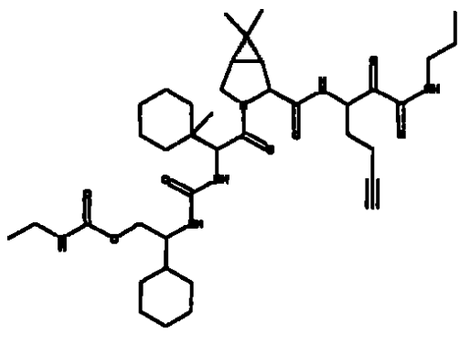
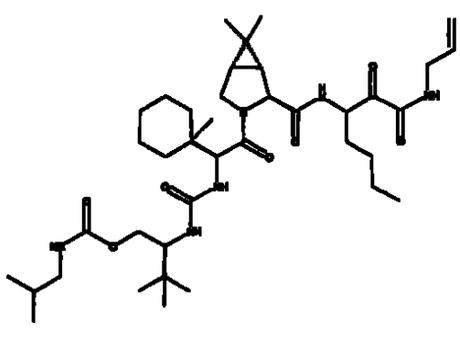
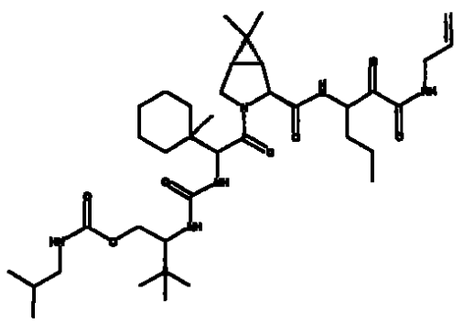
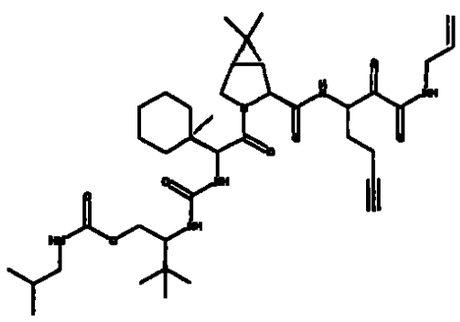
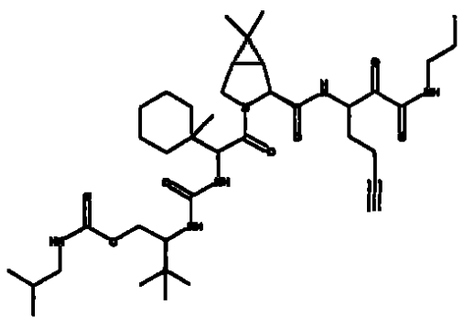
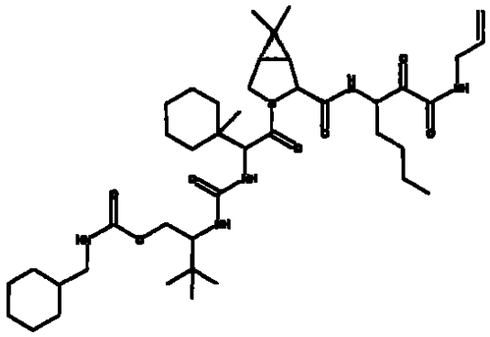
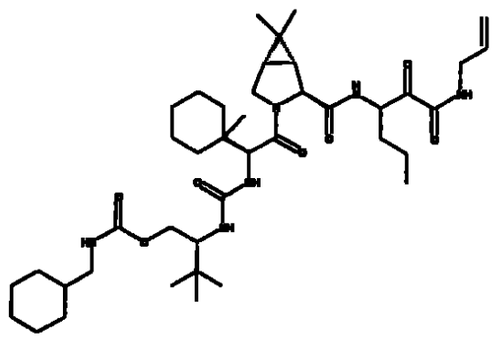
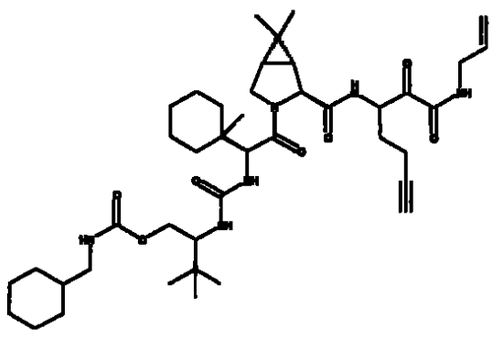
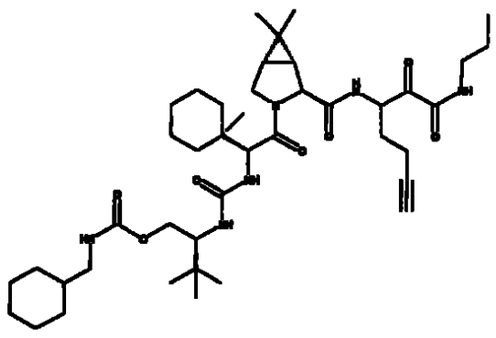
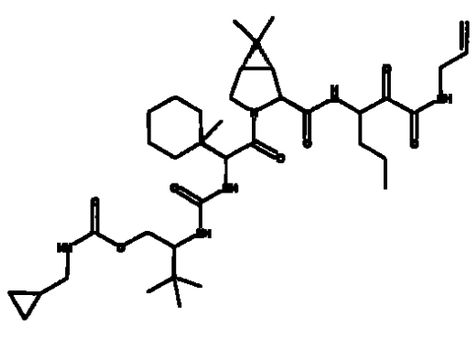
1100		A	700.908
1101		A	710.903

Table 1A

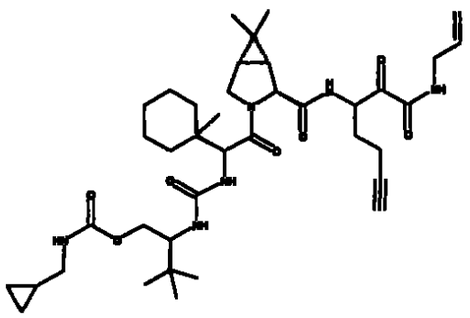
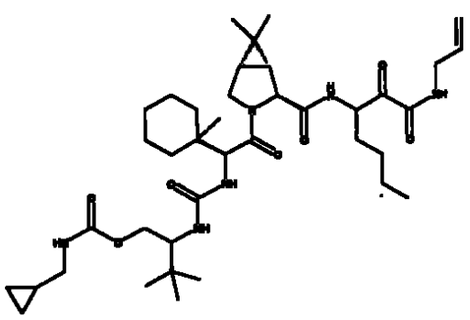
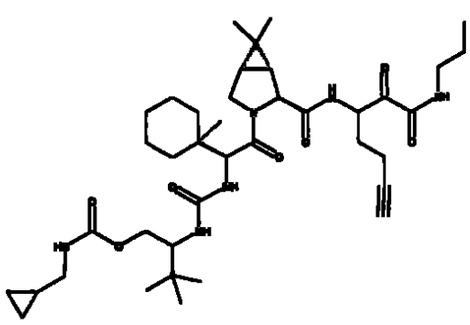
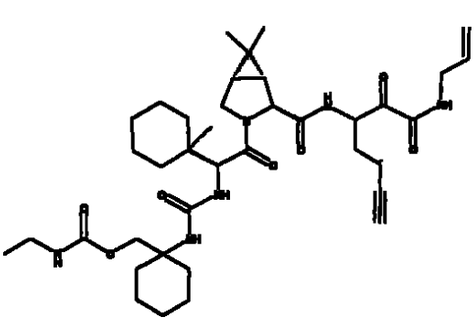
Example #	Structure	KI* (nM)	LC-MS (M+H)
1102		A	729.2

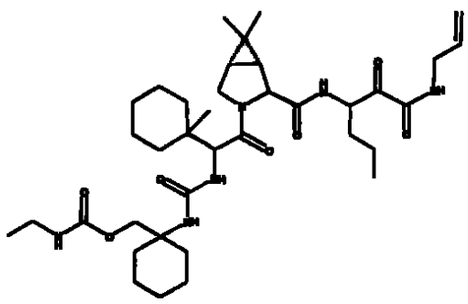
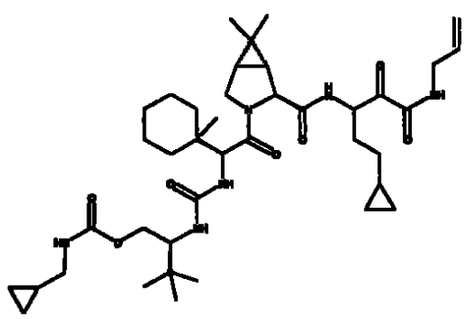
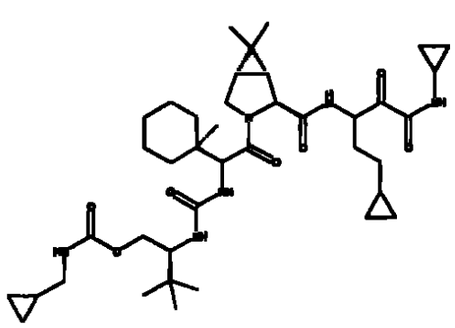
1103		B	715.2
1104		A	725.2
1105		A	727.2
1106		A	731.2

1107		A	717.2
1108		A	727.2
1109		A	729.2
1110		B	772.2

1111		B	757.2
1112		A	767.2
1113		B	769.4
1114		A	715.2

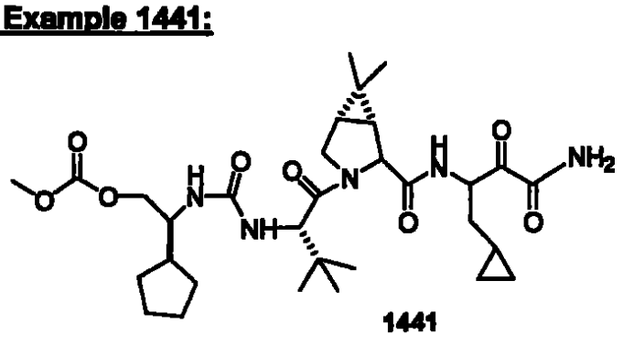
74
74

1115		A	724.939
1116		A	729.2
1117		A	727.2
1118		A	711.2

1119		B	701.2
1120		A	741.2
1121		A	741.4

Ki* range: A = <75 nM, B = 75-250 nM; C = > 250 nM

Preparation of Example 1441:



1441

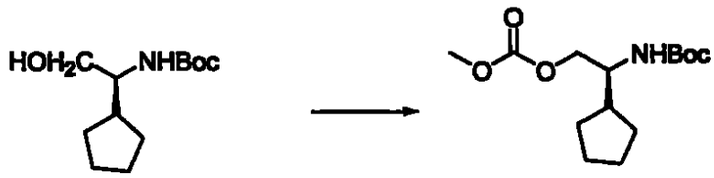
Step 1



1441a 1441b

To a ice cooled solution of **1441a** (4.28 g, 10.08 mmol) in anhydrous ether (100 mL) was added LAH (1.53 g, 40.32 mmol) and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was cooled to 0°C and EtOAc (3 mL) was added to it, followed by aqueous $KHSO_4$ (10 g in 25 mL of H_2O). The gummy residue was extracted with ether (300 mL) and the organic layer was washed with satd. $NaHCO_3$, followed by 10% aq. KH_2PO_4, brine, dried over $MgSO_4$, filtered and concentrated. The crude residue was purified by flash chromatography over SiO_2 using ethyl acetate/DCM (1:4) to yield **1441b** (2.14g, 92%).

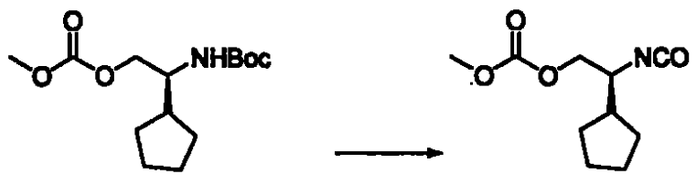
Step2



1441b 1441c

To a ice cooled solution of **1441b** (743 mg, 3.24 mmol) in anhydrous pyridine (10 mL) was added methyl chloroformate (1 mL, 13 mmol), followed by DMAP (1.6 g, 13 mmol) and the reaction mixture was allowed to warm to room temperature over 2 days. The reaction mixture was concentrated and EtOAc (100 mL) was added to it followed by 100 mL of ice-cold (5% KH_2PO_4containing 0.05 volumes of 1M H_3PO_4). The organic layer was washed with brine and dried over $MgSO_4$, filtered and concentrated. The crude was purified by flash chromatography over SiO_2 using ethyl acetate/DCM (1:4) to yield **1441c** (931 mg, 100% yield).

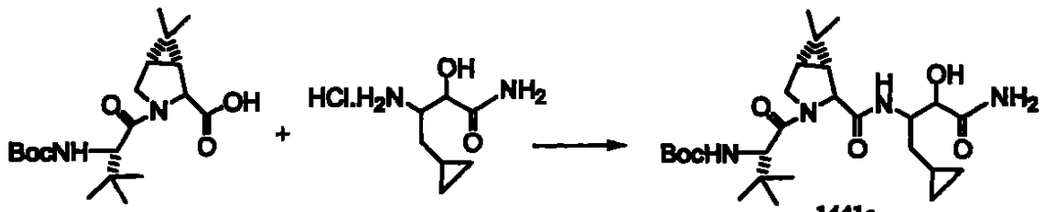
Step 3



1441c 1441d

1441c was dissolved in 4M HCl in dioxane (10 mL) and concentrated after 30 min. Saturated $NaHCO_3$ (25 mL) was added to an ice-cold solution of the crude hydrochloride salt (194 mg, 1 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred vigorously for 10 min and $COCl_2$ (1.85 M solution in PhMe, 4 mL) was added to it and stirring was continued at room temperature for 1h. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to half the volume to yield **1441d** as a 0.05 M solution in CH_2Cl_2.

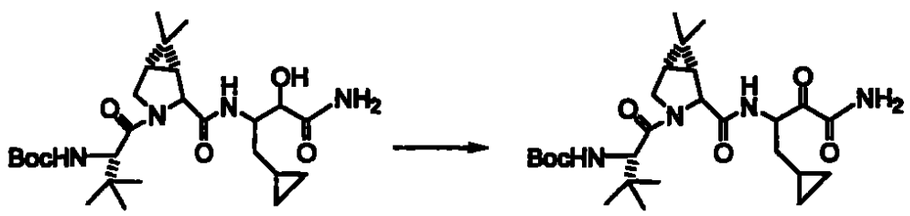
Step 4



1.17 12.03 1441e

To a -20°C solution **1.17** (10.4 g, 28 mmol; obtained by the hydrolysis of **20.06** using the procedure described for Intermediate **20.04**, Step 2) in DCM (300 mL) was added HATU (1.05 equiv, 29.4mmol, 11.2g), amine salt, Intermediate **12.03** (1.0 equiv, 28 mmol, 5.48 g). After 10 min at -20°C, DIPEA (3.6 equiv, 100 mmol, 17.4 mL) was added. Reaction was stirred at this temp for 16 hr. After 16 hr, the reaction was diluted with EtOAc and washed successively with $NaHCO_3$, citric acid (10% w/w) and brine. Organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield 14 g of the required intermediate **1441e**.

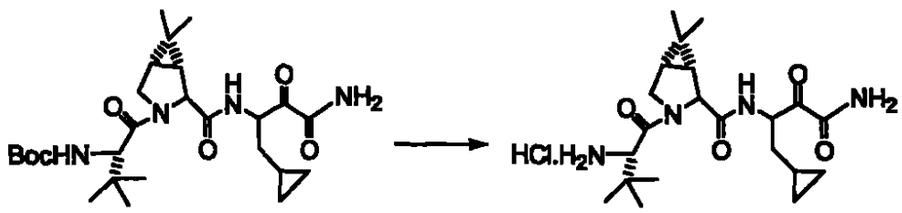
Step 5



1441e 1441f

The hydroxyamide **1441e** was oxidized to the required ketoamide **1441f** in a manner described for Example **1007**, Step 6. LC-MS = 507 $(M+H)^+$

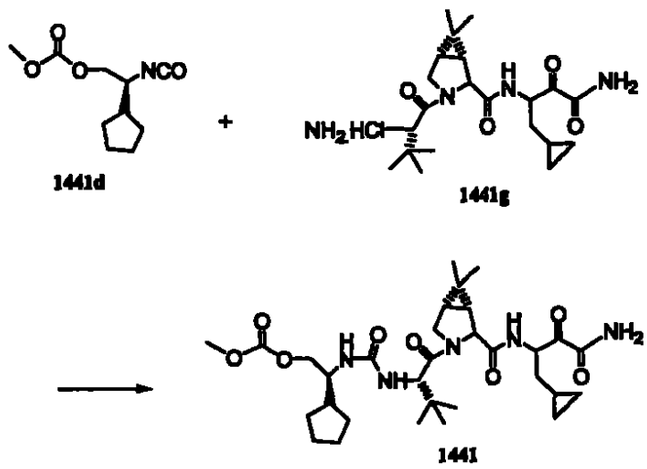
Step 6



1441f 1441g

Deprotection of the t-Boc functionality of **1441f** to give the required material **1441g** was carried out as described for Example **1007**, Step 2.

Step 7

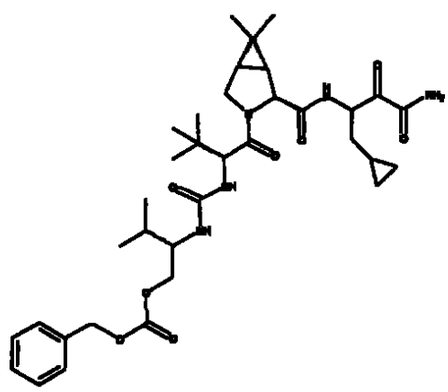
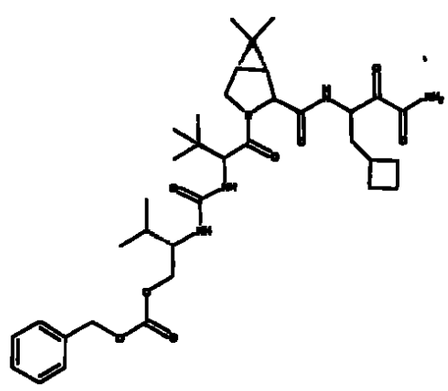
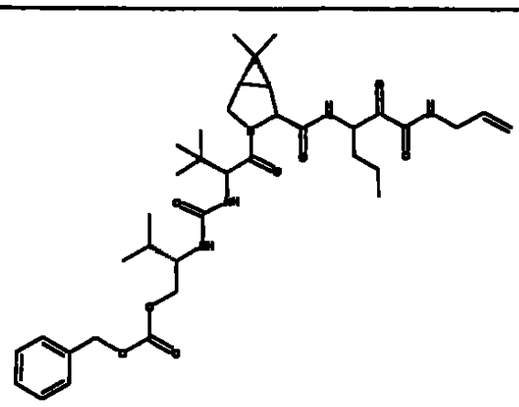


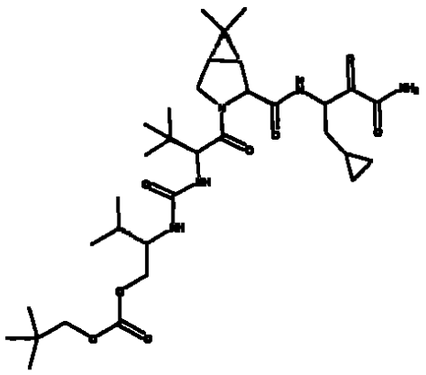
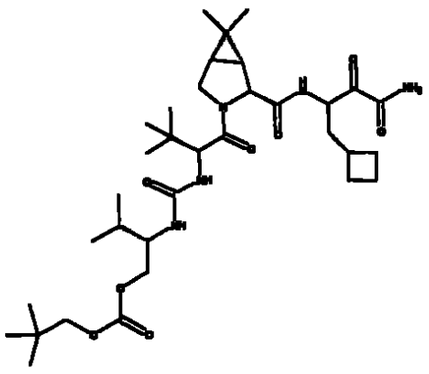
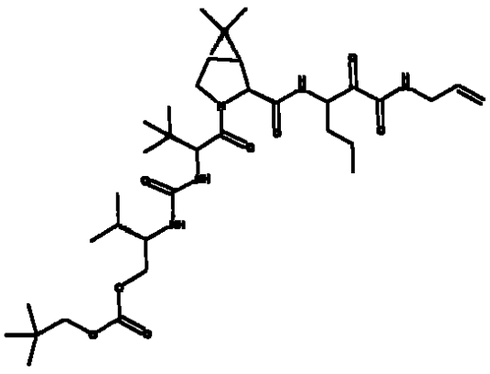
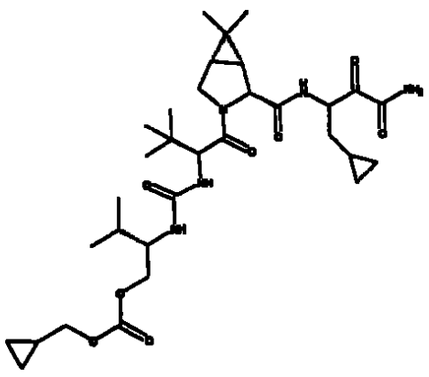
1441d 1441g 1441

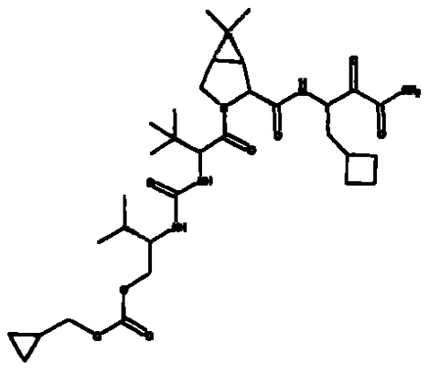
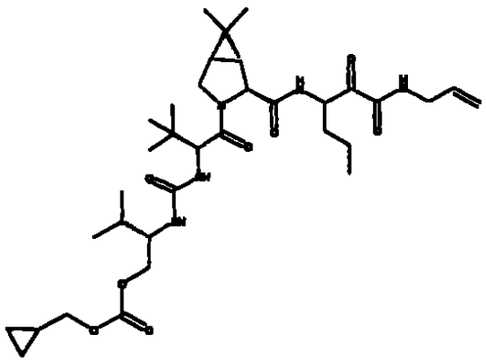
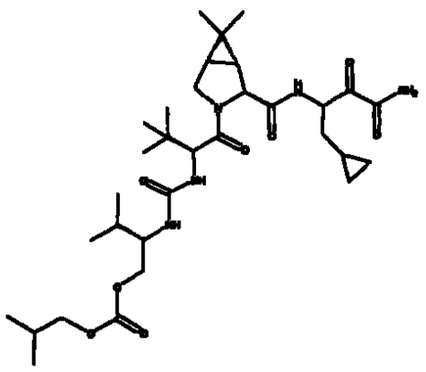
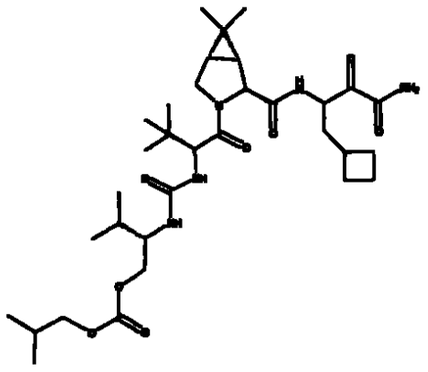
To a cooled solution (O ^{0}C) of the amine hydrochloride **1441g** (20 mg, 0.045 mmol) in CH_2Cl_2 (2.0 mL) was added **1441d** (1.35 mL, 0.135 mmol), followed by DIPEA (63 µL, 0.4 mmol). The reaction mixture was stirred at room temperature for 1.2 h, diluted with ethyl acetate (20 mL), washed with 3% citric acid, brine, dried over $MgSO_4$, filtered , concentrated and purified over SiO_2 using EtOAc/DCM (1:9 to 9:1) to yield **1441** (23 mg). LCMS = 620.3 $(M+H)^+$.

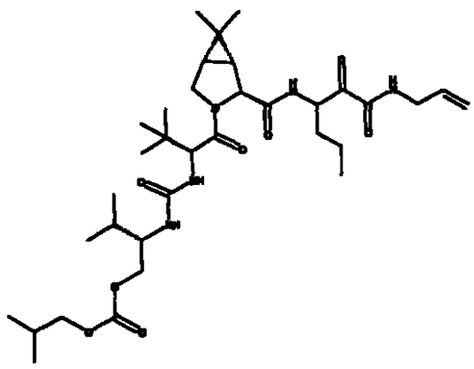
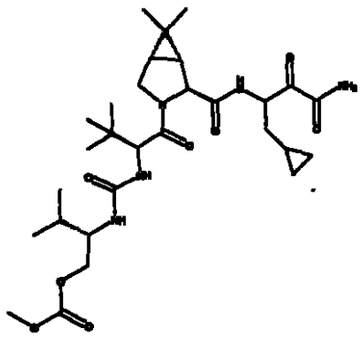
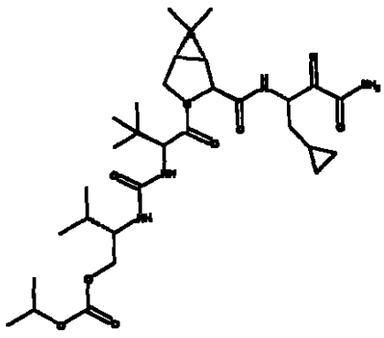
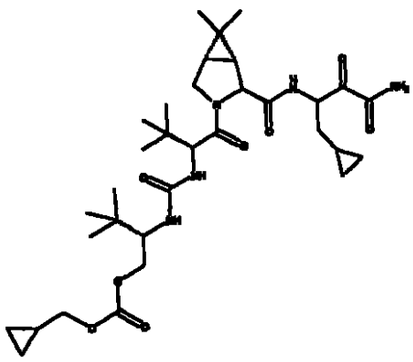
Compounds in the following table (**Table 2**) were essentially prepared using the above described procedures (Preparation of Example **1441**) with appropriate reagents and modifications as described in the General Schemes for Preparation of Target Compounds, Methods A-E.

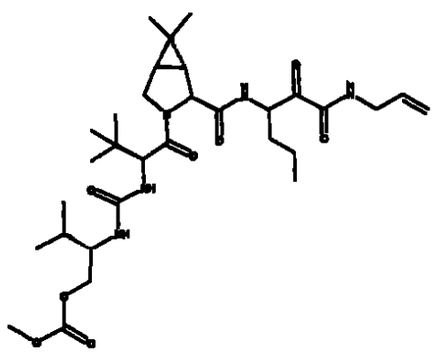
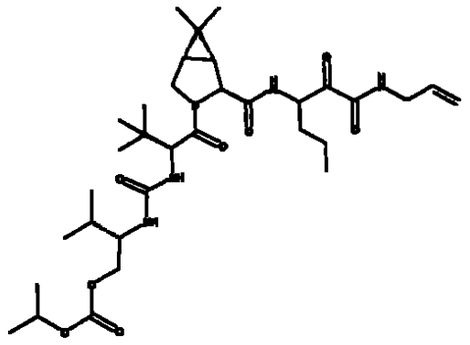
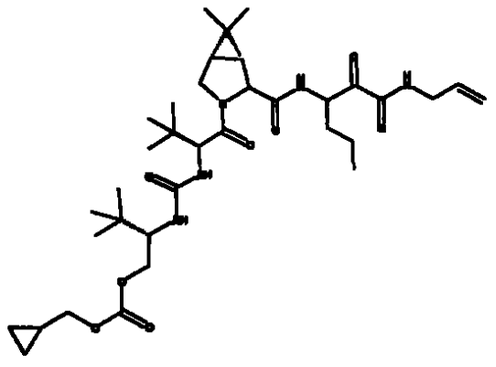
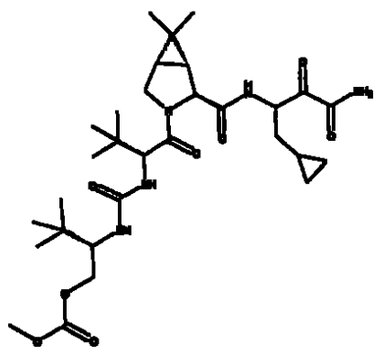
Table 2

Example #	Structure	KI* (nM)	Mol Weight
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1402		A	683.843
1403		B	697.87

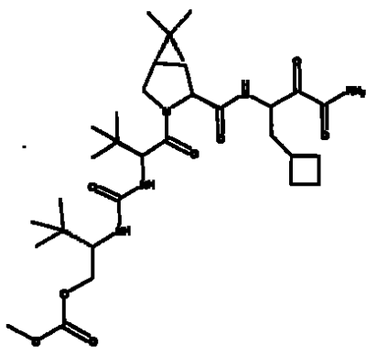
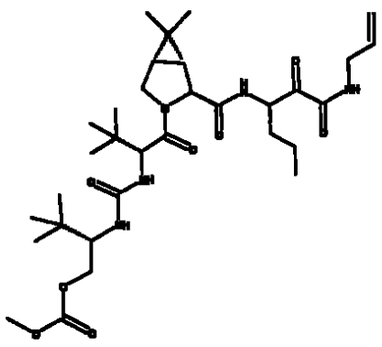
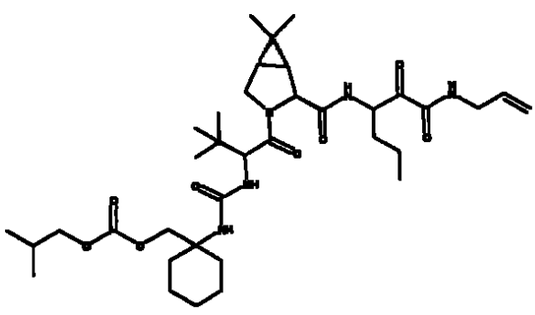
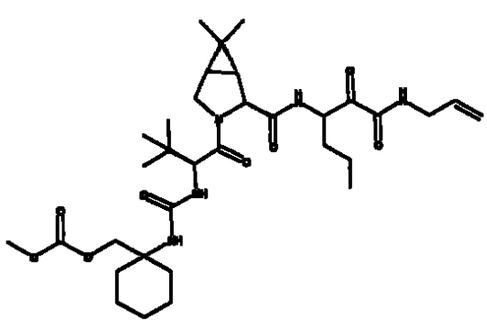
1404		A	649.826
1405		A	663.853
1406		B	677.88
1407		A	633.784

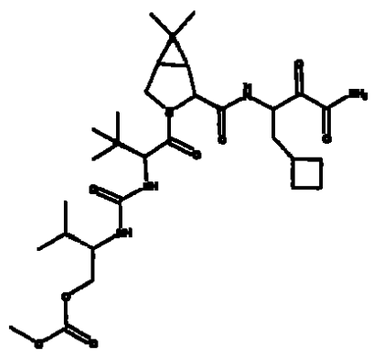
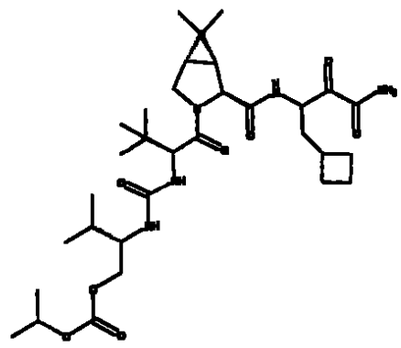
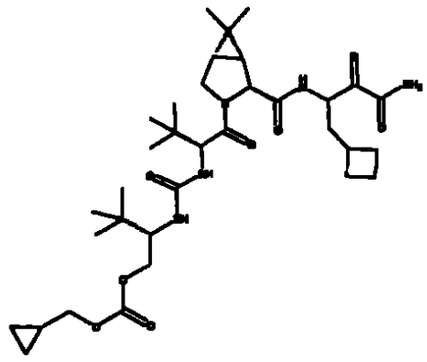
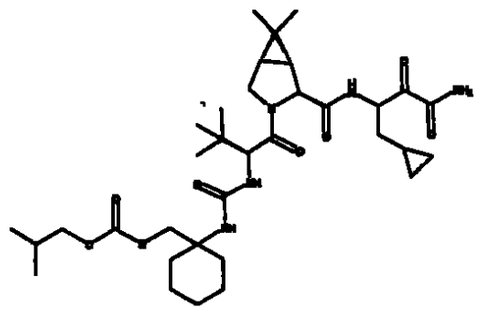
1408		A	647.81
1409		B	661.837
1410		A	635.799
1411		A	649.826

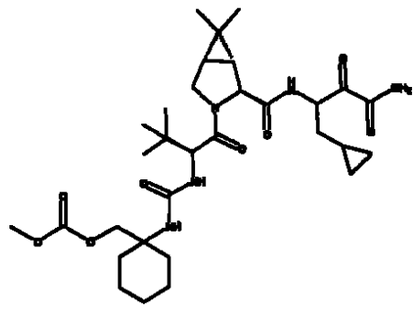
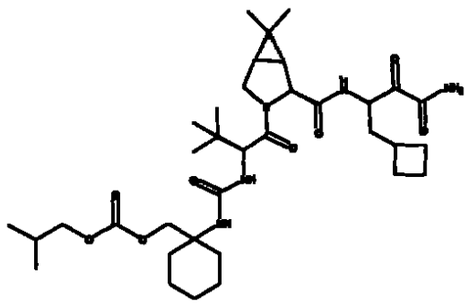
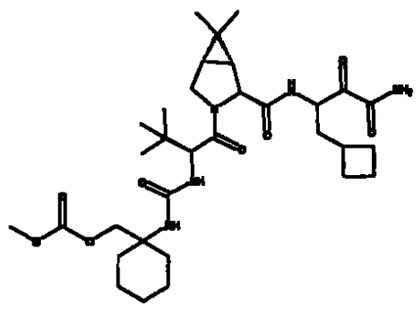
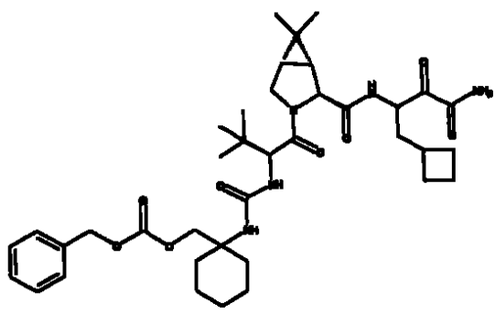
1412		A	663.853
1413		A	593.719
1414		A	621.773
1415		A	647.81

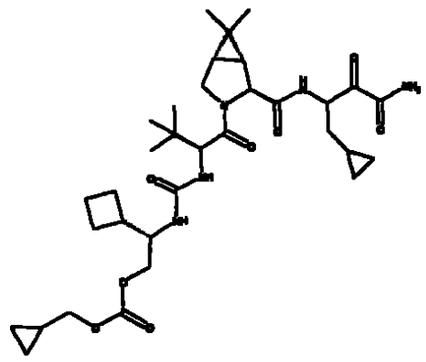
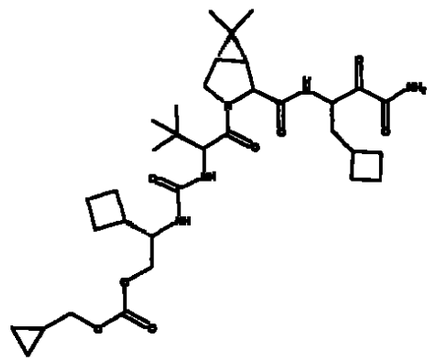
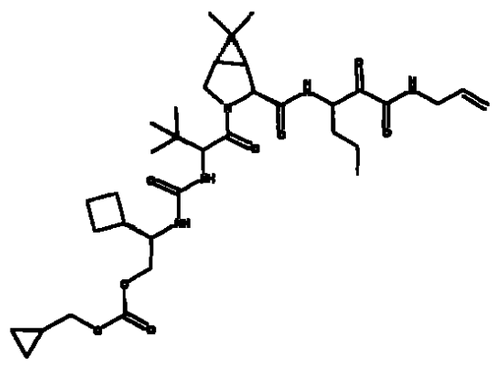
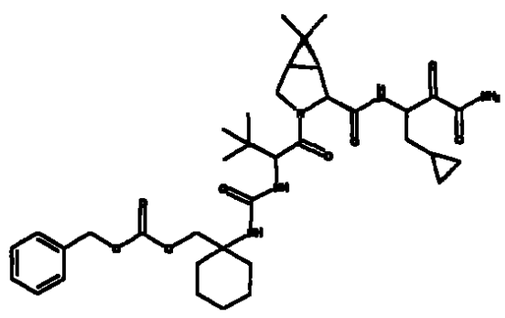
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1417		A	649.826
1418		A	675.864
1419		A	607.746

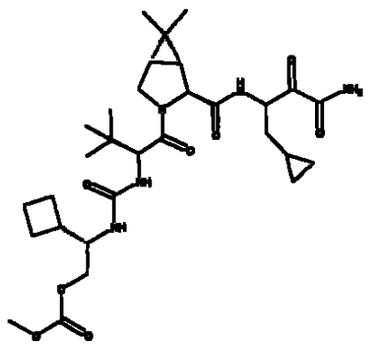
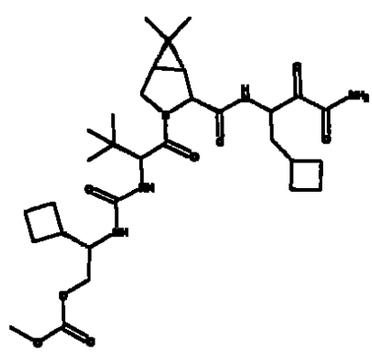
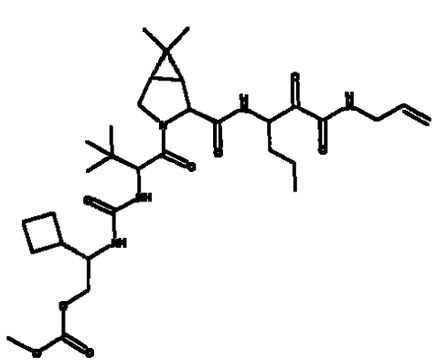
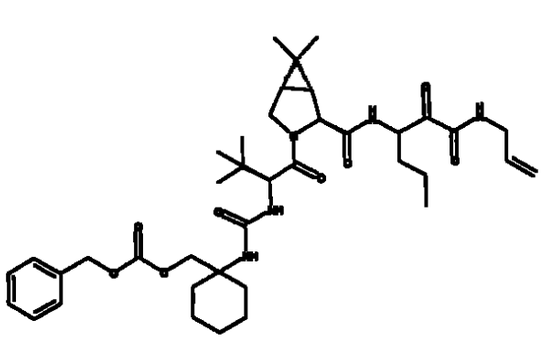
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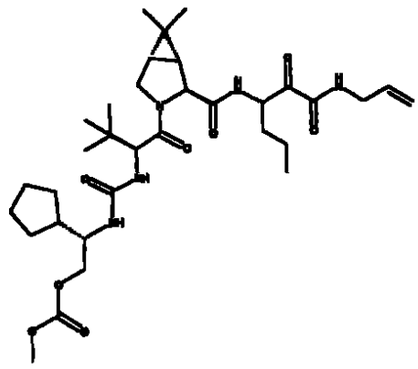
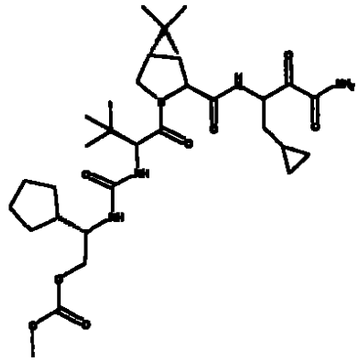
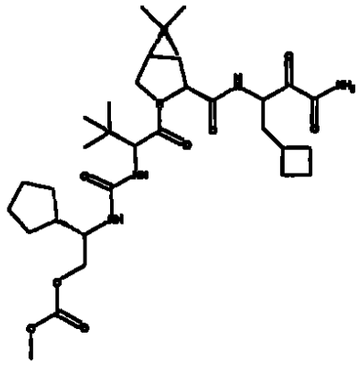
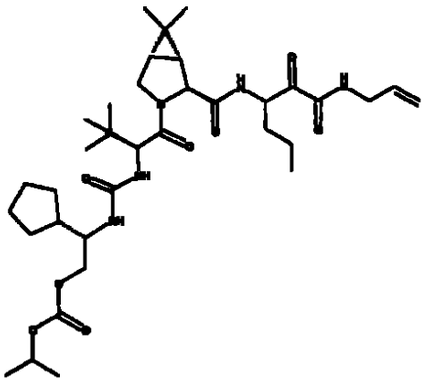
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1421		A	635.799
1422		C	689.891
1423		B	647.81

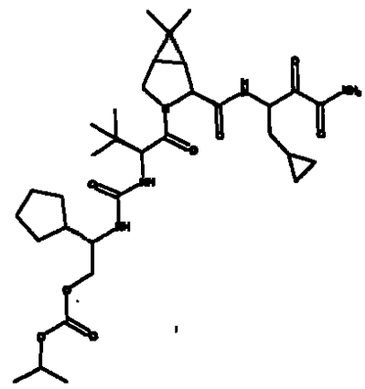
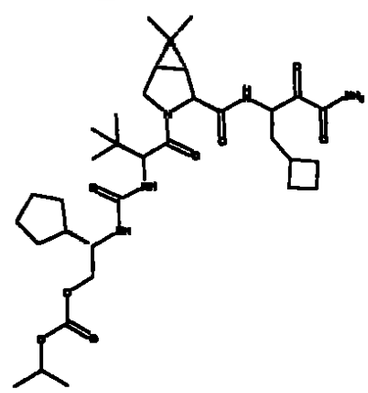
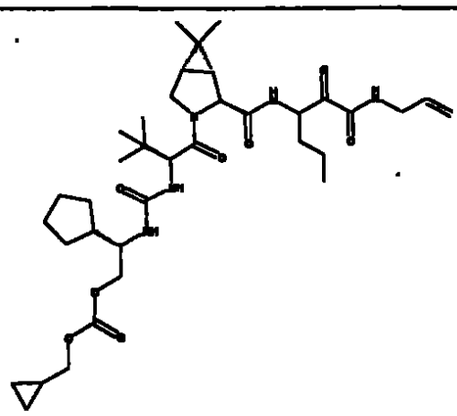
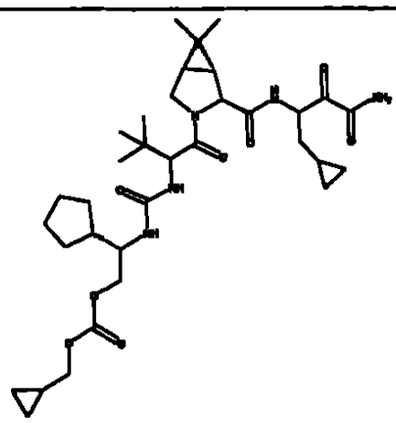
1424		A	607.746
1425		A	635.799
1426		A	661.837
1427		A	661.837

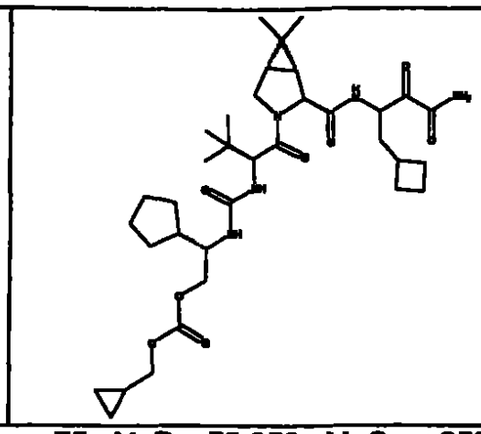
1428		A	619.757
1429		A	675.864
1430		A	633.784
1431		B	709.881

1432		A	645.795
1433		A	659.821
1434		B	673.848
1435		B	695.854

1436		A	605.73
1437		A	619.757
1438		B	633.784
1439		B	723.908

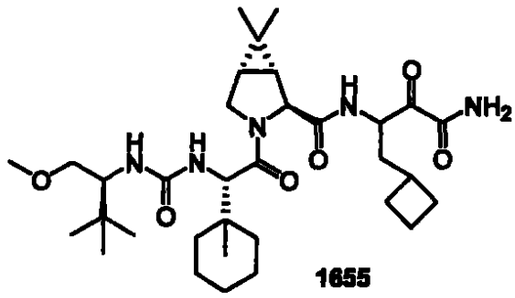
1440		B	647.81
1441		A	619.757
1442		A	633.784
1443		B	675.864

1444		A	647.81
1445		A	661.837
1446		B	687.875
1447		A	659.821

1448		A	673.848

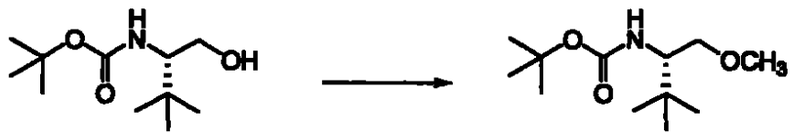
Ki* range A = <75 nM; B = 75-250 nM; C = >250 nM

Preparation of Example 1655



1655

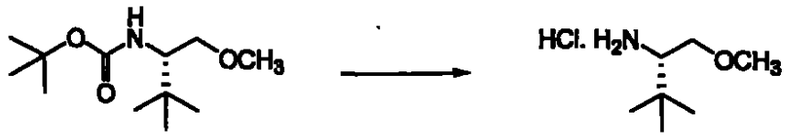
Step 1



1655a 1655b

To a solution of commercially available compound **1655a** (Aldrich Chemical Co., Milwaukee, Wisconsin, USA, 950 mg, 4.38 mmol) in acetonitrile (40 mL) at room temperature was added methyl iodide (4.63 mL, 74.42 mmol). Silver (I) oxide (1.62 g, 7.01 mmol) was then added under nitrogen atmosphere and the reaction mixture was refluxed for approximately 16 hrs. (Note: The reaction flask was covered with aluminum foil). At this time, the reaction mixture was cooled to room temperature and filtered through a pad of celite. The filter cake was rinsed with ethyl acetate several times. The combined filtrate was concentrated and purified by flash column chromatography using 20/80 to 40/60 ethyl acetate/hexanes to afford 720 mg of the expected product, **1655b**.

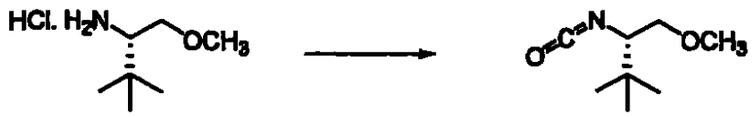
Step 2



1655b 1655c

Conversion of **1655b** to compound **1655c** proceeded in quantitative yield using previously described procedure (Step 2, Example **1007**).

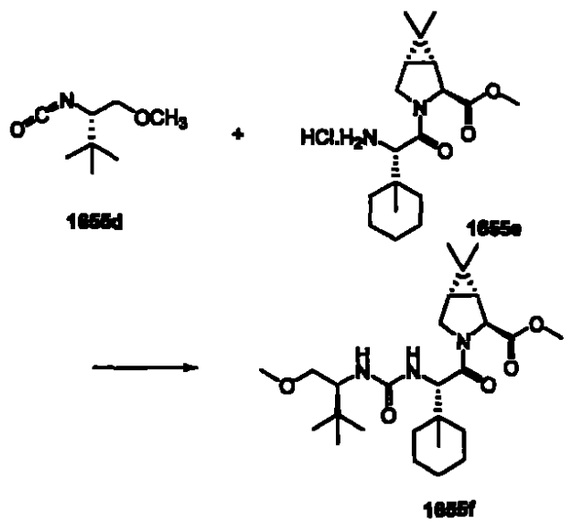
Step 3



1655c 1655d

To a solution of compound **1655c** (514 mg, 3.08 mmol) in dichloromethane (20 mL) was added saturated sodium bicarbonate solution (20 mL). This mixture was stirred vigorously and cooled to 0°C. Phosgene (20 wt% in toluene, 6.5 mL) was added dropwise. The reaction mixture was stirred vigorously for 4.5 hrs while maintaining the temperature at or below 5°C. At this time the reaction mixture was poured into a separatory funnel and the organic layer was separated. The organic layer was washed with saturated ammonium chloride solution (1 x), water (1 x), dried (Na_2SO_4) and concentrated. The residue, **1655d**, was diluted with dichloromethane (10 mL) and used further as a 0.308M solution.

Step 4

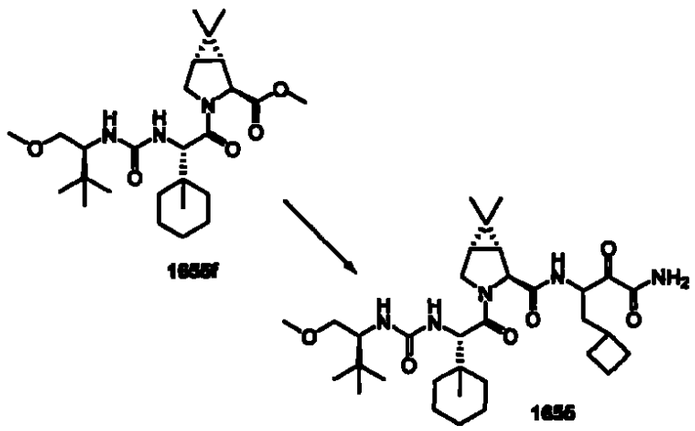


1655d 1655e

1655f

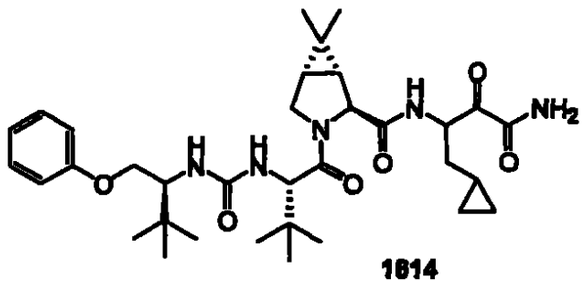
To a cold (0°C) solution of **1655e** (176 mg, 0.5 mmol; **1655e** was prepared as described for Intermediate **20.08**, Steps 1 and 2 using appropriate starting materials) in dichloromethane (4 mL) was added **1655d** (0.308 M solution, 4.87 mL, 1.5 mmol) followed by DIPEA (0.276 mL, 1.5 mmol). The reaction mixture was maintained at 10°C for 16 hrs. The reaction was quenched with saturated ammonium chloride solution and the aqueous layer was extracted with dichloromethane (3 x). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude residue was purified by flash column chromatography using 20/80 acetone/hexanes to provide the required compound **1655f** (240 mg, 100% yield). LC-MS: 480.1 (M+H).

Step 5



Compound **1655f** from above was converted to the required target compound **1655** using the intermediate **10.11** and procedures described above (Steps 4 - 6, Example **1007**). LC-MS of **1655** = 618.1 (M+H).

Preparation of Example 1614



Step 1



1655a 1614a

To a stirred solution of *N*-Boc-*tert*-leucinol **1655a** (2.0 g, 9.22 mmol), phenol (1.0 g, 10.6 mmol) and ADDP (3.8 g, 15.1 mmol) in CH_2Cl_2 (80 mL) at rt was bubbled argon gas for 15 min. Triphenylphosphine was then added in one portion. The resulting solution was stirred at RT for 18 h. The precipitates were filtered off and washed with diethyl ether (2 X 30 mL). The filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with 2-10% EtOAc/hexane to give the desired product **1614a** (0.33 g, 12%).

Step 2



1614a 1614b

Compound **1614a** (0.32 g, 1.13 mmol) was dissolved in a 4 M hydrogen chloride solution in *p*-dioxane (20 mL) and stirred at RT for 3 h. It was concentrated *in vacuo* to give compound **1614b**, which was used without further purification.

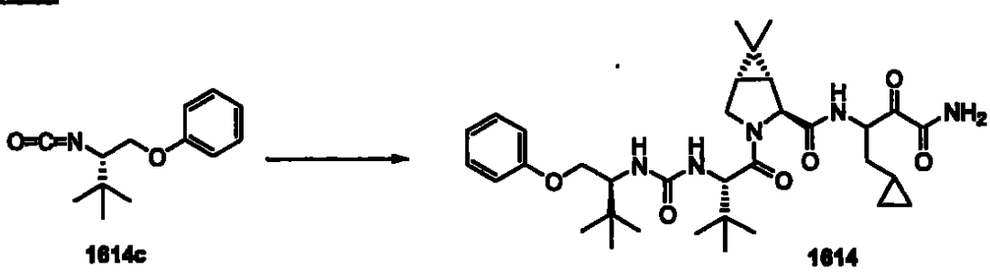
Step 3



1614b 1614c

Compound **1614c** was prepared from **1614b** according to the procedures described for Example **1655**, Step 3.

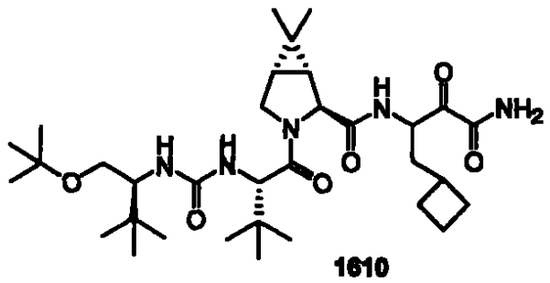
Step 4



1614c 1614

The isocyanate **1614c** was converted to the target compound **1614** as described in the General Schemes, Method C using the appropriate reagents and intermediates.

Preparation of Example 1610



1610

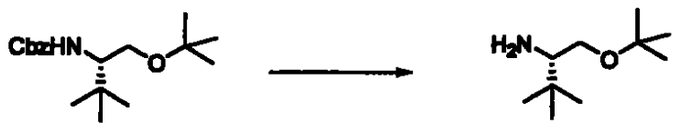
Step 1



1610a **1610b**

To a stirred suspension of anhydrous magnesium sulfate in anhydrous CH_2Cl_2 (40 mL) at RT was added concentrated sulfuric acid (0.32 mL, 5.76 mmol). The mixture was vigorously stirred for 30 min before a solution of **1610a** (2.0 g, 7.90 mmol) in anhydrous CH_2Cl_2 (15 mL) was added. The mixture was then vigorously stirred at RT for 68 h. Saturated $NaHCO_3$ solution (50 mL) was added cautiously, along with CH_2Cl_2 (100 mL) and water (50 mL). Two phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 X 100 mL). The combined organic solution was dried ($MgSO_4$), filtered and concentrated *in vacuo* to give **1610b**.

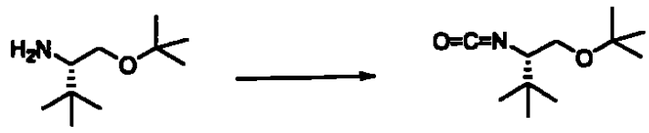
Step 2



1610b **1610c**

A suspension of compound **1610b** and 10% Pd-C in absolute ethanol was vigorously stirred under a hydrogen atmosphere for 4 h. The catalyst was filtered off through a celite pad. The filtrate was concentrated *in vacuo* to afford **1610c** which was used without further purification.

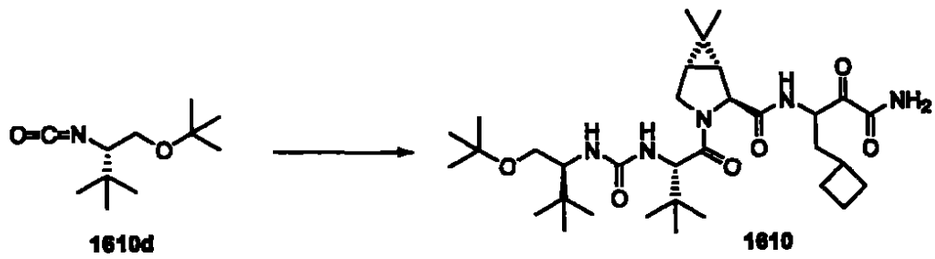
Step 3



1610c 1610d

Compound **1610d** was prepared from **1610c** according to the procedures described for Example **1655**, Step 3.

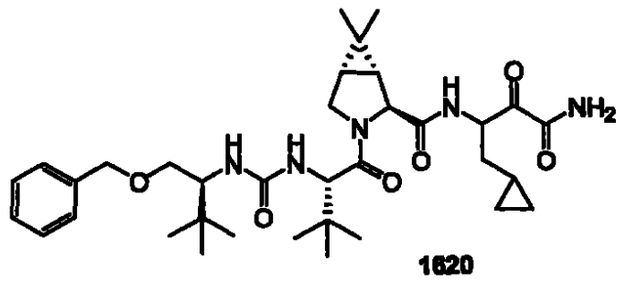
Step 4



1610d 1610

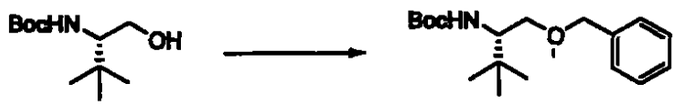
The isocyanate **1610d** was converted to the target compound **1610** as described in the General Schemes, Method C using the appropriate reagents and intermediates.

Preparation of Example 1620



1620

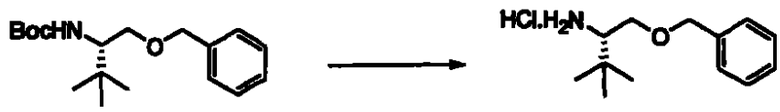
Step 1



1655a 1620a

A suspension of the alcohol **1655a** (3.46 g, 12.8 mmol), benzyl bromide (10 mL, 84.2 mmol) and silver (I) oxide (5.0 g, 21.6 mmol) in acetonitrile was stirred vigorously at 76 °C in an oil bath overnight (18 h), The solid material was filtered off and the solution was concentrated *in vacuo*. The product was purified by flash column chromatography eluting with 5-40% EtOAc/hexane to give the desired product **1620a** (0.78 g, 20%).

Step 2



1620a 1620b

Compound 16120b was prepared from 1620a according to the procedures described for Example 1614, Step 2.

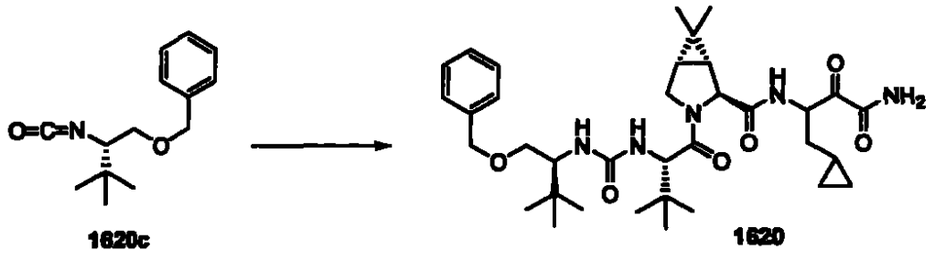
Step 3



1620b 1620c

Compound 1620c was prepared from 1620b according to the procedures described for Example 1655, Step 3.

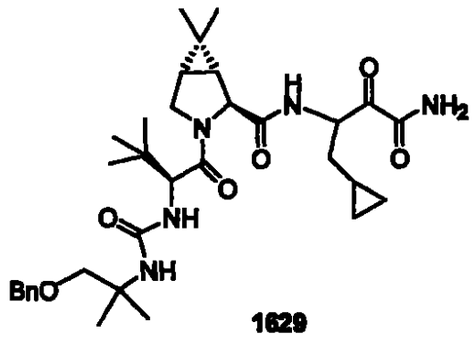
Step 4



1620c 1620

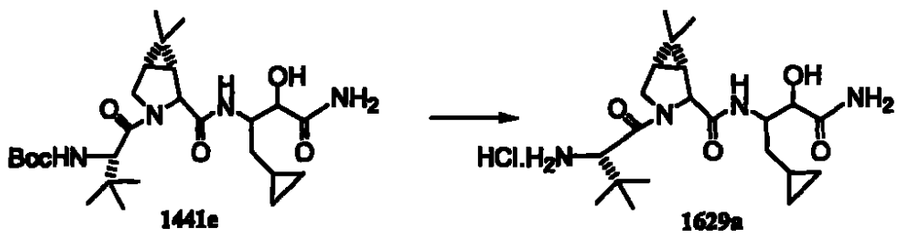
The isocyanate 1620c was converted to the target compound 1620 as described in the General Schemes, Method C using the appropriate reagents and Intermediates.

Preparation of Example 1629



1629

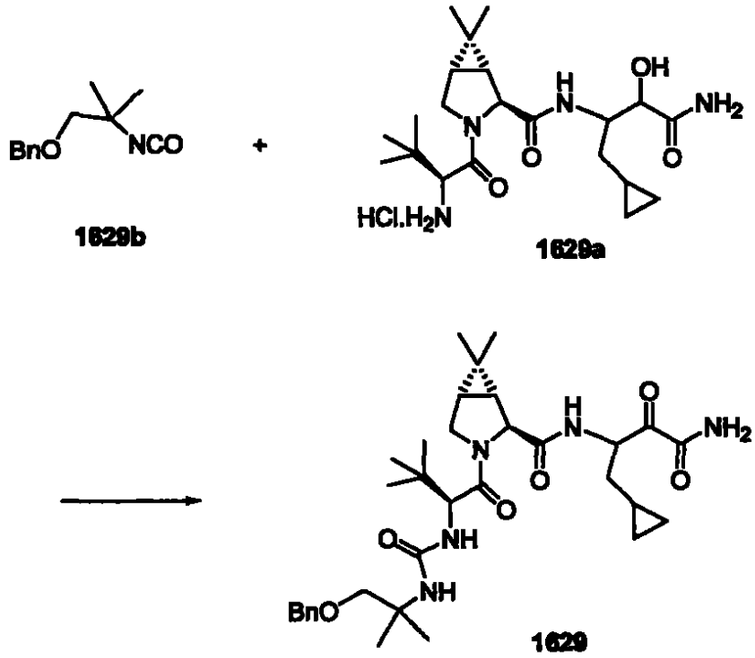
Step 1



1441e 1629a

To **1441e** (600 mg) was added 4M HCl in dioxane (25 mL). The reaction was stirred at room temperature for 30 min. and concentrated to yield a white solid, **1629a** (490 mg), which was carried forward without purification.

Step 2

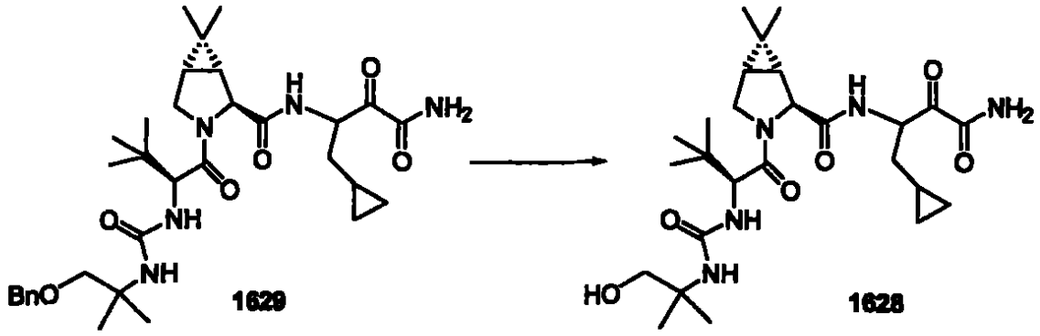


1629b **1629a** **1629**

To a cooled (0 °C) solution of compound **1629a** (395 mg) in CH_2Cl_2 (25 mL) was added Et_3N (0.57 mL), followed by the isocyanate **1629b** (Robinson, Ralph P.; Marfat, Anthony. *Eur. Pat. Appl.* (1991), EP 436333 A2 19910710, 53 pp) in a manner described above (Example **1655**, Step 4). The crude hydroxyamide obtained was used without purification.

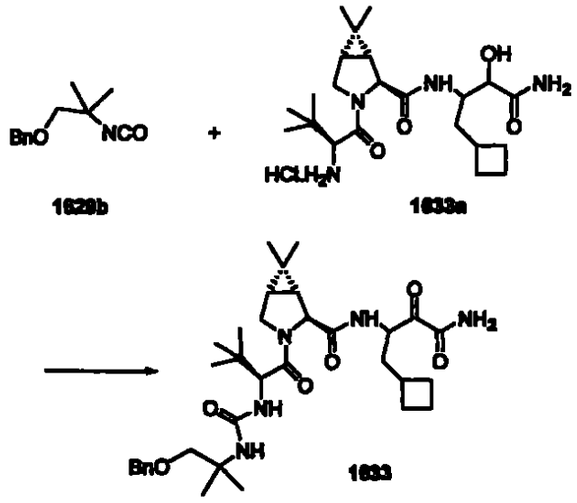
A solution of the crude hydroxyamide in toluene-DMSO (2.0 mL each) was cooled to 0 °C. To the reaction mixture was added EDCI.HCl (410.0 mg), followed by dichloroacetic acetic (0.087 mL), after stirring for 2h at room temperature, it was diluted with EtOAc, washed with 1N HCl, satd. $NaHCO_3$, brine, dried over MgSO4, filtered, concentrated to yield a white solid which was purified by chromatography over silica gel using acetone-hexane (40:60) to afford the title compound **1629** (280.0 mg) as a white solid: Mass spectrum for C33H49N5O6 (611.77); found FAB $(M+H)^+$ = 612.5

Preparation of Example 1628



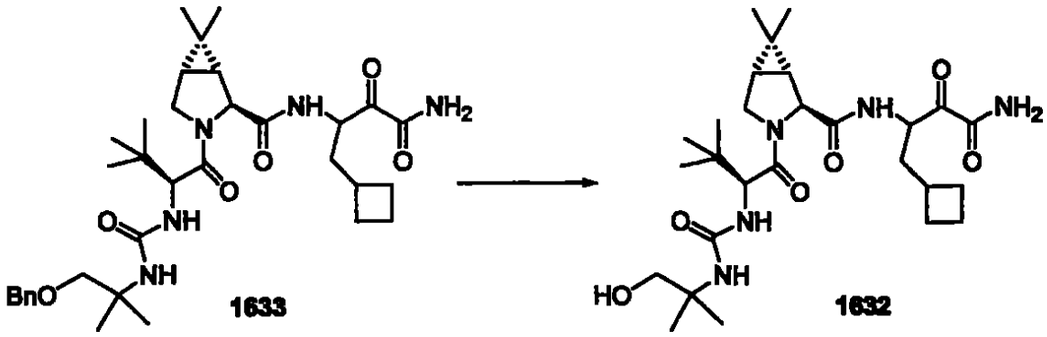
To a solution of compound **1629** (37.0 mg) in MeOH (2.0 mL) was added Pd-C (10 % w/v, 5.0 mg) and the reaction was stirred under hydrogen atmosphere for 1h, filtered through a pad of celite, concentrated and purified by chromatography over silica gel using acetone-hexane (4:6) to yield the required compound **1628** (22.0mg) as a white solid. Mass spectrum for C26H43N5O6 (521.65); found FAB $(M+H)^+$ = 522.6.

Preparation of Example 1633



The required title compound **1633** was obtained from the isocyanate **1629b** and compound **1633a** (prepared from **1.17** and **10.11**) using procedures described for Example **1629**. Mass spectrum for C34H51N5O6 (625.80); found FAB $(M+H)^+$ = 626.8.

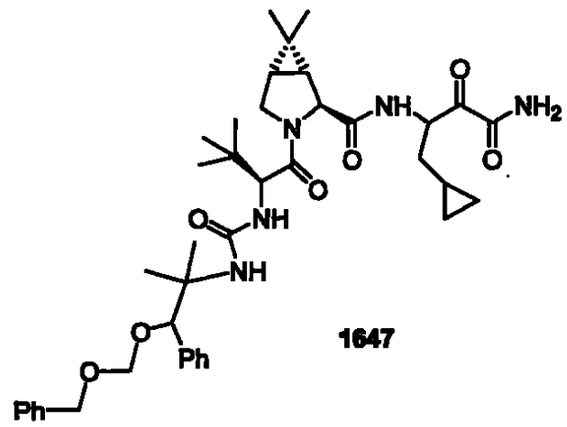
Preparation of Example 1632



1633 1632

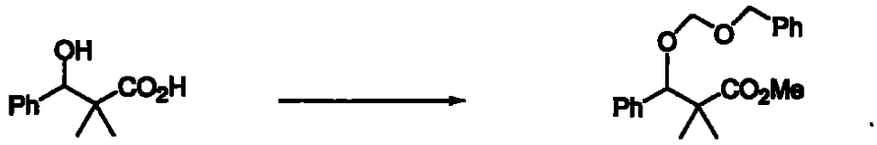
To a solution of compound **1633** (10.0 mg) in MeOH (2.0 mL) was added Pd-C (10 % w/v, 2.0 mg) and the reaction was stirred under hydrogen atmosphere for 1h, filtered through a pad of celite, concentrated and purified by chromatography over silica gel using acetone-hexane (4:6) to yield the title compound **1632** as a white solid (4.2 mg). Mass spectrum for C27H45N5O6 (535.68); found FAB $(M+H)^+$ = 536.7.

Preparation of Example 1647



1647

Step 1

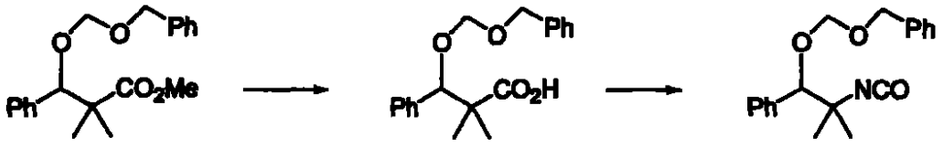


1647a 1647b

To a stirred solution of the commercially available compound **1647a** (Aldrich Chemical Co., Milwaukee, Wisconsin, USA, 250.0 mg) in MeOH was added trimethylsilyl diazomethane (2.0 mL, 2M solution in PhMe). After 20 min the solvent was removed and the crude was redissolved in CH_2Cl_2 (2.0 mL) and Benzyloxymethyl chloride (1.5 equivalent) was added along with Et_3N (1.5 equivalent). The reaction mixture was stirred overnight, diluted with

EtOAc, washed successively with 5 % $Na_2S_2O_3$, satd. $NaHCO_3$, 1N HCl, brine, dried over MgSO4, filtered, concentrated to yield a white solid which was purified by chromatography over silica gel using EtOAc-hexane (1:3) to afford the compound **1647b** (413 mg) as a white solid: Mass spectrum for C20H24O4 (328.40); found FAB $(M+H)^+$ = 329.4.

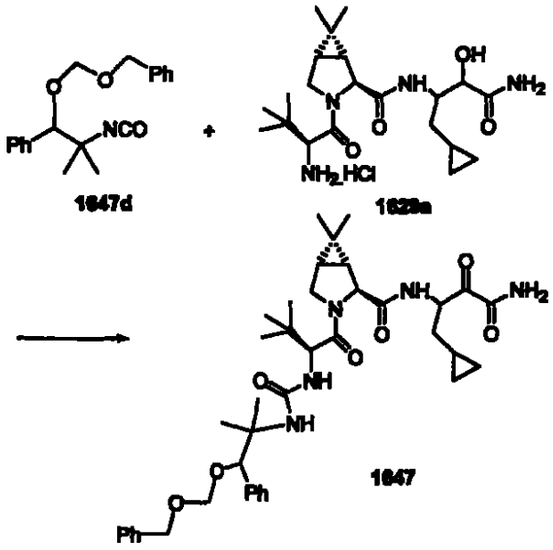
Step 2



1647b **1647c** **1647d**

To a solution of 0.413 g of compound **1647b** in MeOH/H_2O (5.0/0.5 mL) was added 0.735 g of KOH. The reaction mixture was refluxed overnight, cooled to room temperature and concentrated. The crude was redissolved in H_2O (10.0 mL) and acidified with 10 % aqueous HCl and extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated to afford the corresponding carboxylic acid **1647c** (392 mg). The crude was directly used in the next step. To a solution of 123.2 mg of acid **1647c** in toluene (5.0 mL) was added DPPA (0.09 mL) and Et_3N (0.055 mL). The reaction mixture was heated at 110 °C for 40 min, cooled and washed with satd. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to afford the isocyanate **1647d**. The crude obtained was used without purification.

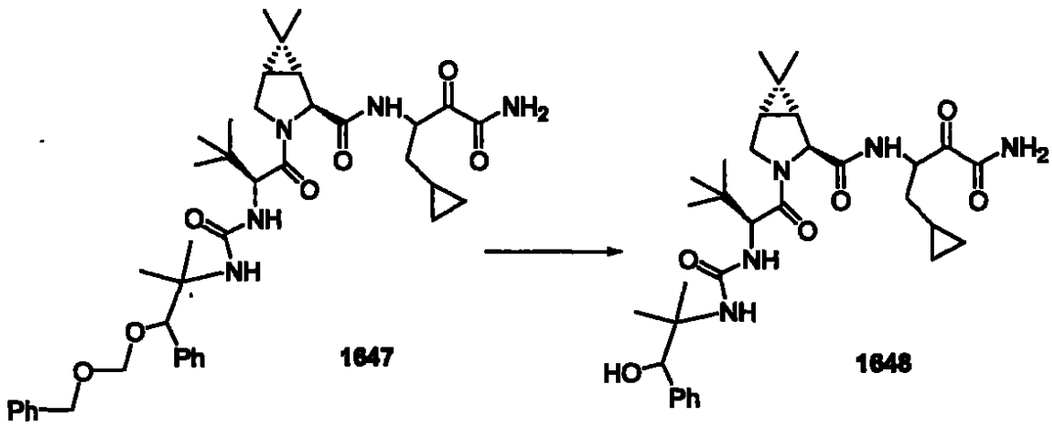
Step 3



1647

The isocyanate **1647d** was treated with compound **1629a** (90.0 mg) in a manner described in Example **1629** to provide the title compound **1647**. Mass spectrum for C40H55N5O7 (717.89); found FAB $(M+H)^+$ = 718.8.

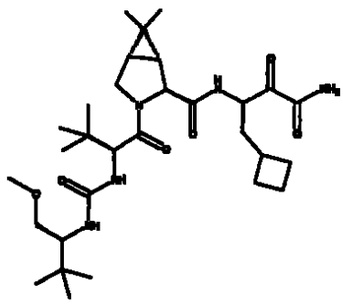
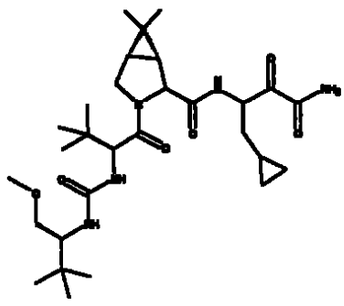
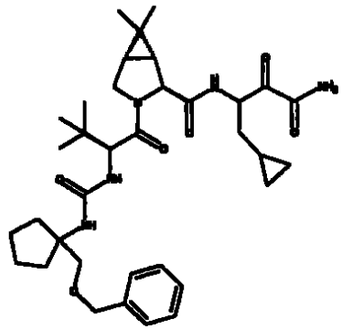
Preparation of Example 1648

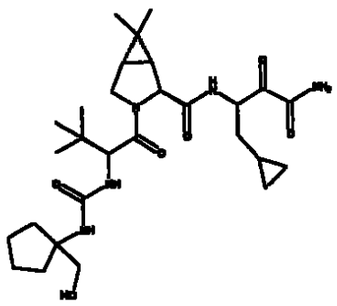
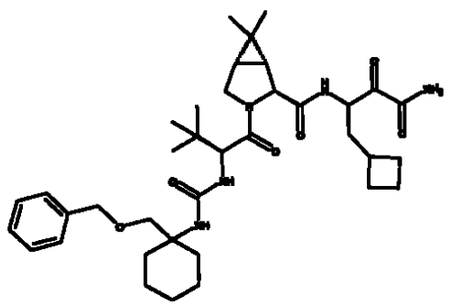
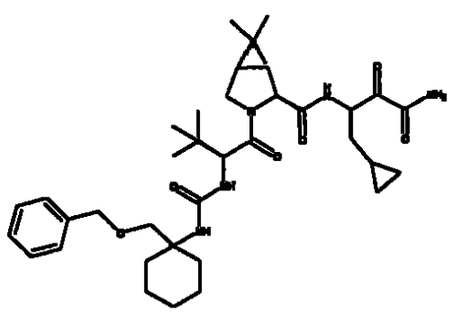
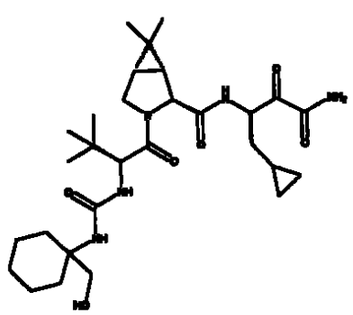


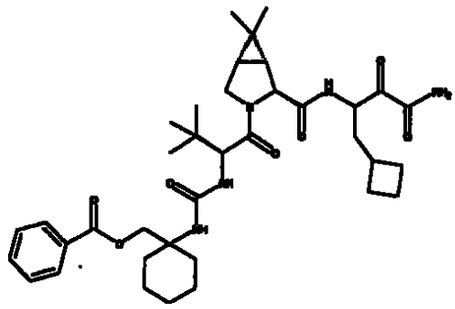
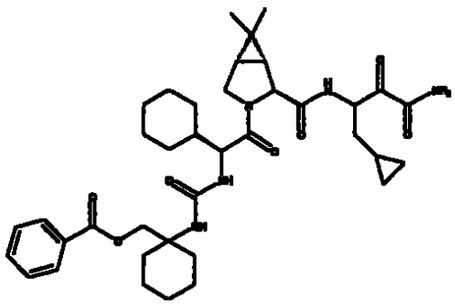
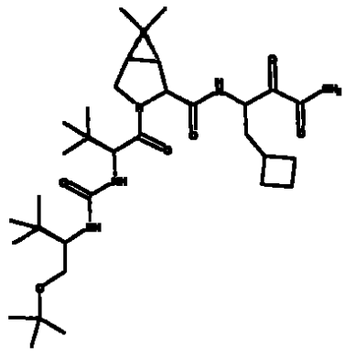
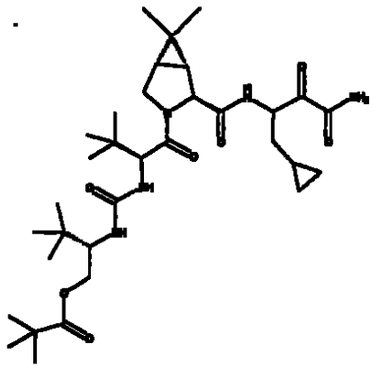
To a solution of compound **1647** in MeOH was added 6N HCl after 30 min, the MeOH was removed and the crude was redissolved in ethyl acetate and washed with satd. $NaHCO_3$. The crude was purified by chromatography over silica gel using acetone-hexane (40:60) to afford the title compound **1648** (25.0 mg) as a white solid: Mass spectrum for C32H47N5O6 (597.75); found FAB $(M+H)^+$ = 598.7.

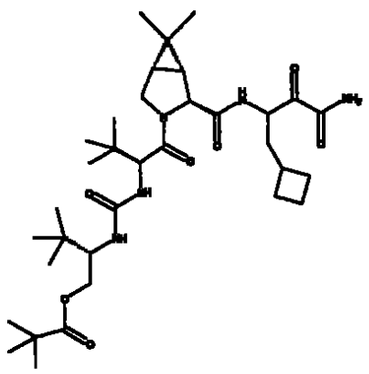
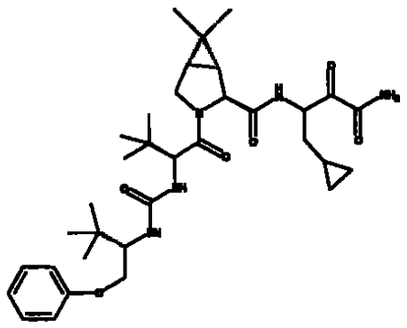
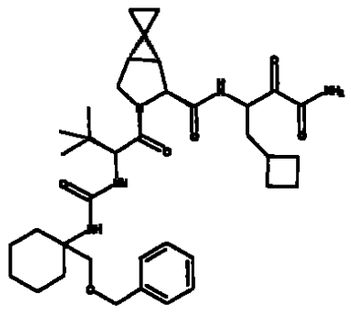
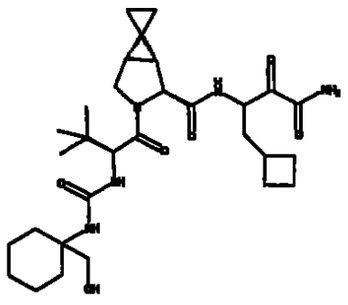
Compounds in the following table (**Table 3**) were essentially prepared using the above described procedures (Preparation of Examples **1610, 1614, 1620, 1628, 1629, 1632, 1633, 1647, 1648, 1655**) with appropriate reagents and modifications as described in the General Schemes for Preparation of Target Compounds, Methods A-E.

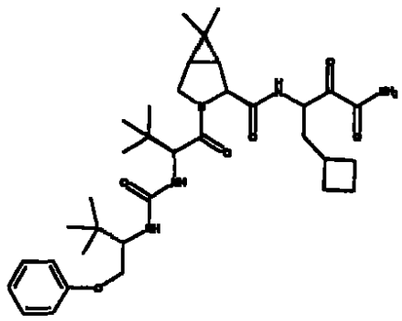
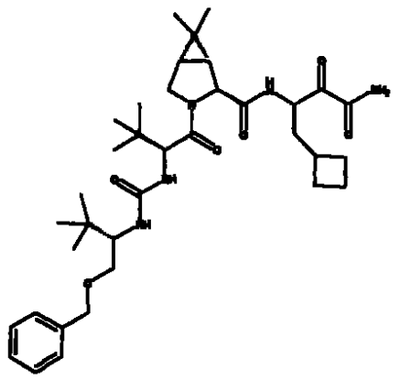
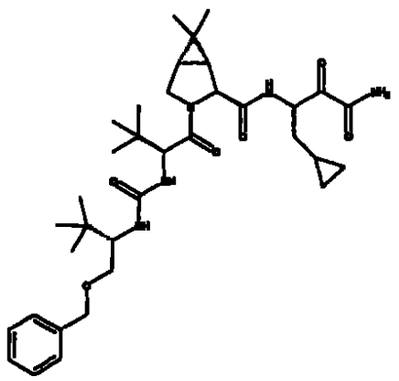
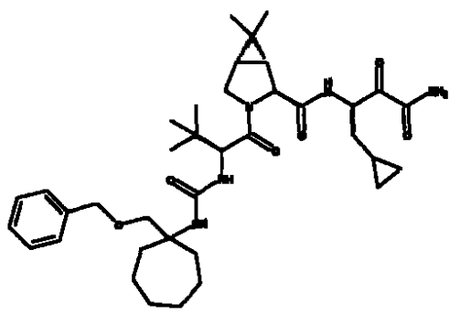
Table 3

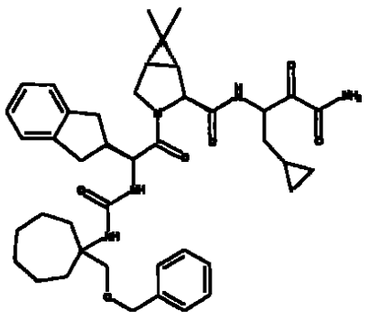
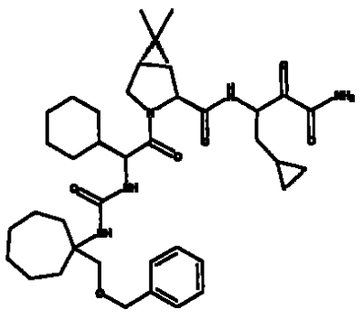
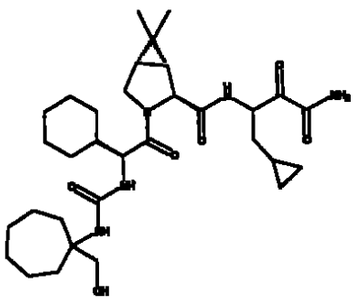
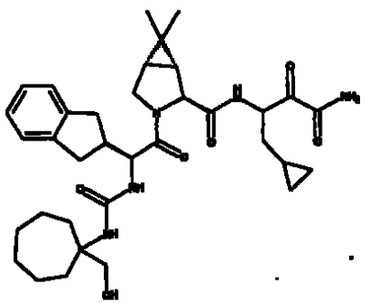
Example #	Structure	KI* (nM)	Mol Weight
1601		B	577.763
1602		B	563.736
1603		A	637.818

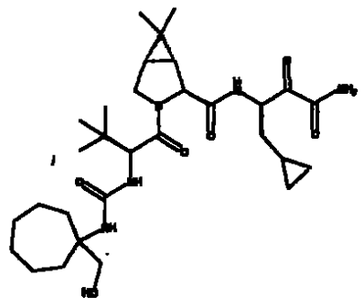
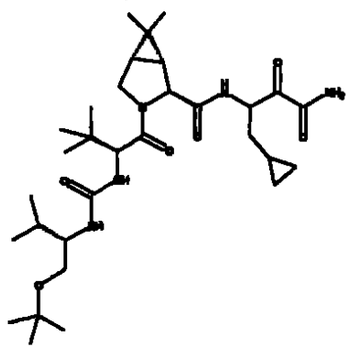
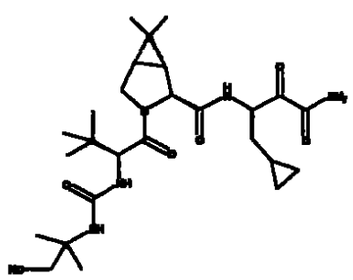
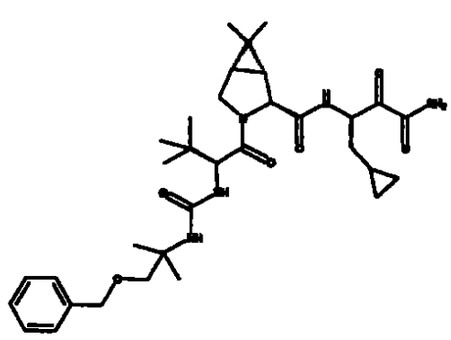
1604		A	547.693
1605		A	665.871
1606		A	651.845
1607		A	561.72

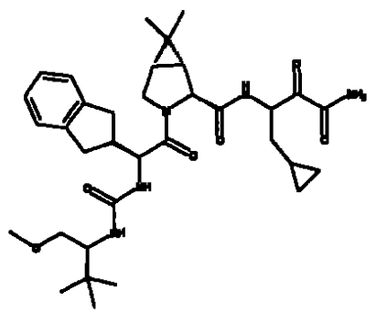
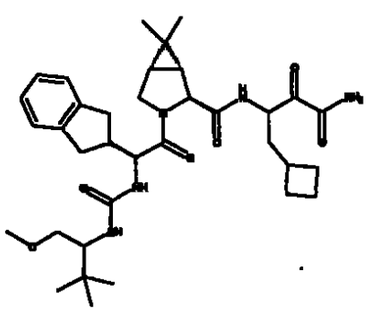
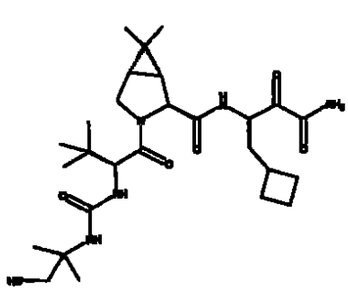
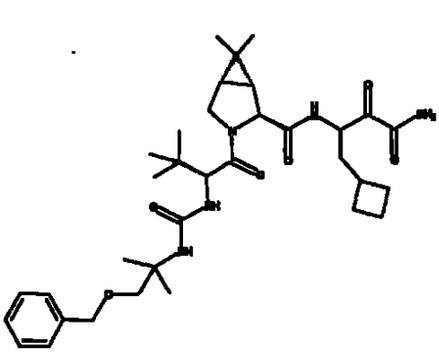
1608		B	679.855
1609		B	691.866
1610		A	619.843
1611		A	633.827

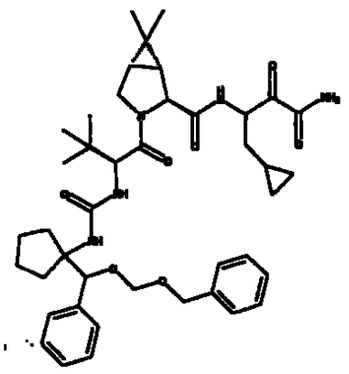
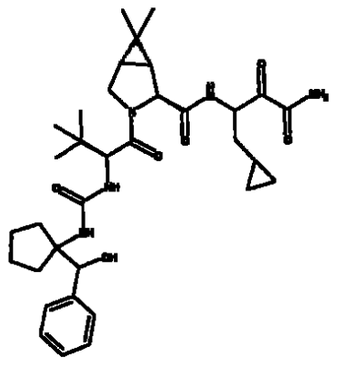
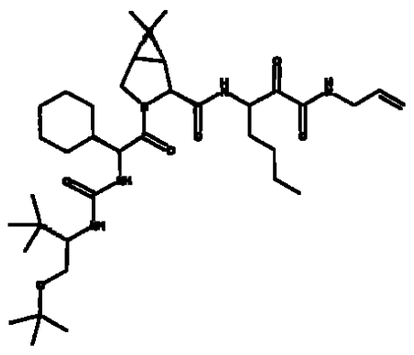
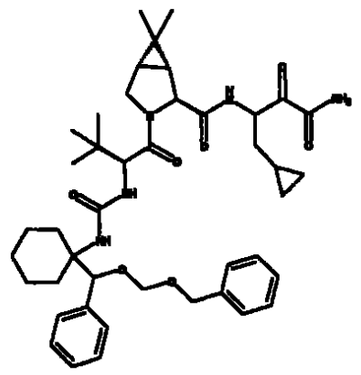
1612		A	647.854
1614		B	625.807
1616		C	663.856
1617		B	573.731

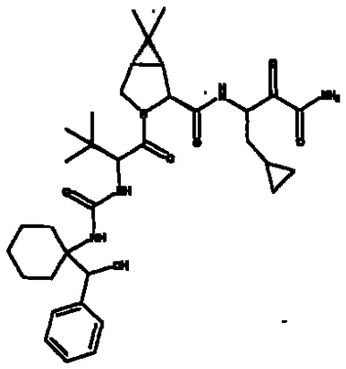
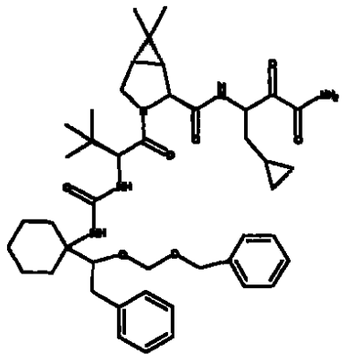
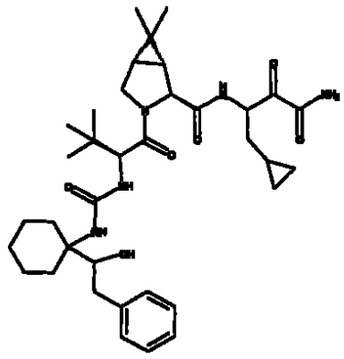
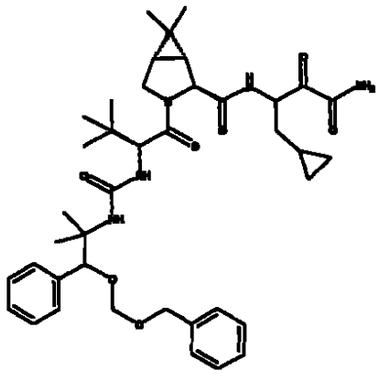
1618		B	639.834
1619		B	653.86
1620		B	639.834
1621		A	665.871

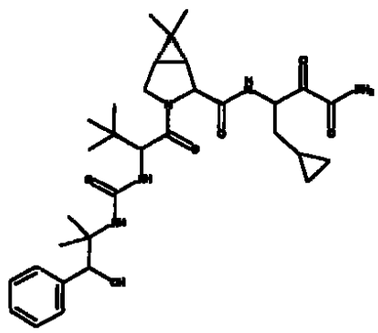
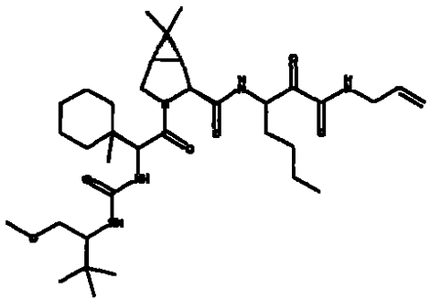
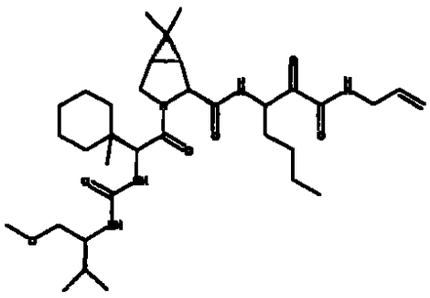
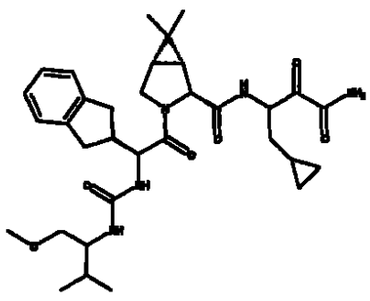
1622		C	725.926
1623		B	691.909
1624		A	601.785
1625		B	635.802

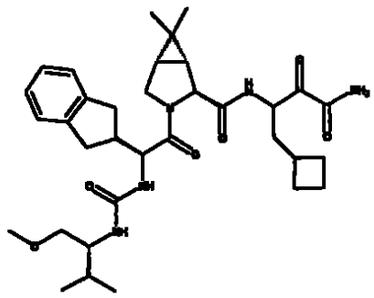
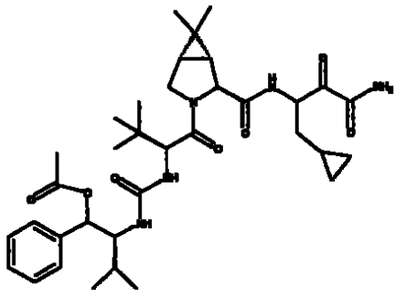
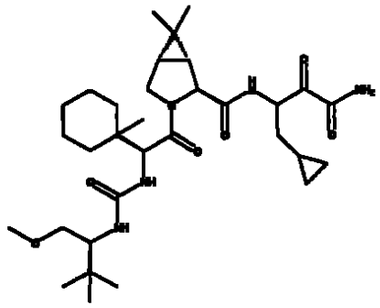
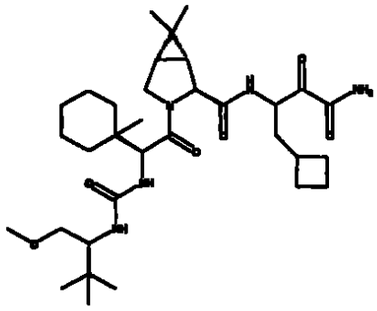
1626		A	575.747
1627		A	591.79
1628		A	521.656
1629		B	611.78

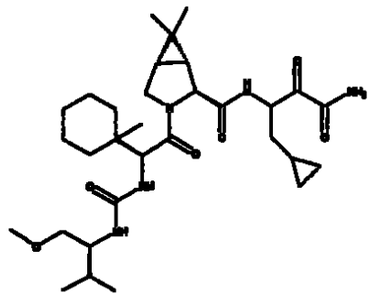
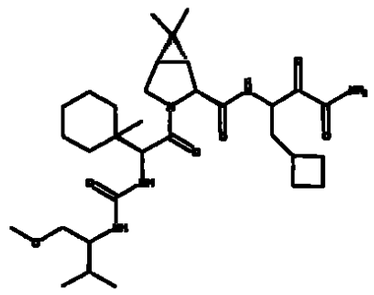
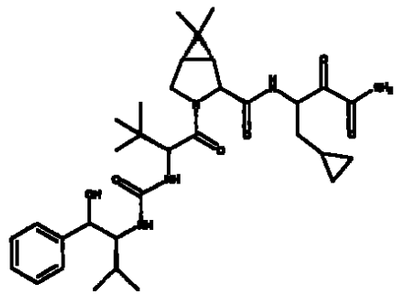
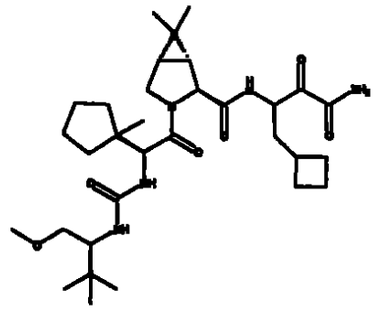
1630		A	623.791
1631		A	637.818
1632		A	535.682
1633		B	625.807

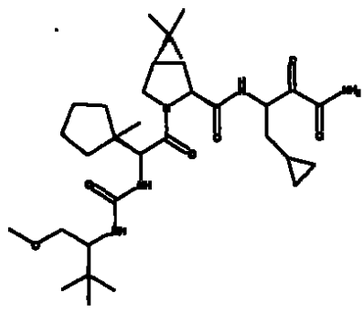
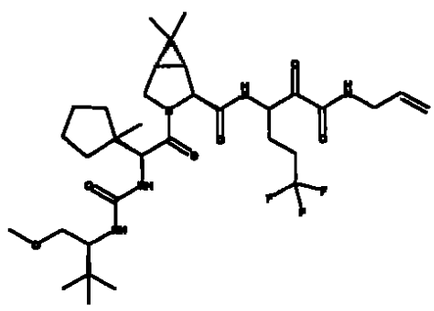
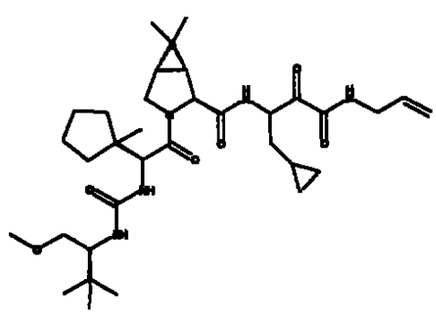
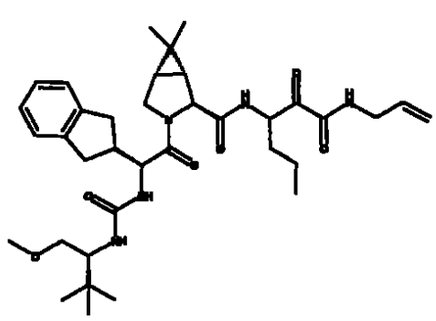
1634		B	743.942
1635		A	623.791
1636		B	673.935
1641		A	757.968

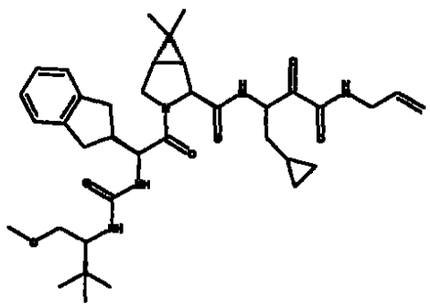
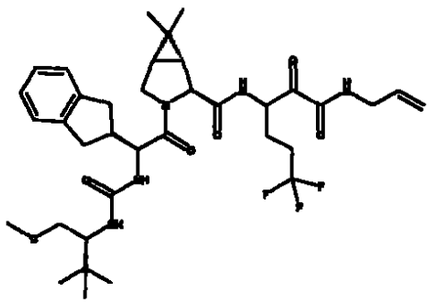
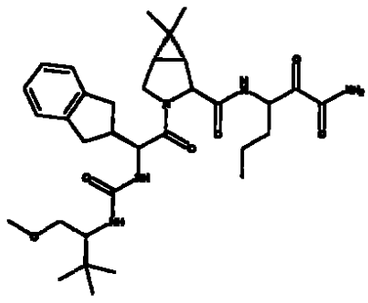
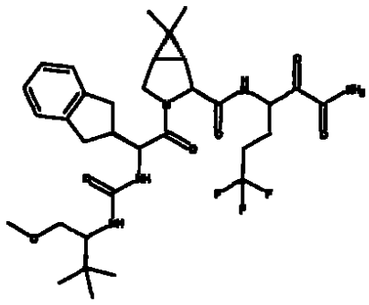
1642		A	637.818
1643		B	771.995
1644		A	651.845
1647		B	717.904

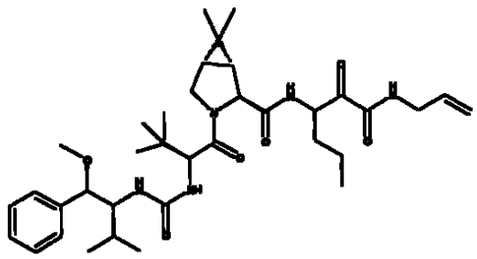
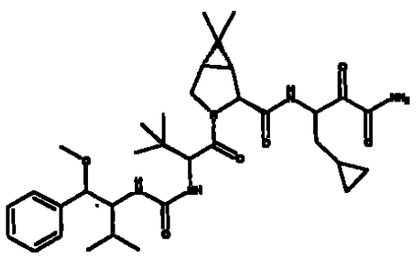
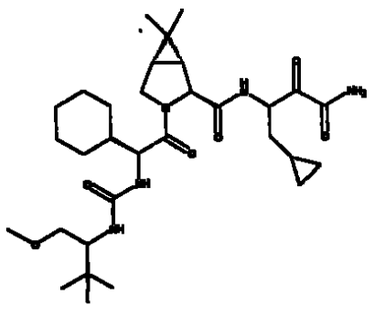
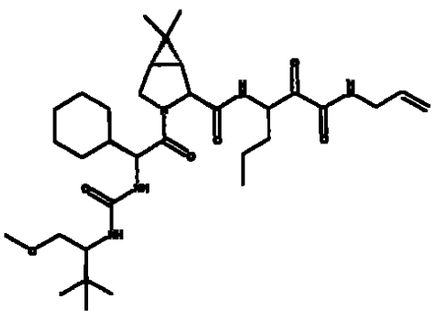
1648		B	597.753
1649		A	645.881
1650		B	631.854
1651		A	609.764

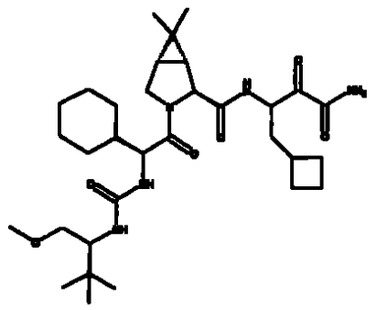
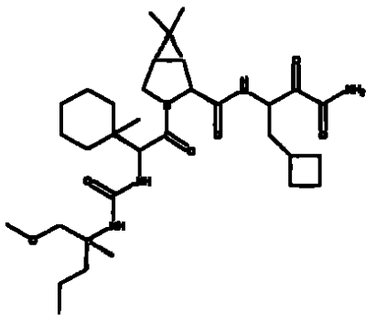
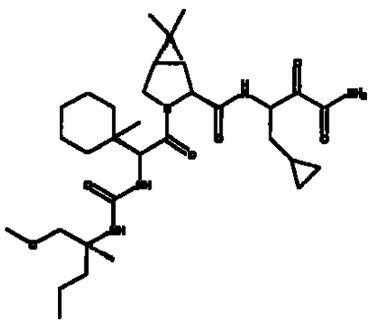
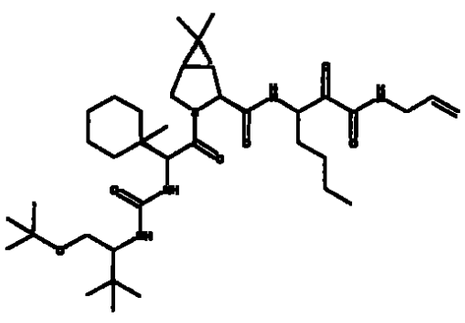
1652		A	623.791
1653		B	653.817
1654		A	603.801
1655		A	617.827

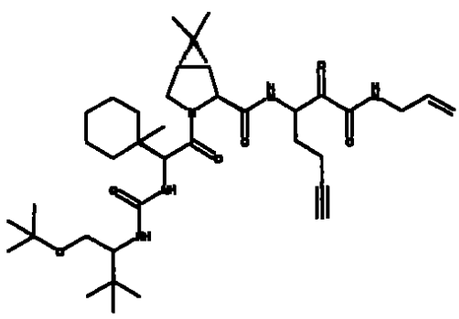
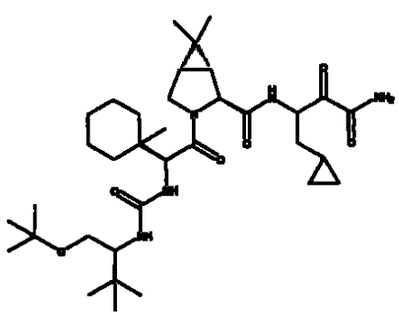
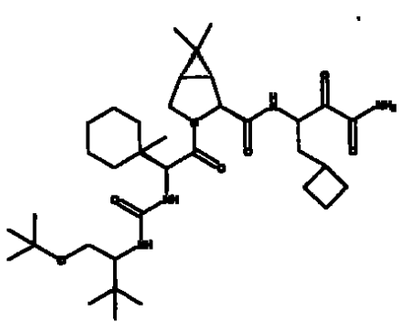
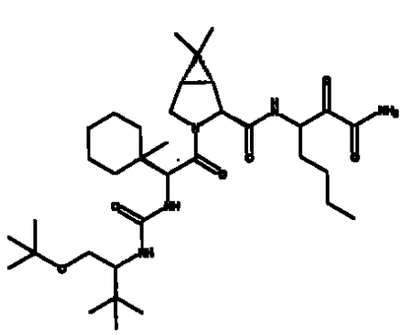
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1657		A	603.801
1658		B	611.78
1659		A	603.801

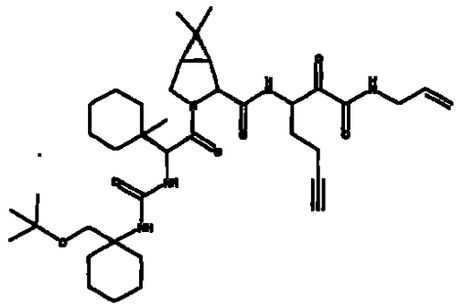
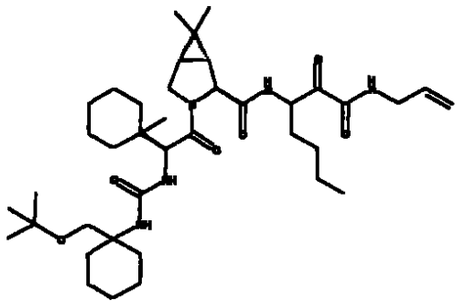
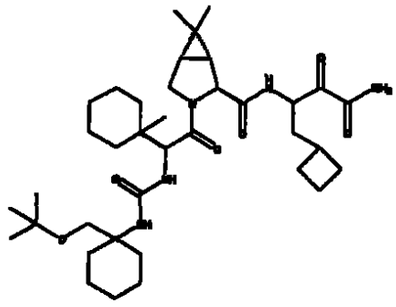
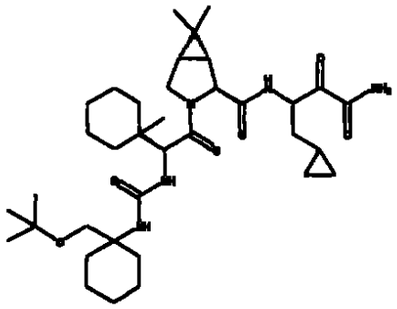
1660		A	589.774
1661		B	671.799
1662		B	629.838
1663		B	651.845

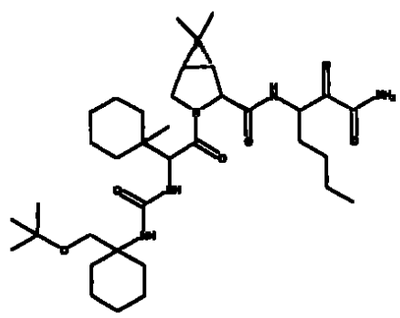
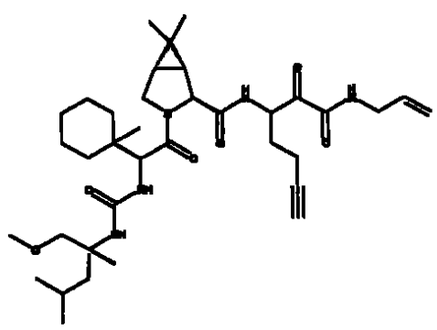
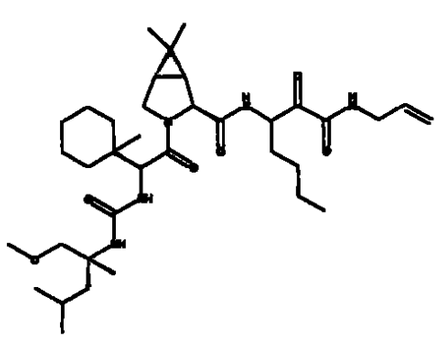
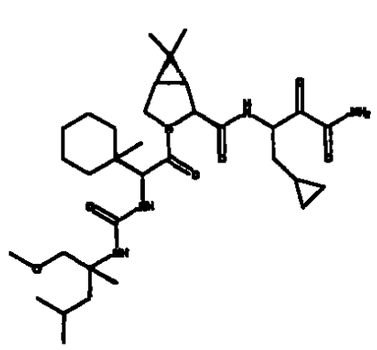
1664		B	663.856
1665		B	705.816
1666		A	611.78
1667		A	665.751

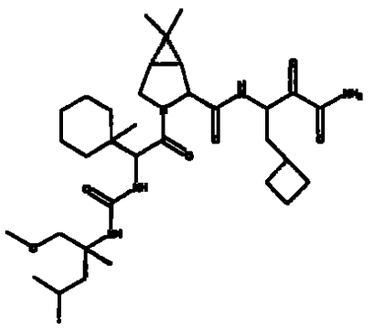
1668		B	653.86
1669		A	625.807
1670		A	589.774
1671		B	617.827

1672		A	603.801
1673		B	617.827
1674		B	603.801
1675		C	687.953

1676		B	683.921
1677		A	645.873
1678		B	659.899
1679		B	647.889

1680		A	695.932
1681		C	699.963
1682		B	671.910
1683		A	657.884

1684		B	659.899
1685		B	655.868
1686		C	659.899
1687		A	617.820

1688		A	631.846

KI* range A = <75 nM; B = 75-250 nM; C = >250 nM

The present invention relates to novel HCV protease inhibitors. This utility can be manifested in their ability to inhibit the HCV NS2/NS4a serine protease. A general procedure for such demonstration is illustrated by the following *in vitro* assay.

Assay for HCV Protease Inhibitory Activity:

Spectrophotometric Assay: Spectrophotometric assay for the HCV serine protease can be 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 are derived from the P side of the NS5A-NS5B junction sequence (Ac-DTEDVVX(Nva), where X = A or P) whose C-terminal carboxyl groups are esterified with one of four different chromophoric alcohols (3- or 4-nitrophenol, 7-hydroxy-4-methyl-coumarin, or 4-phenylazophenol). Illustrated 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 are 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 are synthesized manually or on an

98
99

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 can be from USA Scientific (Ocala, Florida) and the 96-well plate vortexer is from Labline Instruments (Melrose Park, Illinois). A Spectramax Plus microtiter plate reader with monochrometer is obtained from Molecular Devices (Sunnyvale, California).

Enzyme Preparation: Recombinant heterodimeric HCV NS3/NS4A protease (strain 1a) is prepared by using the procedures published previously (D. L. Sall *et al*, *Biochemistry*, 37 (1998) 3392-3401). Protein concentrations are 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) is 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 is done as reported by R. Zhang *et al*, (*ibid.*) and is 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 are subsequently assembled, using Fmoc chemistry, either manually or on an automatic ABI model 431 peptide synthesizer. The N-acetylated and fully protected peptide fragments are 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 is evaporated azeotropically (or repeatedly extracted by aqueous Na_2CO_3 solution) to remove the acid used in cleavage. The DCM phase is dried over Na_2SO_4 and evaporated.

The ester substrates are assembled using standard acid-alcohol coupling procedures (K. Holmber *et al*, *Acta Chem. Scand.*, B33 (1979) 410-412). Peptide fragments are 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.) is added to initiate the coupling reactions. Product formation is monitored by HPLC and can be found to be complete following 12-72 hour reaction at room temperature. Pyridine solvent is evaporated under vacuum and further removed by azeotropic evaporation with toluene. The peptide ester is deprotected with 95% TFA in DCM for two hours and extracted three times with anhydrous ethyl ether to remove excess chromophore. The deprotected substrate is 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 can be approximately 20-30%. The molecular mass can be confirmed by electrospray ionization mass spectroscopy. The substrates are stored in dry powder form under desiccation.

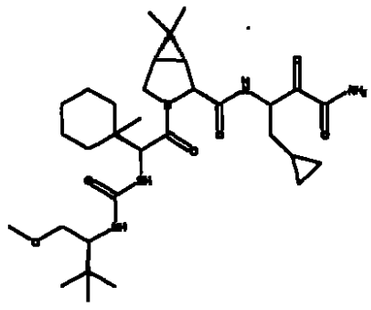
Spectra of Substrates and Products: Spectra of substrates and the corresponding chromophore products are obtained in the pH 6.5 assay buffer. Extinction coefficients are determined at the optimal off-peak wavelength in 1-cm cuvettes (340 nm for 3-Np and HMC, 370 nm for PAP and 400 nm for 4-Np) using multiple dilutions. The optimal off-peak wavelength is defined as that wavelength yielding the maximum fractional difference in absorbance between substrate and product (product OD - substrate OD)/substrate OD).

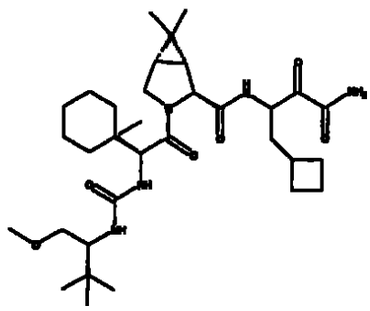
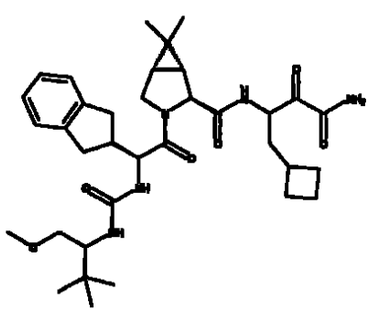
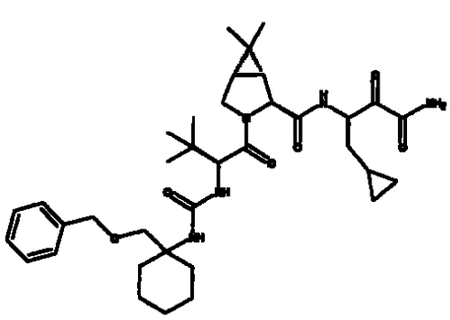
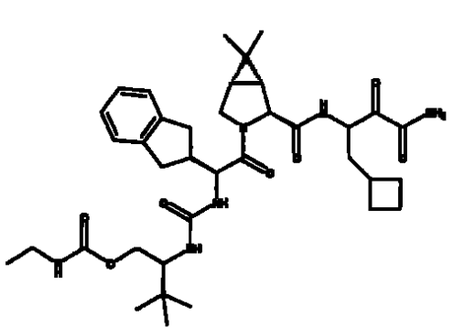
Protease Assay: HCV protease assays are performed at 30°C using a 200 µl reaction mix in a 96-well microtiter plate. Assay buffer conditions (25 mM MOPS pH 6.5, 300 mM NaCl, 10% glycerol, 0.05% lauryl maltoside, 5 µM EDTA and 5 µM DTT) are optimized for the NS3/NS4A heterodimer (D. L. Sali *et al, Ibid.*)). Typically, 150 µl mixtures of buffer, substrate and inhibitor are 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, is then used to initiate the reaction (final volume 200 µl).The plates are 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

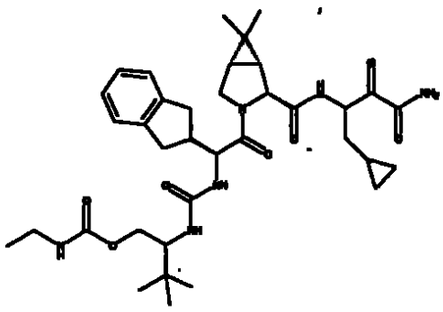
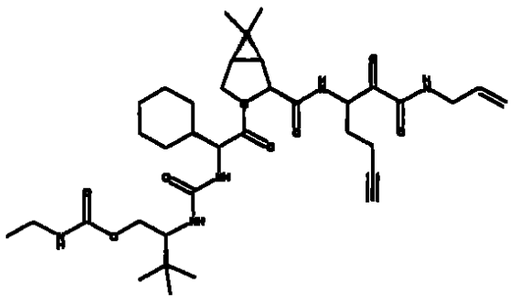
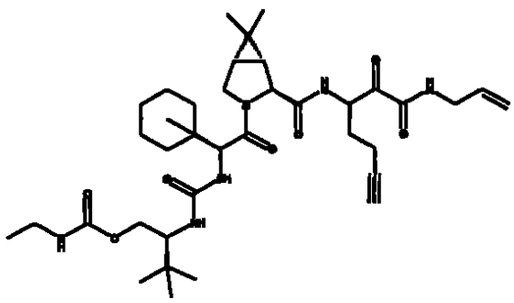
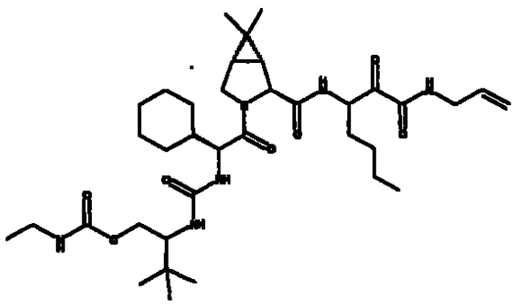
chromophore is monitored at the appropriate wavelength against a no enzyme blank as a control for non-enzymatic hydrolysis. The evaluation of substrate kinetic parameters is performed over a 30-fold substrate concentration range (~6-200 μM). Initial velocities are determined using linear regression and kinetic constants are 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}) are calculated assuming the enzyme is fully active.

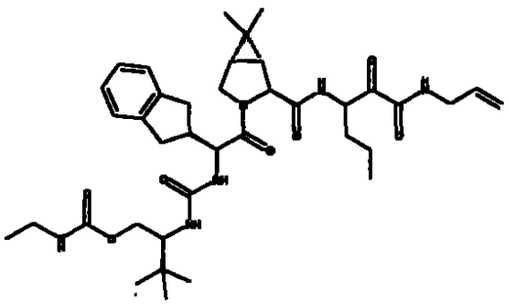
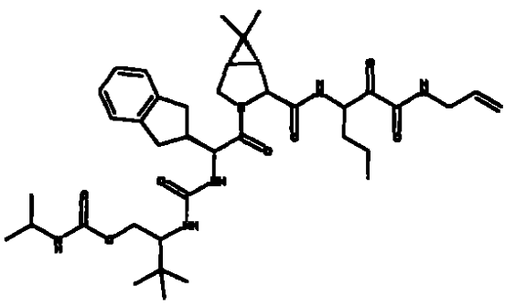
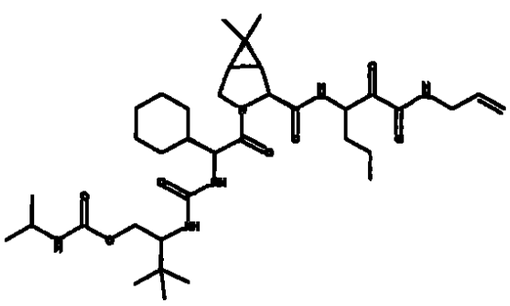
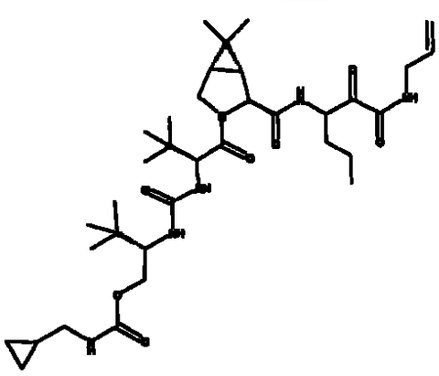
Evaluation of Inhibitors and Inactivators: The inhibition constants (K_i) for the competitive inhibitors Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH and Ac-DTEDVVP(Nva)-OH are determined experimentally at fixed concentrations of enzyme and substrate by plotting v_o/v_i vs. inhibitor concentration ($[I]_o$) according to the rearranged Michaelis-Menten equation for competitive inhibition kinetics: $v_o/v_i = 1 + [I]_o/(K_i(1 + [S]_o/K_m))$, 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 are fitted using linear regression and the resulting slope, $1/(K_i(1+[S]_o/K_m)$, is used to calculate the K_i value. The K_i^* values of some of the inventive compounds are shown in **Table 6** and **Table 6A** below:

Table 6

Example #	Structure	K_i^* (nM)
1654		12

1655		24
1631		15
1606		16
1025		6.7

1024		7.3
1086		8
1090		9
1085		11

1023		33
1012		40
1056		30
1029		14

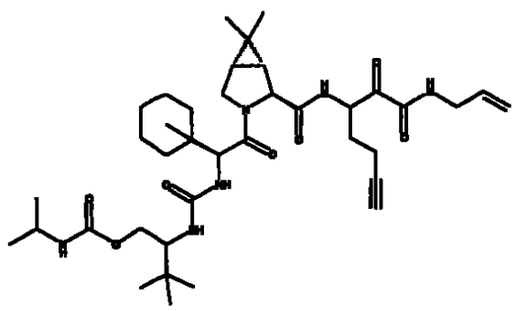
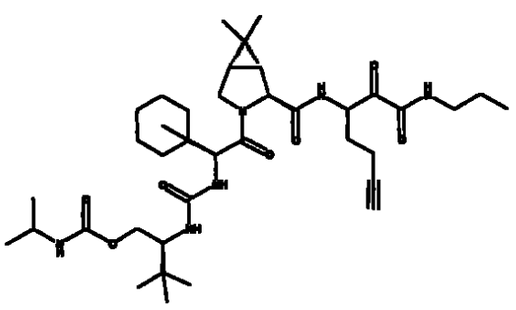
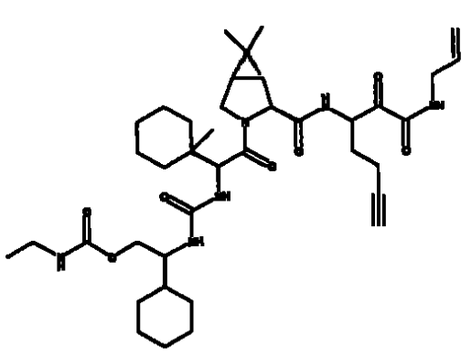
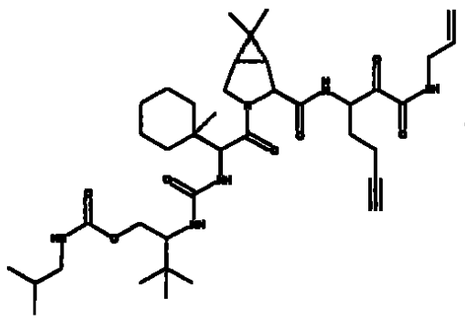
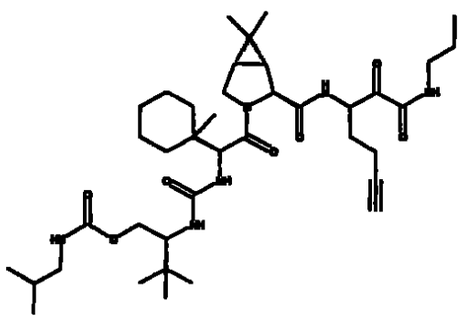
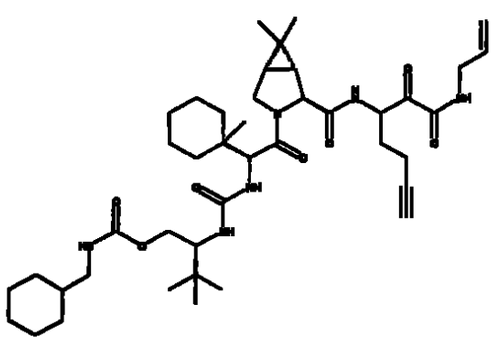
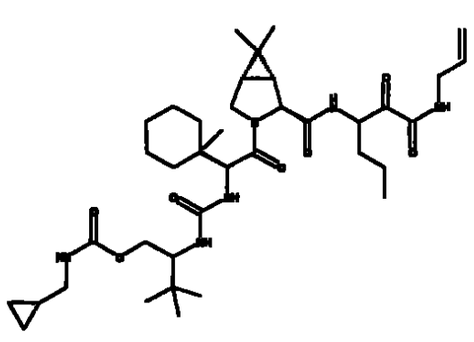
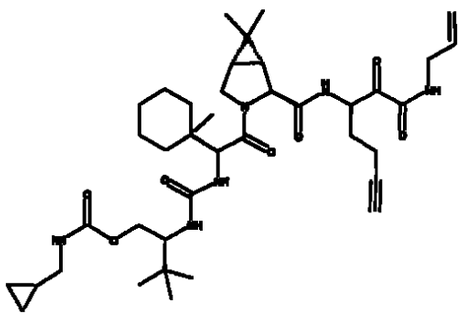
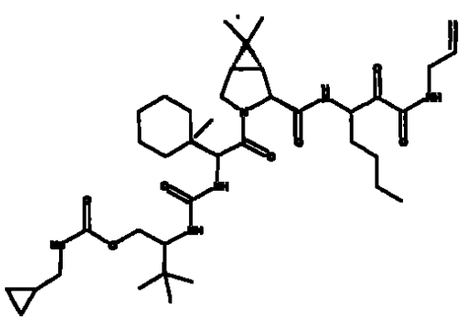
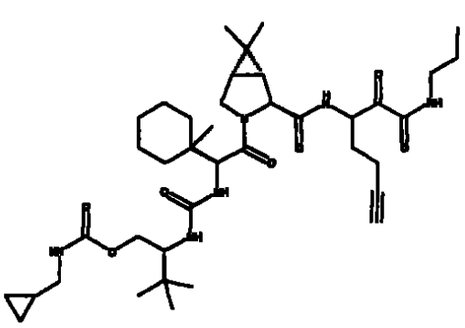
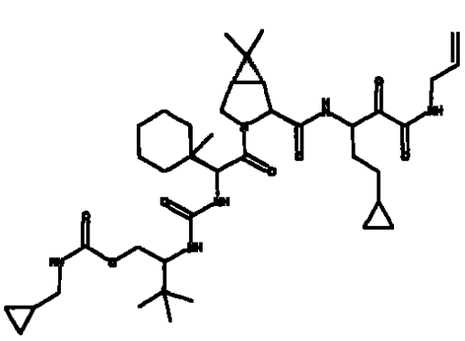
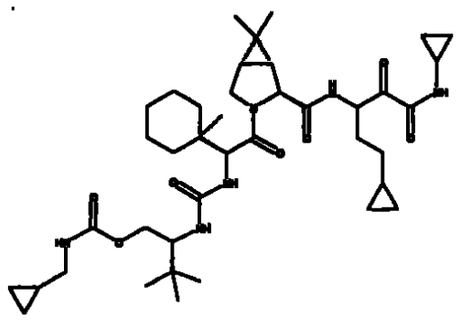
1095		8
1098		15

Table 6A

Example #	Structure	KI* (nM)
1104		13

1108		9
1109		27
1112		20
1114		32

1115		7.4
1116		34
1117		19
1120		30

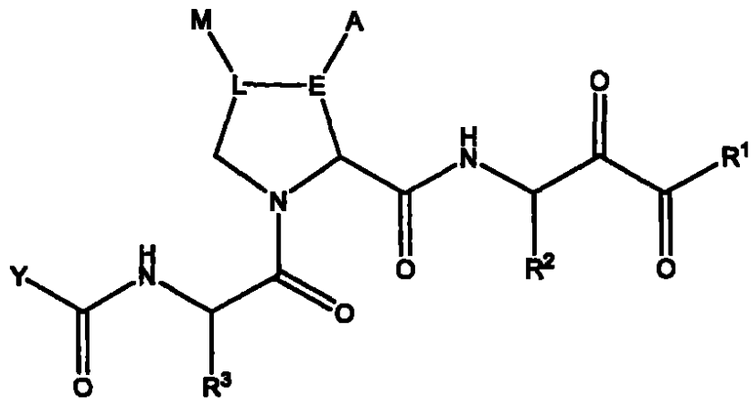
1121		22

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.

Claims

What is claimed is:

1. A compound, or enantiomers, stereoisomers, rotamers, tautomers, or racemates of said compound, or a pharmaceutically acceptable salt, solvate or ester of said compound, said compound having the general structure shown in Formula I:

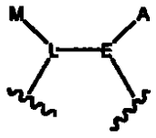


Formula I

wherein:

R^1 is H, OR^8, NR^9R^{10}, or CHR^9R^{10}, wherein R^8, R^9 and R^{10} can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, aryl-, heteroalkyl-, heteroaryl-, cycloalkyl-, heterocyclyl-, arylalkyl-, and heteroarylalkyl;

A and M can be the same or different, each being independently selected from R, OR, NHR, NRR', SR, SO_2R, and halo; or A and M are connected to each other such that the moiety:



shown above in Formula I forms either a three, four, six, seven or eight-membered cycloalkyl, a four to eight-membered heterocyclyl, a six to ten-membered aryl, or a five to ten-membered heteroaryl;

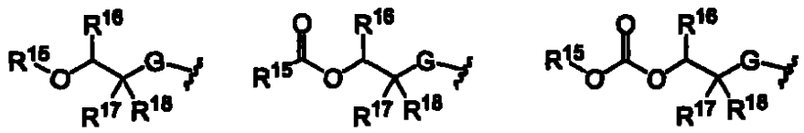
E is C(H) or C(R);

L is C(H), C(R), $CH_2C(R)$, or $C(R)CH_2$;

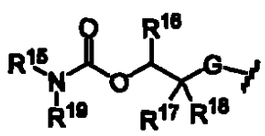
R, R', R^2, and R^3 can be the same or different, each being independently selected from the group consisting of H, alkyl-, alkenyl-, alkynyl-, cycloalkyl-, heteroalkyl-, heterocyclyl-, aryl-, heteroaryl-,

(cycloalkyl)alkyl-, (heterocyclyl)alkyl-, aryl-alkyl-, and heteroaryl-alkyl-; or alternately R and R' in NRR' are connected to each other such that NRR' forms a four to eight-membered heterocyclyl;

and Y is selected from the following moieties:



or

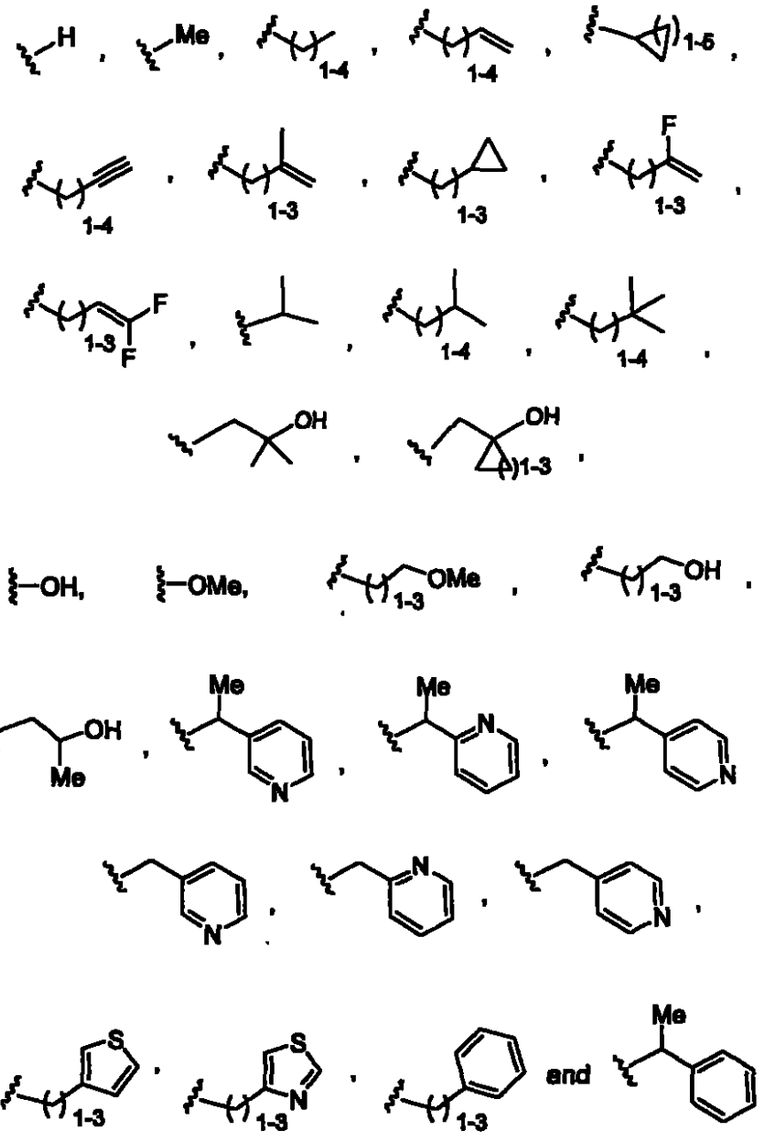


wherein G is NH or O; and R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, and heteroarylalkyl, or alternately, (i) either R^{15} and R^{16} are connected to each other to form a four to eight-membered cyclic structure, or R^{15} and R^{19} are connected to each other to form a four to eight-membered cyclic structure, and (ii) likewise, independently, R^{17} and R^{18} are connected to each other to form a three to eight-membered cycloalkyl or heterocyclyl;

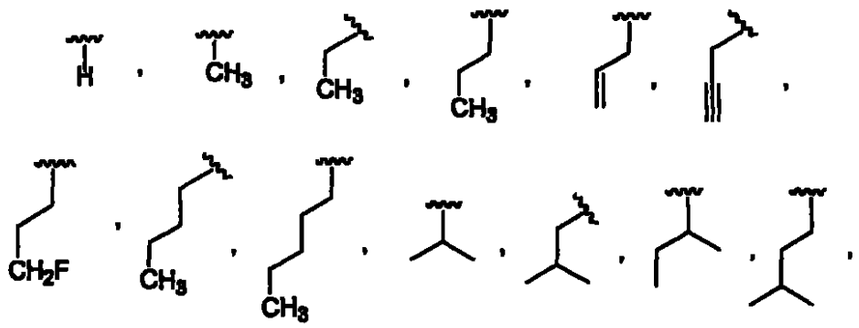
wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio, alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, sulfonamido, alkylsulfonamido, arylsulfonamido, alkyl, aryl, heteroaryl, keto, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

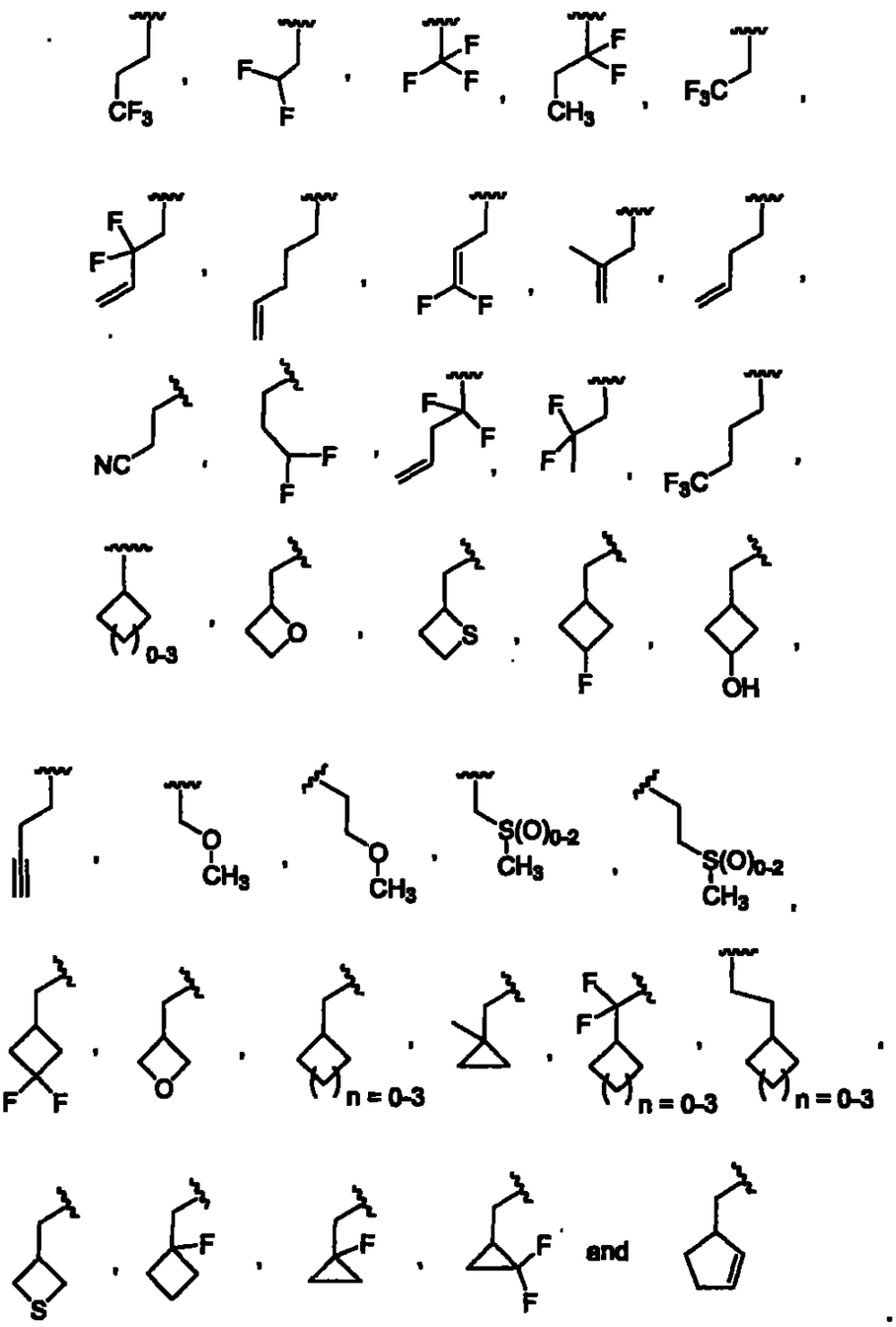
2. The compound of claim 1, wherein R^1 is NR^9R^{10}, and R^9 is H, R^{10} is H, or R^{14} wherein R^{14} is H, alkyl, aryl, heteroalkyl, heteroaryl, cycloalkyl, alkyl-aryl, alkyl-heteroaryl, aryl-alkyl, alkenyl, alkynyl or heteroaryl-alkyl.

3. The compound of claim 2, wherein R^{14} is selected from the group consisting of:

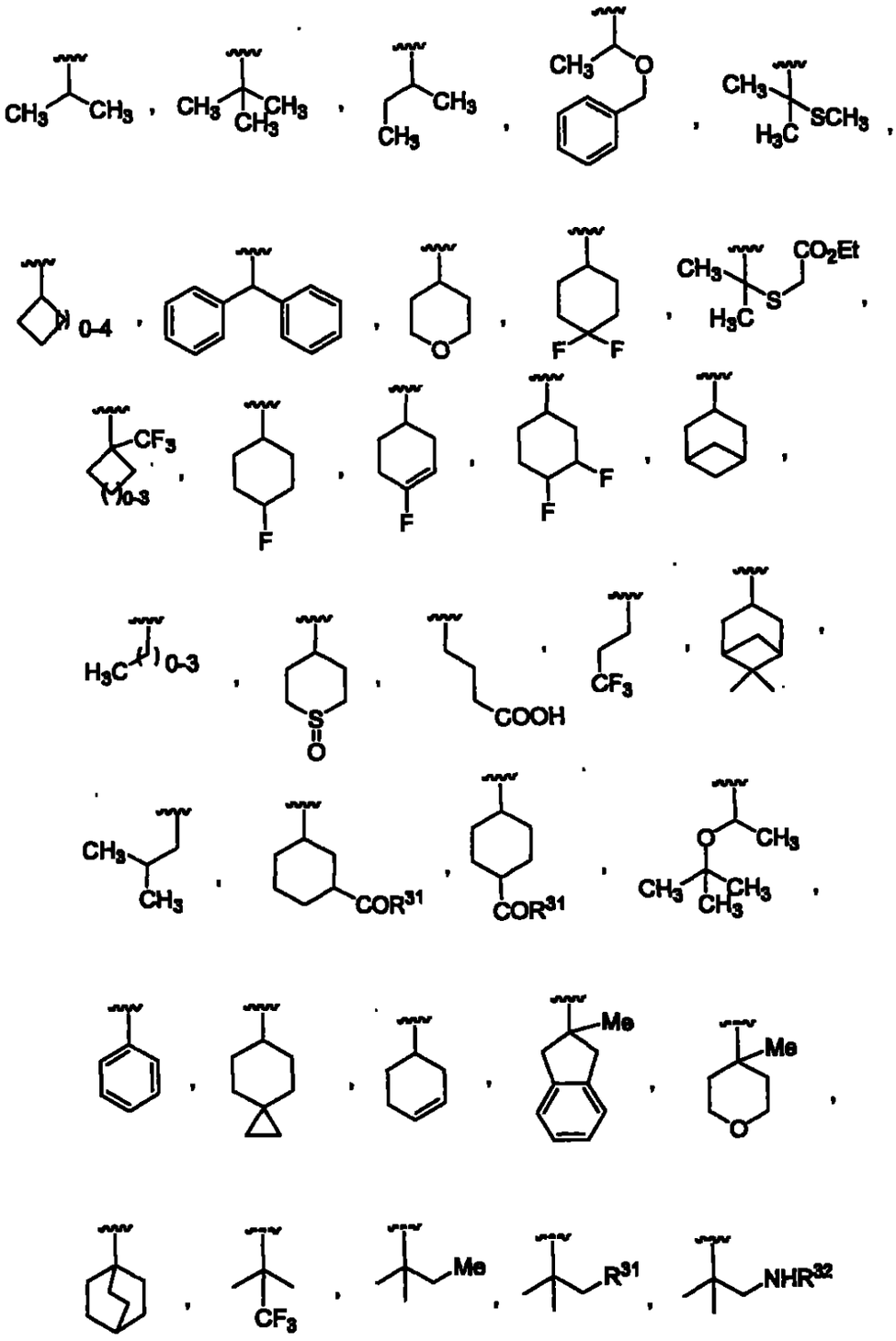


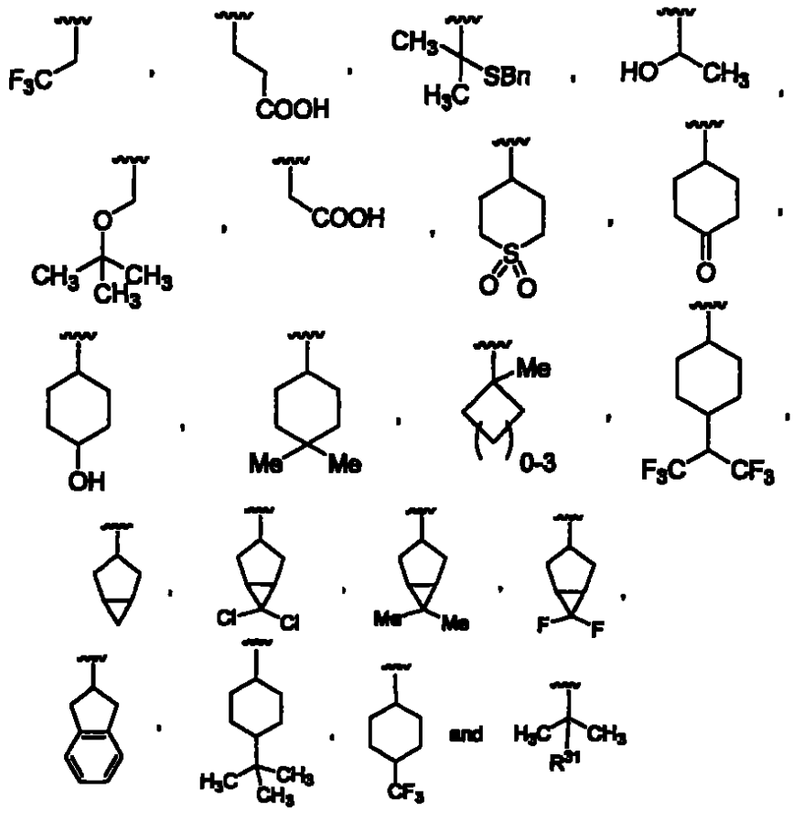
4. The compound of claim 1, wherein R^2 is selected from the group consisting of the following moieties:





5. The compound of claim 1, wherein R^3 is selected from the group consisting of:

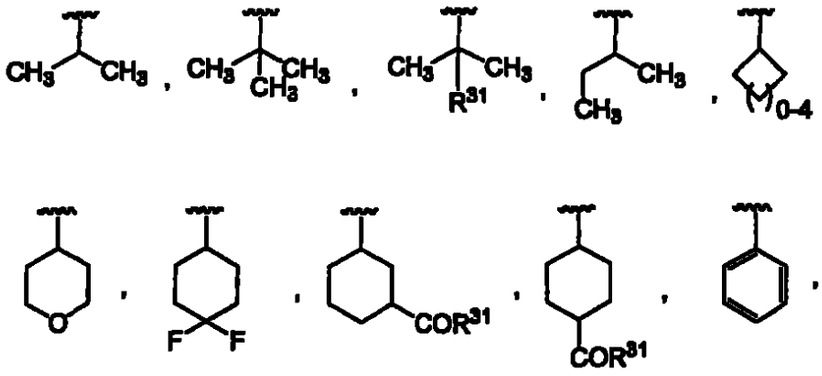

CH3
CH3
CH3
CH3
CH3
CH3
CH3
O
CH3
H3C
SCH3
0-4
O
F
F
CH3
CO2Et
S
H3C
CF3
0-3
F
F
F
H3C
0-3
S
O
COOH
CF3
CH3
CH3
COR31
COR31
O
CH3
CH3
CH3
Me
Me
O
CF3
Me
R31
NHR32

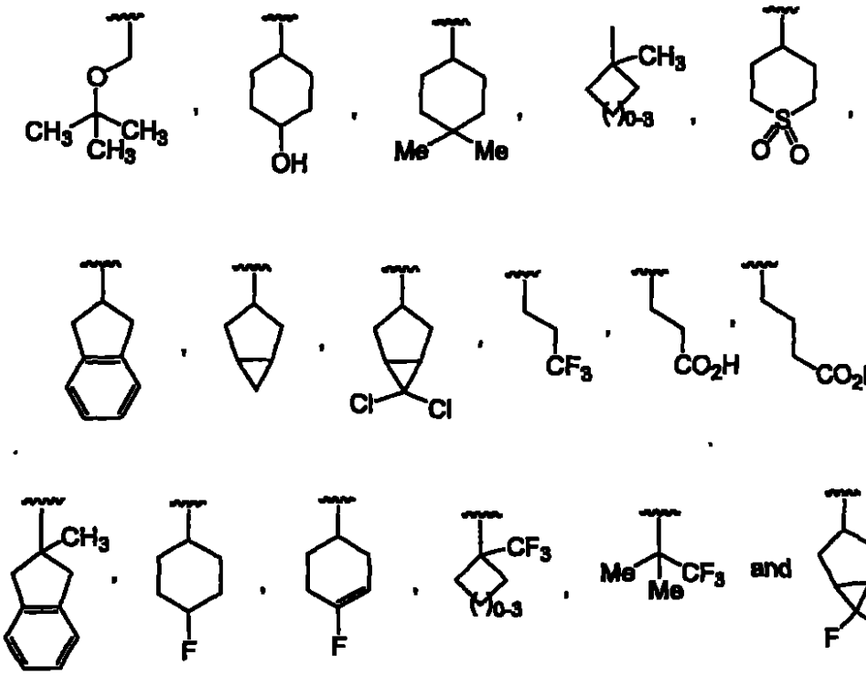


wherein R^{31} is OH or O-alkyl; and

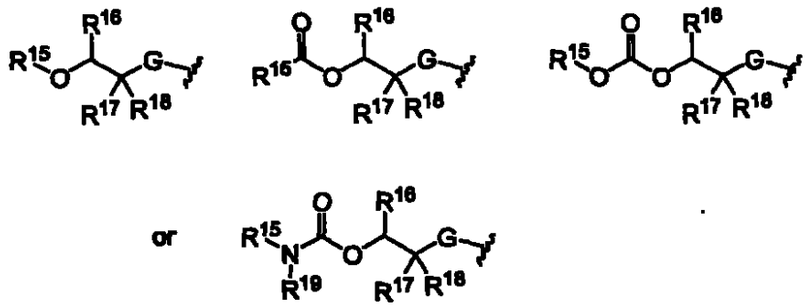
R^{32} is H, $C(O)CH_3$, C(O)OtBu or C(O)N(H)tBu.

6. The compound of claim 5, wherein R^3 is selected from the group consisting of the following moieties:





7. The compound of claim 1, wherein Y is selected from the following moieties:



wherein G = NH or O; and

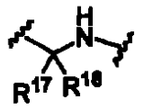
R^{15}, R^{16}, R^{17}, R^{18}, and R^{19} can be the same or different, each being independently selected from the group consisting of H, alkyl, heteroalkyl, alkenyl, heteroalkenyl, alkynyl, heteroalkynyl, cycloalkyl, heterocyclyl, aryl, and heteroaryl, or alternately, (i) either R^{15} and R^{16} are directly connected to form a four to eight-membered cyclic structure, or R^{15} and R^{19} are directly connected to form a four to eight-membered cyclic structure, and (ii) likewise, independently, R^{17} and R^{18} are directly connected to form a three to eight-membered cycloalkyl or heterocyclyl;

wherein each of said alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl can be unsubstituted or optionally independently substituted with one or more moieties selected from the group consisting of: hydroxy, alkoxy, aryloxy, thio,

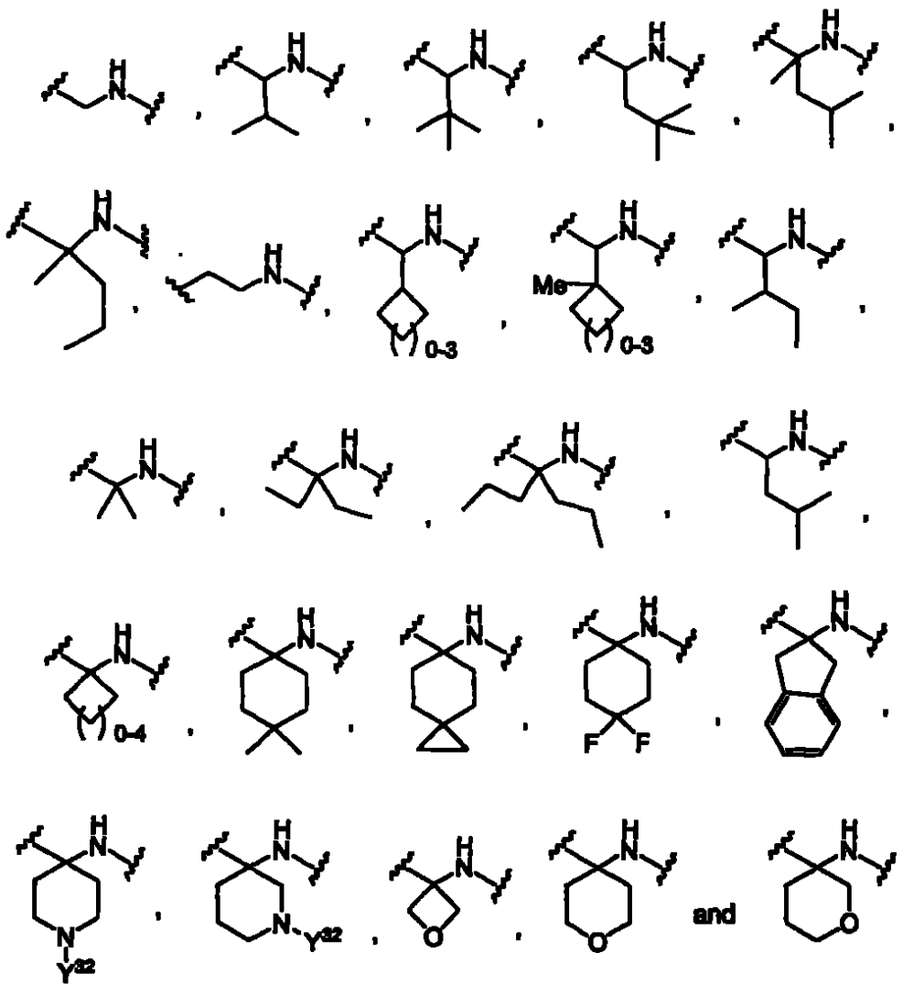
alkylthio, arylthio, amino, amido, alkylamino, arylamino, alkylsulfonyl, arylsulfonyl, sulfonamido, alkylsulfonamido, arylsulfonamido, keto, carboxy, carbalkoxy, carboxamido, alkoxycarbonylamino, alkoxycarbonyloxy, alkylureido, arylureido, halo, cyano, and nitro.

8. The compound of claim 7, wherein G is NH.

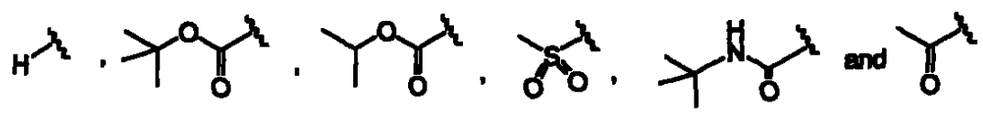
9. The compound of claim 8, wherein



is selected from the group consisting of:

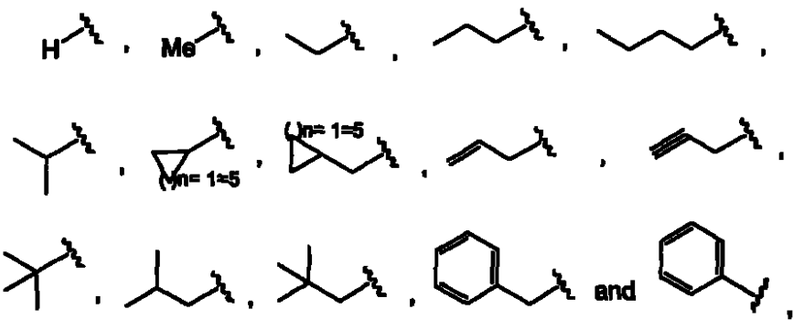


wherein Y^{32} is selected from the group consisting of:

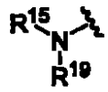


R^{16} is selected from H, methyl, phenyl, benzyl; and

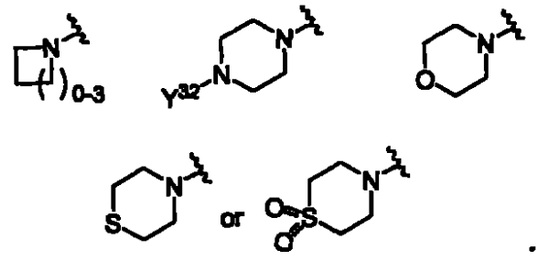
R^{15} and R^{19} maybe the same or different, each being independently selected from the following:



or alternately, the moiety:

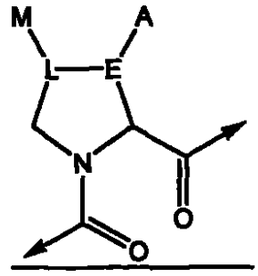


is selected from the following moieties:

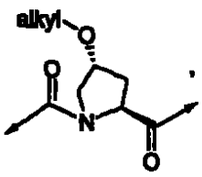


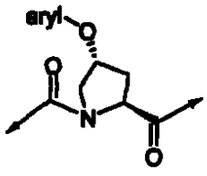
10. The compound of claim 9, wherein R^{16} is H.

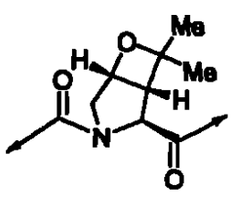
11. The compound of claim 1, wherein the moiety:

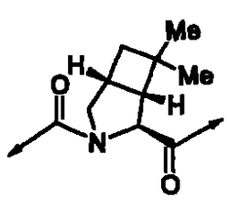


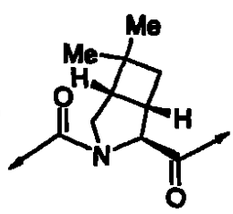
is selected from the following structures:

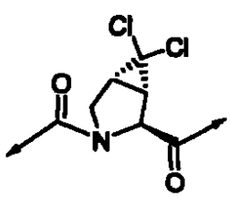

alkyl
O
O
N
O

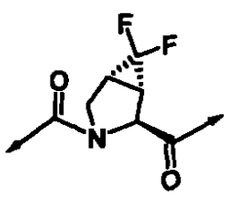

aryl
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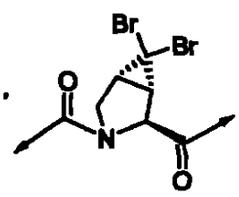

Me
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O
Me
H
O
N
O

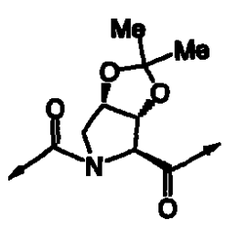

Me
H
O
Me
H
O
N
O

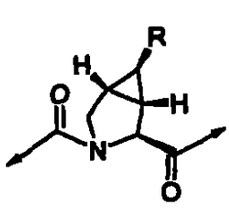

Me
Me
H
O
H
O
N
O

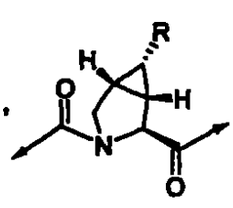

Cl
Cl
O
O
N
O

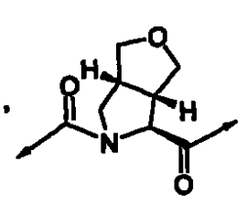

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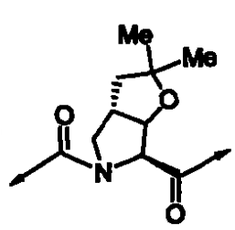

Br
Br
O
O
N
O

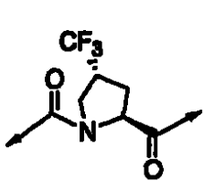

Me
Me
O
O
O
N
O

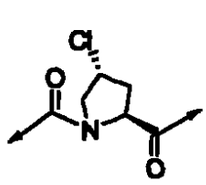

R
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H
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N
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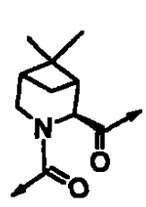

R
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O
H
O
N
O

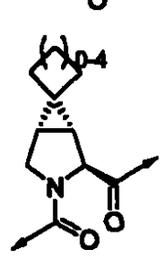

O
H
O
H
O
N
O


Me
Me
O
O
O
N
O

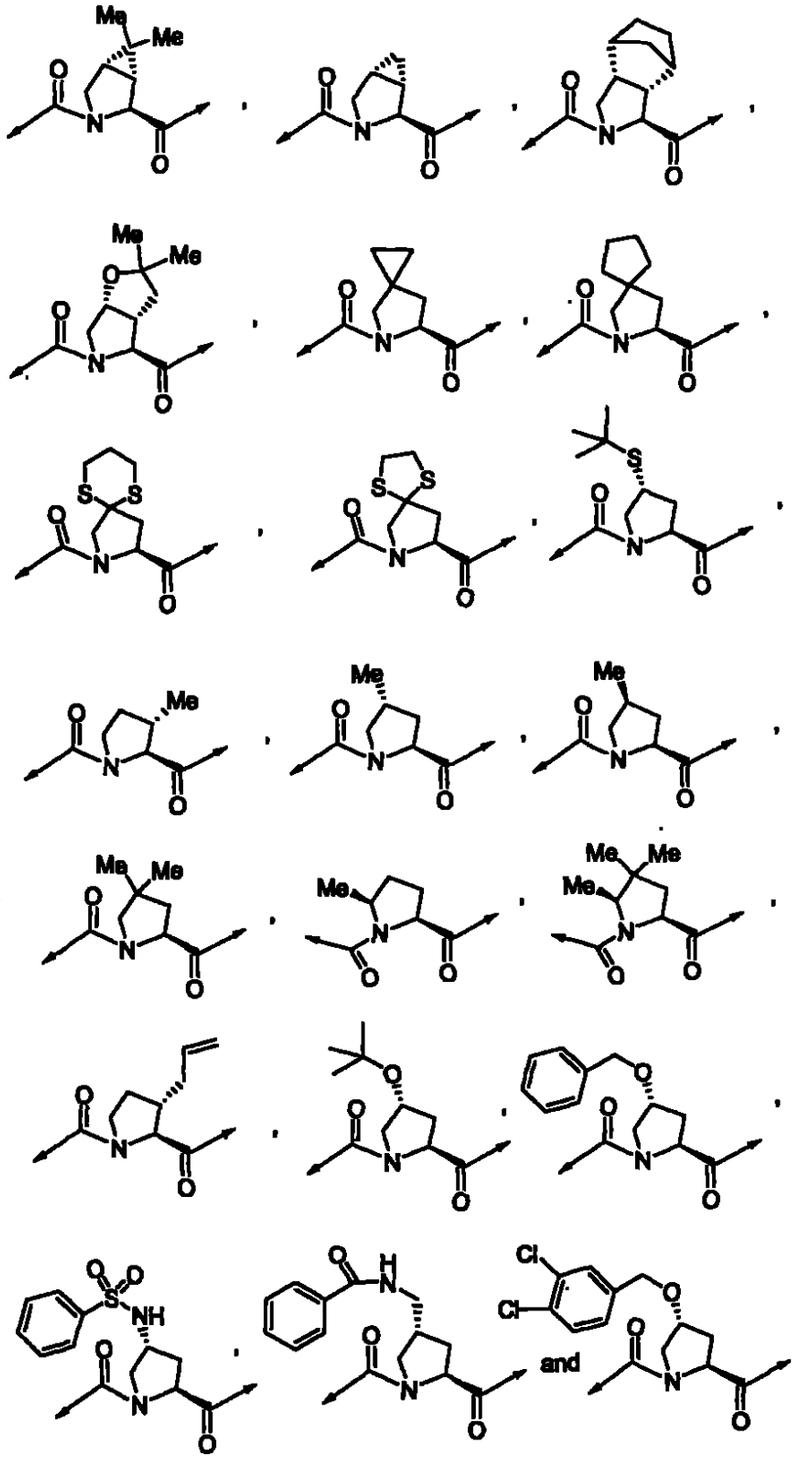

CF3
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O
N
O


Cl
O
O
N
O

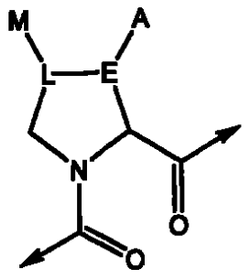

N
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O


0-4
N
O
O

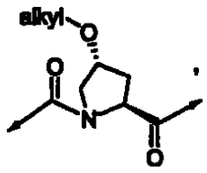
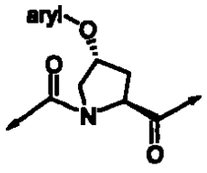
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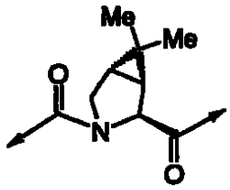
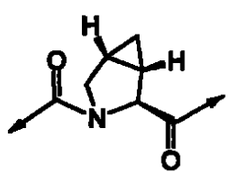
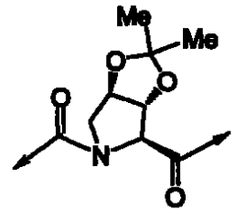
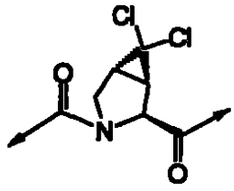
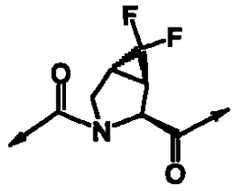
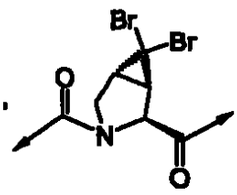
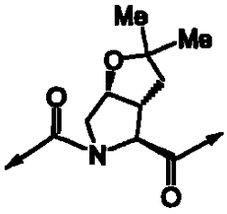
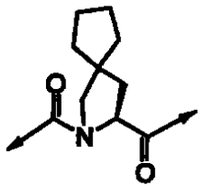
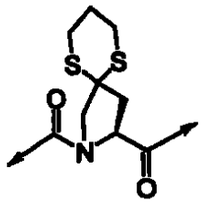
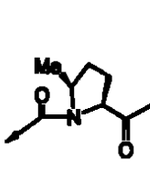
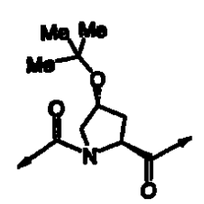
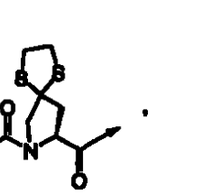
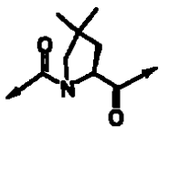
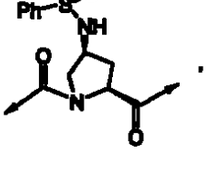
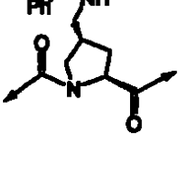


12. The compound of claim 11, wherein the moiety:

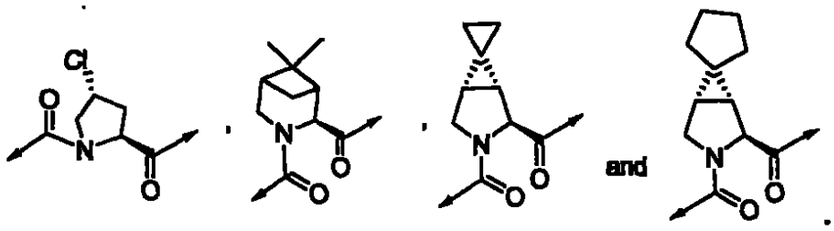


is selected from the following structures:

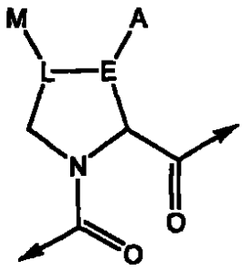



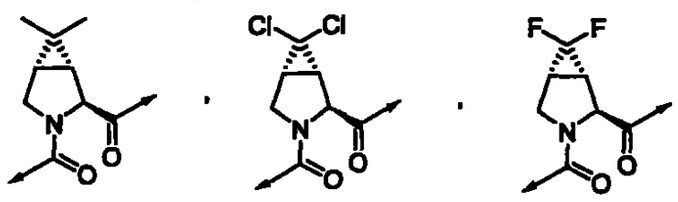
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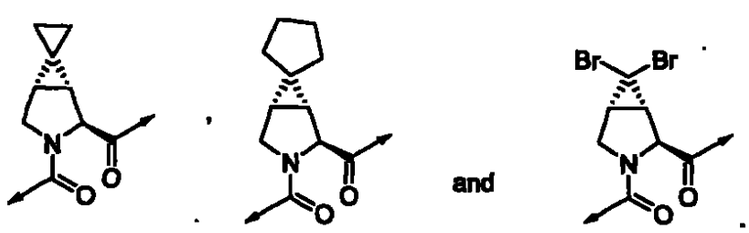


13. The compound of claim 12, wherein the moiety:

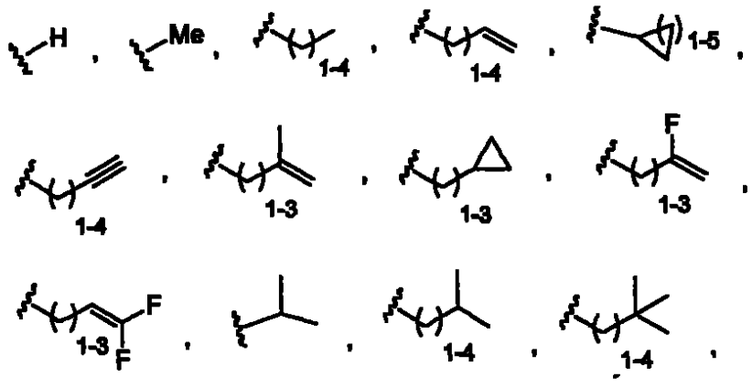


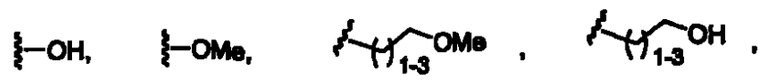
is selected from the following structures:

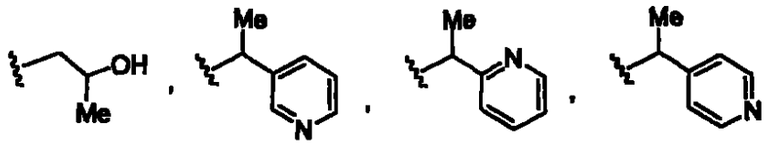


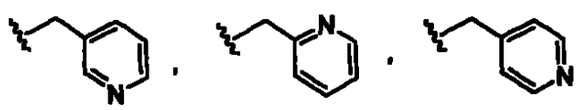


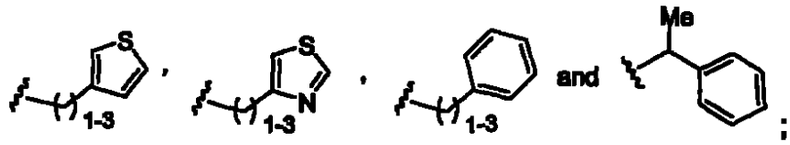
14. The compound of claim 1, wherein R^{14} is selected from the group consisting of:



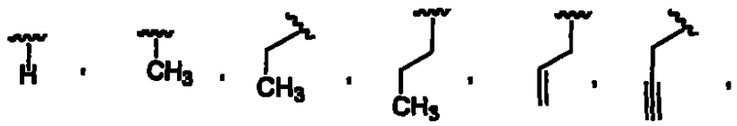


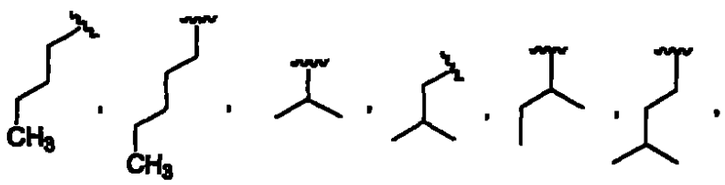


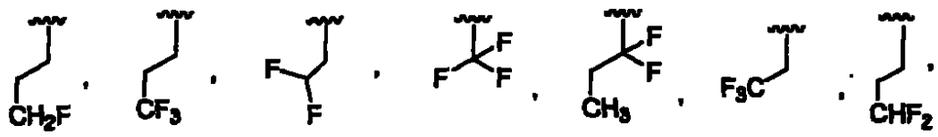


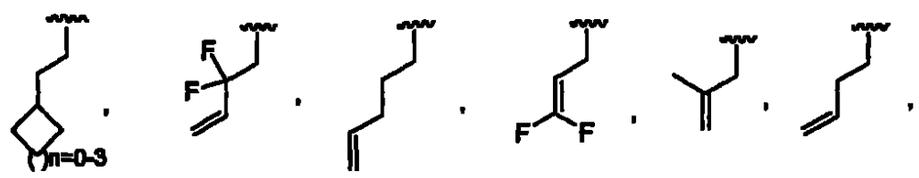


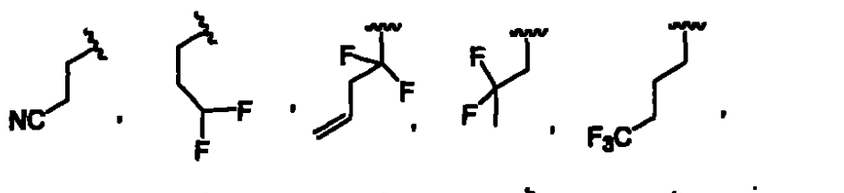
R^2 is selected from the group consisting of the following moieties:

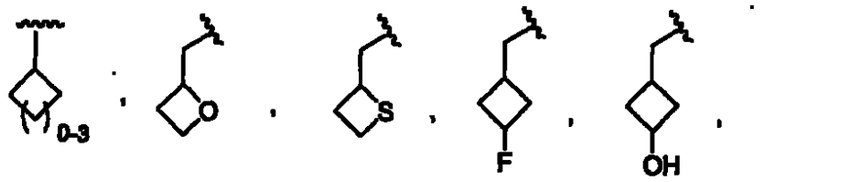


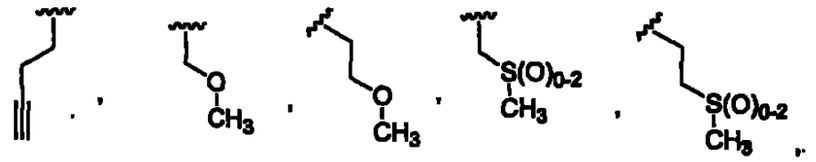


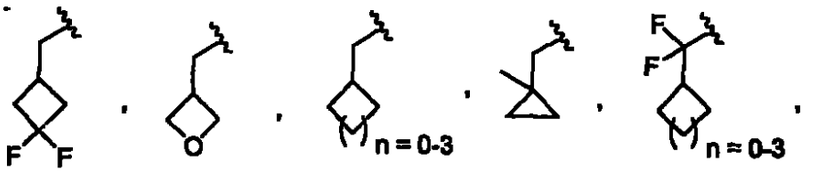


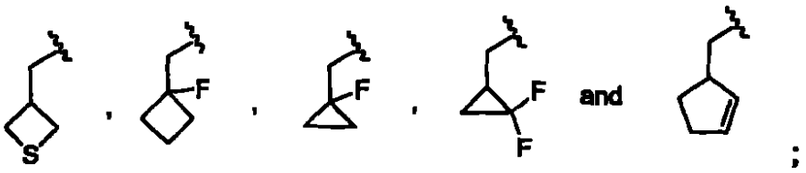






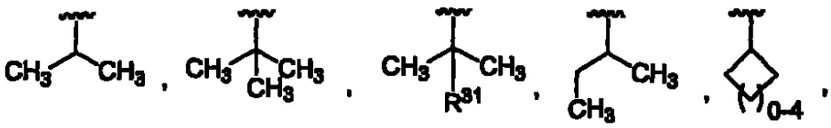


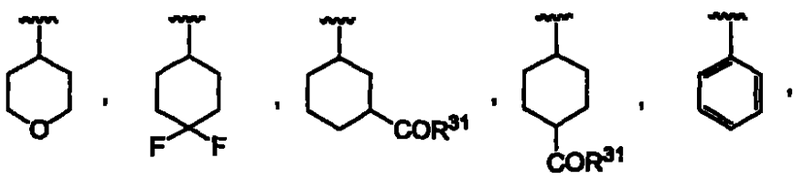


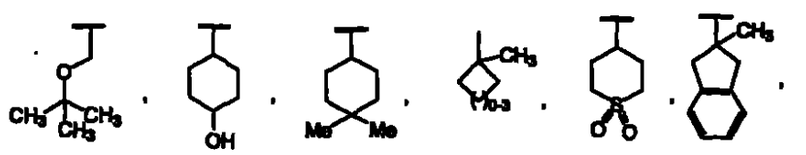


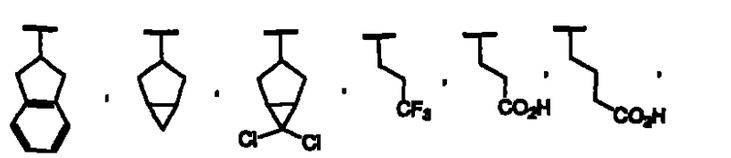
;

R^3 is selected from the group consisting of the following moieties:

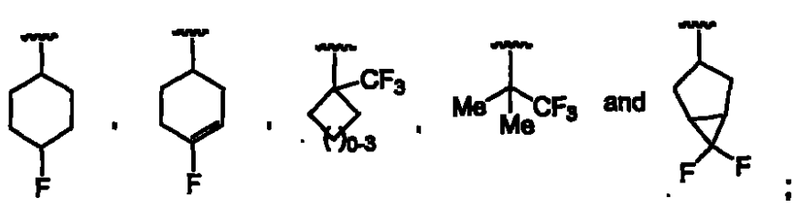






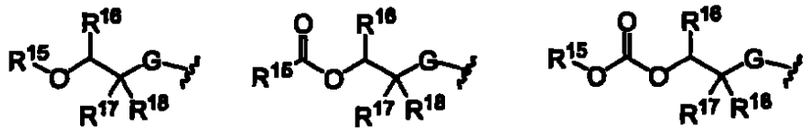


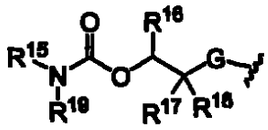
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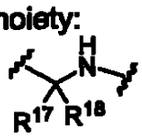
;

Y is selected from the group consisting of:

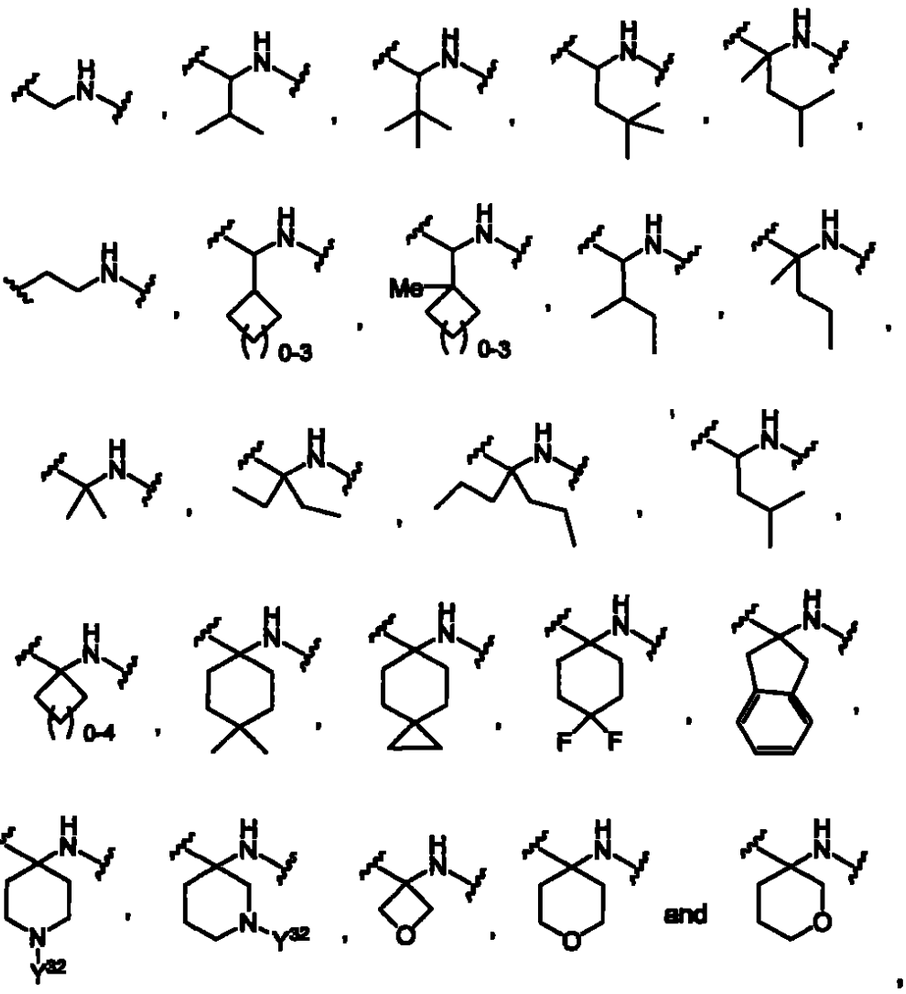


and 

wherein G = NH; and the moiety:

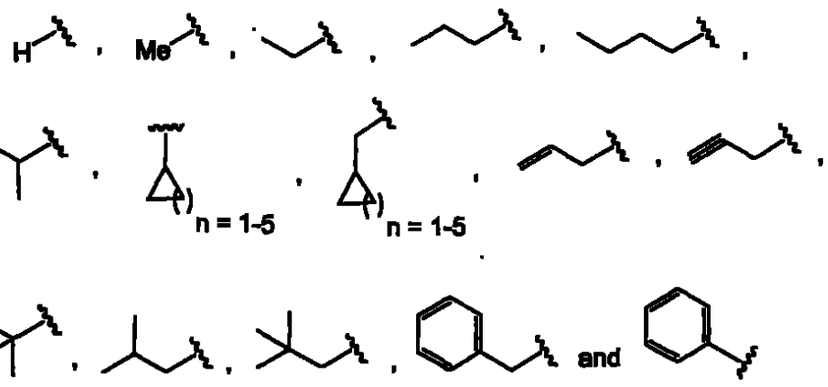


is selected from the group consisting of:

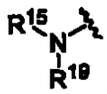


R^{16} = H; and

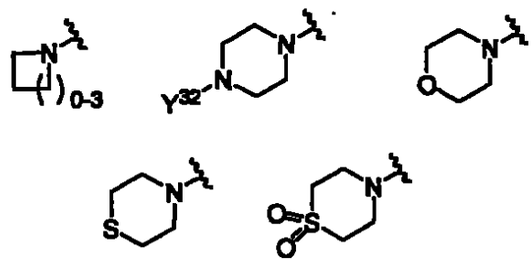
R^{15} and R^{19} maybe the same or different, and is selected from one of the following:



or alternately, the moiety:

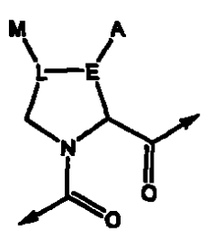


is represented by one of the following moieties,

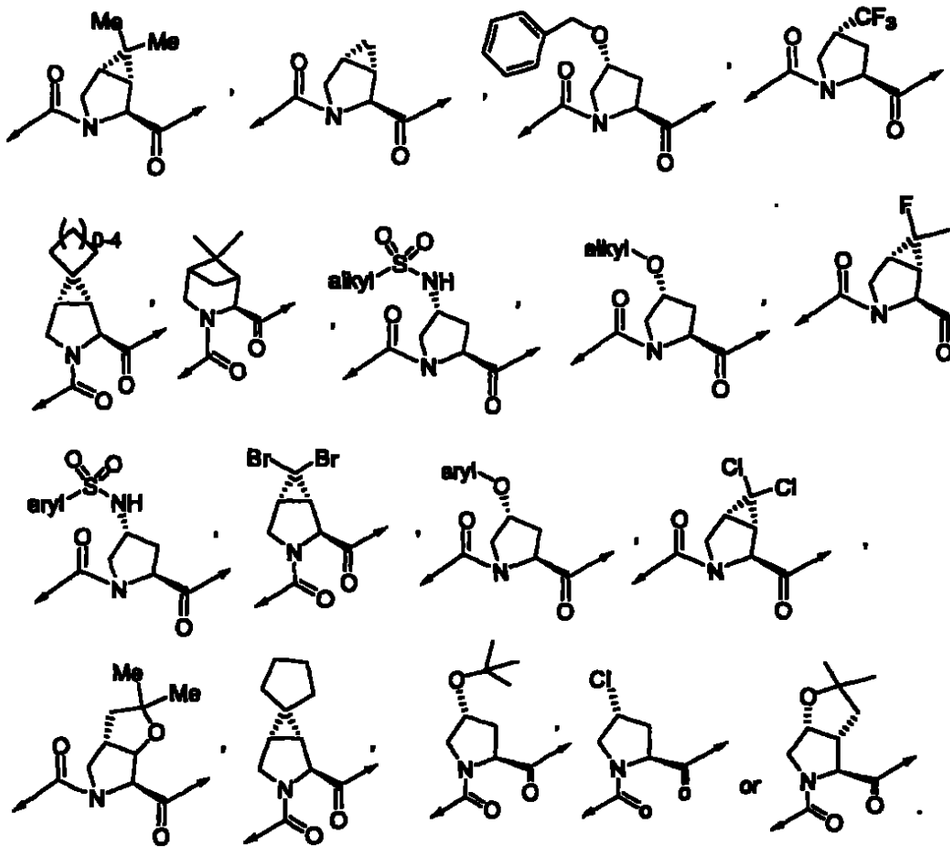


;

and the moiety:



is:



15. A pharmaceutical composition comprising as an active ingredient at least one compound of claim 1.

16. The pharmaceutical composition of claim 15 for use in treating disorders associated with HCV.

17. The pharmaceutical composition of claim 16 additionally comprising at least one pharmaceutically acceptable carrier.

18. The pharmaceutical composition of claim 17, additionally containing at least one antiviral agent.

19. The pharmaceutical composition of claim 18, still additionally containing at least one interferon.

20. The pharmaceutical composition of claim 19, wherein said at least one antiviral agent is ribavirin and said at least one interferon is α-interferon or pegylated interferon.

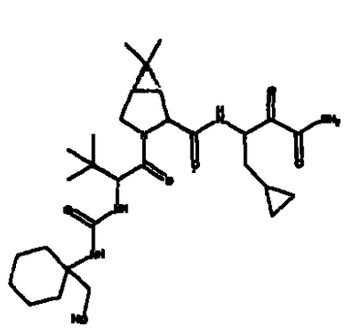
21. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound of claim 1.

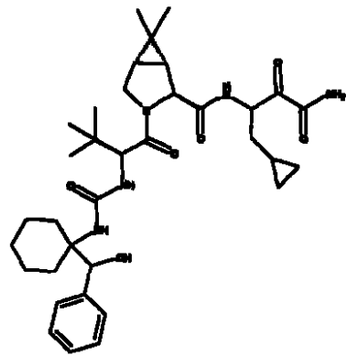
22. The method of claim 21, wherein said administration is oral or subcutaneous.

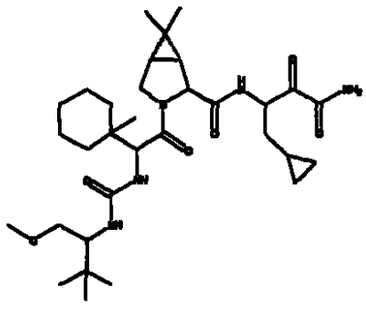
23. The use of a compound of claim 1 for the manufacture of a medicament to treat disorders associated with the HCV.

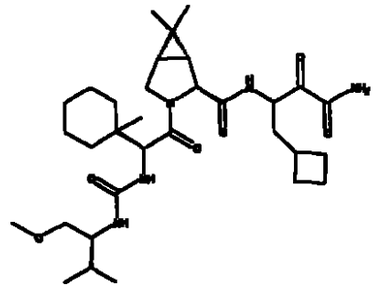
24. A method of preparing a pharmaceutical composition for treating the disorders associated with the HCV, said method comprising bringing into intimate physical contact at least one compound of claim 1 and at least one pharmaceutically acceptable carrier.

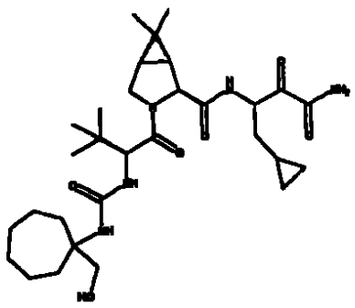
25. A compound exhibiting HCV protease inhibitory activity, or enantiomers, stereoisomers, rotamers, tautomers, diastereomers, or racemates of said compound, or a pharmaceutically acceptable salt, solvate or ester of said compound, said compound being selected from the compounds of structures listed below:

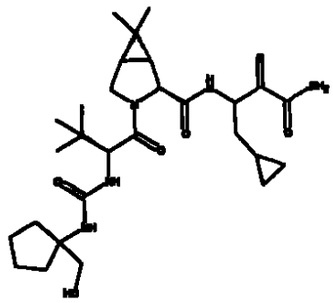


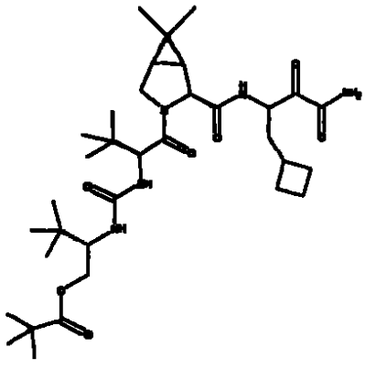


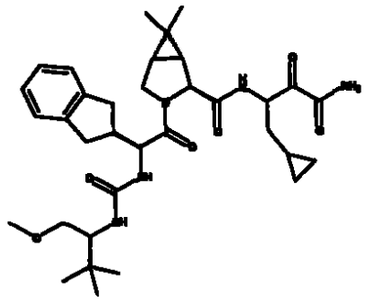


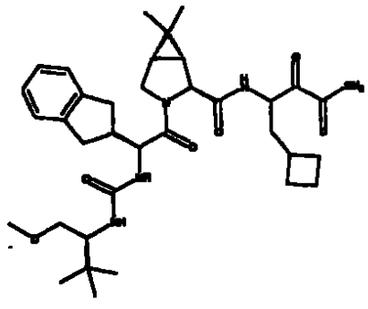


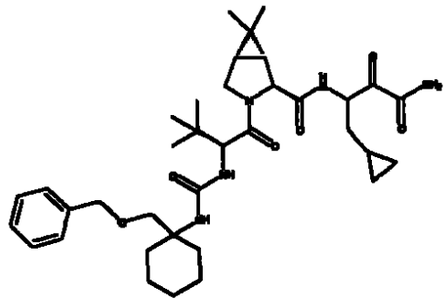


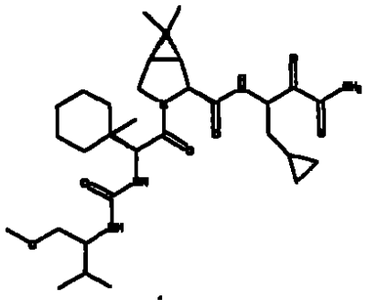


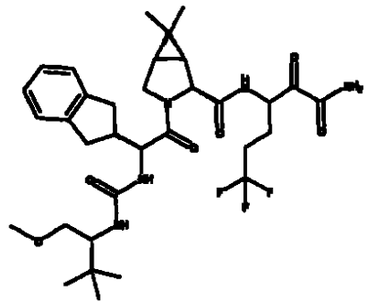


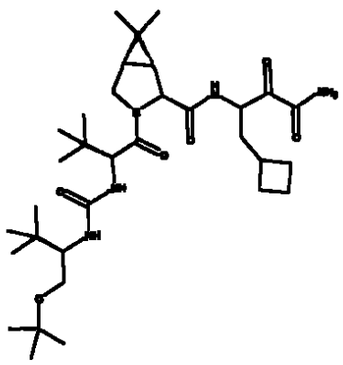


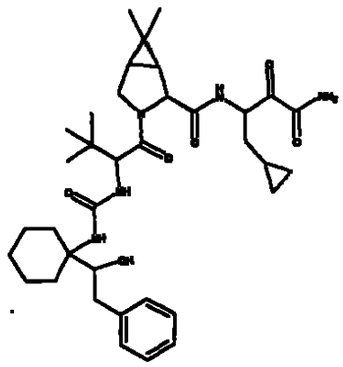


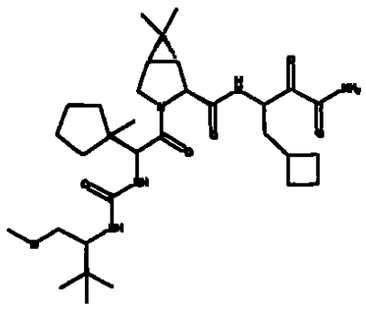


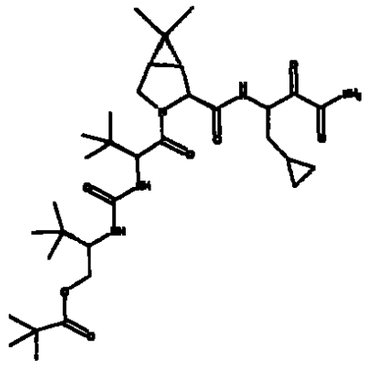


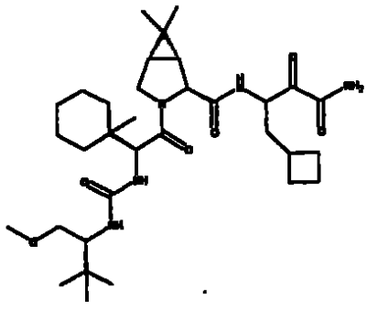


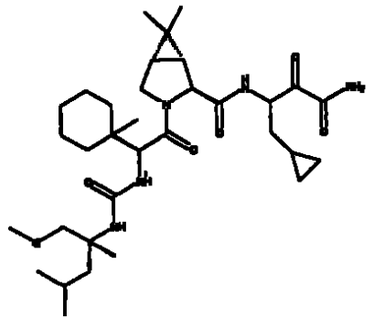


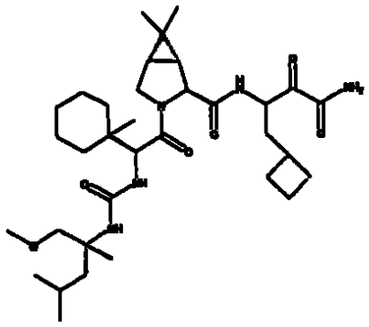


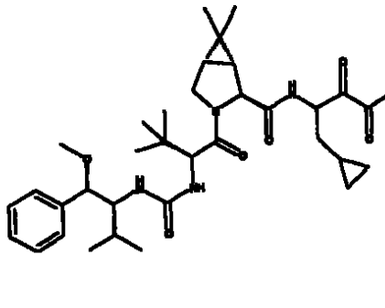


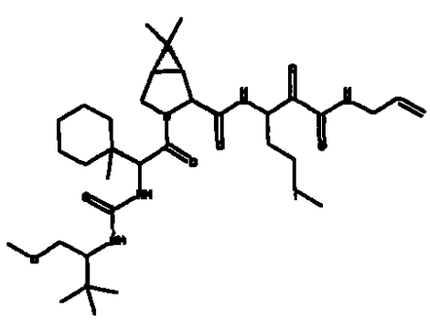


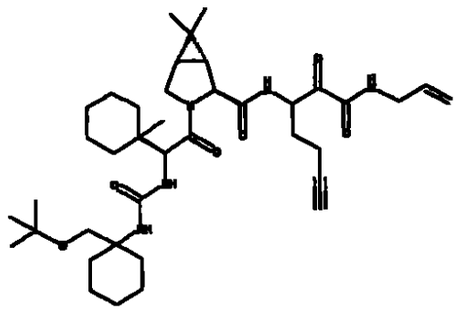


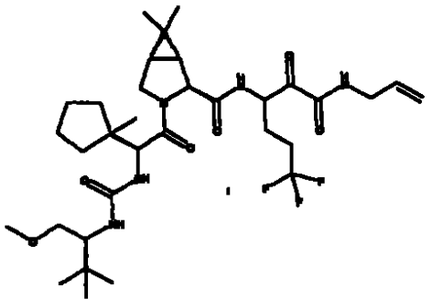


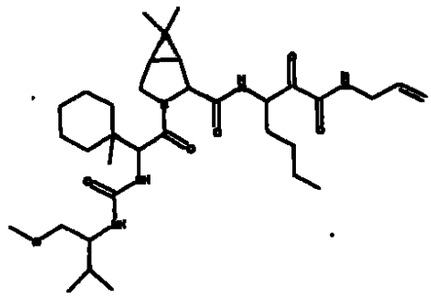


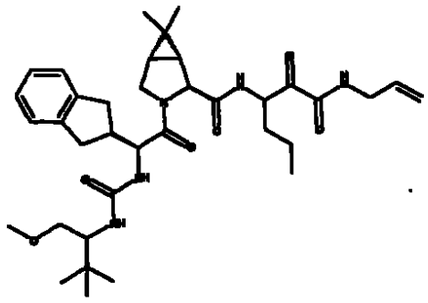


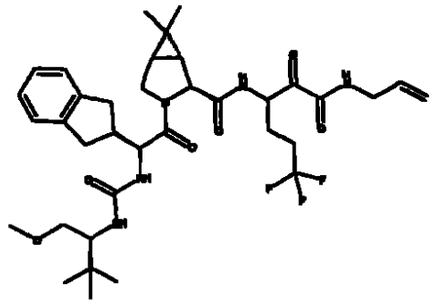


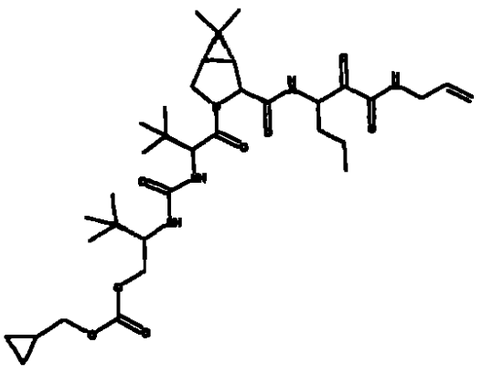


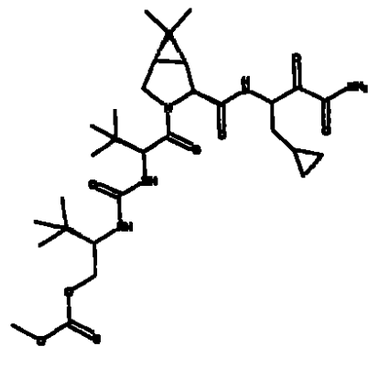


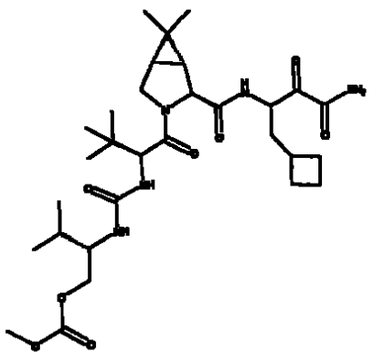


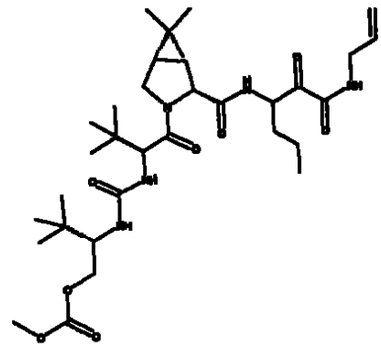


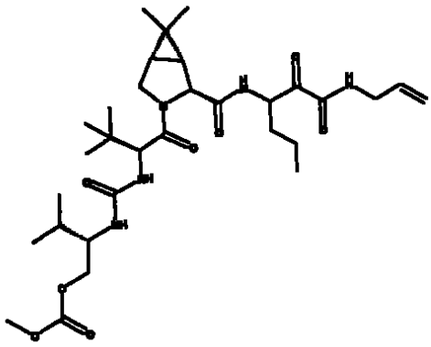


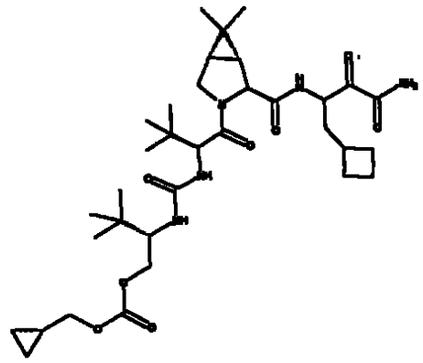


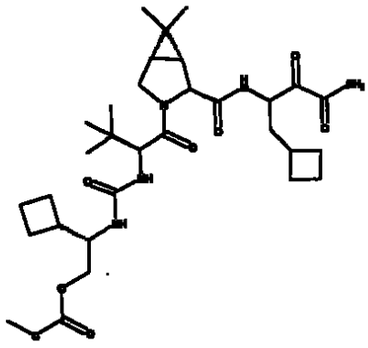


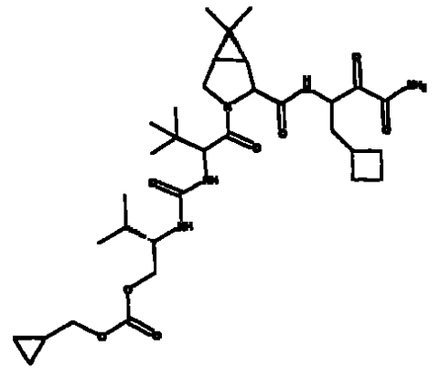


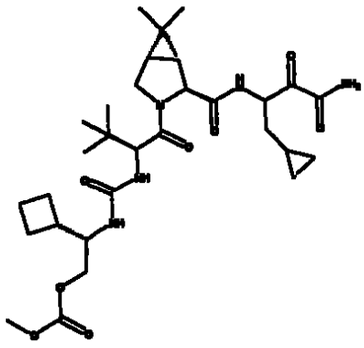


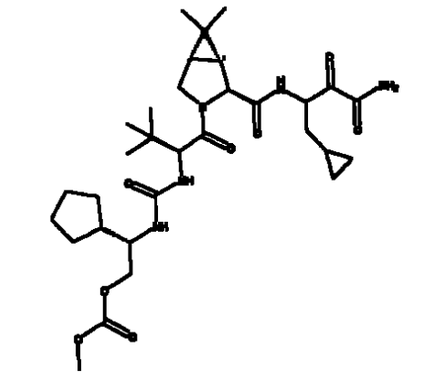


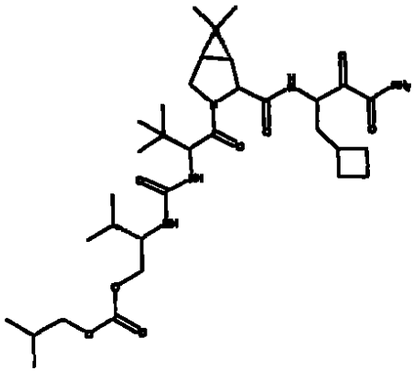


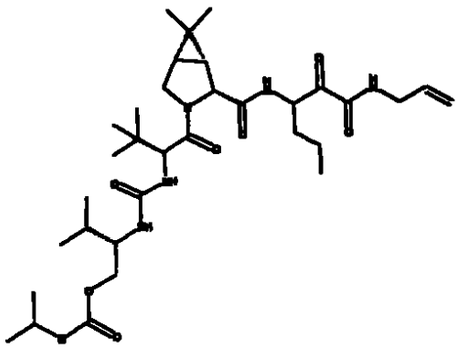


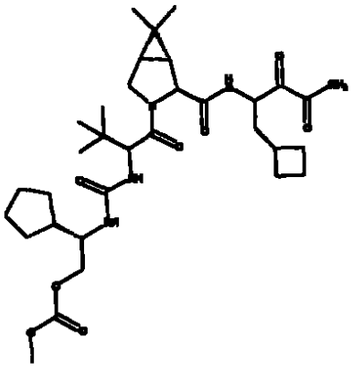


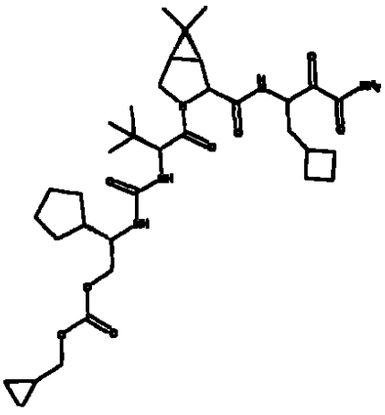


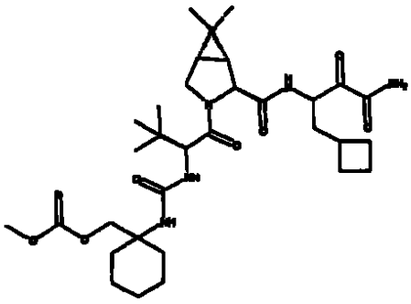


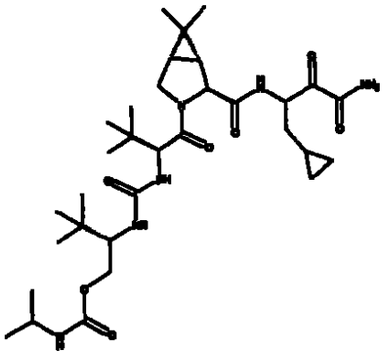


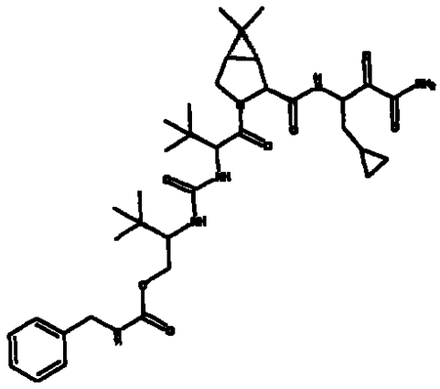


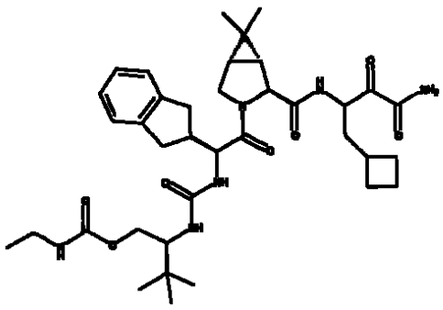


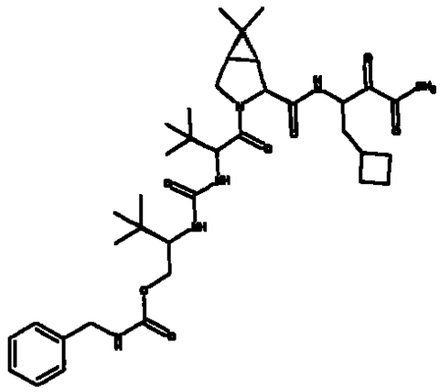


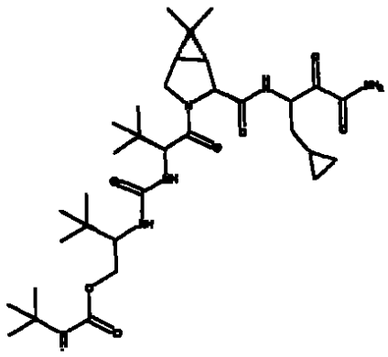


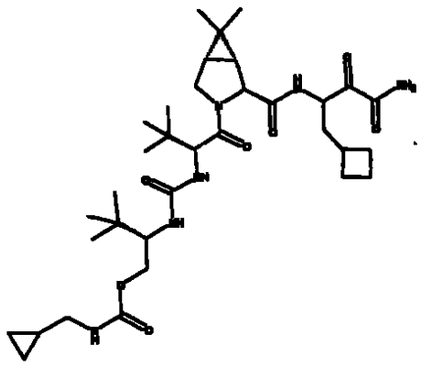


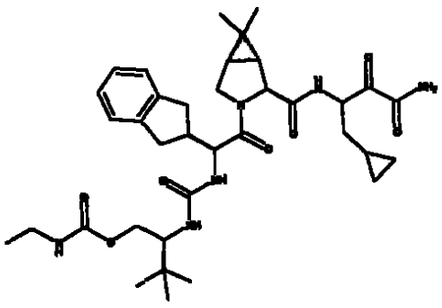


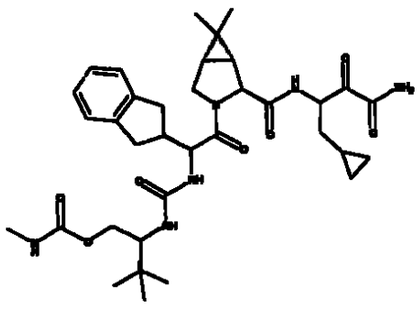


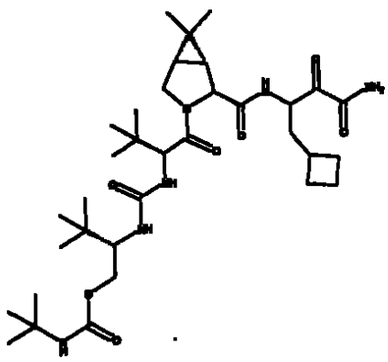


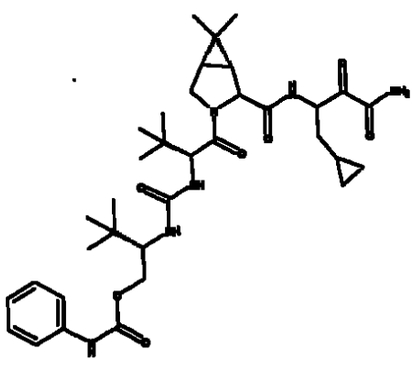


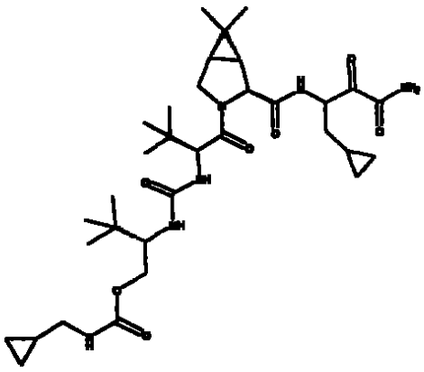


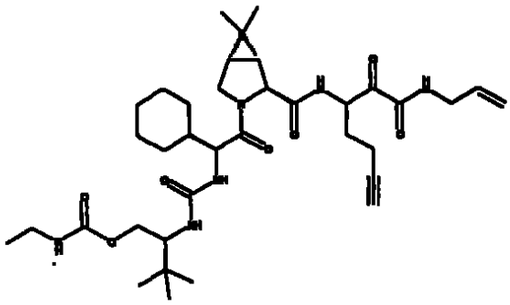


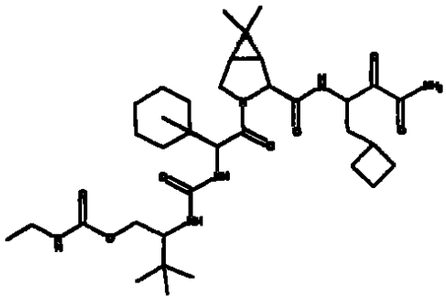


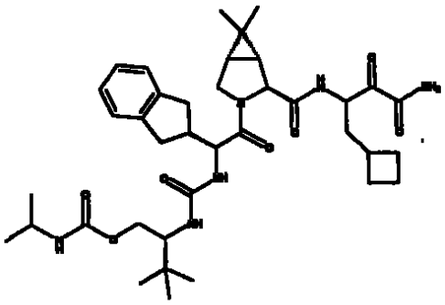


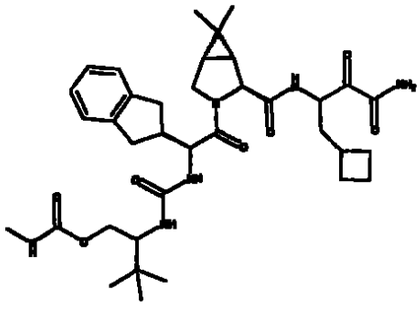


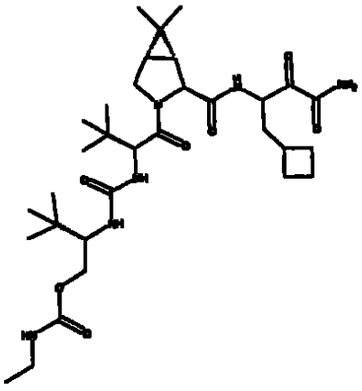


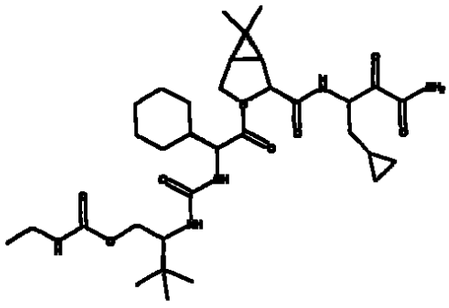


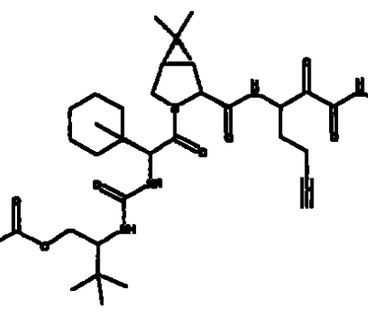


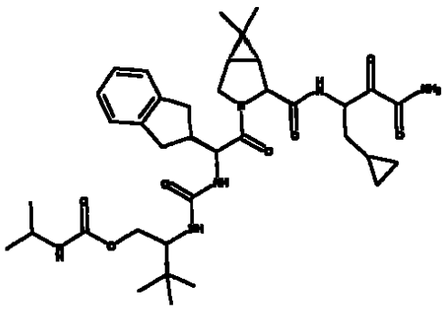


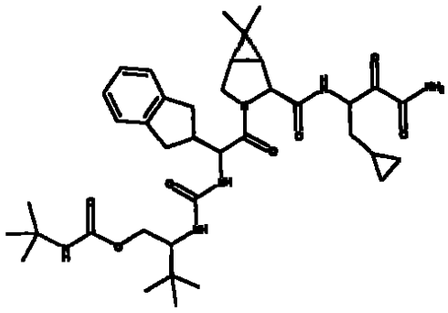


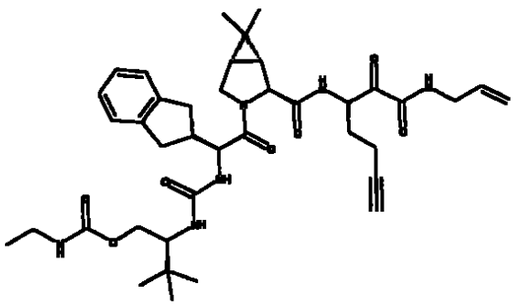


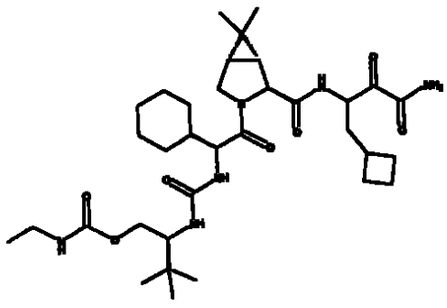


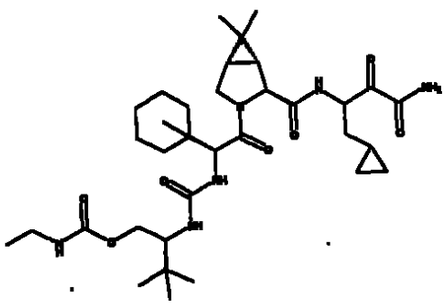


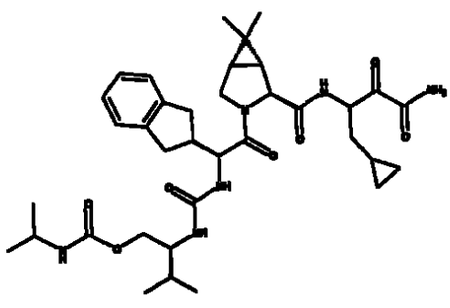


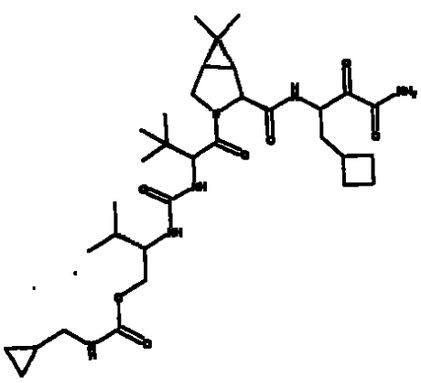


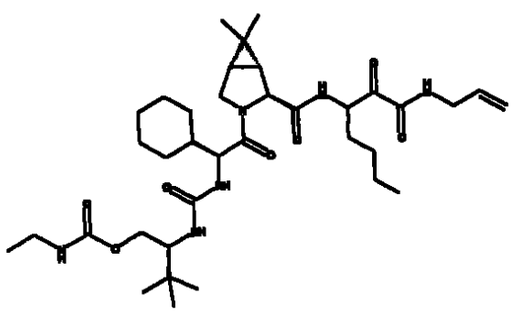


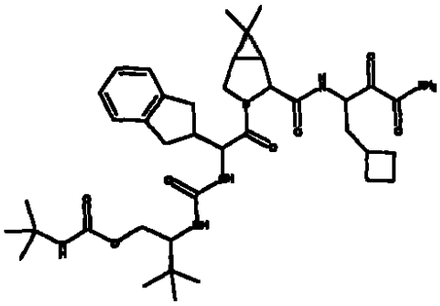


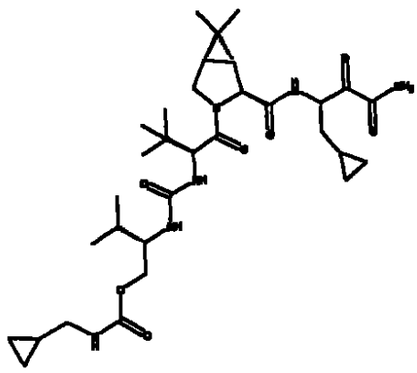


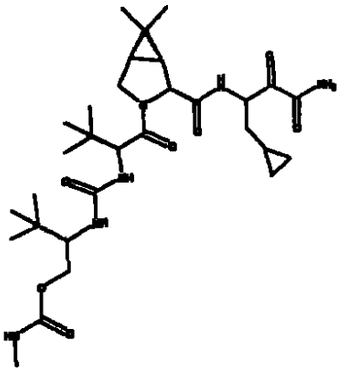


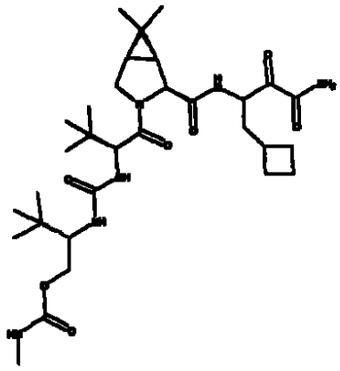


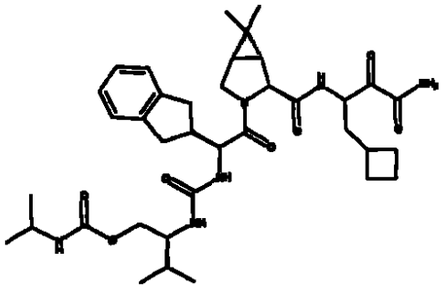


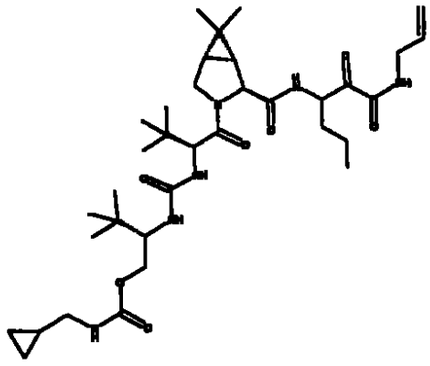


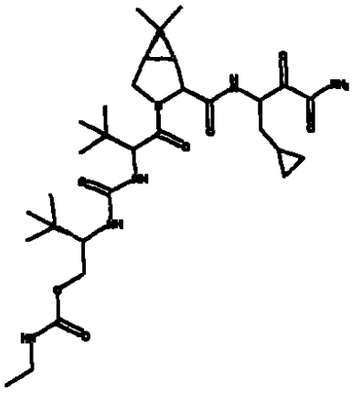


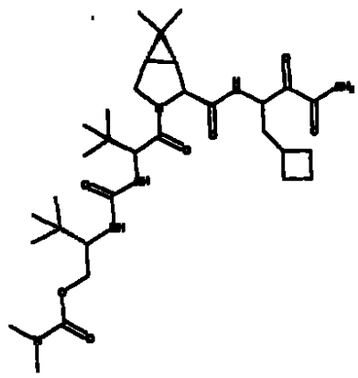


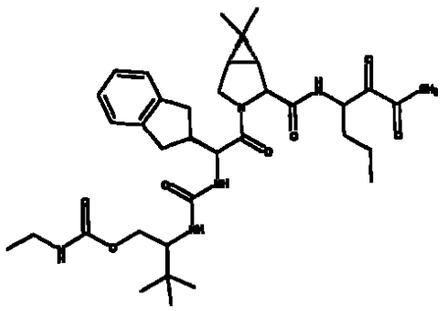


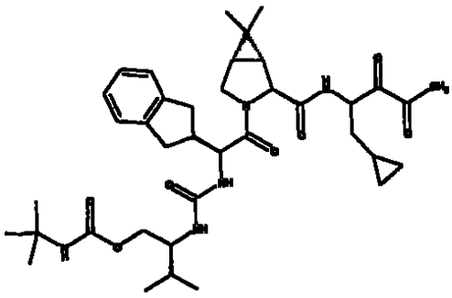


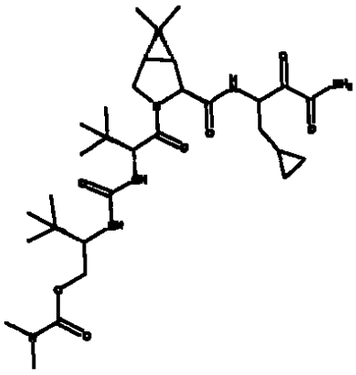


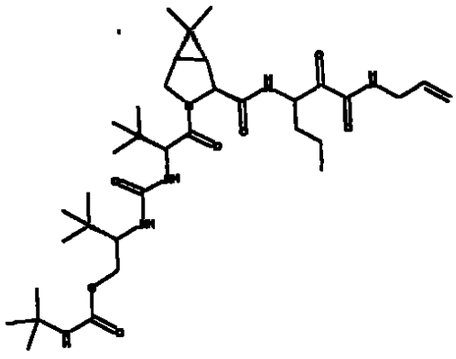


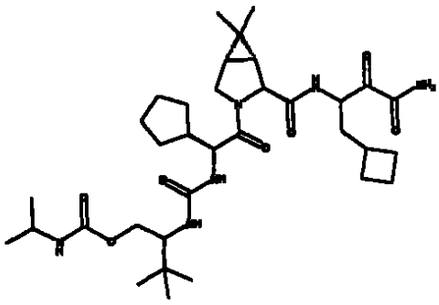


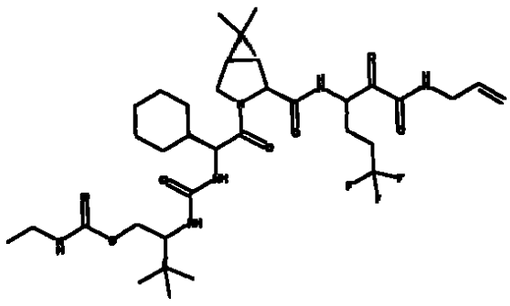


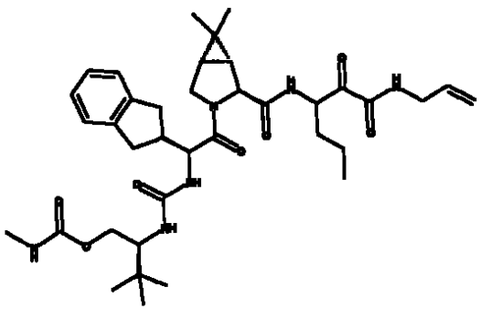


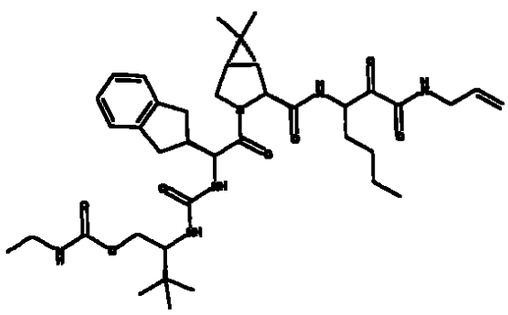


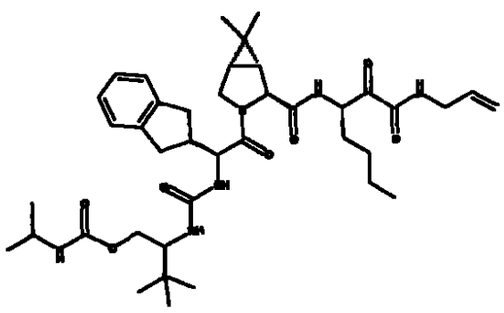


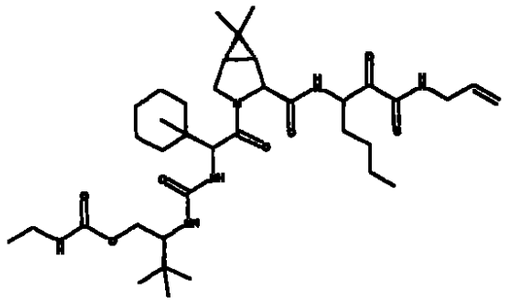


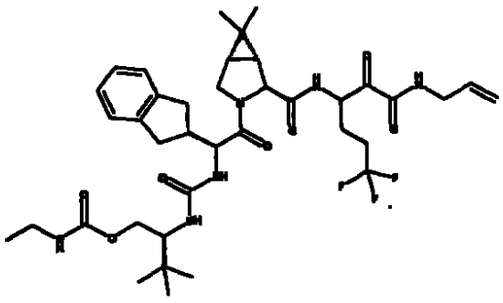


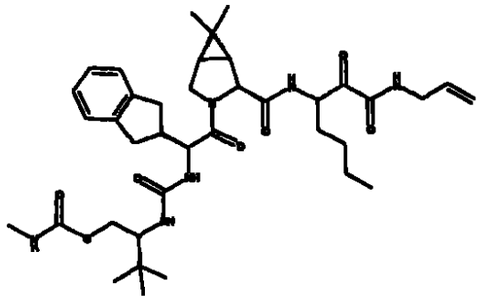


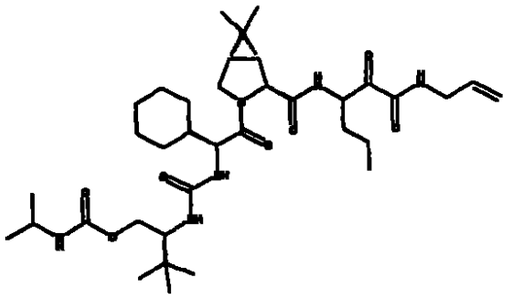


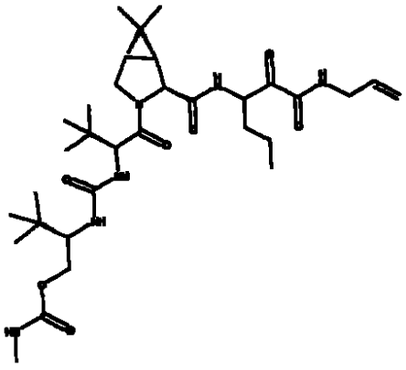


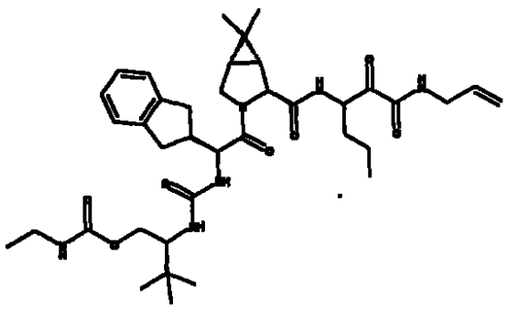


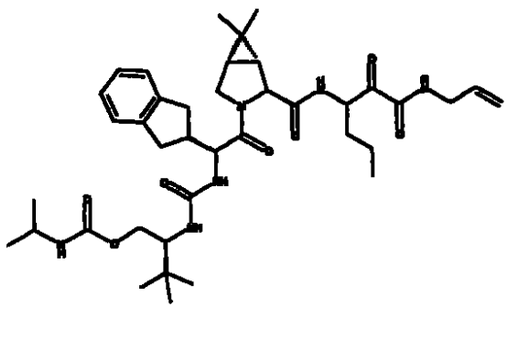


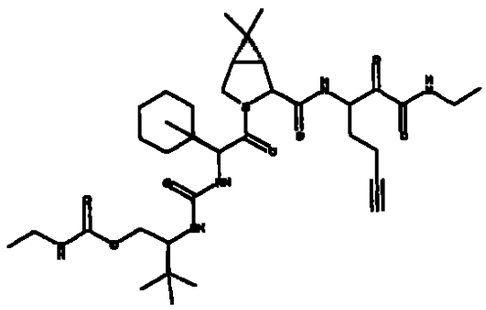


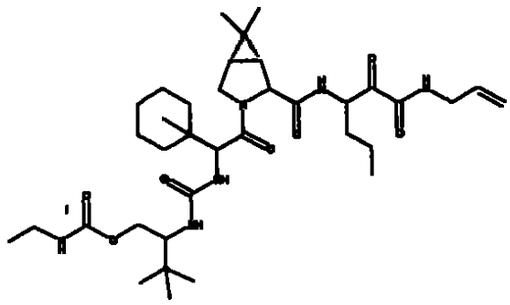


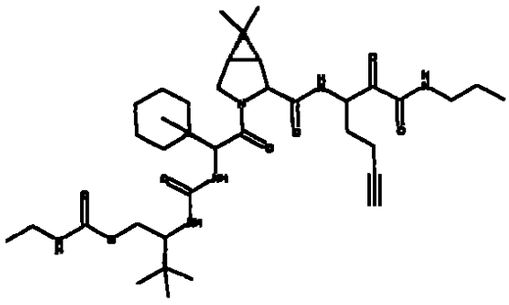


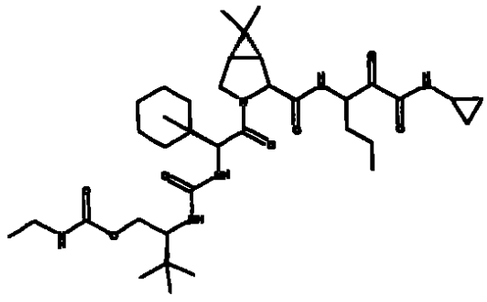


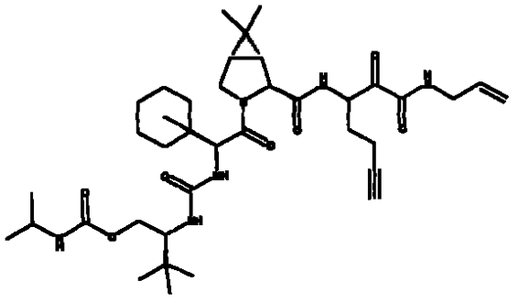


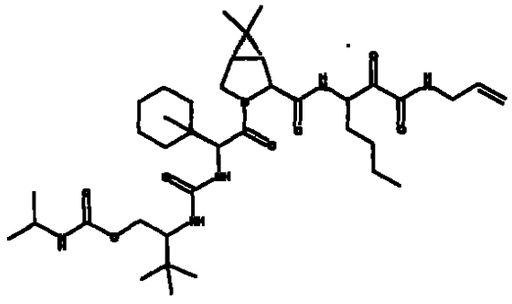


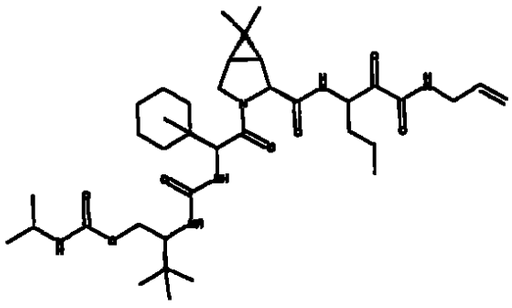


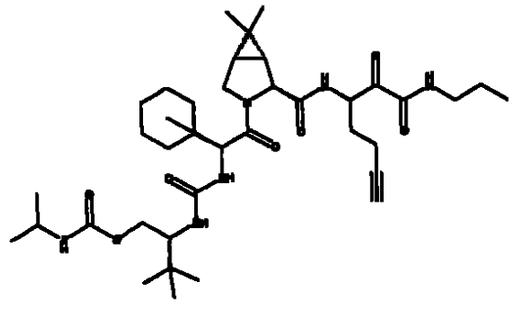


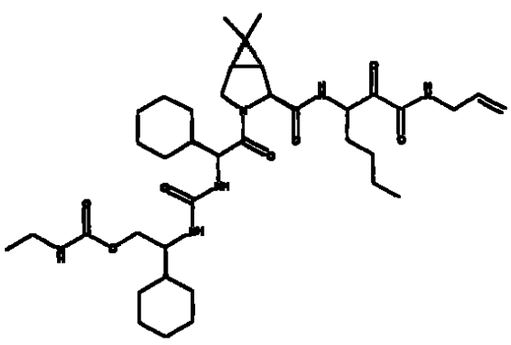


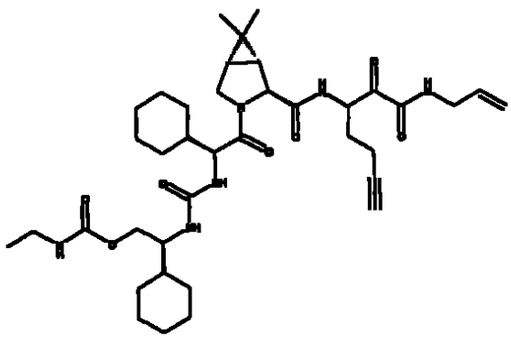


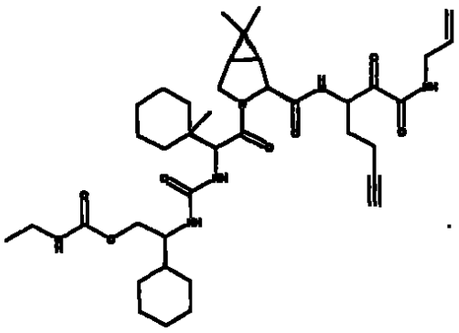


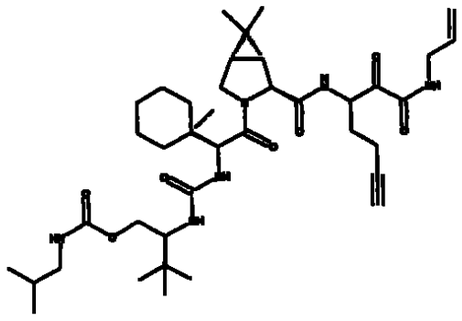


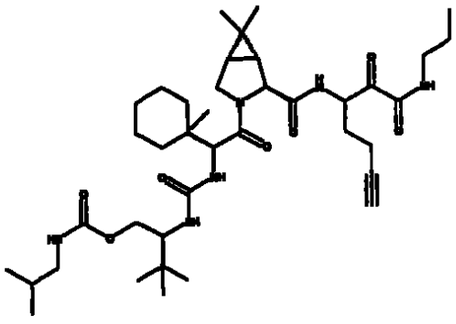


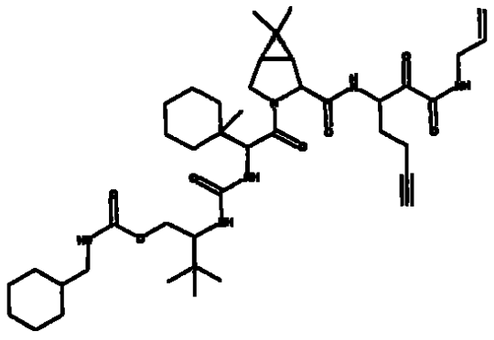


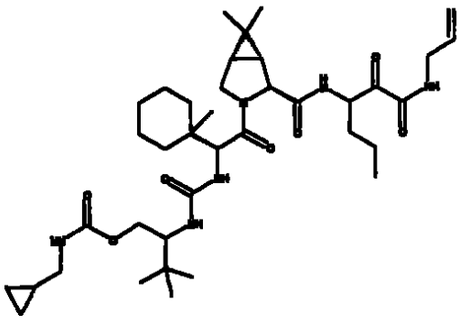


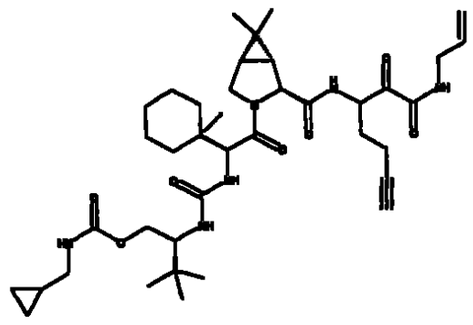


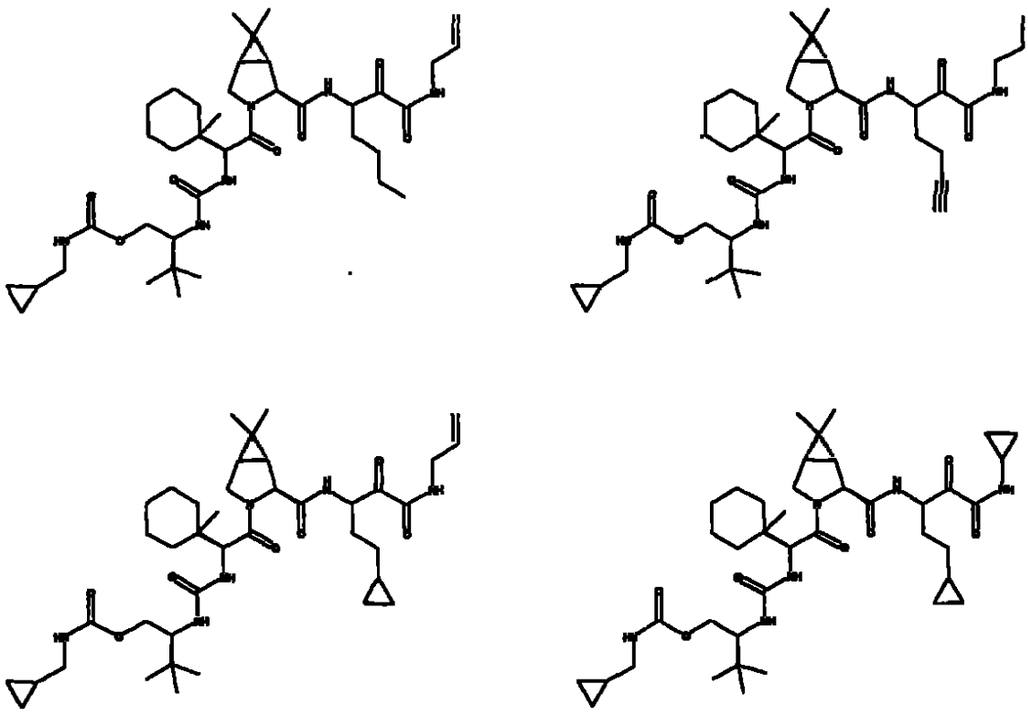












26. A pharmaceutical composition for treating disorders associated with the HCV, said composition comprising therapeutically effective amount of one or more compounds in claim 25 and a pharmaceutically acceptable carrier.

27. The pharmaceutical composition of claim 26, additionally containing at least one antiviral agent.

28. The pharmaceutical composition of claim 27, additionally containing at least one interferon or PEG-interferon alpha conjugate.

29. The pharmaceutical composition of claim 28, wherein said at least one antiviral agent is ribavirin and said at least one interferon is α-interferon or pegylated interferon.

30. A method of treatment of a hepatitis C virus associated disorder, comprising administering an effective amount of one or more compounds of claim 25.

31. A method of modulating the activity of hepatitis C virus (HCV) protease, comprising contacting HCV protease with one or more compounds of claim 25.

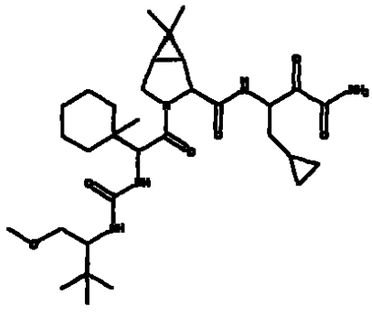
32. A method of treating, preventing, or ameliorating one or more symptoms of hepatitis C, comprising administering a therapeutically effective amount of one or more compounds of claim 25.

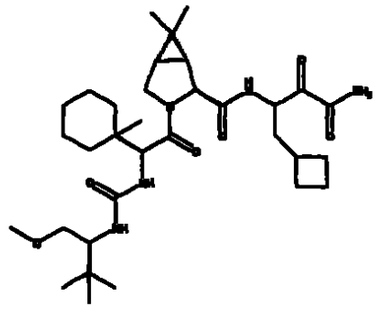
33. The method of claim 32, wherein the HCV protease is the NS3/NS4a protease.

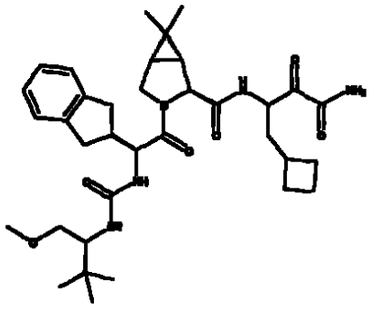
34. The method of claim 33, wherein the compound or compounds inhibit HCV NS3/NS4a protease.

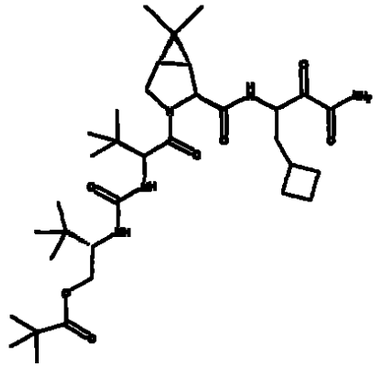
35. A method of modulating the processing of hepatitis C virus (HCV) polypeptide, comprising contacting a composition containing the HCV polypeptide under conditions in which said polypeptide is processed with one or more compounds of claim 25.

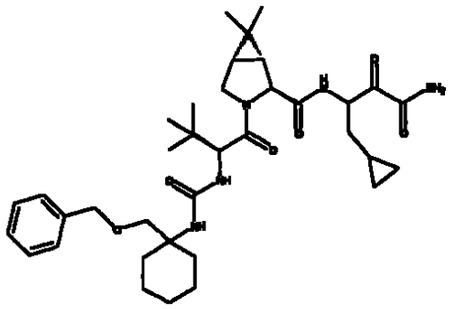
36. A method of treating disorders associated with the HCV, said method comprising administering to a patient in need of such treatment, a pharmaceutical composition which comprises therapeutically effective amounts of at least one compound, or enantiomers, stereoisomers, rotamers, tautomers, diastereomers or racemates of said compound, or a pharmaceutically acceptable salt, solvate or ester of said compound, said compound being selected from the following:

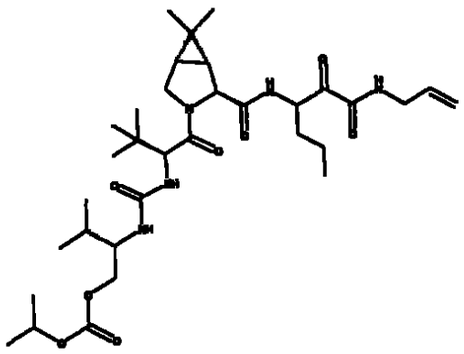


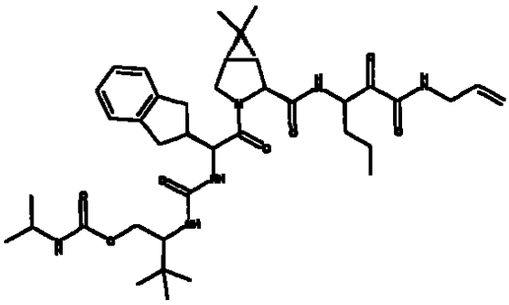


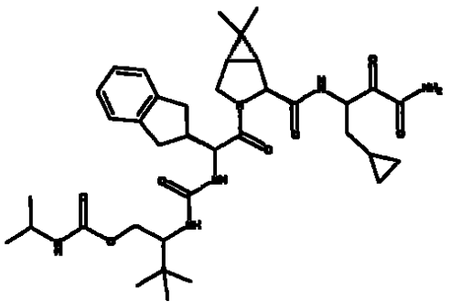


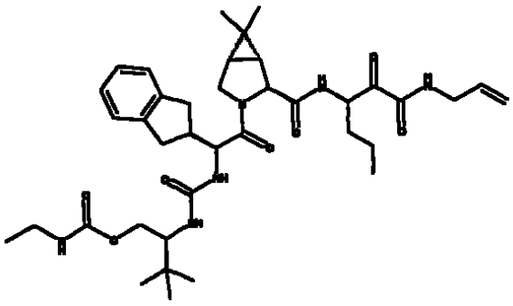


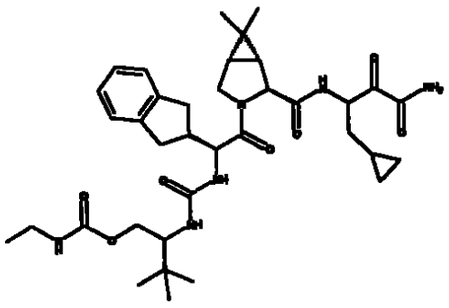


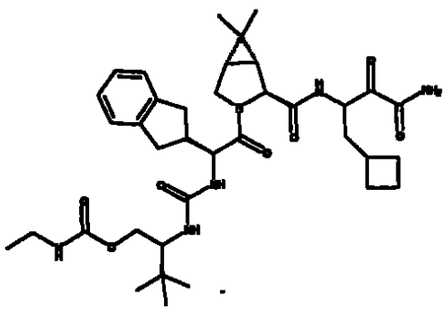


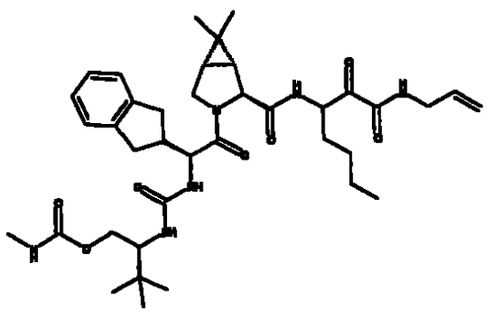


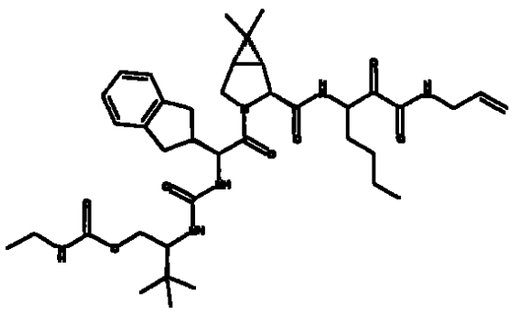


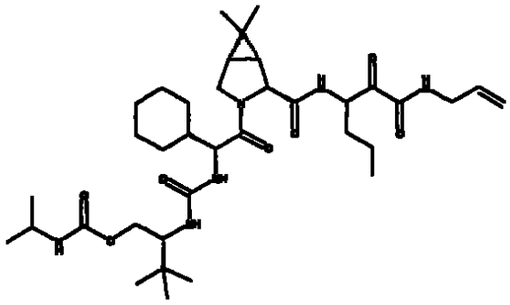


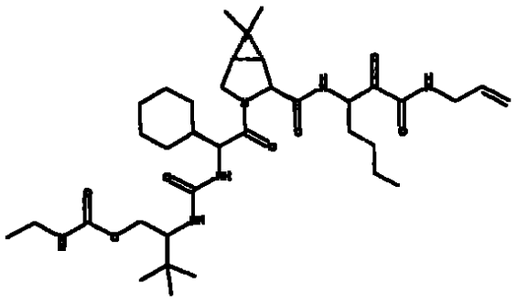


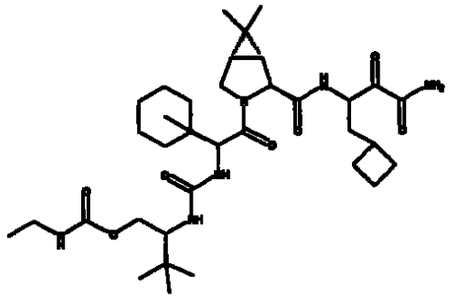


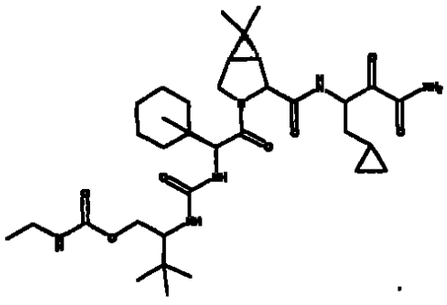


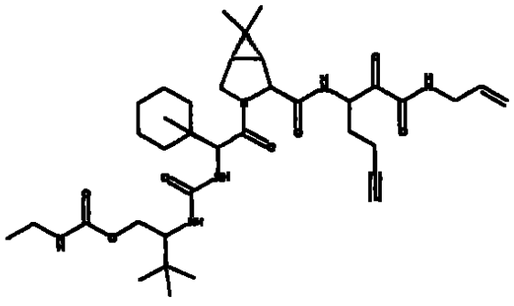


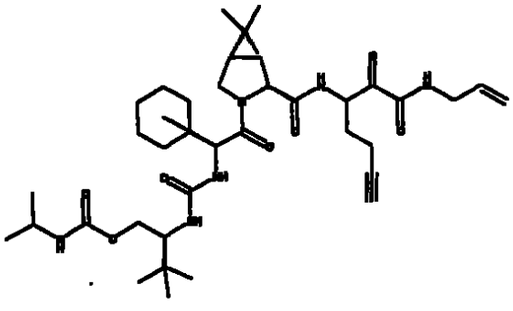


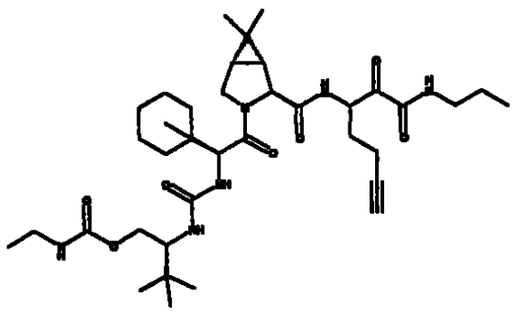


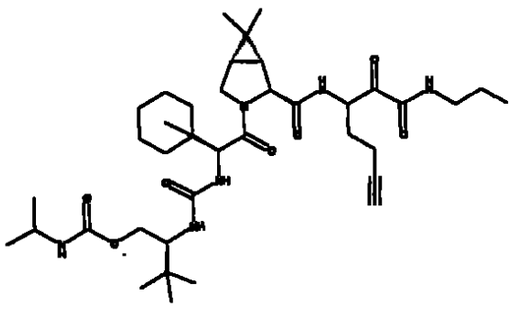


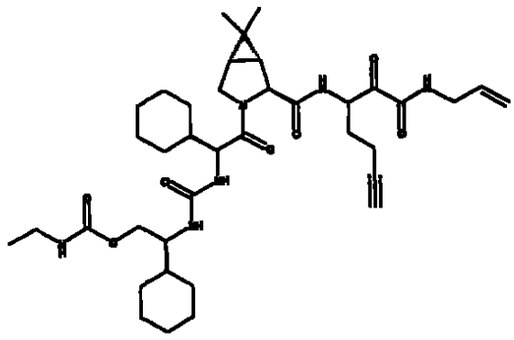


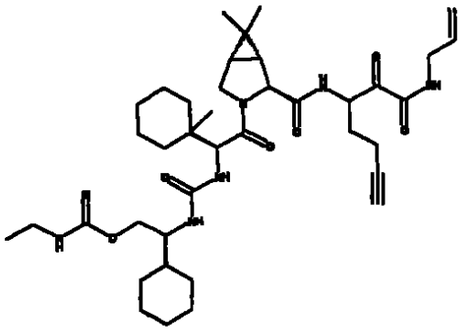


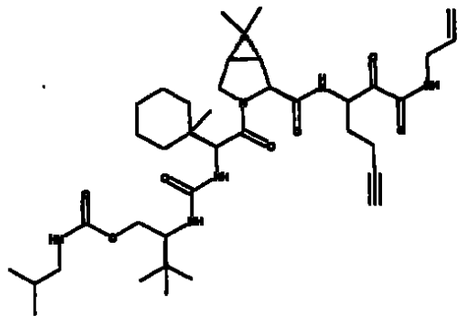


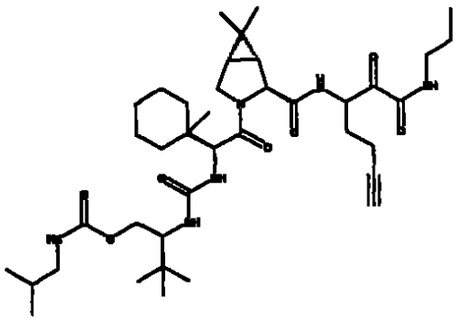


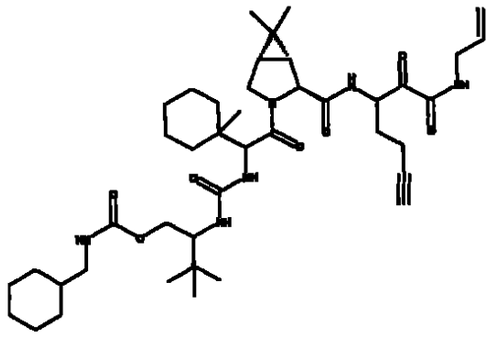


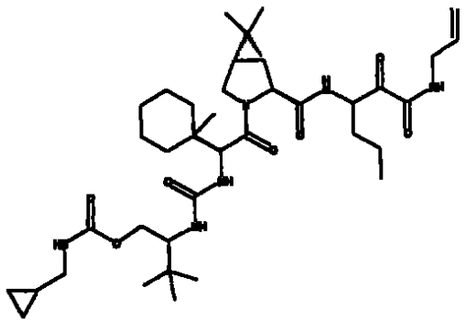


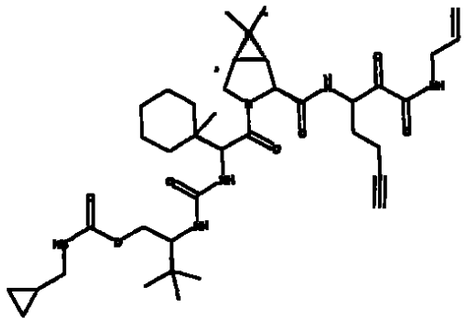


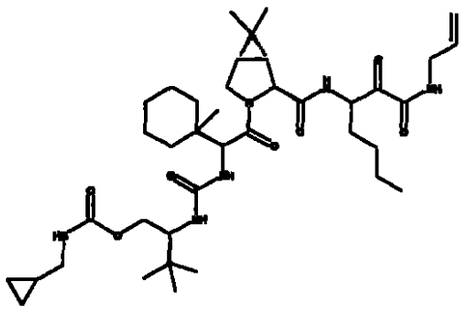
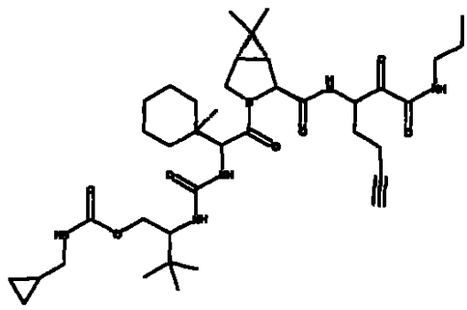
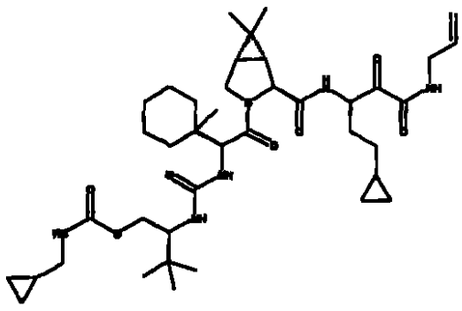
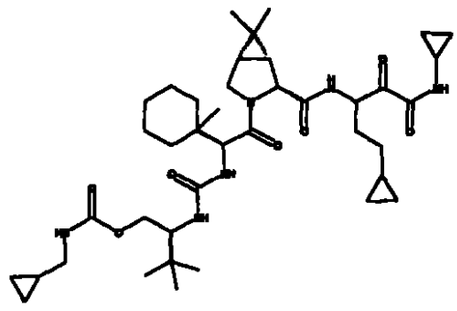










37. A compound of claim 1 in purified form.

IN06133 - AR ref

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Memoria Descriptiva

de la

Patente de Invención

Sobre

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

Solicitada por:

SCHERING CORPORATION, residente en
2000 Galloping Hill Road Kenilworth, NUEVA JERSEY 07033-0530, E. U. DE NORTEAMERICA

212129
US/JPV

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

Campo de la Invención

La presente invención se refiere a nuevos inhibidores de proteasa del virus de la hepatitis C ("HCV"), a las composiciones farmacéuticas que contienen uno o más de dichos inhibidores, a los métodos de preparación de dichos inhibidores y a los métodos de uso de dichos inhibidores para tratar la hepatitis C y desórdenes relacionados. Esta invención describe adicionalmente nuevos compuestos como inhibidores de la serina proteasa NS3/NS4a de HCV. Esta solicitud reivindica prioridad de la solicitud de patente norteamericana provisional Acta Número 60/548.535 presentada el 27 de febrero de 2004.

Antecedentes de la Invención

El virus de la hepatitis C (HCV) es un virus de ARN de un solo filamento de (+)-sentido, que ha sido implicado como agente causante principal de la hepatitis no A, no B (NANBH), particularmente la NANBH asociada a la sangre (BB-NANBH) (*ver*, Publicación de la Solicitud de Patente Internacional No. WO 89/04669 y Publicación de la Solicitud de Patente Europea No. EP 381.216). Debe distinguirse la NANBH de otros tipos de enfermedades hepáticas inducidas por virus, tales 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), así como también de otras formas de enfermedades hepáticas, tales como el alcoholismo y la cirrosis biliar primaria. Recientemente, una proteasa de HCV necesaria para el procesamiento de los polipéptidos y para la replicación viral ha sido identificada, clonada y expresada. (*Ver*, por ejemplo, la Patente Norteamericana No. 5.712.145). Esta poliproteína de aproximadamente 3000 aminoácidos contiene, desde el término amino hasta el término carboxi, una proteína de nucleocápsida (C), proteínas de envoltura (E1 y E2) y varias proteínas no estructurales (NS1, 2, 3, 4a, 5a y 5b). La NS3 es una proteína de aproximadamente 68 kda, codificada por aproximadamente 1893

nucleótidos del genoma HCV, y tiene dos dominios distintos: (a) un dominio de serina proteasa que consiste en aproximadamente 200 de los aminoácidos N-terminales; y (b) un dominio de ATPasa que depende de ARN en el término C de la proteína. La proteasa NS3 se considera un miembro del anillo de las quimiotripsinas debido a la similitud en la secuencia de la proteína, la estructura tridimensional general y el mecanismo de catálisis. Otras enzimas del tipo de la quimiotripsina son elastasa, factor Xa, trombina, tripsina, plasmina, urokinasa, tPA y PSA. La serina proteasa de HCV NS3 es responsable de la proteólisis del polipéptido (poliproteína) en las uniones NS3/NS4a, NS4a/NS4b, NS4b/NS5a y NS5a/NS5b y por lo tanto es responsable de generar cuatro proteínas virales durante la replicación viral. Esto ha convertido a la serina proteasa HCV NS3 en un atractivo objetivo para quimioterapia antiviral. Los compuestos de la invención pueden inhibir dicha proteasa. También pueden modular el procesamiento del polipéptido del virus de la hepatitis C (HCV).

Se ha determinado que la proteína NS4a, un polipéptido de aproximadamente 6 kda, es un co-factor para la actividad de la serina proteasa de NS3. La autodisociación de la unión NS3/NS4a con la serina proteasa NS3/NS4a ocurre intramolecularmente (es decir, *cis*) mientras que los otros sitios de disociación son procesados intermolecularmente (es decir, *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 están estrictamente conservados en las uniones NS4a/NS4b, NS4b/NS5a y NS5a/NS5b. La unión NS3/NS4a contiene una treonina en P1 y una resina en P1'. Se ha postulado que la sustitución Cys→Thr en NS3/NS4a es la responsable del requisito del procesamiento *cis* en vez de *trans* en esta unión. *Ver*, por ejemplo, Pizzi et al. (1994) Proc. Natl. Acad. Sci. (USA) 91:888-892, Failla et al. (1996) Folding & Design 1:35-42. El sitio de disociación NS3/NS4a es también más tolerante a la mutagénesis que los otros sitios. *Ver*, por ejemplo, Kollykhalov et al. (1994) J. Virol. 68:7525-7533. Se ha hallado también que se requieren residuos ácidos en la región cadena

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arriba del sitio de disociación, para una disociación eficiente. *Ver*, por ejemplo, Komoda et al. (1994) J. Virol. 68:7351-7357.

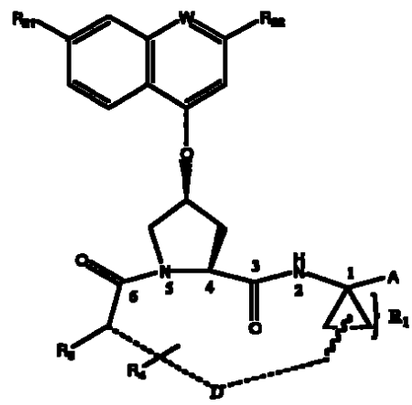
Los inhibidores de la proteasa HCV que se han mencionado incluyen antioxidantes (*ver*, Publicación de la Solicitud de Patente Internacional No. WO 98/14181), algunos péptidos y análogos peptídicos (*ver*, Publicación de la Solicitud de Patente Internacional No. WO 98/17679, Landro et al. (1997) Biochem. 36:9340-9348, Ingallinella et al. (1998) Biochem. 37:8906-8914, Llinàs-Brunet et al. (1998) Bioorg. Med. Chem. Lett. 8:1713-1718), inhibidores basados en el polipéptido de 70 aminoácidos eglina c (Martin et al. (1998) Biochem. 37:11459-11468, inhibidores de afinidad seleccionados del inhibidor de la secreción de tripsina pancreática humana (hPSTI-C3) y repertorios de minicuerpos (MBip) (Dimasi et al. (1997) J. Virol. 71:7461-7469), cV_HE2 (un fragmento de anticuerpo de dominio variable "camelizado") (Martin et al. (1997) Protein Eng. 10:607-614), y α1-antiquimiotripsina (ACT) (Elzouki et al.) (1997). J. Hepat. 27:42-28). Una ribozima diseñada para destruir selectivamente el ARN del virus de la hepatitis C, ha sido recientemente dada a conocer (*ver*, *BioWorld Today* 9(217): 4 (10 de Noviembre de 1998)).

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.).

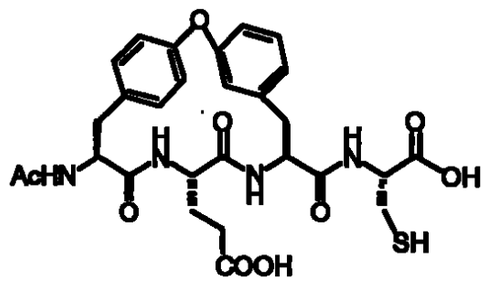
El HCV ha sido implicado en la cirrosis del hígado y en la inducción del carcinoma hepatocelular. El pronóstico para pacientes que sufren de infección de HCV es corrientemente malo. La infección de HCV es más difícil de tratar que otras formas de hepatitis, debido a la falta de inmunidad o remisión asociadas con la infección de HCV. Los datos corrientes indican una tasa de supervivencia inferior al 50% a los cuatro años post diagnóstico de cirrosis. Pacientes a los cuales se les diagnosticaron un carcinoma hepatocelular resectable localizado, tienen una tasa de supervivencia de 10-30% en cinco años, mientras que aquellos con carcinoma hepatocelular no resectable localizado tienen una tasa de supervivencia de menos del 1% en cinco años.

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Se hace referencia a la WO 00/59929 (US 6.608.027, Titular: Boehringer Ingelheim (Canadá) Ltd.; Publicada el 12 de octubre del 2000) que describe derivados peptídicos de la fórmula:

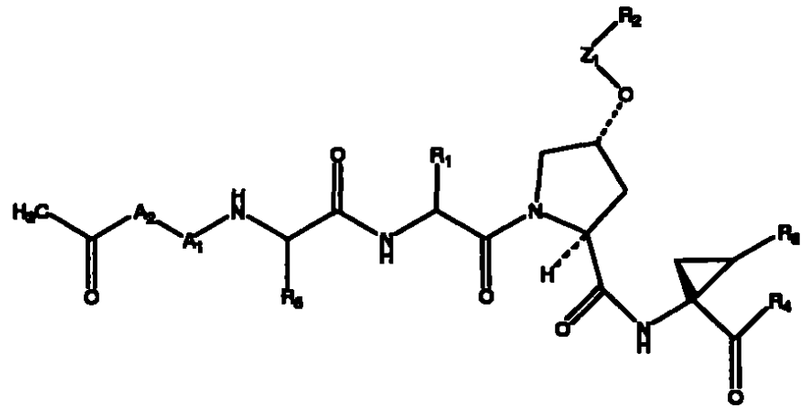


Se hace referencia a A. Marchetti *et al*, *Synlett*, S1, 1000-1002 (1999) que describe la síntesis de análogos bicíclicos de un inhibidor de proteasa NS3 de HCV. Un compuesto descripto allí tiene la fórmula:

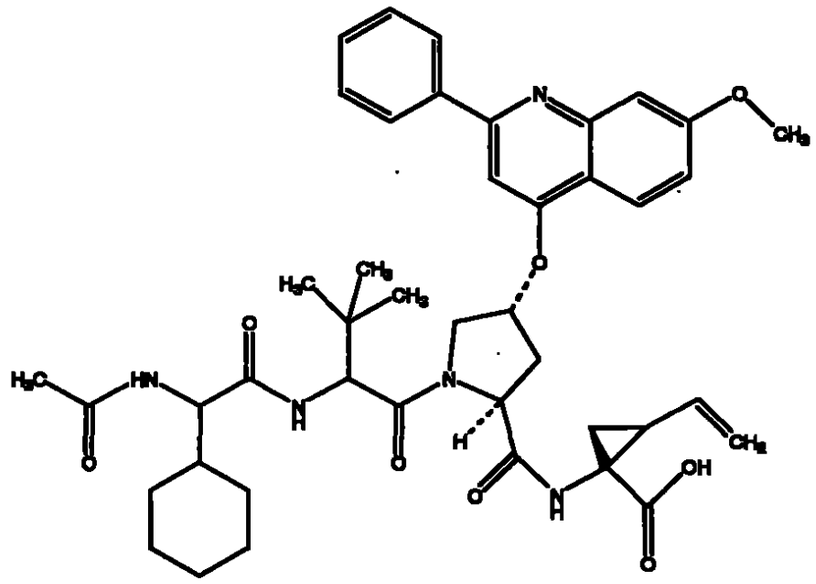


También se hace referencia a W. Han *et al*, *Bioorganic & Medicinal Chem. Lett*, (2000) 10, 711-713, que describe la preparación de ciertas α-cetoamidas, α-cetoésteres y α-dicetonas que contienen funcionalidades alilo y etilo.

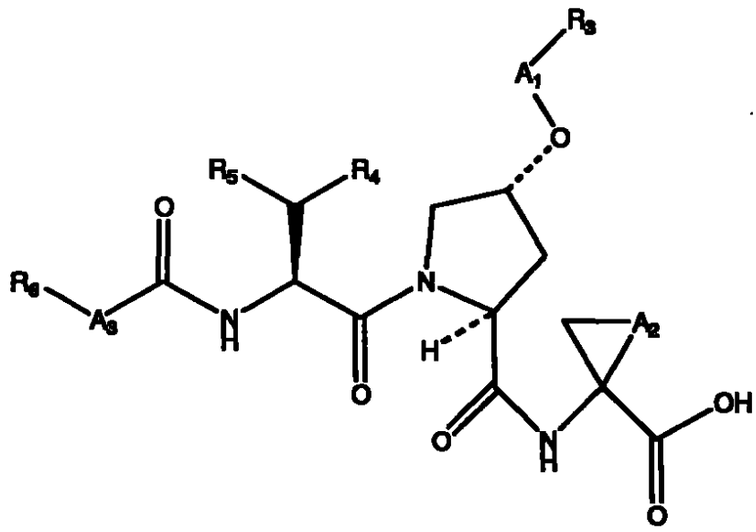
Se hace referencia también a la WO 00/09558 (Titular: Boehringer Ingelheim Limited; publicada el 24 de febrero de 2000) que describe derivados peptídicos de la fórmula:



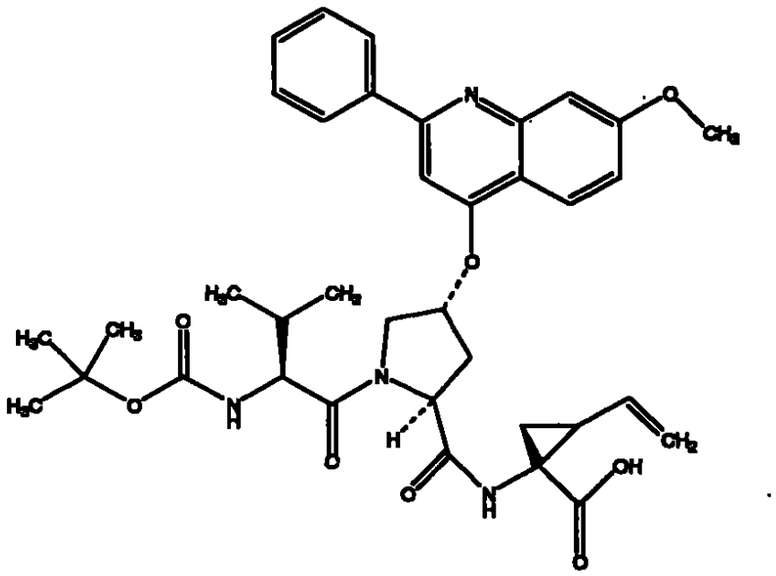
donde los varios elementos están definidos allí. Un compuesto ilustrativo de esa serie es:



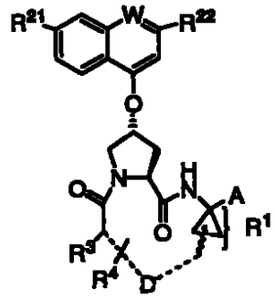
También se hace referencia a la WO 00/09543 (Titular: Boehringer Ingelheim Limited; publicada el 24 de febrero de 2000) que describe derivados peptídicos de la fórmula:



donde los varios elementos están definidos allí. Un compuesto ilustrativo de esa serie es:



Se hace referencia a la patente norteamericana 6.608.027 (Boehringer Ingelheim, Canadá) que describe inhibidores de proteasa NS3 del tipo:



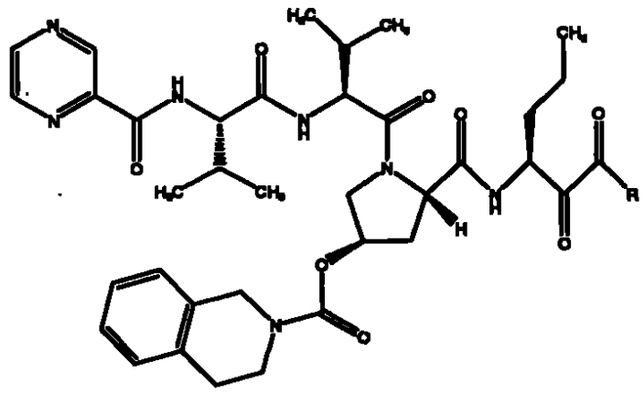
donde las varias porciones se definen allí.

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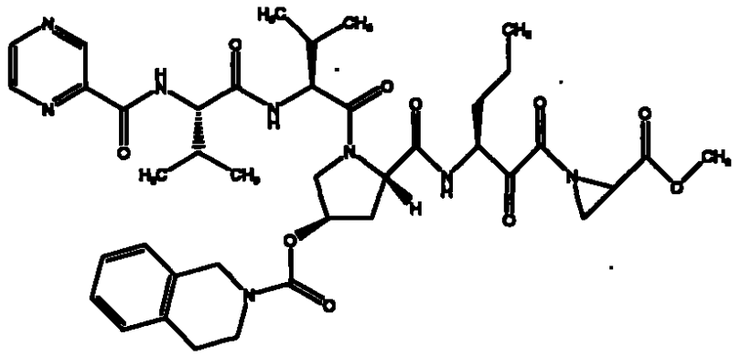
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Las t rapias corrientes para la hepatitis C incluyen interferón-α (INF_α) y terapias de combinación para la ribavirina y el interferón. *Ver*, por ejemplo, Beremguer et al. (1998) Proc. Assoc. Am. Physicians 110(2):98-112. Estas terapias sufren de bajo régimen de respuesta sostenida y frecuentes efectos secundarios. *Ver*, por ejemplo, Hoofnagle et al. (1997) N. Engl. J. Med. 336:347. Corrientemente, no se encuentra ninguna vacuna disponible para la infección de HCV.

Se hace referencia además a la WO 01/74768 (Titular: Vertex Pharmaceuticals Inc) publicada el 11 de octubre de 2001, que describe ciertos compuestos de la siguiente fórmula general (R se define allí) como inhibidores de la serina proteasa NS3 del virus de la Hepatitis C:



Un compuesto específico descripto en la WO 01/74768 antes mencionada tiene la fórmula siguiente:



Las publicaciones PCT WO 01/77113; WO 01/081325; WO 02/08198; WO 02/08256; WO 02/08187; WO 02/08244; WO 02/48172; WO 02/08251; y la solicitud de patente norteamericana pendiente Acta N° 10/052.386, presentada el 18 de enero de 2002, describen varios tipos de péptidos y/o compuestos como inhibidores de serina proteasa NS-3 del virus de la

hepatitis C. Las descripciones de esas solicitudes se incorporan aquí como referencia.

Existe la necesidad de disponer de los tratamientos y terapias para la infección de HCV. Existe una necesidad de disponer de compuestos útiles en el tratamiento o prevención o mejoramiento de uno o más síntomas de la hepatitis C.

Existe la necesidad de disponer de métodos de tratamiento o prevención o mejoramiento de uno o más síntomas de la hepatitis C.

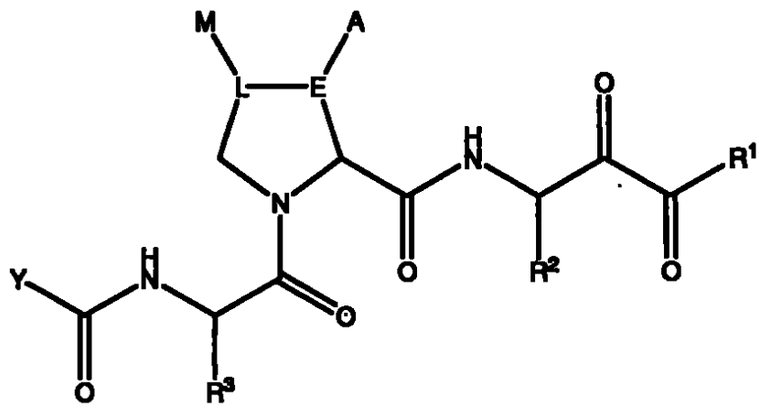
Existe una necesidad de disponer de métodos para modular la actividad de serina proteasas, particularmente la serina proteasa NS3/NS4a de HCV, usando los compuestos provistos aquí.

Existe la necesidad de disponer de métodos para modular el procesamiento del polipéptido HCV usando los compuestos provistos aquí.

Compendio de la Invención

En sus muchas realizaciones, la presente invención provee una nueva clase de inhibidores de la proteasa HCV, de las composiciones farmacéuticas que contienen uno o más de los compuestos, de los métodos de preparación de las formulaciones farmacéuticas que comprenden uno o más de dichos compuestos, y de los métodos de tratamiento o prevención de HCV o mejoramiento de uno o más de los síntomas de la hepatitis C usando uno o más de dichos compuestos o una o más de dichas formulaciones. Asimismo se proveen métodos para modular la interacción de polipéptido de HCV con la proteasa HCV. Entre los compuestos provistos aquí, se prefiere los compuestos que inhiben la actividad de la serina proteasa NS3/NS4a de HCV. La presente invención describe compuestos, o enantiómeros, estereoisómeros, rotámeros, tautómeros, diastereómeros o racematos de dichos compuestos, o una sal, solvato o éster farmacéuticamente aceptable de dichos compuestos, donde dichos compuestos tienen la estructura general que se muestra en la Fórmula estructural 1:

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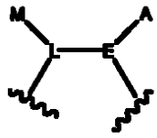


Fórmula I

en la cual:

R^1 es H, OR^8, NR^9R^{10}, o CHR^9R^{10}, donde R^8, R^9 y R^{10} pueden ser iguales o diferentes, y cada uno está independientemente seleccionado del grupo que consiste en H, alquil-, alquenil-, alquinil-, aril-, heteroalquil-, heteroaril-, cicloalquil-, heterociclil-, arilalquil- y heteroarilalquilo;

A y M pueden ser iguales o diferentes y cada uno está independientemente seleccionado de R, OR, NHR, NRR', SR, SO_2R y halo; o A y M están conectados entre sí de manera que la porción:



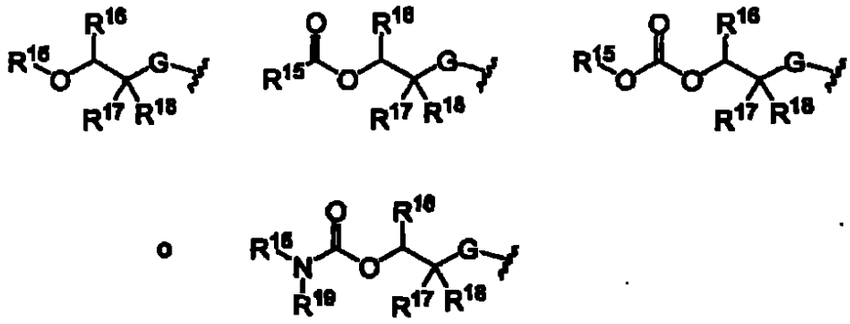
que se muestra anteriormente en la Fórmula I forma un cicloalquilo de tres, cuatro, seis, siete u ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros, o un heteroarilo de cinco a diez miembros;

E es C(H) o C(R);

L es C(H), C(R), $CH_2C(R)$, o $C(R)CH_2$;

R, R', R^2 y R^3 pueden ser iguales o diferentes, y cada uno está independientemente seleccionado del grupo que consiste en H, alquil-, alquenil-, alquinil-, cicloalquil-, heteroalquil-, heterociclil-, aril-, heteroaril-, (cicloalquil)alquil-, (heterociclil)alquil-, aril-alquil- y heteroaril-alquil-; o alternativamente R y R' en NRR' están conectados entre sí de manera que el NRR' forma un heterociclilo de cuatro a ocho miembros;

e Y está seleccionado entre las siguientes porciones:

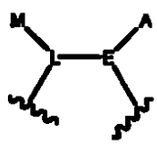


o

en las cuales G es NH u O; y R^{15}, R^{16}, R^{17}, R^{18} y R^{19} pueden ser iguales o diferentes, y cada una está independientemente seleccionado del grupo que consiste en H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo y heteroarilalquilo, o alternativamente, (I) cualquiera de R^{15} y R^{16} está conectado uno al otro para formar una estructura cíclica de cuatro a ocho miembros, o R^{15} y R^{19} están conectados uno al otro para formar una estructura cíclica de cuatro a ocho miembros, y (II) asimismo, independientemente, R^{17} y R^{18} están conectados uno al otro para formar un cicloalquilo o heterociclilo de tres a ocho miembros;

donde cada uno de dichos alquilo, arilo, heteroarilo, cicloalquilo o heterociclilo pueden estar no sustituidos u opcionalmente independientemente sustituidos con una o más porciones seleccionadas del grupo que consiste en hidroxi, alcoxi, ariloxi, tio, alquiltio, ariltio, amino, amido, alquilamino, arilamino, alquilsulfonilo, arilsulfonilo, sulfonamido, alquilsulfonamido, arilsulfonamido, alquilo, arilo, heteroarilo, ceto, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halo, ciano y nitro.

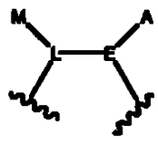
La manifestación previamente citada "A y M están conectados entre sí de manera que la porción:



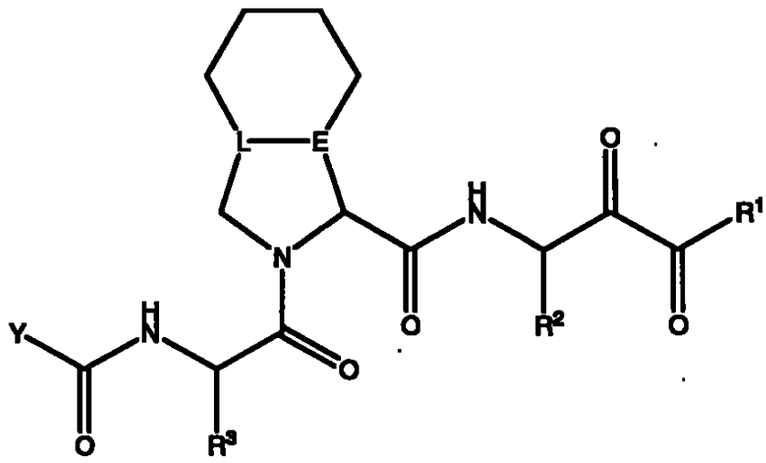
que se muestra anteriormente en la Fórmula I, forma un cicloalquilo de tres, cuatro, seis, siete u ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros, o un heteroarilo de cinco a diez

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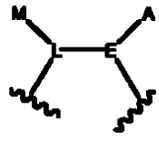
miembros", puede ilustrarse de manera no limitativa tal como sigue. Por lo tanto, por ejemplo, en el caso en el cual A y M están conectados de manera que la porción:



mostrada anteriormente en la Fórmula I forma un cicloalquilo de seis miembros (ciclohexilo), la Fórmula I puede describirse como:



Una persona con experiencia en la materia apreciará que puede llegarse a descripciones similares para la Fórmula I cuando A y M, tal como se muestran anteriormente en la porción:



están conectados para formar un cicloalquilo de tres, cuatro, siete u ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros, o un heteroarilo de cinco a diez miembros.

La manifestación anterior: "alternativamente, (i) cualquiera de R^{15} y R^{16} están conectados uno al otro para formar una estructura cíclica de cuatro a ocho miembros, o R^{15} y R^{19} están conectados uno al otro para formar una estructura cíclica de cuatro a ocho miembros, y (ii) asimismo, independientemente, R^{17} y R^{18} están conectados entre sí para formar un cicloalquilo o heterociclilo de tres a ocho miembros" significa las siguientes

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135

posibilidades: (i) que R^{15} y R^{16} están conectados para formar una estructura cíclica mientras que R^{15} y R^{19} no lo están; (ii) que R^{15} y R^{19} están conectados para formar una estructura cíclica, mientras que R^{16} y R^{17} no lo están; y que (iii) R^{17} y R^{18} están independientemente conectados para formar una estructura cíclica, independientemente de si existen o no las posibilidades en (i) e (ii).

En las definiciones previamente mencionadas de R, R', R^2 y R^3, el alquilo preferido se prepara con uno a diez átomos de carbono, el alquenilo o alquinilo preferido se preparan con dos a diez átomos de carbono, el cicloalquilo preferido se prepara con tres a ocho átomos de carbono, y el heteroalquilo, heteroarilo o heterocicloalquilo preferido tienen de uno a seis átomos de oxígeno, nitrógeno, azufre o fósforo.

Los compuestos representados por la Fórmula I, por sí mismos o en combinación con uno o más de otros agentes apropiados descriptos aquí, pueden ser útiles para tratar enfermedades tales como por ejemplo HCV, HIV, SIDA (Síndrome de Inmunodeficiencia Adquirida) y desórdenes relacionados, así como también para modular la actividad de la proteasa del virus de la hepatitis C (HCV), prevenir la HCV, o mejorar uno o más de los síntomas de la hepatitis C. Dicha modulación, tratamiento, prevención o mejoramiento, pueden efectuarse con los compuestos de la invención así como también con las composiciones o formulaciones farmacéuticas que comprende dichos compuestos. Sin limitarnos a ninguna teoría, creemos que la proteasa HCV puede ser la proteasa NS3 o NS4a. Los compuestos de la invención pueden inhibir dicha proteasa. Pueden modular también el procesamiento del polipéptido del virus de la hepatitis C (HCV).

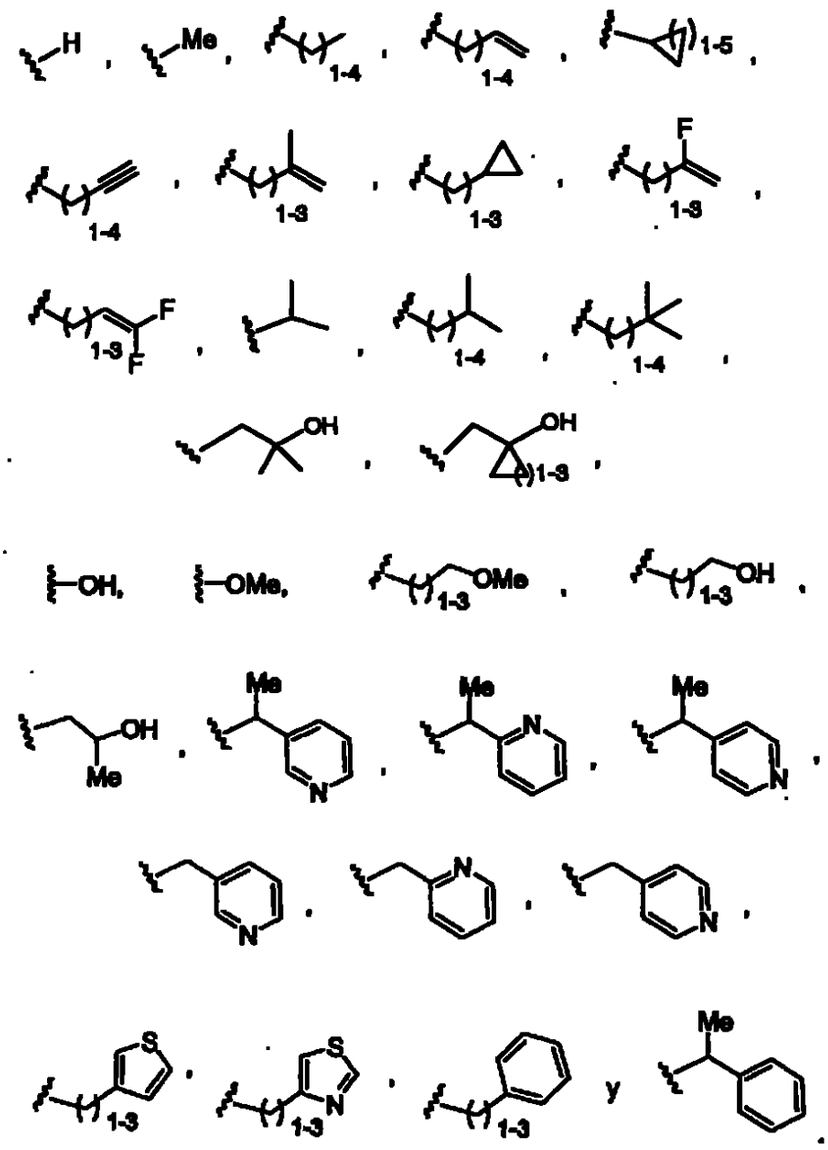
Descripción Detallada

En una realización, la presente invención describe compuestos que están representados por la fórmula estructural 1 o por una sal, solvato o éster del mismo farmacéuticamente aceptable, donde las varias porciones son tal como se han definido anteriormente.

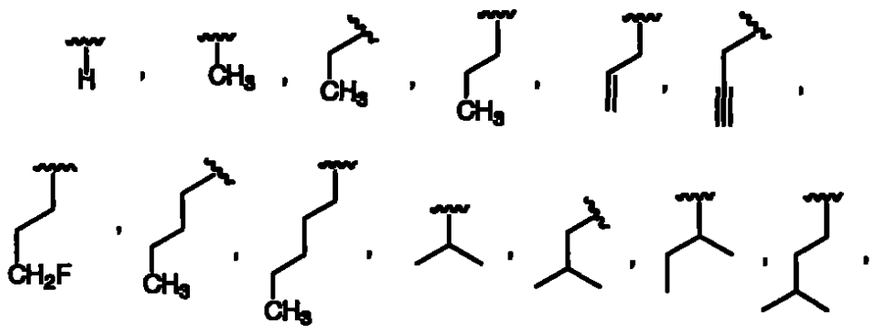
En otra realización, R^1 es NR^9R^{10}, y R^9 es H, R^{10} es H, o R^{14} donde R^{14} es H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arlo, alquil-heteroarilo, aril-alquilo, alquenilo, alquinilo o heteroaril-alquilo.

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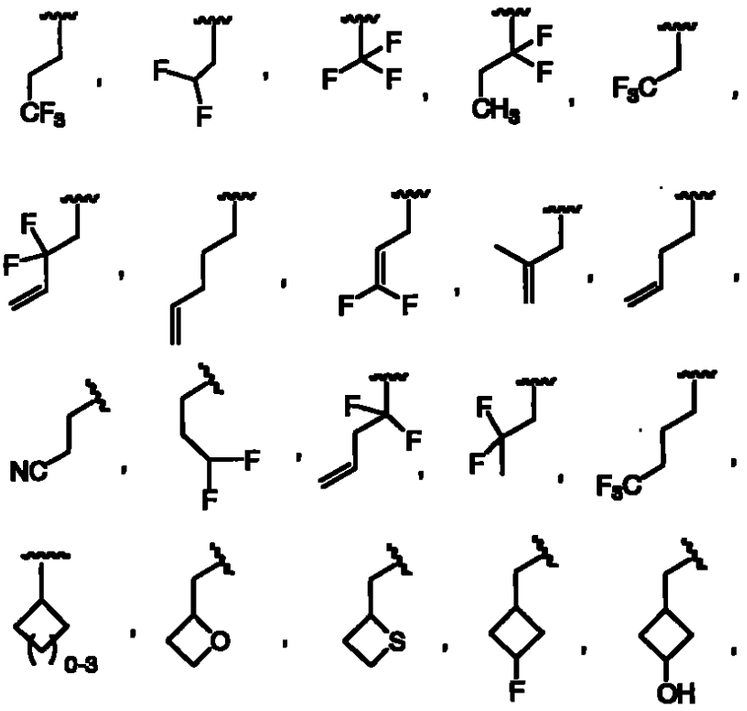
En otra realización, R^{14} está seleccionado del grupo que consiste en:



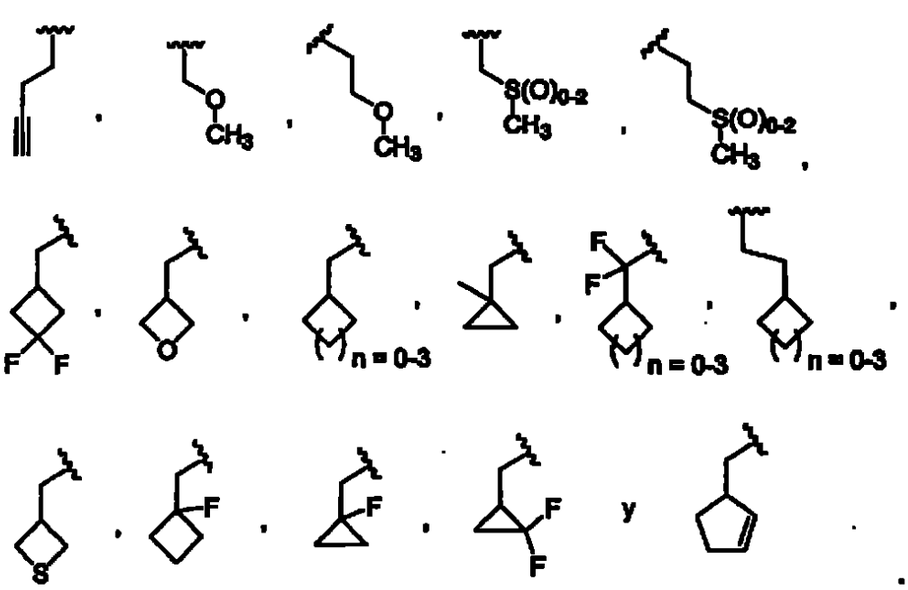
En otra realización, R^2 está seleccionado del grupo que consiste en las porciones siguientes:



137

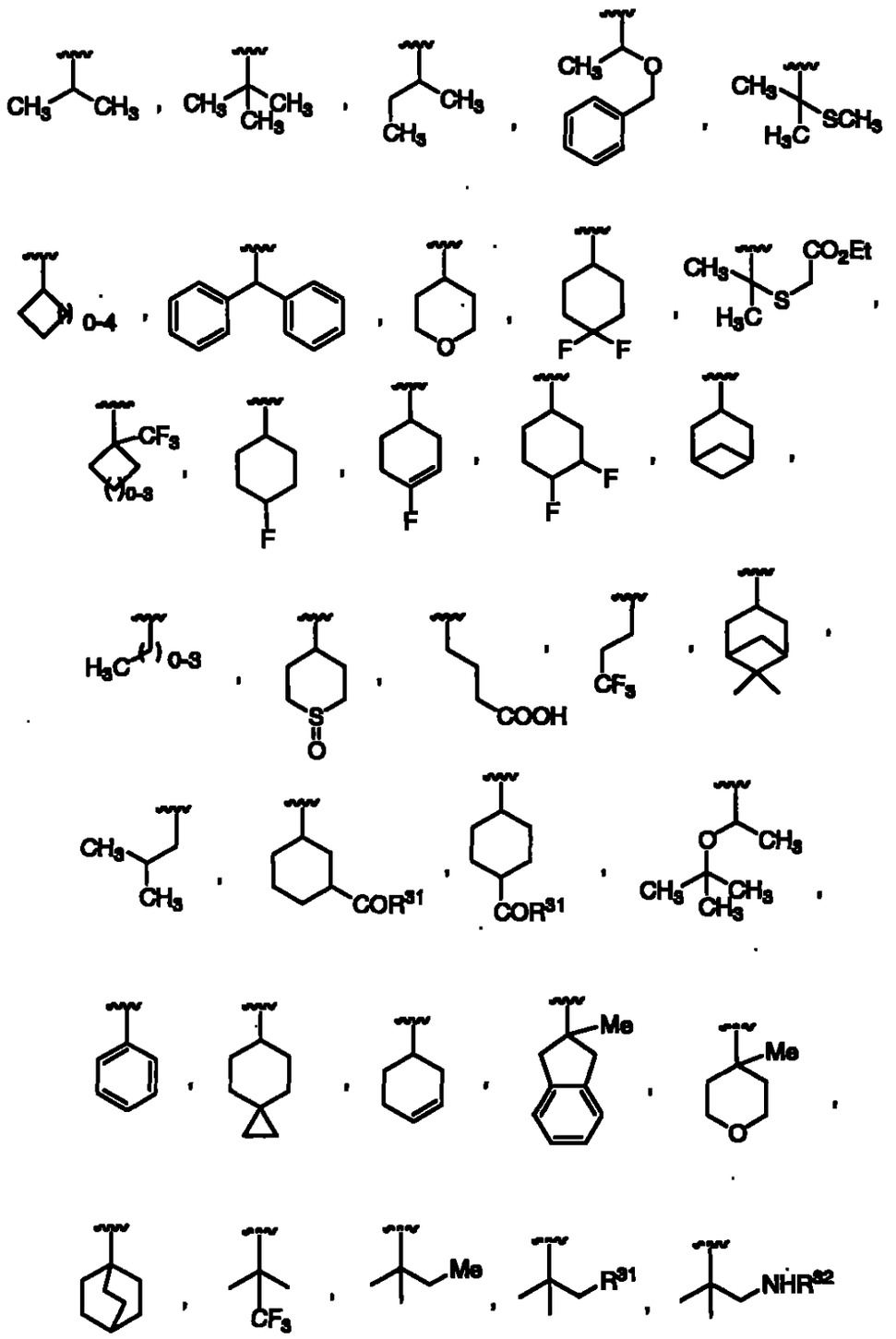


y

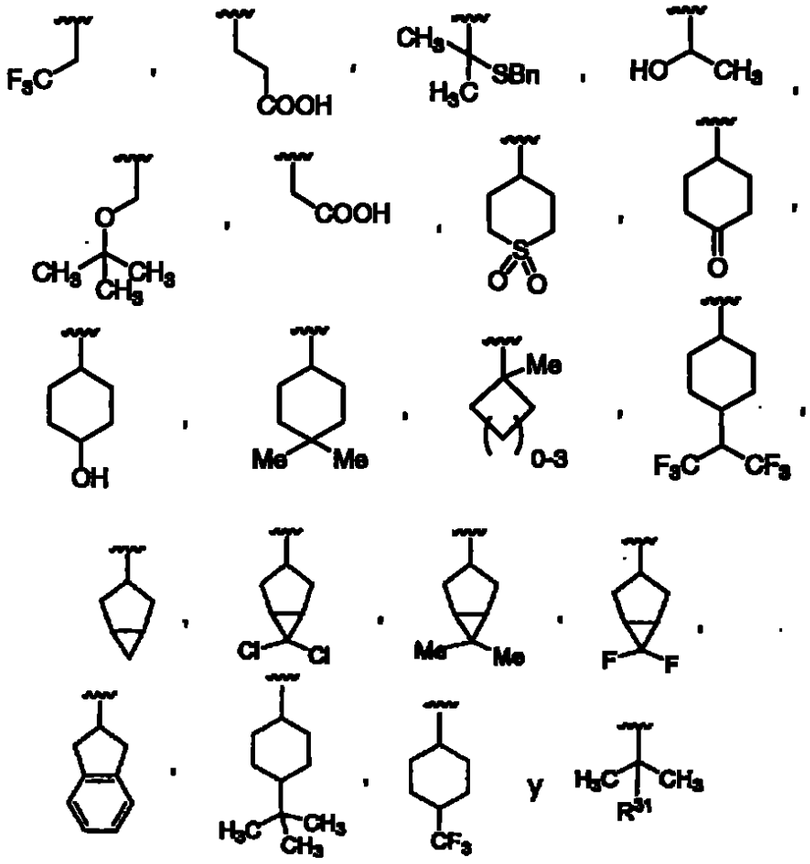


138

En otra realización, R^3 está seleccionado del grupo que consiste en:



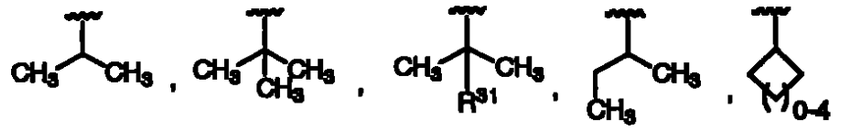
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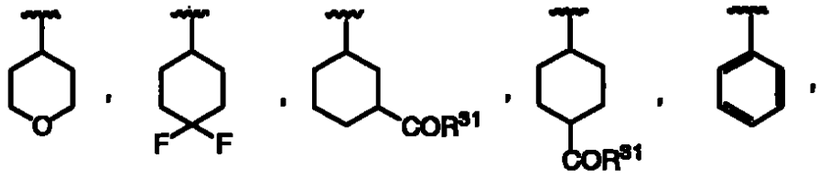


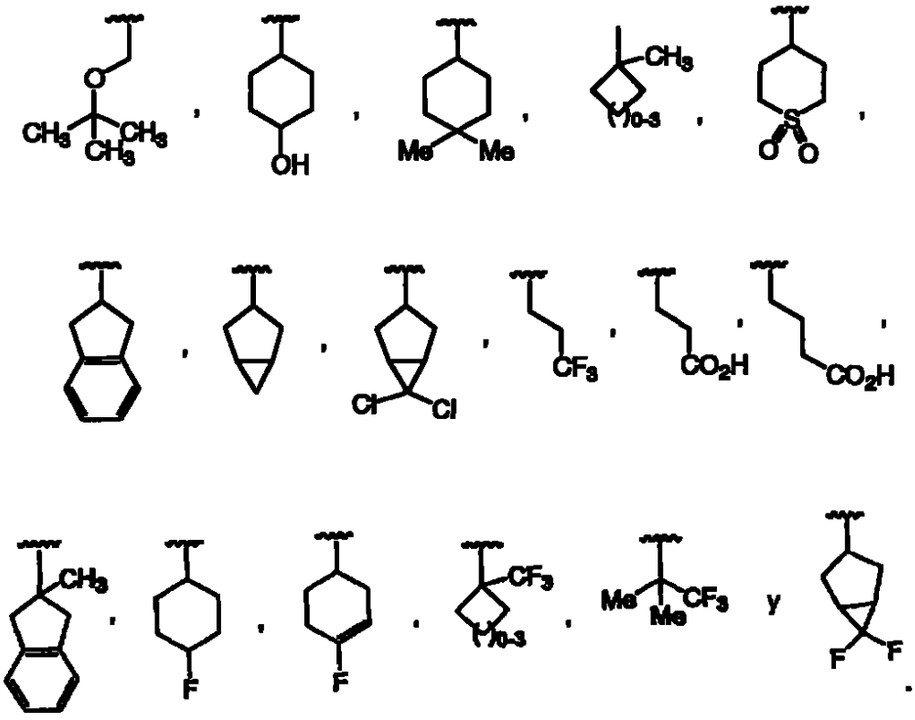
en las cuales R^{31} es OH u O-alquilo; y

R^{32} es H, C(O)CH_3, C(O)OtBu o C(O)N(H)tBu.

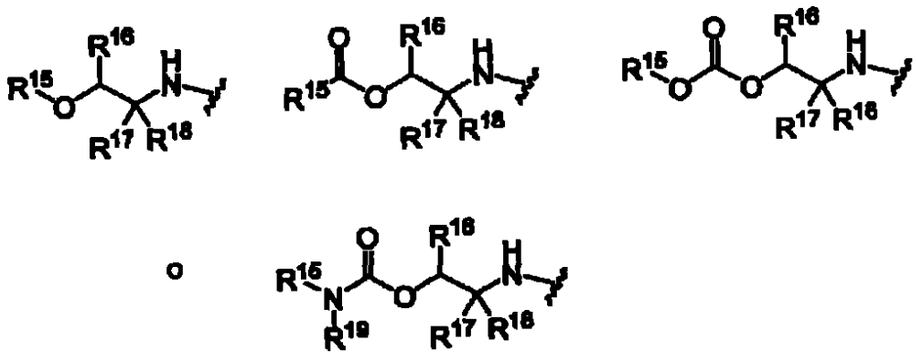
En una realización adicional, R^3 está seleccionado del grupo que consiste en las porciones siguientes:







En otra realización, Y está seleccionado de las siguientes porciones:

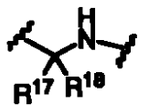


en las cuales R^{15}, R^{16}, R^{17}, R^{18} y R^{19} pueden ser iguales o diferentes, y cada uno está independientemente seleccionado del grupo que consiste en H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo y heteroarilo, o alternativamente, (i) o bien R^{15} y R^{16} están conectados para formar una estructura cíclica de cuatro a ocho miembros, o R^{15} y R^{19} están conectados para formar una estructura cíclica de cuatro a ocho miembros, y (ii) asimismo, independientemente, R^{17} y R^{18} están conectados para formar un cicloalquilo o heterociclilo de tres a ocho miembros;

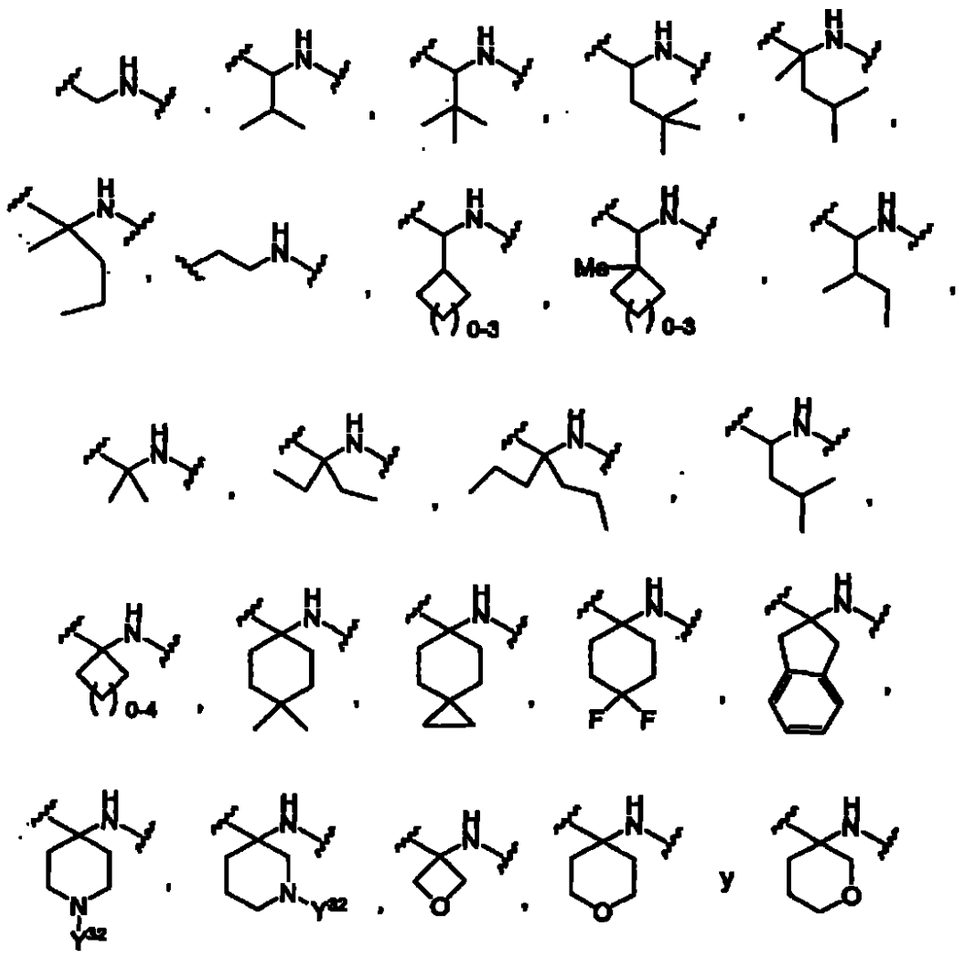
794
141

donde cada uno de dichos alquilo, arilo, heteroarilo, cicloalquilo o heterocicli pueden estar no sustituidos o pueden estar opcionalmente independientemente sustituidos con una o más porciones seleccionadas del grupo que consiste en: hidroxi, alcoxi, ariloxi, tio, alquiltio, ariltio, amino, amido, alquilamino, arilamino, alquilsulfonilo, arilsulfonilo, sulfonamido, alquilsulfonamido, arilsulfonamido, ceto, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halo, ciano y nitro.

En una realización adicional, la porción:

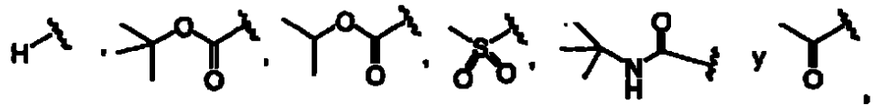


está seleccionada del grupo que consiste en:



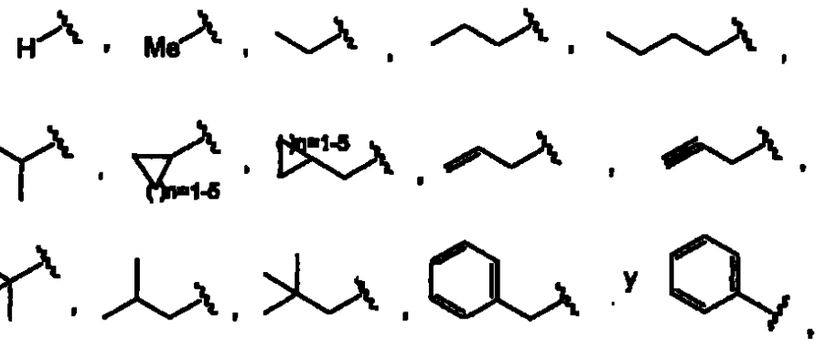
en las cuales Y^{32} está seleccionado del grupo que consiste en:

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R^{16} está seleccionado de H, metilo, fenilo, bencilo; y

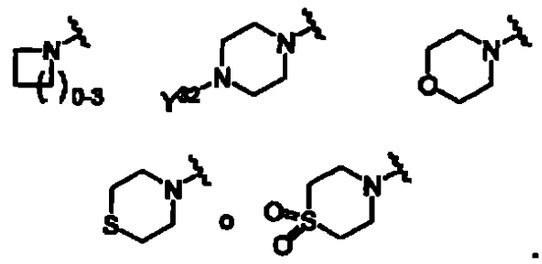
R^{15} y R^{19} pueden ser iguales o diferentes, y cada uno está independientemente seleccionado de las siguientes:



o alternativamente, la porción:

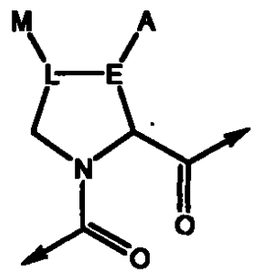


se selecciona de las porciones siguientes:



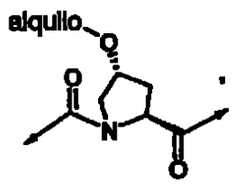
En una realización adicional, R^{16} es H.

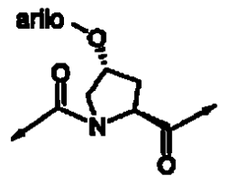
En otra realización, la porción:

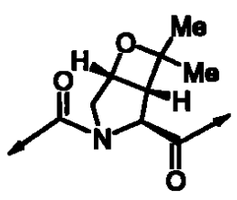


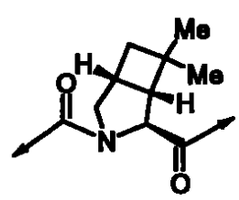
está seleccionada de las estructuras siguientes:

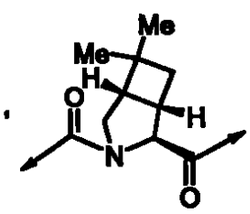
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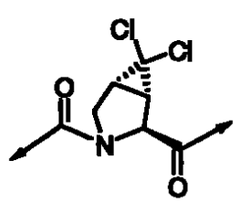

alquilo
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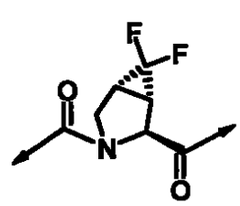

arilo
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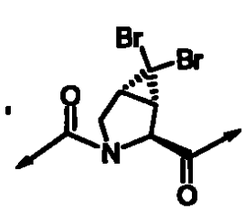

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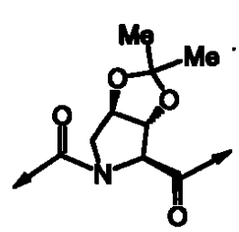

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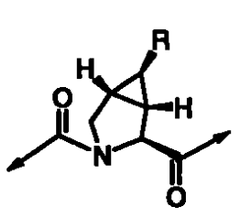

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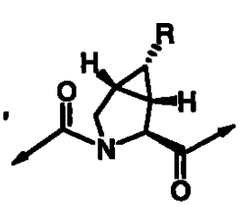

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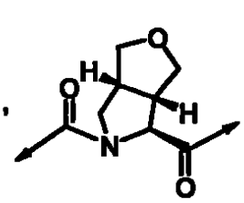

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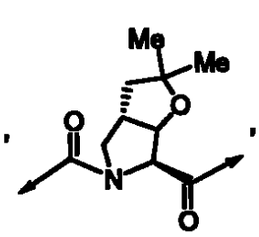

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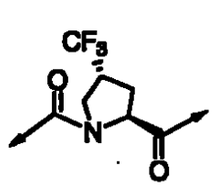

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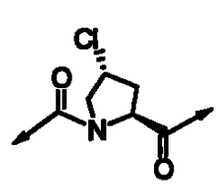

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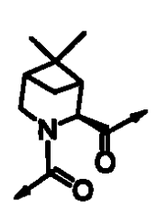

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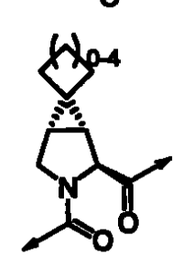

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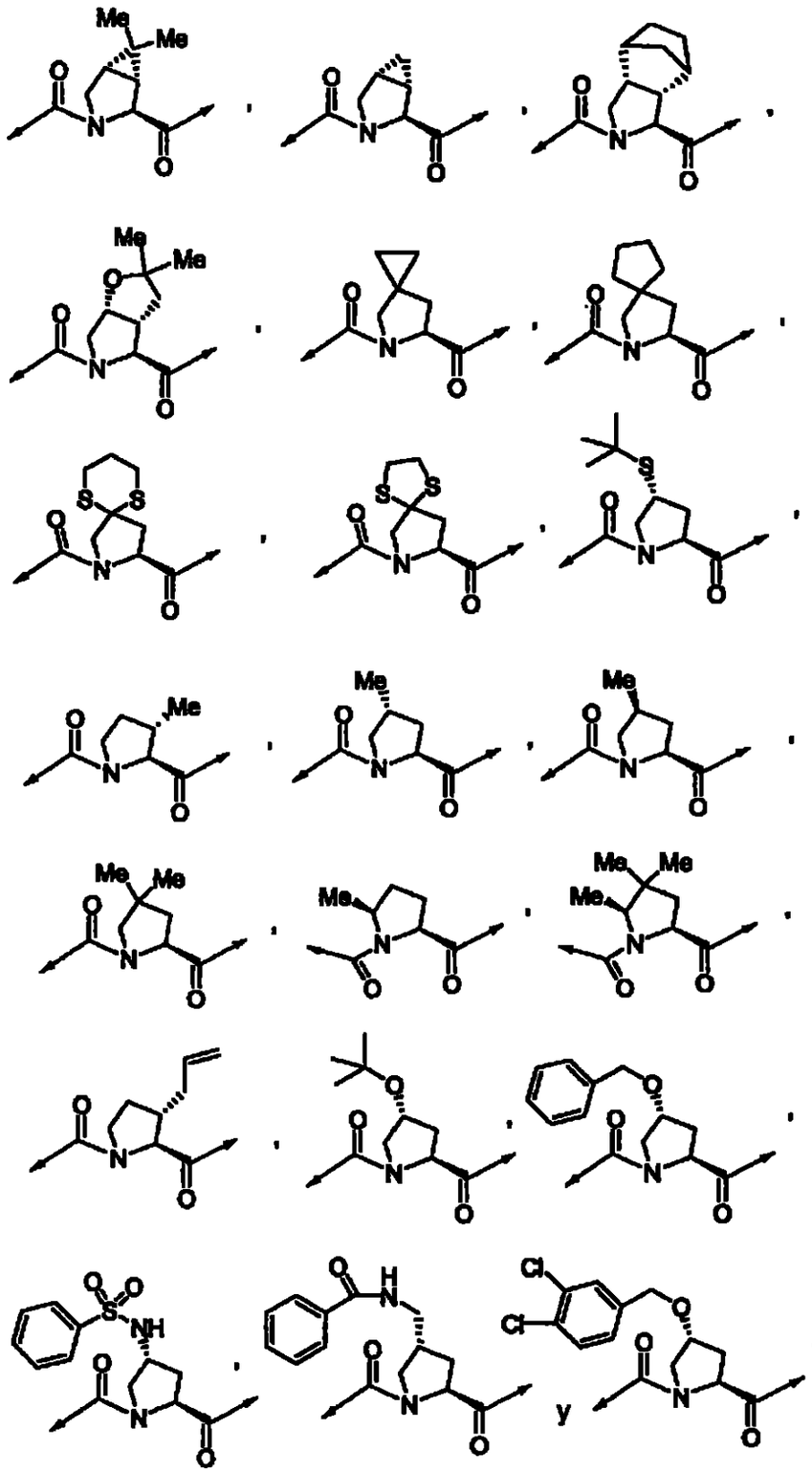

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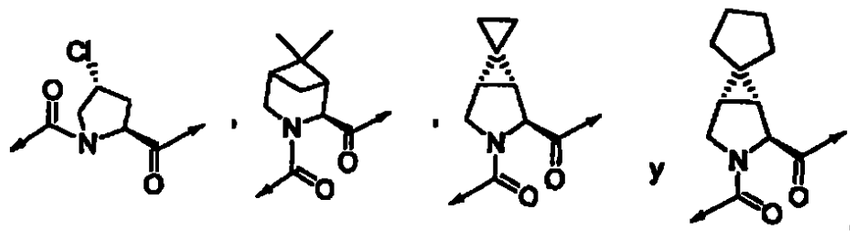

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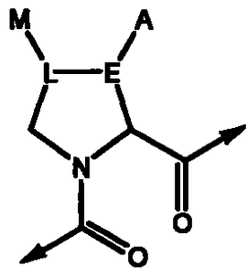
144



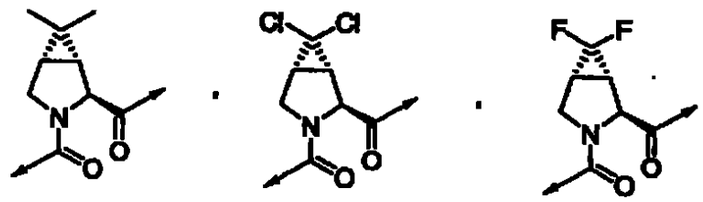
En una realización adicional, la porción:

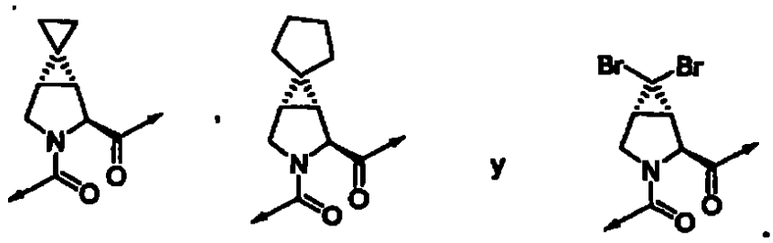


En una realización más, la porción:

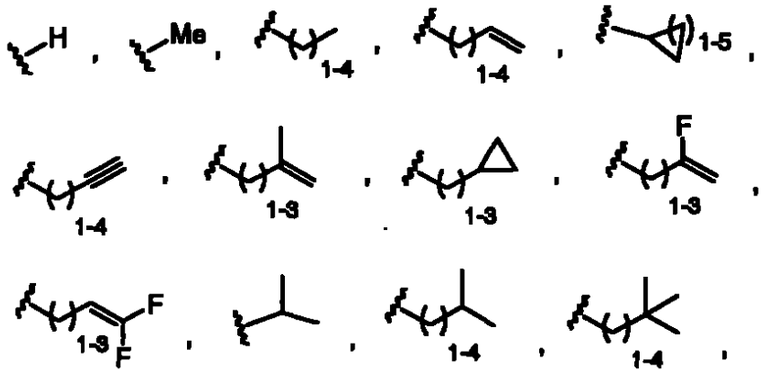


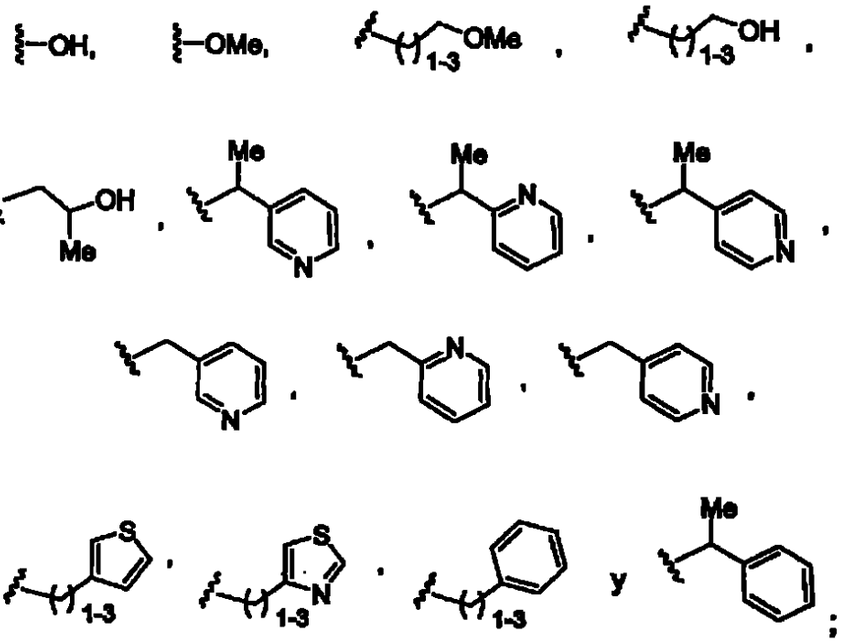
se selecciona de las siguientes estructuras:



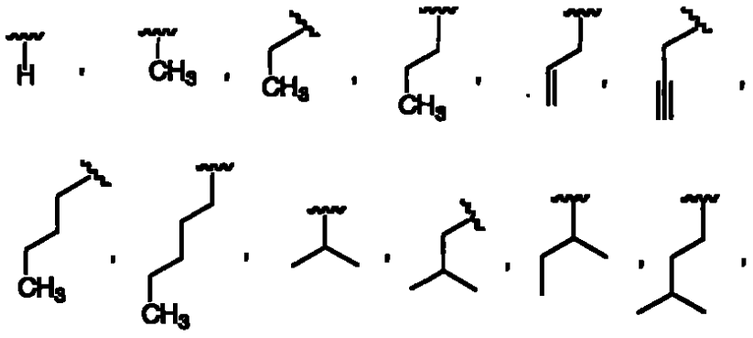


En una realización adicional más, R^1 es NHR^{14}, donde R^{14} está seleccionado del grupo que consiste en:

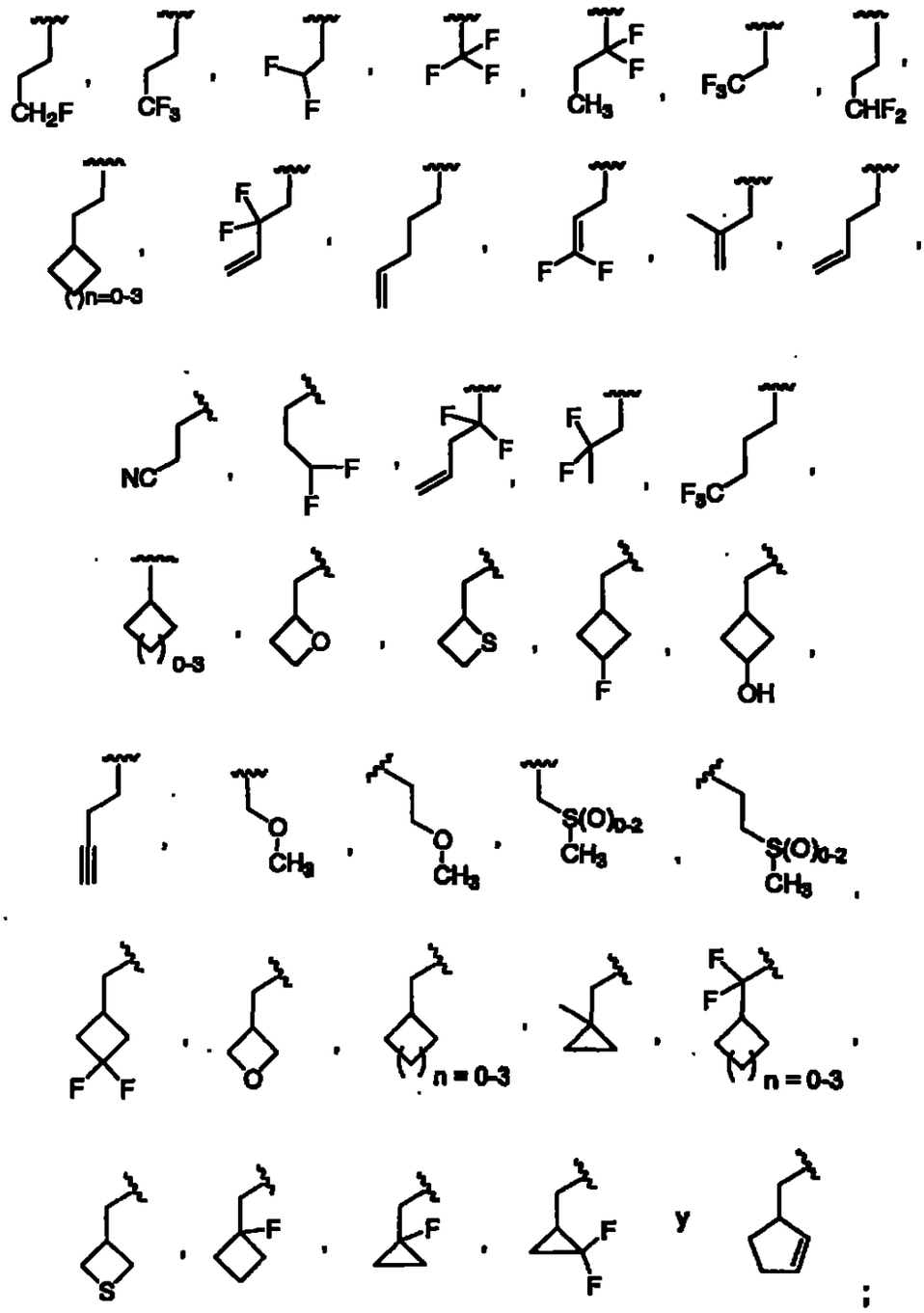




R^2 está seleccionado del grupo que consiste en las siguientes porciones:



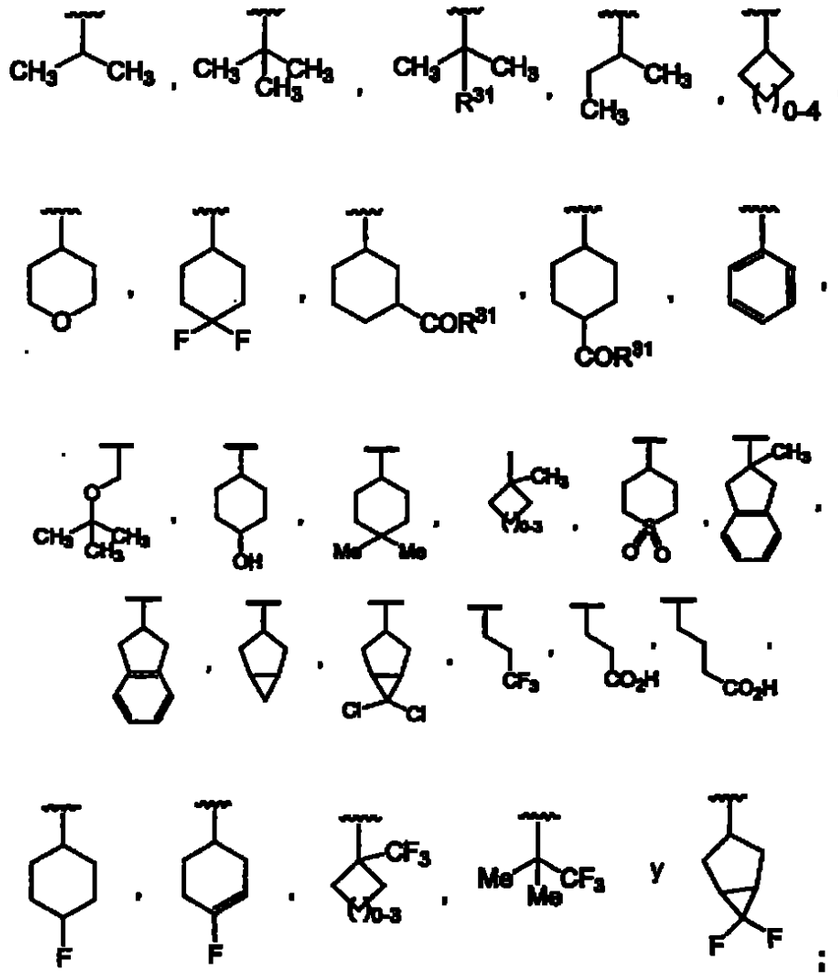
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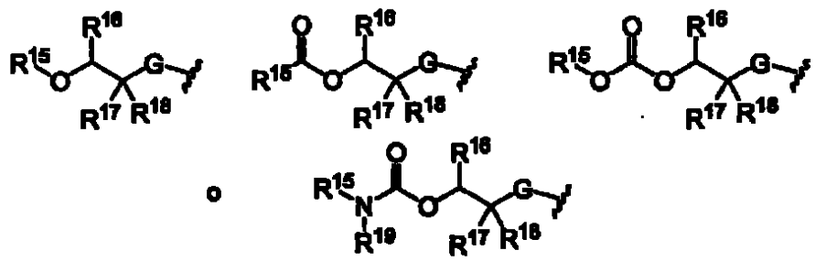
;

R^3 está seleccionado del grupo que consiste en las siguientes porciones:

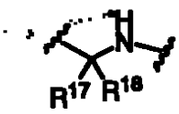
148



Y está seleccionado del grupo que consiste en:

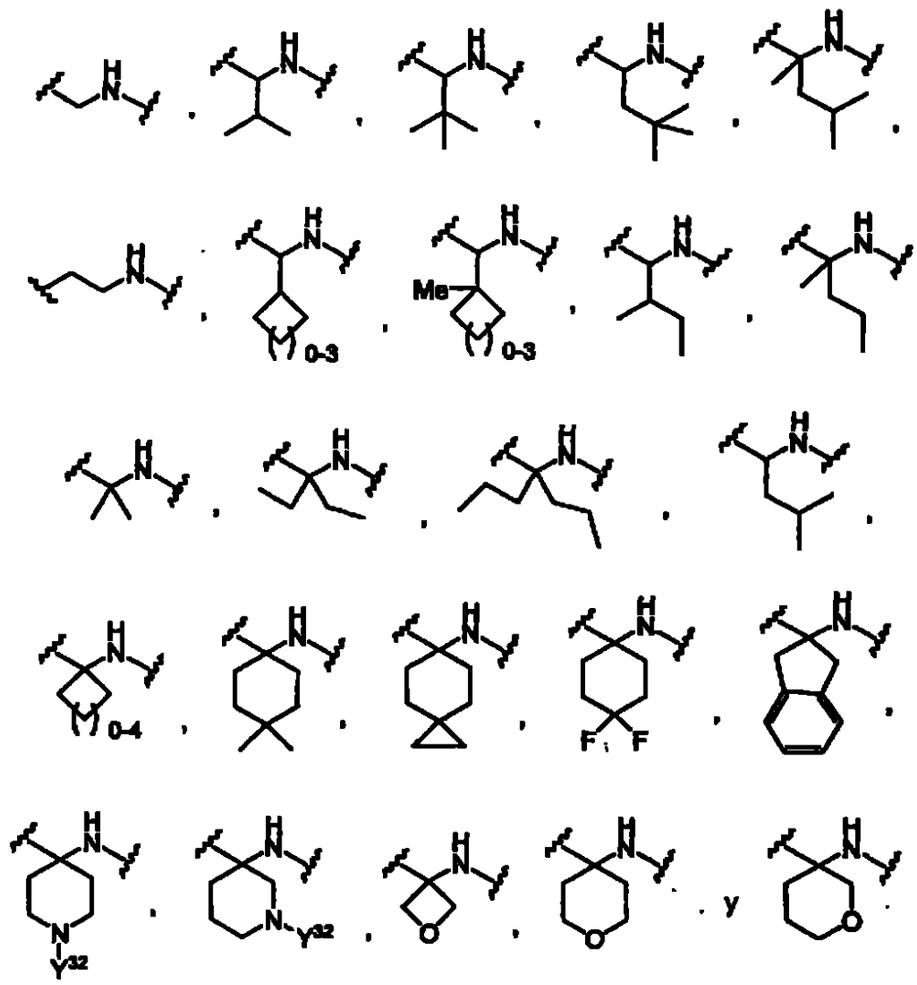


en las cuales G = NH, y la porción



está seleccionada del grupo que consiste en:

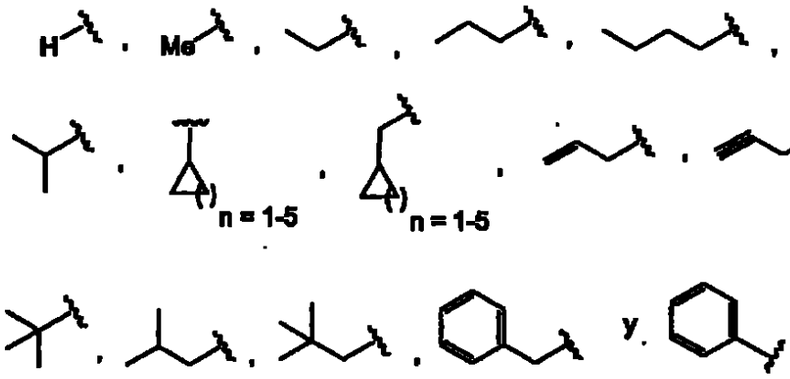
7469
149



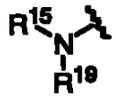
R^{16} = H, y

R^{15} y R^{19} pueden ser iguales o diferentes, y cada una está independientemente seleccionada de las siguientes:

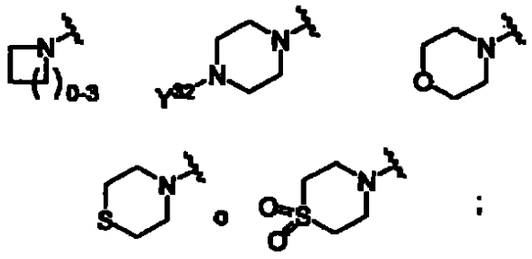
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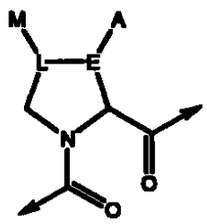
o alternativamente, la porción:



está representada por una de las porciones siguientes,

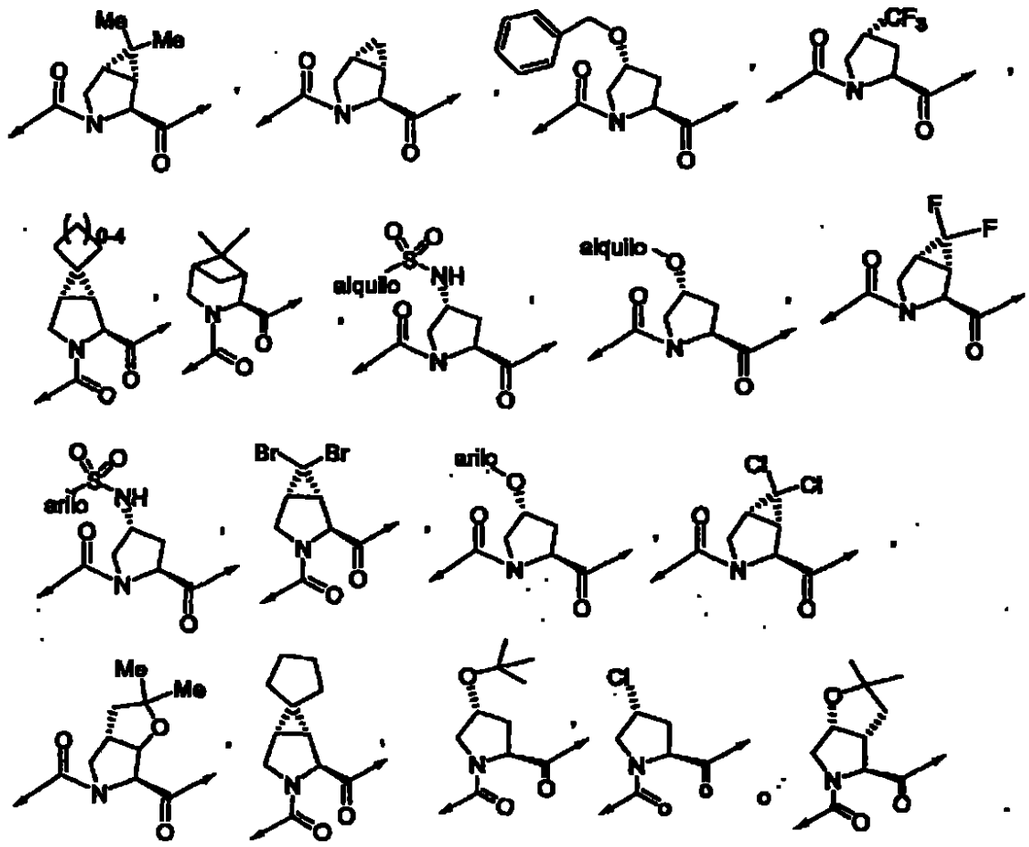


y la porción:



es:

151

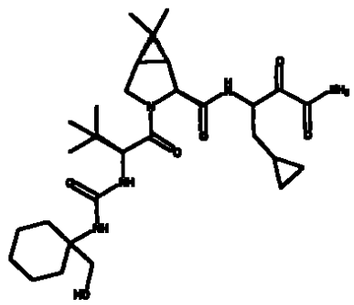


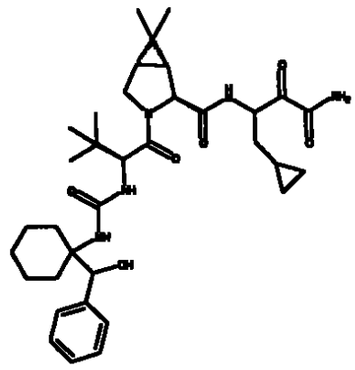
Otra realización de la invención describe compuestos que se muestran en las **Tabla 1, Tabla 1A, Tabla 2 y Tabla 3** más adelante en esta Descripción. Asimismo en las **Tablas** se muestran las actividades biológicas de varios compuestos de la invención (como valores Ki*).

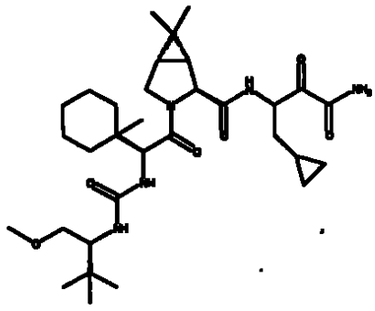
En una realización adicional, esta invención describe los compuestos siguientes en la **Tabla 4:**

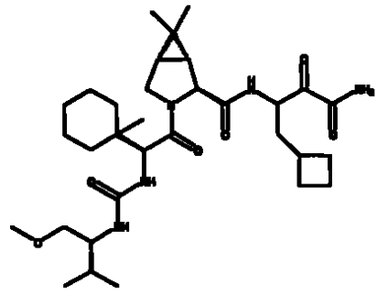
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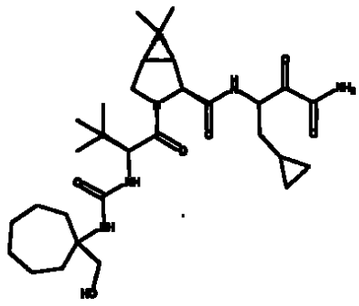
Tabla 4

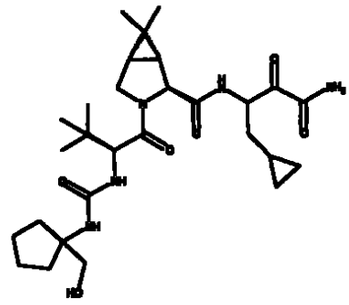


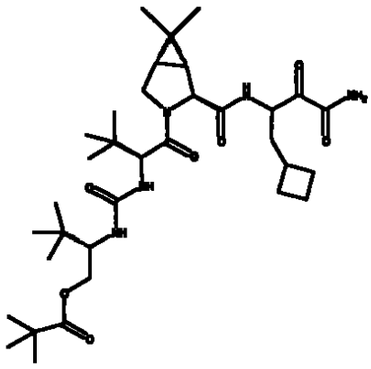


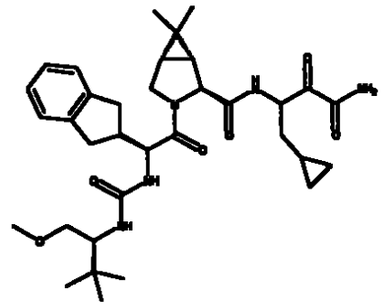






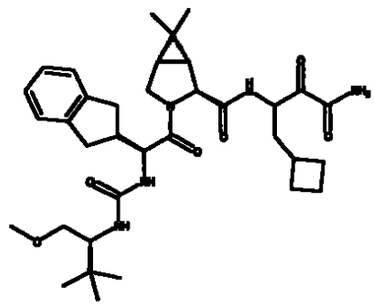


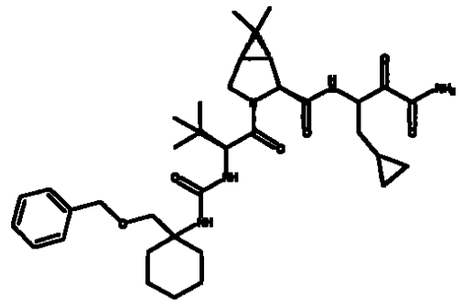


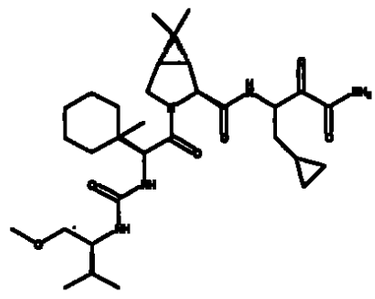


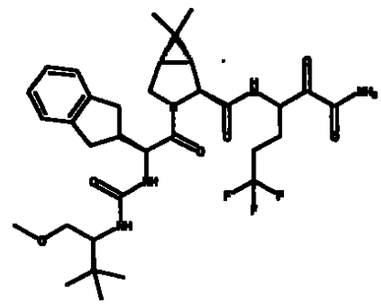
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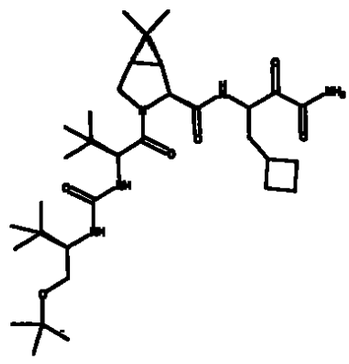
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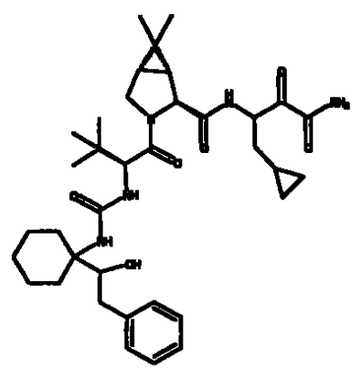


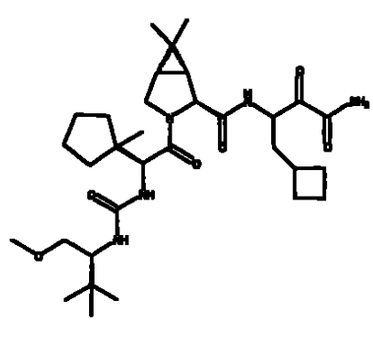


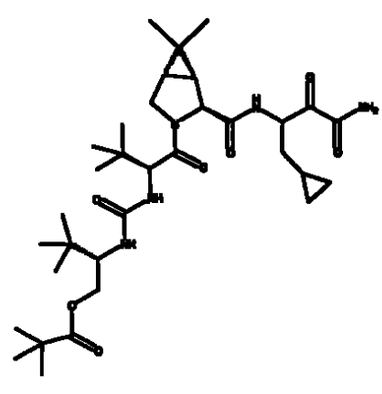


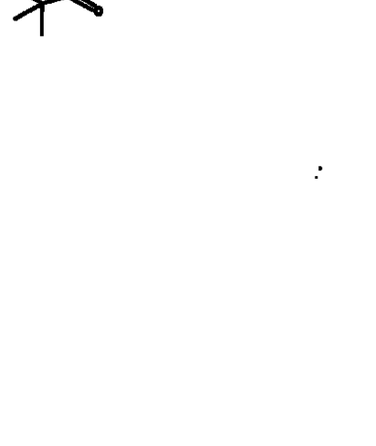




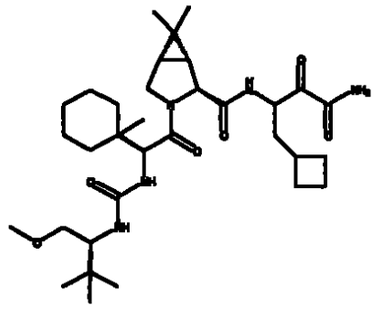


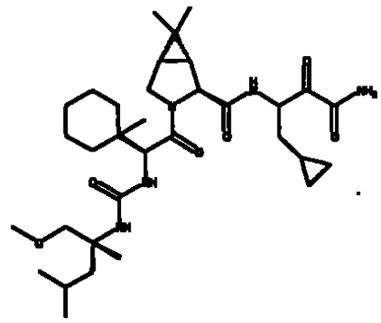


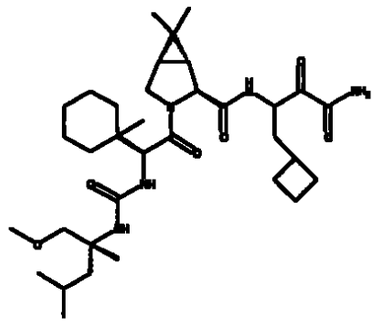


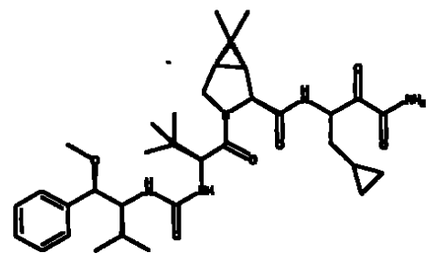


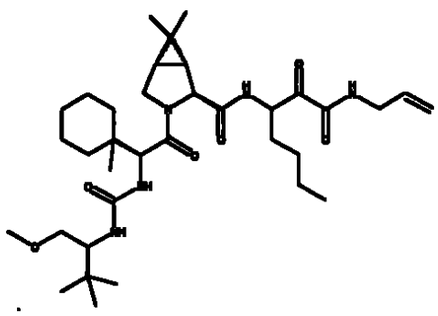
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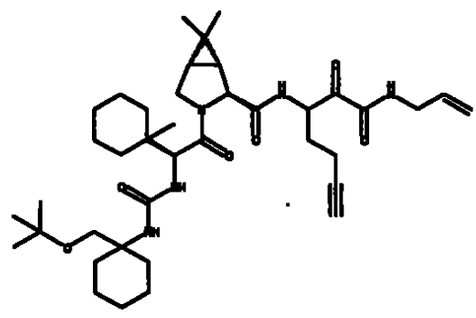


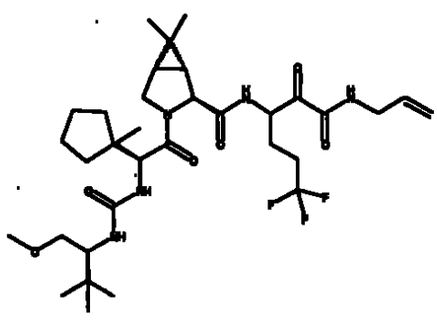


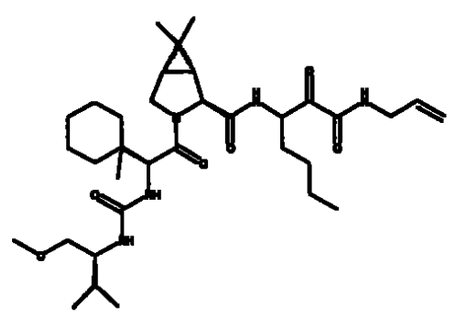




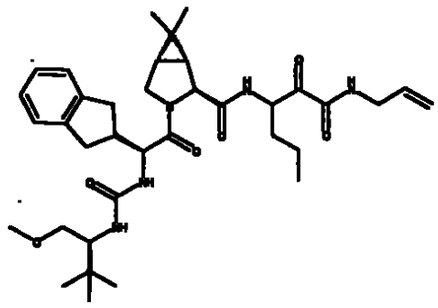


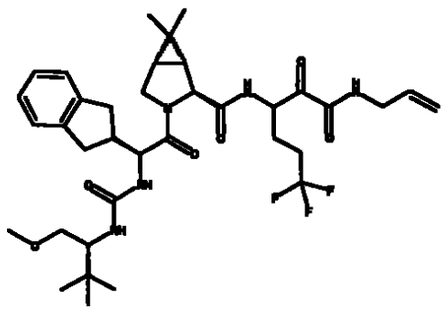


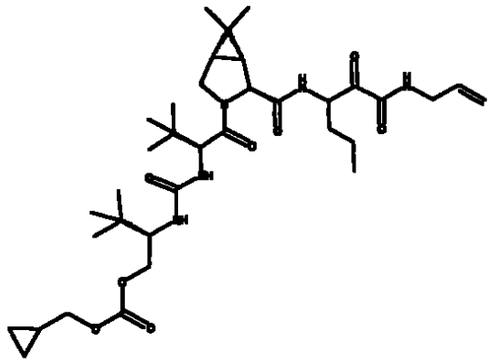


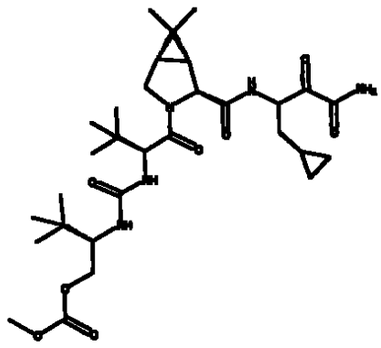


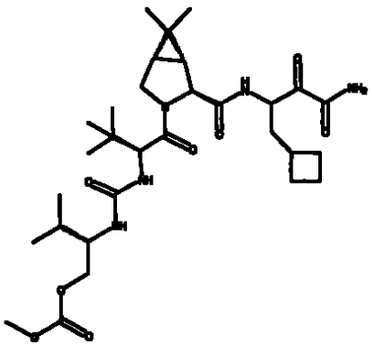
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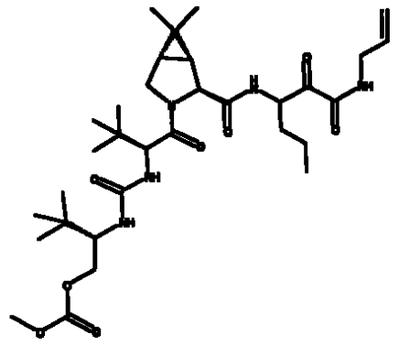


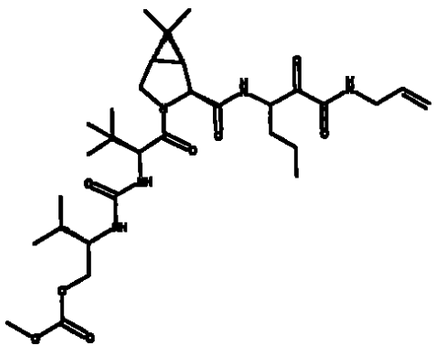


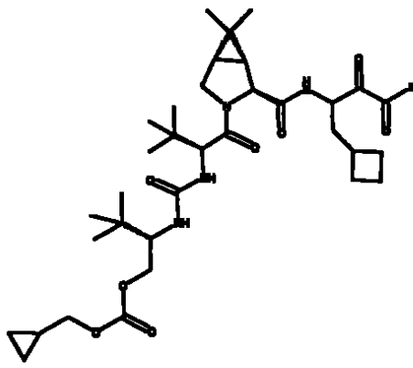




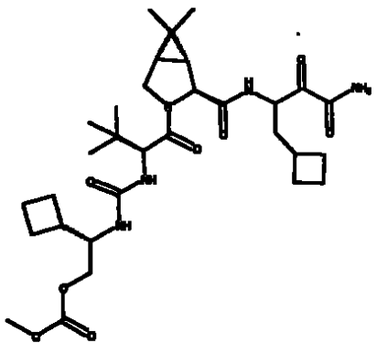


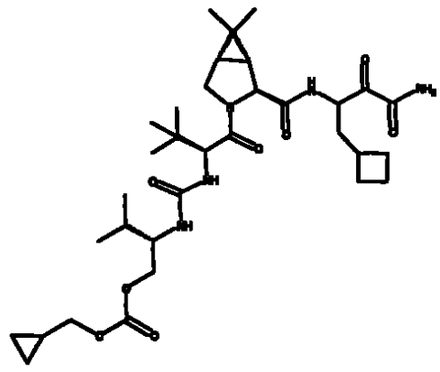


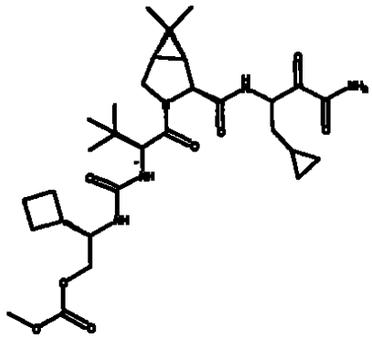


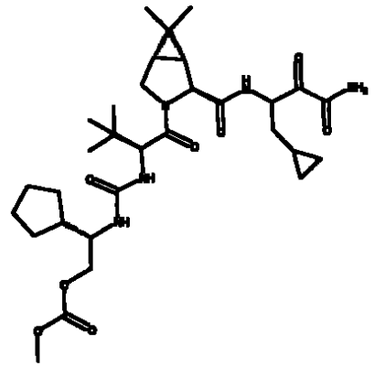


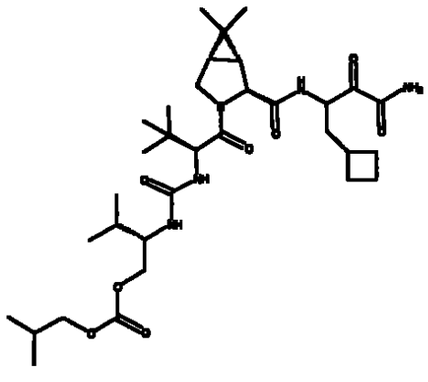
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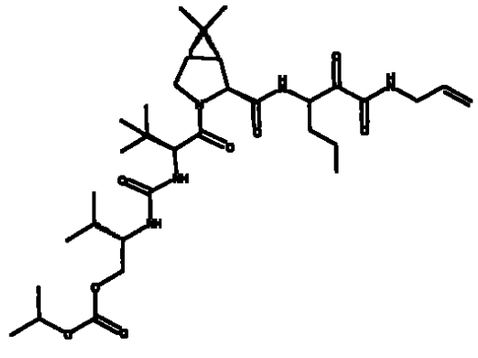


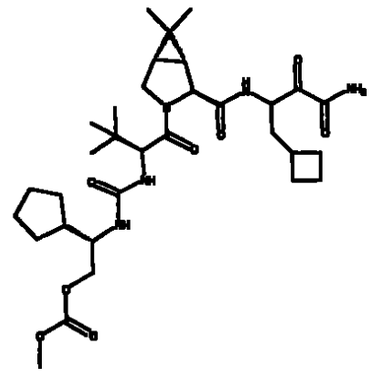


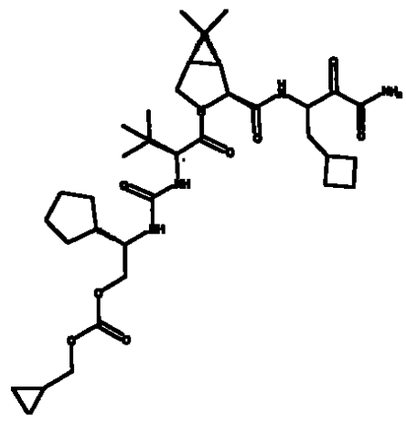




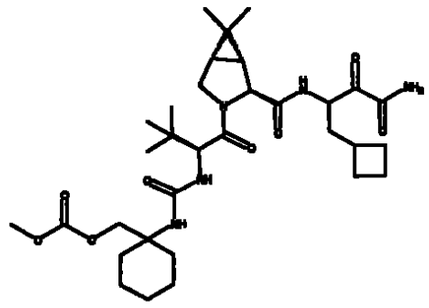


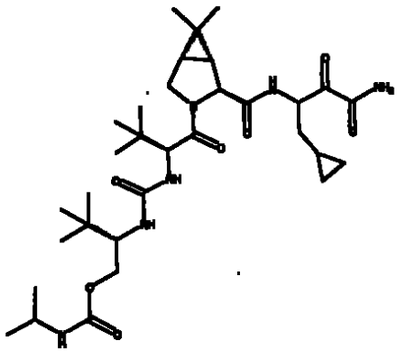


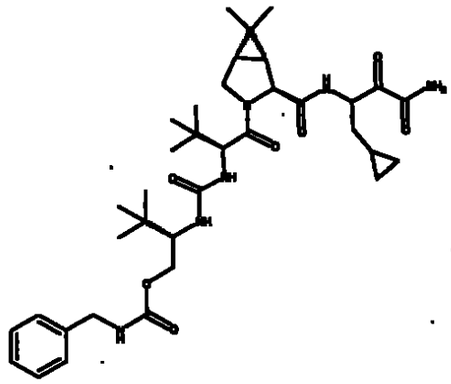


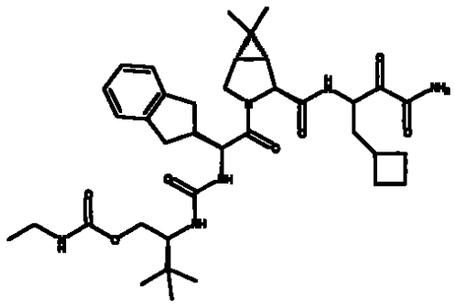


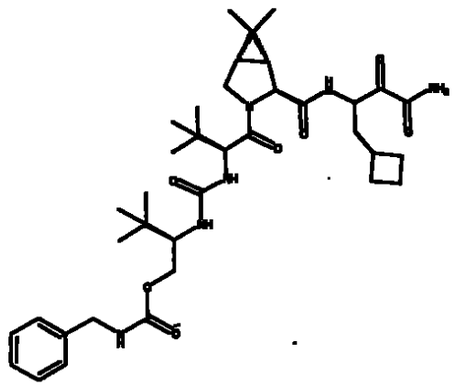
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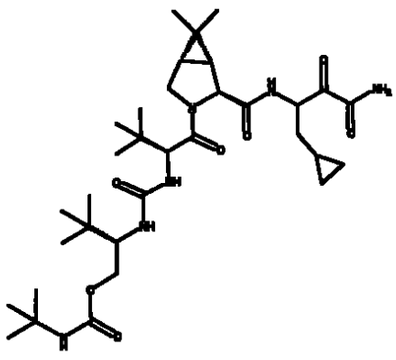


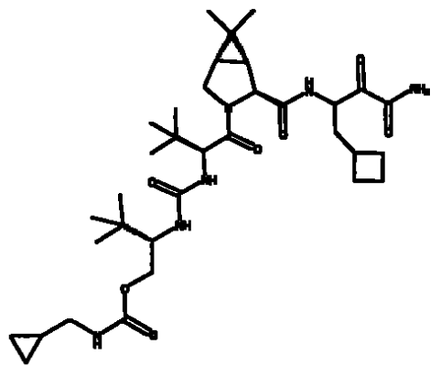






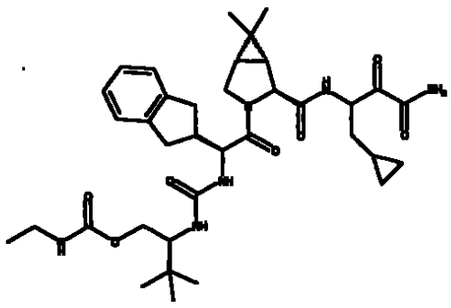


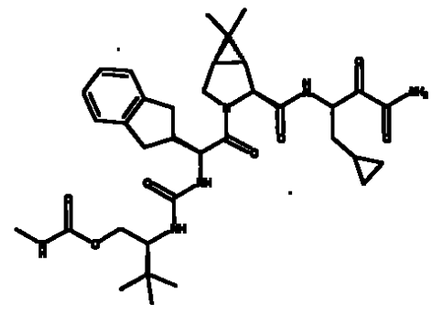


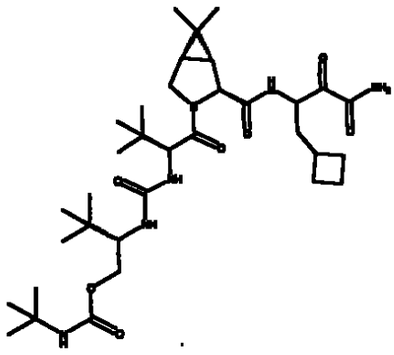


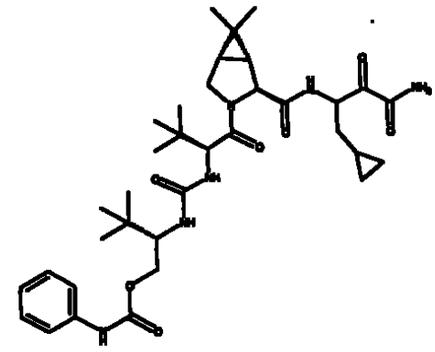
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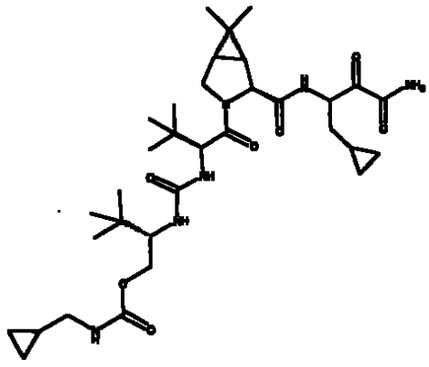
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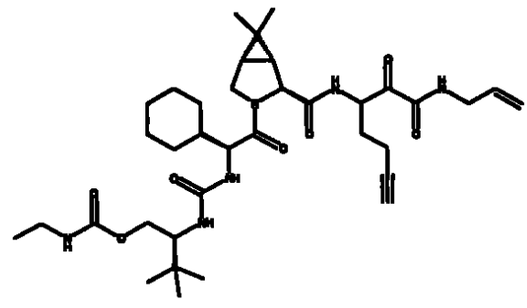


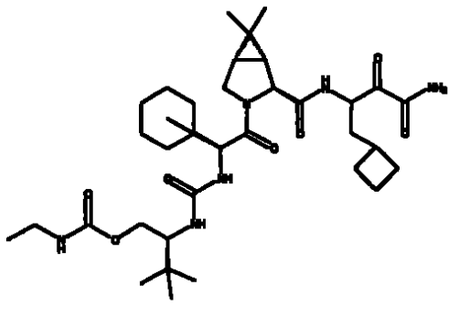


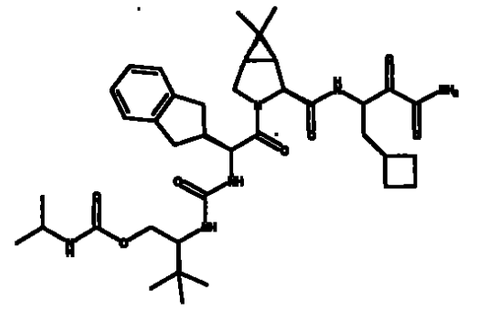


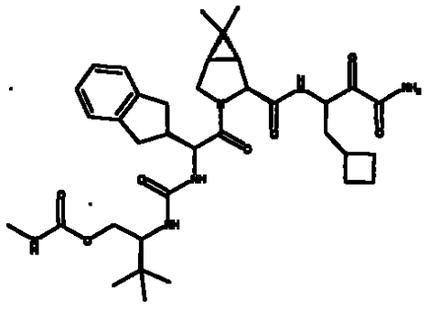


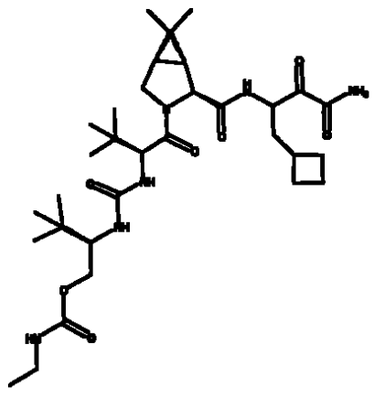


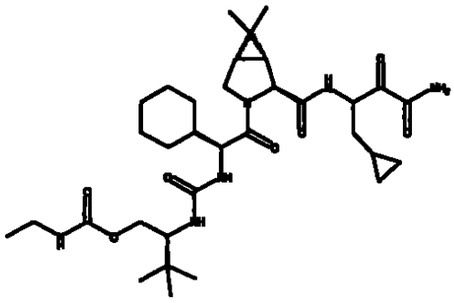


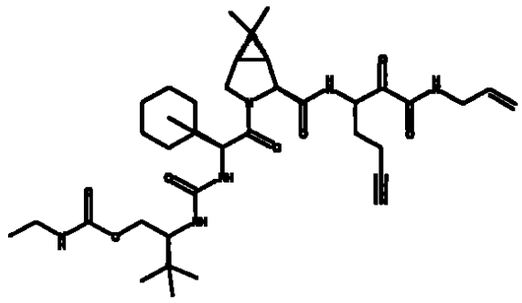


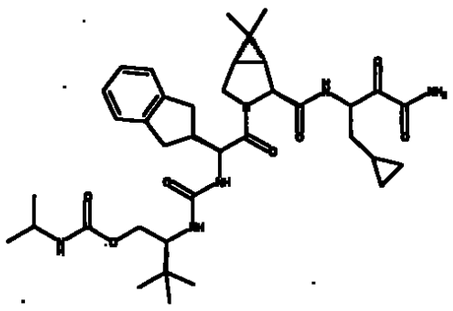


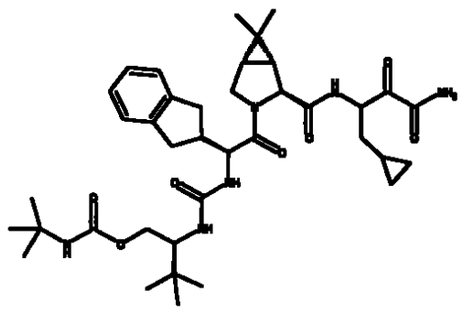


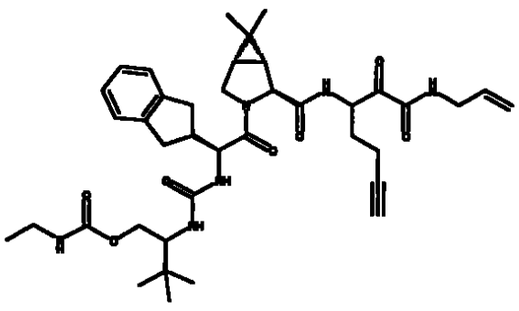


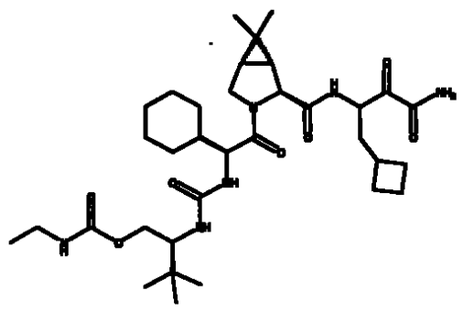




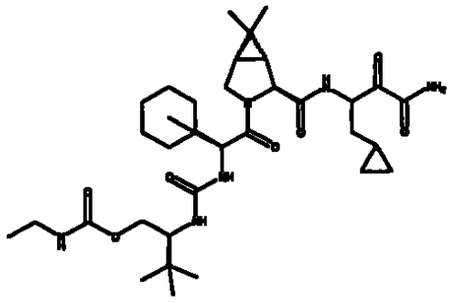


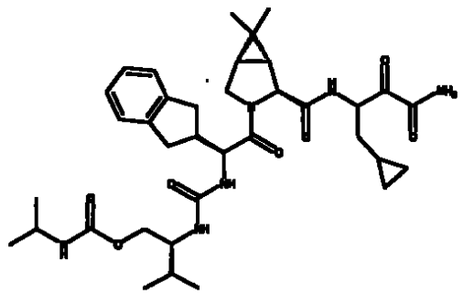


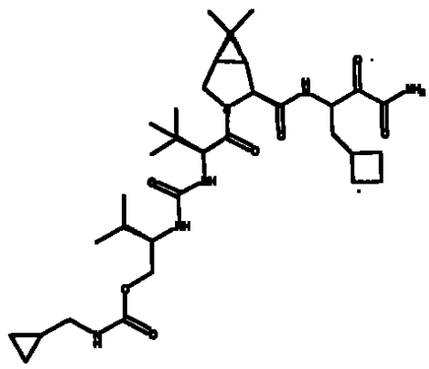


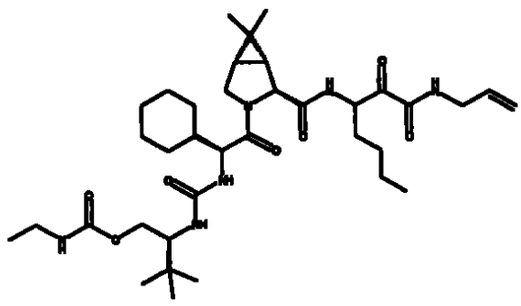


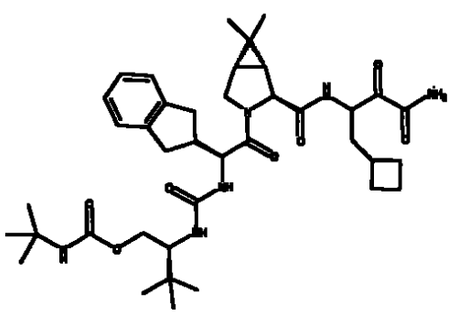
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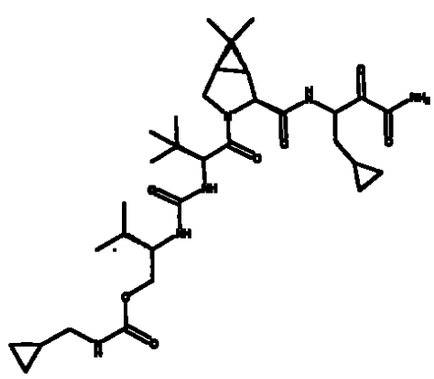


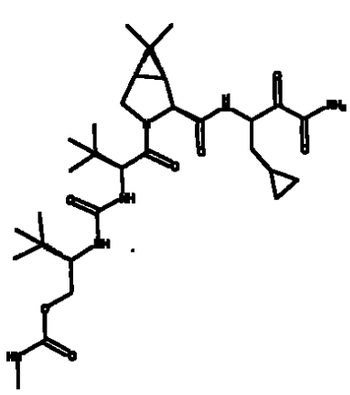


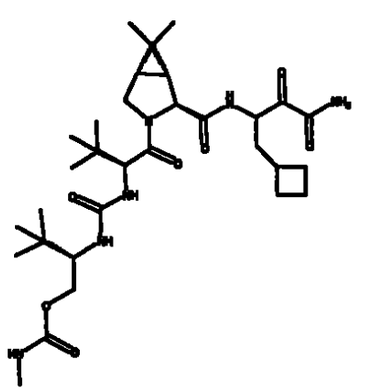


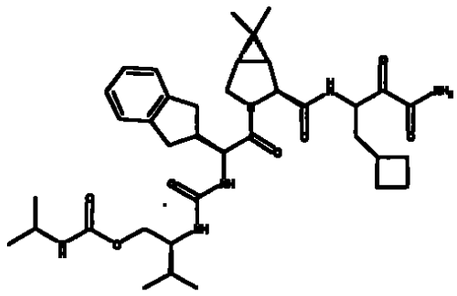


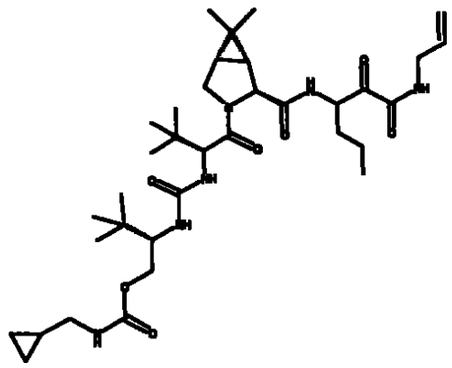


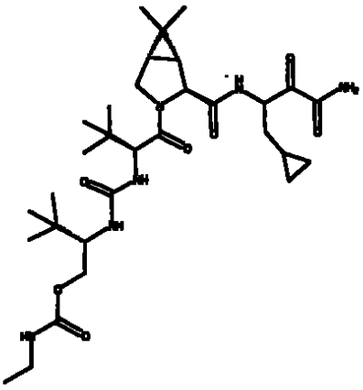


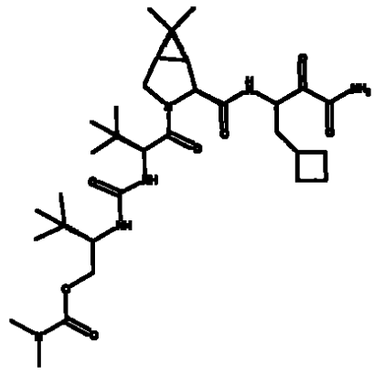


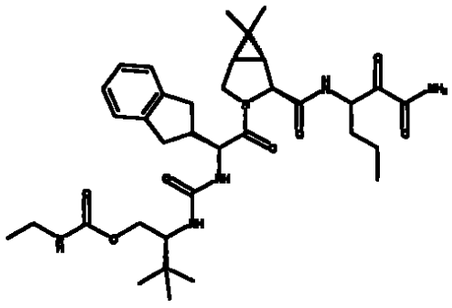


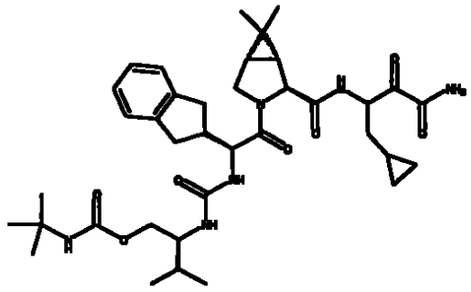


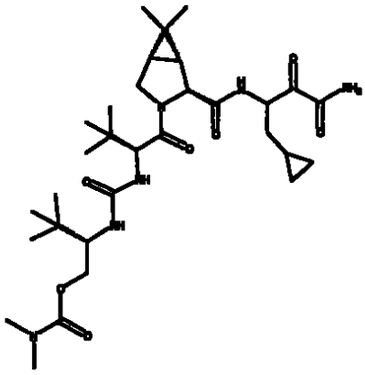


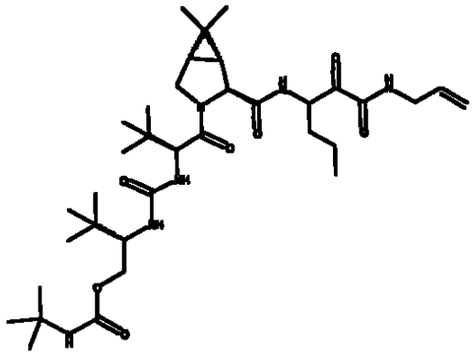




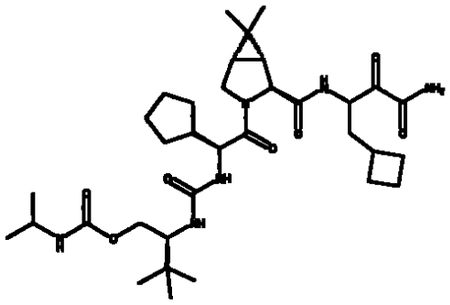


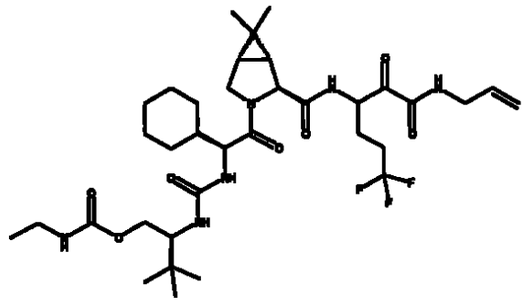


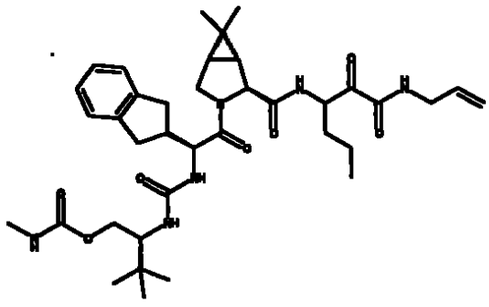


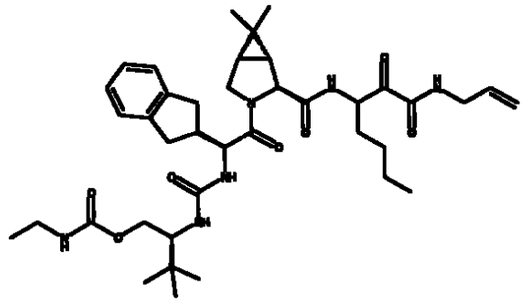


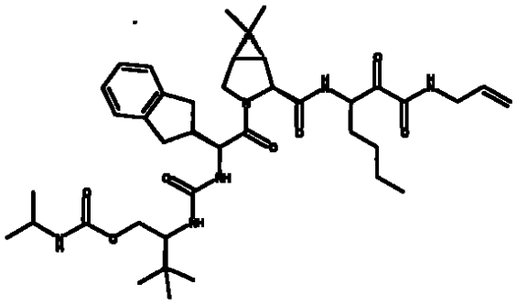
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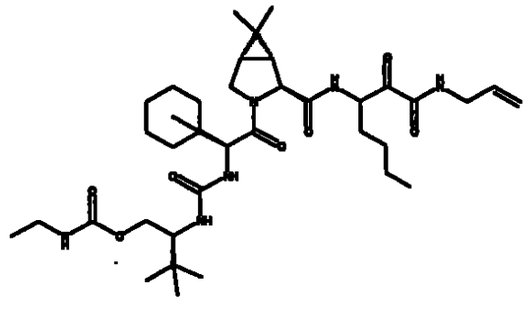


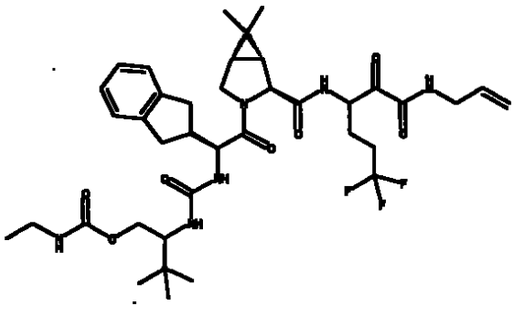


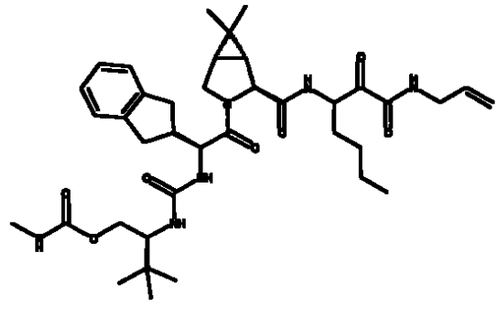


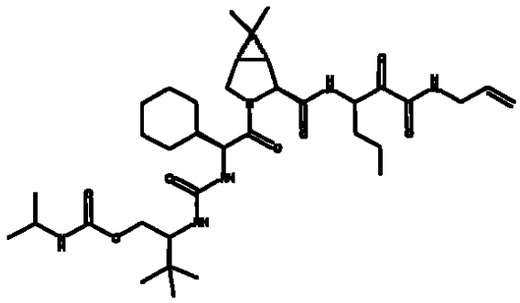


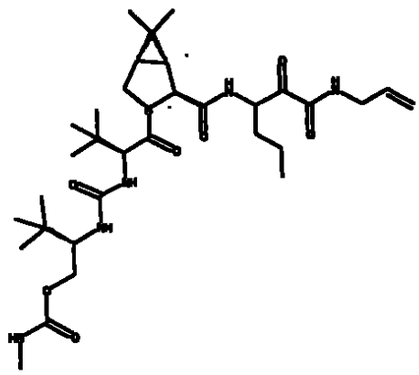


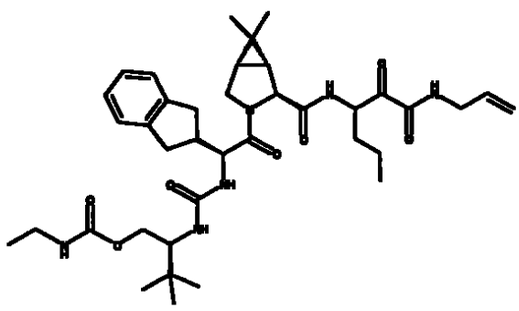


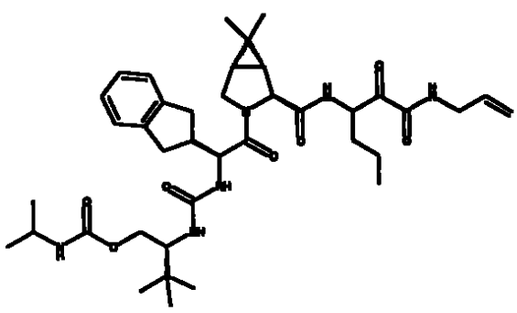


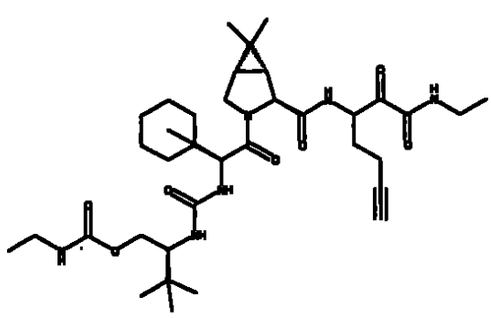


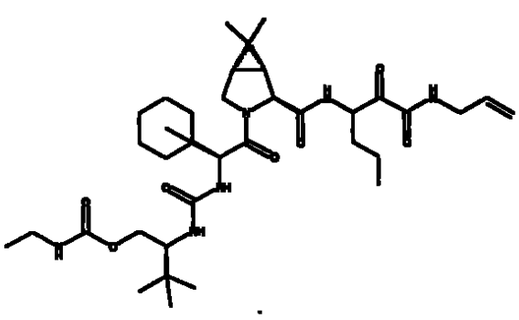


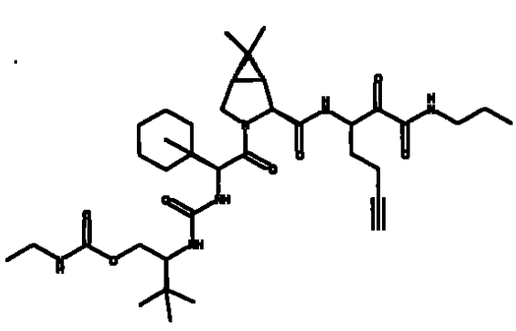


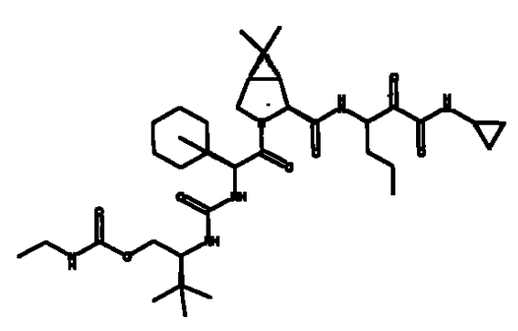




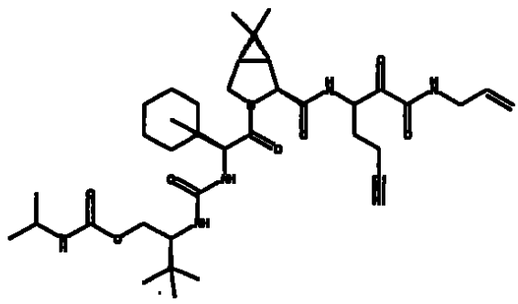


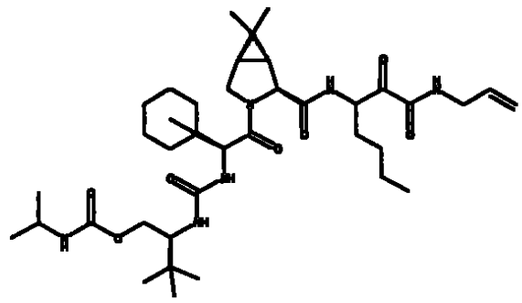


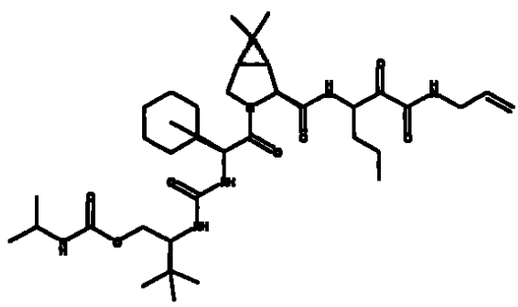


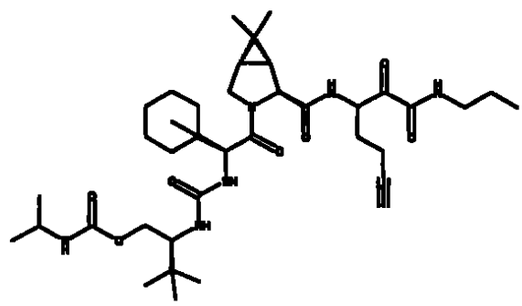


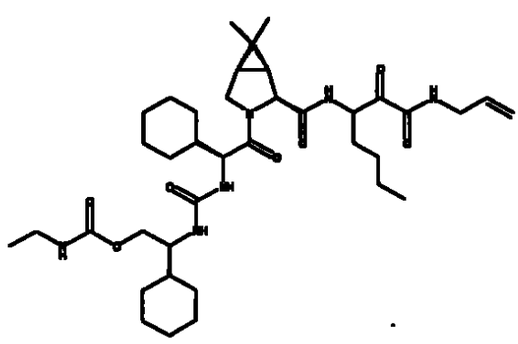
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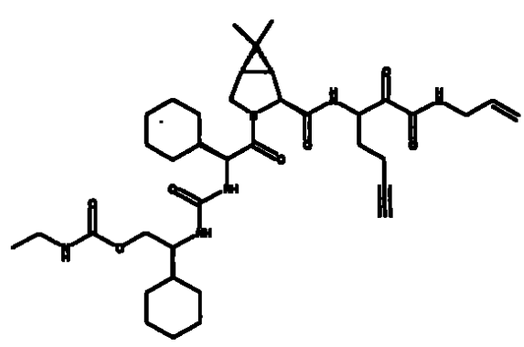


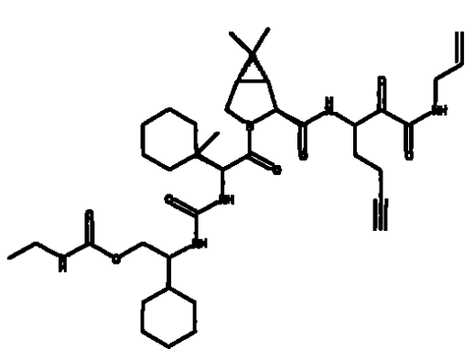


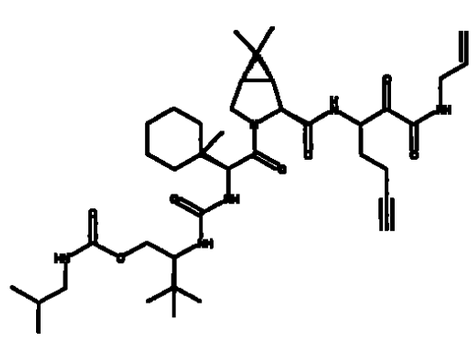


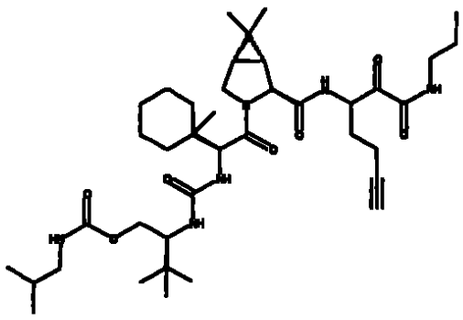


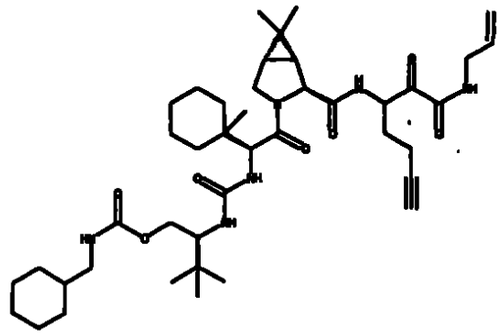


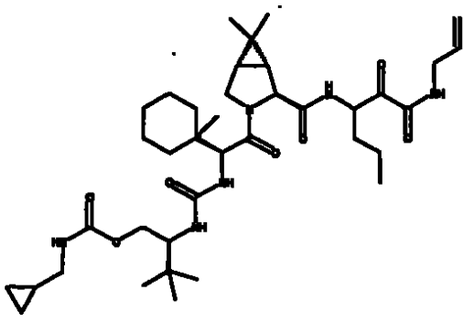


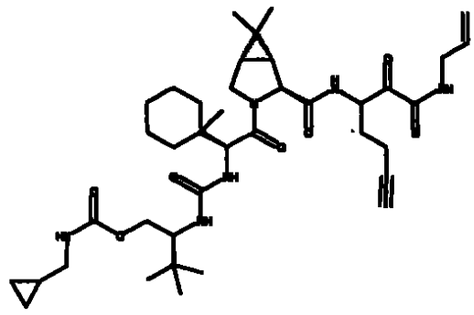


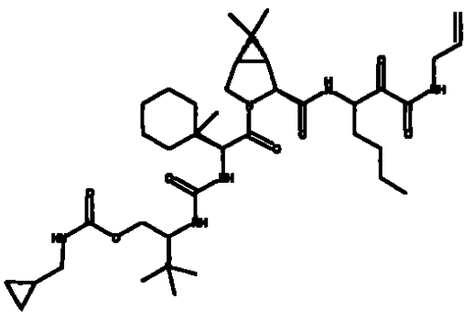


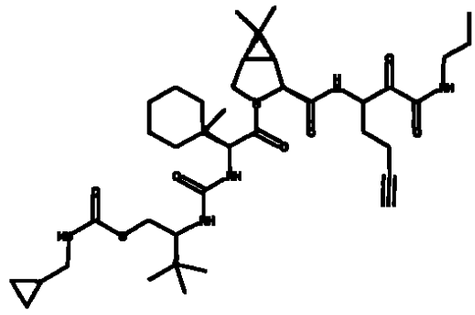


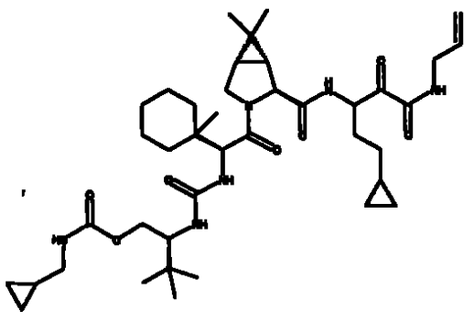


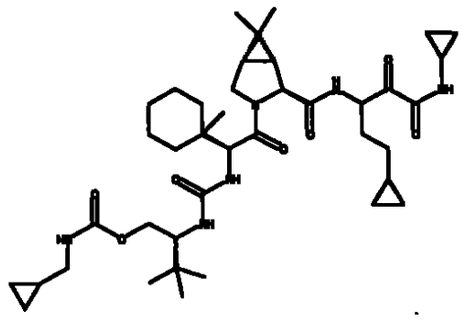








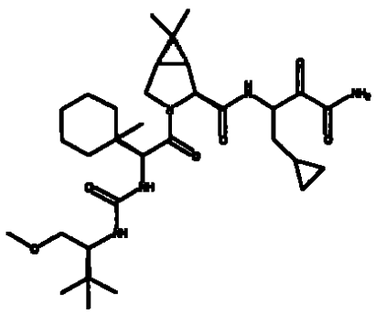


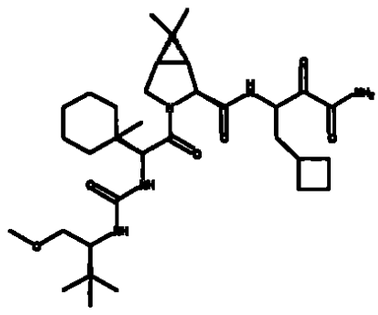


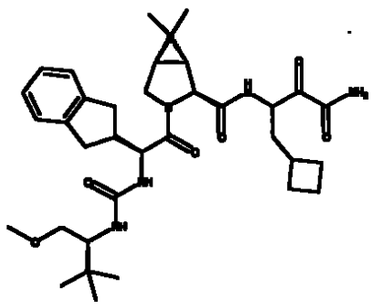
En una realización adicional, la presente invención describe los siguientes compuestos en la **Tabla 5**:

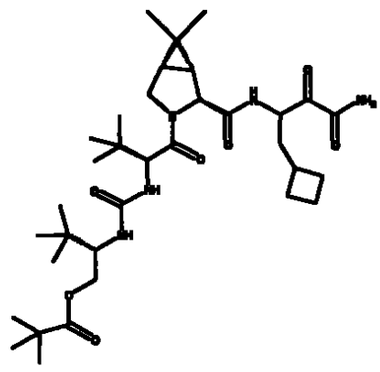
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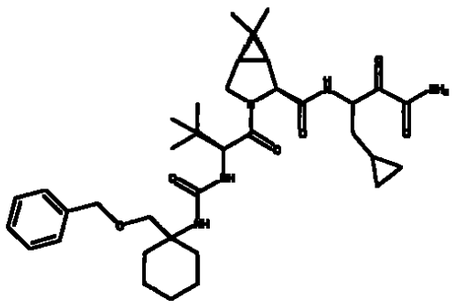
Tabla 5

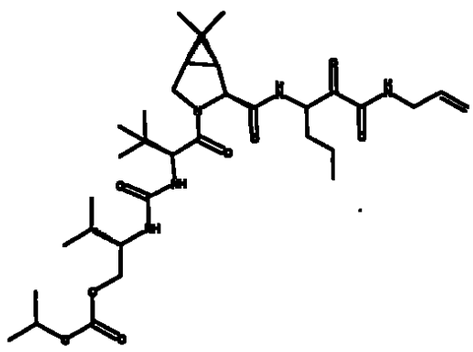


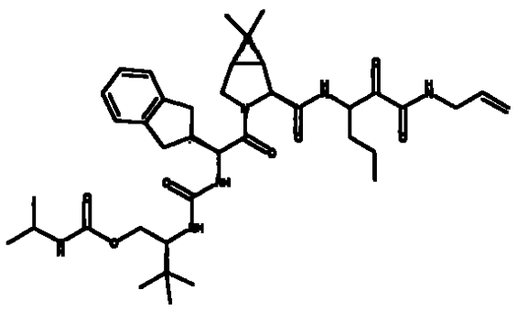


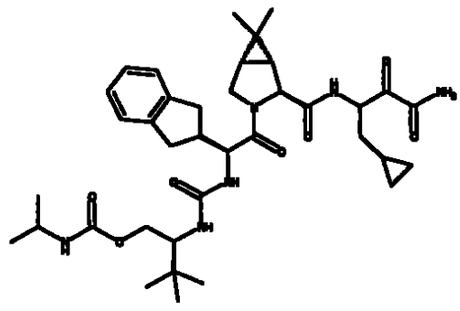




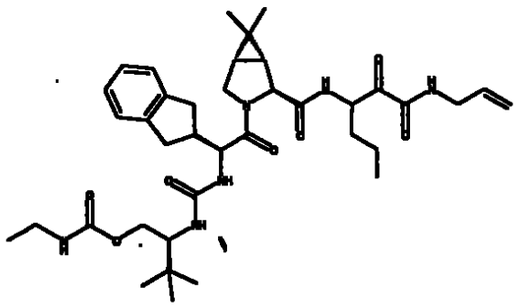


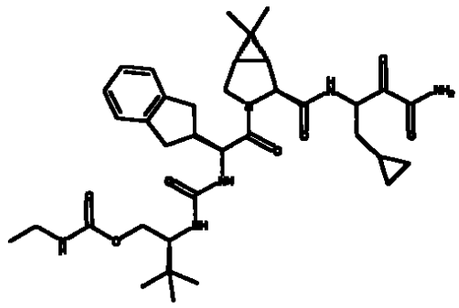


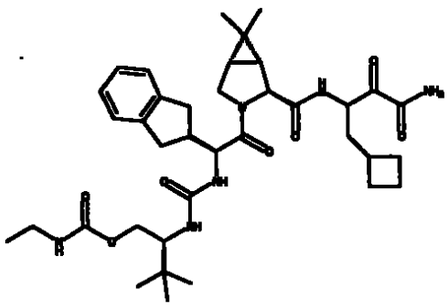


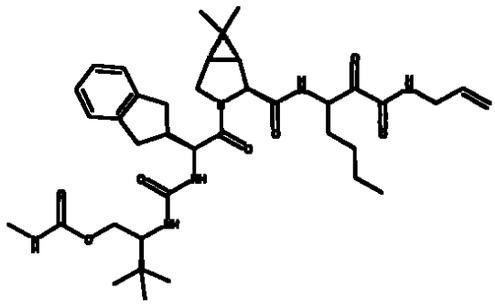


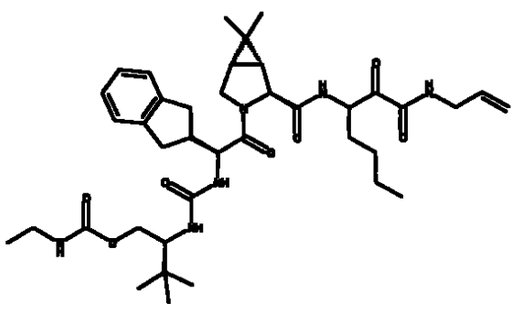
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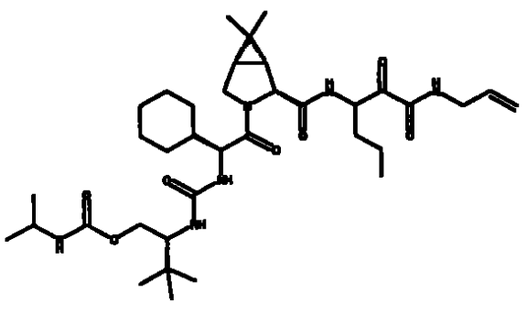


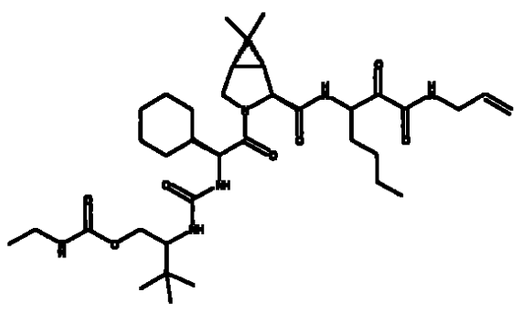


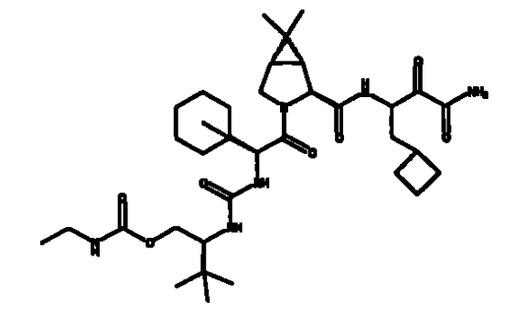




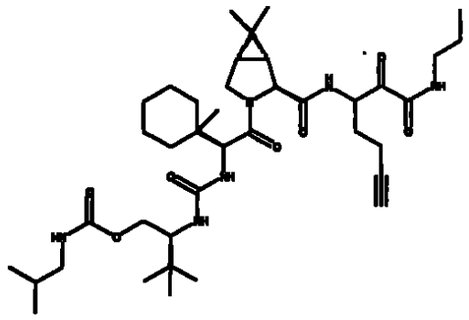


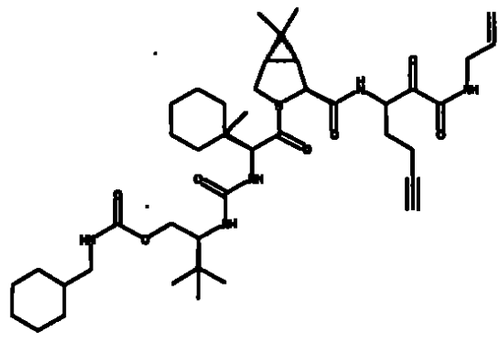


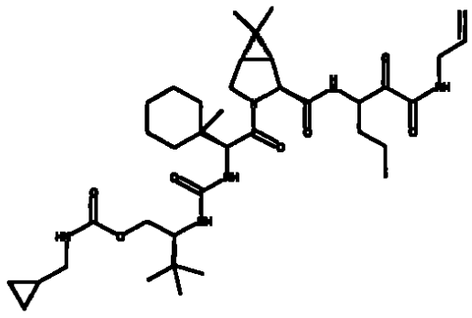


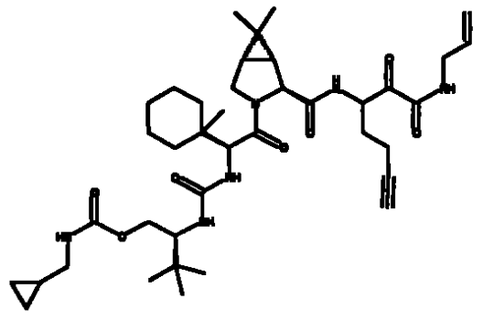


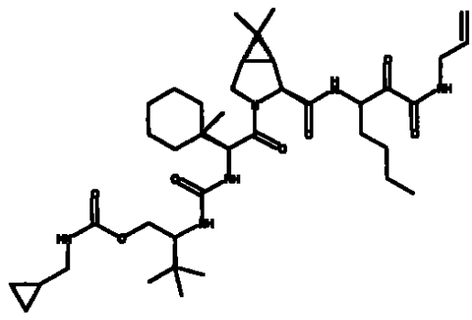
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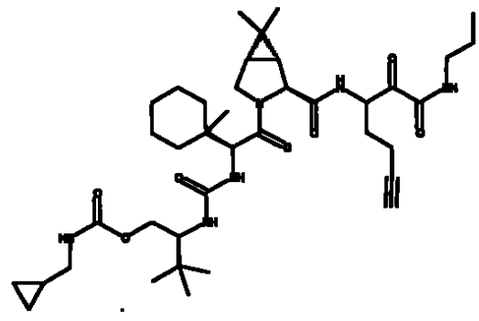


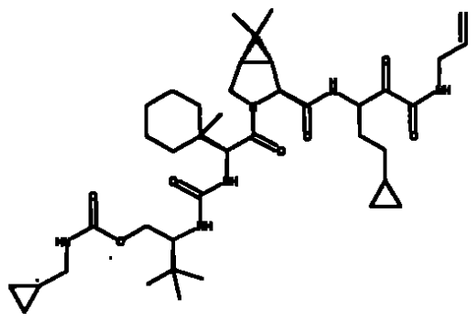


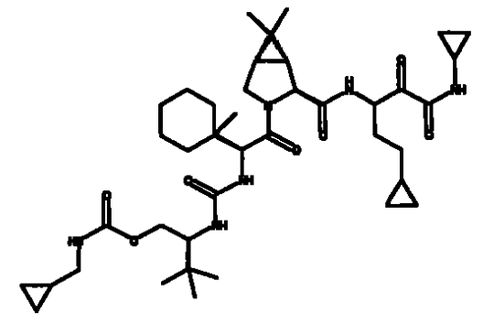












Tal como se usó anteriormente y a través de toda esta descripción, los siguientes términos, a menos que se indique lo contrario, se interpretarán con los siguientes significados:

"Paciente" incluye tanto a los seres humanos como a los animales.

"Mamífero" significa seres humanos y otros animales mamíferos.

"Alquilo" significa un grupo hidrocarbonado alifático que puede ser recto o ramificado y que comprende aproximadamente 1 hasta aproximadamente 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen aproximadamente 1 hasta aproximadamente 12 átomos de carbono en la cadena. Los grupos alquilo más preferidos contienen aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferiores tales como metilo, etilo o propilo, están unidos a una cadena alquilo lineal. "Alquilo inferior" significa un grupo que tiene aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recta o ramificada. El término "alquilo sustituido" significa que el grupo alquilo puede estar sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, y cada sustituyente está independientemente seleccionado del grupo que consiste en halo, alquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -N(alquilo)$_2$, carboxi y -C(O)O-alquilo. Ejemplos no limitativos de grupos alquilo apropiados incluyen metilo, etilo, n-propilo, isopropilo y t-butilo.

"Alquenilo" significa un grupo hidrocarbonado alifático que contiene por lo menos un doble enlace de carbono a carbono y que puede ser recto o ramificado y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena. Los grupos alquenilo preferidos tienen aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y más preferiblemente aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferiores tales como metilo, etilo o propilo están unidos a una cadena alquenilo lineal. "Alquenilo inferior" significa aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena, la cual puede ser recta o ramificada. El término "alquenilo sustituido" significa que el grupo alquenilo puede estar sustituido con uno o más sustituyentes que pueden ser iguales o

diferentes y cada sustituyente está independientemente seleccionado del grupo que consiste en halo, alquilo, arilo, cicloalquilo, ciano, alcoxi y -S(alquilo). Ejemplos no limitativos de grupos alquenilo apropiados incluyen etenilo, propenilo, *n*-butenilo, 3-metilbut-2-enilo, *n*-pentenilo, octenilo y decenilo.

"Alquinilo" significa un grupo hidrocarbonado alifático que contiene por lo menos un triple enlace de carbono a carbono y que puede ser recto o ramificado y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos tienen aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y más preferiblemente aproximadamente 2 hasta aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferiores tales como metilo, etilo o propilo están unidos a una cadena alquinilo lineal. "Alquinilo inferior" significa aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena, la cual puede ser recta o ramificada. Ejemplos no limitativos de dichos grupos alquinilo apropiados incluyen etinilo, propinilo, 2-butinilo y 3-metilbutinilo. El término "alquinilo sustituido" significa que el grupo alquinilo puede estar sustituido con uno o más sustituyentes que pueden ser iguales o diferentes y donde cada sustituyente está independientemente seleccionado del grupo que consiste en alquilo, arilo y cicloalquilo.

"Arilo" significa un sistema de anillo aromático monocíclico o multicíclico que comprende aproximadamente 6 hasta aproximadamente 14 átomos de carbono, preferiblemente aproximadamente 6 hasta aproximadamente 10 átomos de carbono. El grupo arilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillo" que puede ser iguales o diferentes y son tal como se definen aquí. Ejemplos no limitativos de grupos arilo apropiados incluyen fenilo y naftilo.

"Heteroarilo" significa un sistema de anillo monocíclico o multicíclico que comprende aproximadamente 5 hasta aproximadamente 14 átomos en el anillo, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, en los cuales uno o más de los átomos del anillo es un elemento distinto de carbono, por ejemplo, nitrógeno, oxígeno o azufre, solo o en combinación. Los heteroarilos preferidos contienen aproximadamente 5

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hasta aproximadamente 6 átomos en el anillo. El "heteroarilo" puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes y son tal como se han definido aquí. Los prefijos aza, oxa o tia antes del nombre de raíz heteroarilo significan que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente, está presente como átomo del anillo. Un átomo de nitrógeno de un heteroarilo puede estar opcionalmente oxidado al correspondiente N-óxido. Ejemplos no limitativos de heteroarilos apropiados incluyen piridilo, pirazinilo, furanilo, tienilo, pirimidinilo, piridona (incluyendo piridonas N-sustituidas), isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazanilo, pirrolilo, pirazolilo, triazolilo, 1,2,4-tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, oxindolilo, imidazo[1,2-a]piridinilo, imidazo[2,1-b]tiazolilo, benzofurazanilo, indolilo, azaindolilo, bencimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo y similares. El término "heteroarilo" se refiere también a porciones heteroarilo parcialmente saturadas tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares.

"Aralquilo" o "arilalquilo" significa un grupo aril-alquilo en el cual el arilo y el alquilo son tal como se han descripto previamente. Los aralquilos preferidos comprenden un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo apropiados incluyen bencilo, 2-fenetilo y naftalenilmetilo. El enlace con la porción principal es a través del alquilo.

"Alquilarilo" significa un grupo alquil-arilo en el cual el alquilo y el arilo son tal como se han descripto previamente. Los alquilarilos preferidos comprenden un grupo alquilo inferior. Un ejemplo no limitativo de un grupo alquilarilo apropiado es tolilo. El enlace con la porción principal es a través del arilo.

"Cicloalquilo" significa un sistema de anillo mono- o multicíclico no aromático que comprende aproximadamente 3 hasta aproximadamente 10 átomos de carbono, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos de carbono. Los anillos cicloalquilo preferidos contienen aproximadamente 5 hasta aproximadamente 7 átomos en el anillo. El cicloalquilo puede estar opcionalmente sustituido con uno o más

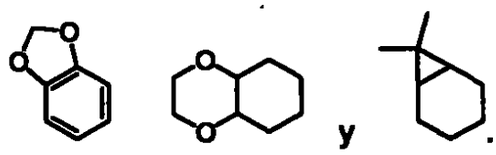
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"sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y son tal como se han definido anteriormente. Ejemplos no limitativos de cicloalquilos monocíclicos apropiados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Ejemplos no limitativos de cicloalquilos multicíclicos apropiados incluyen 1-decalinilo, norbornilo, adamantilo y similares, así como también las especies parcialmente saturadas tales como, por ejemplo, indanilo, tetrahidronaftilo y similares.

"Halógeno" o "halo" significa flúor, cloro, bromo o yodo. Se prefiere flúor, cloro y bromo.

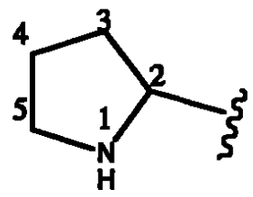
"Sustituyentes del sistema de anillo" significa un sustituyente unido a un sistema de anillo aromático o no aromático, el cual, por ejemplo, reemplaza un hidrógeno disponible en el sistema de anillo. Los sustituyentes del sistema de anillo pueden ser iguales o diferentes y cada uno está independientemente seleccionado del grupo que consiste en alquilo, alquenilo, alquinilo, arilo, heteroarilo, aralquilo, alquilarilo, heteroaralquilo, heteroarilalquenilo, heteroarilalquinilo, alquilheteroarilo, hidroxi, hidroxialquilo, alcoxi, ariloxi, aralcoxi, acilo, aroílo, halo, nitro, ciano, carboxi, alcoxicarbonilo, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsulfonilo, heteroarilsulfonilo, alquiltio, ariltio, heteroariltio, aralquiltio, heteroaralquiltio, cicloalquilo, heterociclilo, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH$(alquilo), Y_1Y_2N-, Y_1Y_2N-alquil-, $Y_1Y_2NC(O)-$, $Y_1Y_2NSO_2-$ y $-SO_2NY_1Y_2$, donde Y_1 e Y_2 pueden ser iguales o diferentes y están independientemente seleccionados del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo y aralquilo. "Sustituyente del sistema de anillo" puede significar también una porción única la cual reemplaza simultáneamente dos hidrógenos disponibles en dos átomos de carbono adyacentes (un H en cada carbono) en un sistema de anillo. Ejemplos de dicha porción son metilendioxi, etilendioxi, $-C(CH_3)_2-$ y similares que forman porciones tales como, por ejemplo:



"Heterociclilo" significa un sistema de anillo monocíclico o multicíclico no aromático saturado que comprende aproximadamente 3 hasta aproximadamente 10 átomos en el anillo, preferiblemente aproximadamente 5

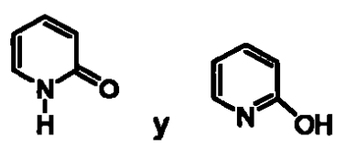
hasta aproximadamente 10 átomos en el anillo, en el cual uno o más de los átomos del sistema de anillo es un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, solos o en combinación. No hay ningún átomo de oxígeno y/o azufre adyacente presente en el sistema de anillo. Los heterociclilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. Los prefijos aza, oxa o tia antes del nombre de raíz heterociclilo significan que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente están presentes como átomo de un anillo. Cualquier -NH en un anillo heterociclilo puede existir protegido tal como por ejemplo un grupo -N(Boc), -N(CBz), -N(Tos) y similares; dichas protecciones se consideran también partes de esta invención. El heterociclilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes y que son tal como se definen aquí. El átomo de nitrógeno o azufre del heterociclilo puede estar opcionalmente oxidado al correspondiente N-óxido, S-óxido o S,S-dióxido. Ejemplos no limitativos de anillos de heterociclilo monocíclicos apropiados incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona y similares.

Cabe observar que en los sistemas de anillo que contienen heteroátomos, de esta invención, no hay ningún grupo hidroxilo en los átomos de carbono adyacente a N, O o S, como así tampoco a ningún grupo N o S en el carbono adyacente a otro heteroátomo. Por lo tanto, por ejemplo, en el anillo:



no hay ningún -OH unido directamente a los carbonos marcados 2 y 5.

Cave observar también que las formas tautoméricas tales como, por ejemplo, las porciones:



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se consideran equivalentes en ciertas realizaciones de esta invención.

"Alquinilalquilo" significa un grupo alquinil-alquil- en el cual el alquinilo y el alquilo son tal como se han descripto previamente. Los alquinilalquilos preferidos contienen un grupo alquinilo inferior y un grupo alquilo inferior. El enlace con la porción principal es a través del alquilo. Ejemplos no limitativos de grupos alquinilalquilo apropiados incluyen propargilmetilo.

"Heteroaralquilo" significa un grupo heteroaril-alquil- en el cual el heteroarilo y el alquilo son tal como se han descripto previamente. Los heteroaralquilos preferidos contienen un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo apropiados incluyen piridilmetilo y quinolin-3-ilmetilo. El enlace con la porción principal se efectúa a través del alquilo.

"Hidroxialquilo" significa un grupo HO-alquil- en el cual el alquilo es tal como se ha definido previamente. Los hidroxialquilos preferidos contienen alquilo inferior. Ejemplos no limitativos de grupos hidroxialquilo apropiados incluyen hidroximetilo y 2-hidroxietilo.

"Acilo" significa un grupo H-C(O)-, alquil-C(O)- o cicloalquil-C(O)-, en el cual los varios grupos son tal como se han descripto previamente. Este enlace con la porción principal es a través del carbonilo. Los acilos preferidos contienen un alquilo inferior. Ejemplos no limitativos de grupos acilo apropiados incluyen formilo, acetilo y propanoílo.

"Aroílo" significa un grupo aril-C(O)- en el cual el grupo arilo es tal como se ha descripto previamente. El enlace con la porción principal es a través del carbonilo. Ejemplos no limitativos de grupos apropiados incluyen benzoílo y 1-naftoílo.

"Alcoxi" significa un grupo alquil-O- en el cual el grupo alquilo es tal como se ha descripto previamente. Ejemplos no limitativos de grupos alcoxi apropiados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi. El enlace con la porción principal es a través del oxígeno del éter.

"Ariloxi" significa un grupo aril-O- en el cual el grupo arilo es tal como se ha descripto previamente. Ejemplos no limitativos de grupos ariloxi apropiados incluyen fenoxi y naftoxi. El enlace con la porción principal es a través del oxígeno del éter.

"Aralquiloxi" significa un grupo aralquil-O- en el cual el grupo aralquilo es tal como se ha descripto previamente. Ejemplos no limitativos de grupos

aralquiloxi apropiados incluyen benciloxi y 1- o 2-naftalenmetoxi. El enlace con la porción principal es a través del oxígeno del éter.

"Alquiltio" significa un grupo alquil-S- en el cual el grupo alquilo es tal como se ha descripto previamente. Ejemplos no limitativos de grupos alquiltio apropiados incluyen metiltio y etiltio. El enlace con la porción principal es a través del azufre.

"Ariltio" significa un grupo aril-S- en el cual el grupo arilo es tal como se ha descripto previamente. Ejemplos no limitativos de grupos ariltio apropiados incluyen feniltio y naftiltio. El enlace con la porción principal es a través del azufre.

"Aralquiltio" significa un grupo aralquil-S- en el cual el grupo aralquilo es tal como se ha descripto previamente. Un ejemplo no limitativo de un grupo aralquiltio apropiado es benciltio. El enlace con la porción principal es través del azufre.

"Alcoxicarbonilo" significa un grupo alquil-O-CO-. Ejemplos no limitativos de grupos alcoxicarbonilo apropiados incluyen metoxicarbonilo y etoxicarbonilo. El enlace con la porción principal es través del carbonilo.

"Ariloxicarbonilo" significa un grupo aril-O-C(O)-. Ejemplos no limitativos de grupos ariloxicarbonilo apropiados incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace con la porción principal es través del carbonilo.

"Aralcoxicarbonilo" significa un grupo aralquil-O-C(O)-. Un ejemplo no limitativo de un grupo aralcoxicarbonilo apropiado es benciloxicarbonilo. El enlace con la porción principal es través del carbonilo.

"Alquilsulfonilo" significa un grupo alquil-S(O_2)-. Los grupos preferidos son aquellos en los cuales el grupo alquilo es alquilo inferior. El enlace con la porción principal es a través del sulfonilo.

"Arilsulfonilo" significa un grupo aril-S(O_2)-. El enlace con la porción principal es a través del sulfonilo.

El término "sustituido" significa que uno o más hidrógenos en el átomo designado están reemplazados con una selección del grupo indicado, con la condición de no exceder la valencia normal del átomo designado bajo las circunstancias existentes, y que la sustitución proporcione un compuesto estable. Las combinaciones de sustituyentes y/o variables son permisibles únicamente si dichas combinaciones proveen compuestos estables. Mediante

"compuesto estable" o "estructura estable" se indica un compuesto que es suficientemente fuerte para sobrevivir al aislamiento hasta un grado de pureza útil a partir de una mezcla de reacción y su formulación en un agente terapéutico eficaz.

El término "uno o más" o "por lo menos uno", cuando se indica la cantidad de sustituyentes, compuestos, agentes de combinación y similares, se refiere a por lo menos uno y hasta una cantidad máxima de sustituyentes, compuestos, agentes de combinación y similares química y físicamente permisibles, que están presentes o que se agregan, dependiendo del contexto. Dichas técnicas y conocimientos son bien conocidos por los expertos en la materia.

El término "opcionalmente sustituido" significa una sustitución opcional con los grupos radicales o porciones especificadas.

El término "aislado" o "en forma aislada" para un compuesto se refiere al estado físico de dicho compuesto después de ser aislado a partir de un procedimiento de síntesis o de una fuente natural o combinación de los mismos. El término "purificado" o "en forma purificada " para un compuesto se refiere al estado físico de dicho compuesto después de haber sido obtenido mediante un procedimiento o procedimientos de purificación descriptos aquí o bien conocidos por un experto en la materia, con una pureza suficiente para ser caracterizable mediante técnicas analíticas convencionales aquí descriptas o bien conocidas por los expertos en la materia.

Cabe observar que cualquier heteroátomo con valencias insatisfechas en el texto, esquemas, ejemplos y Tablas presentes se considera que tiene átomos de hidrógeno para satisfacer las valencias.

Cuando un grupo funcional en un compuesto se denomina "protegido", esto significa que el grupo está en una forma modificada que evita reacciones secundarias indeseables en el sitio protegido cuando el compuesto es sometido a una reacción. Los grupos protectores apropiados serán reconocidos por los expertos en la materia así como también por las referencias en los libros de texto convencionales, tales como, por ejemplo, T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

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Cuando cualquier variable (por ejemplo, arilo, heterociclo, R^2, etc.) ocurre más de una vez en cualquier constituyente o en la Fórmula 1, su definición cada vez que ocurre es independiente de su definición cada vez que debe ocurrir.

Tal como se usa aquí, el término "composición" abarca un producto que comprende los ingredientes especificados en las cantidades especificadas, así como también cualquier producto resulte, directa o indirectamente, de la combinación de los ingredientes especificados en las cantidades especificadas.

Los profármacos y solvatos de los compuestos de la invención están también contemplados aquí. El término "profármaco" tal como se emplea aquí denota un compuesto que es precursor de un fármaco, el cual por administración o sujeto, sufre una conversión química por procedimientos metabólicos o químicos que proporcionan un compuesto de Fórmula 1 o una sal y/o solvato del mismo. Una discusión de los profármacos se provee en T. Higuchi y V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, que se incorporan aquí como referencia.

"Solvato" significa una asociación física de un compuesto de esta invención con una o más moléculas de solvente. Esta asociación física involucra varios grados de unión iónica y covalente que incluye unión de hidrógeno. En algunos casos el solvato será capaz de aislación, por ejemplo cuando se incorporan una o más moléculas de solvente en el retículo cristalino del sólido cristalino. "Solvato" abarca tanto los solvatos en fase de solución como los aislables. Ejemplos no limitativos de solvatos apropiados incluyen etanolatos, metanolatos, y similares. "Hidrato" es un solvato en el cual la molécula de solvente es H_2O.

"Cantidad eficaz" o "cantidad terapéuticamente eficaz" describe una cantidad de compuesto o una composición de la presente invención que es eficaz para inhibir los CDK(s) y por lo tanto para producir el efecto terapéutico, mejorador, inhibidor o preventivo deseado.

Los compuestos de la Fórmula 1 pueden formar sales que están también dentro del alcance de esta invención. La referencia a un compuesto

de Fórmula I aquí se interpreta incluyendo referencias a las sales del mismo, a menos que se indique lo contrario. Los términos "sales", tal como se emplean aquí, denotan sales ácidas formadas con ácidos inorgánicos y/o orgánicos, así como también sales básicas formadas con bases inorgánicas y/o orgánicas. Además, cuando un compuesto de Fórmula 1 contiene tanto una porción básica tal como pero sin limitarla a una piridina o imidazol, y una porción ácida tal como pero sin limitarla a un ácido carboxílico, pueden formarse zwitteriones ("sales internas") y se incluirán dentro del término "sales" tal como se usa aquí. Se prefieren las sales farmacéuticamente aceptables (es decir., no tóxicas, fisiológicamente aceptables), aunque también son útiles otras sales. Las sales de los compuestos de la Fórmula I pueden formarse por ejemplo por reacción de un compuesto de Fórmula I con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como aquel en el cual se precipita la sal o en un medio acuoso seguido de liofilización.

Ejemplos de sales de adición de ácido incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, fumaratos, clorhidratos, bromhidratos, iodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartratos, tiocianatos, toluensulfonatos (conocidos también como tosilatos,) y similares. Adicionalmente, los ácidos que generalmente se consideran apropiados para la formación de sales farmacéuticamente útiles a partir de compuestos farmacéuticos básicos han sido discutidos por ejemplo por P. Stahl *et al*, Camille G. (eds.) *Handbook of Pharmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al*, *The Practice of Medicinal Chemistry* (1996), Academic Press, New York; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. en sitio de la red). Estas descripciones se incorporan aquí como referencia.

Ejemplos de sales básicos incluyen sales de amonio, sales de metales alcalinos, tales como sales de sodio, litio y potasio, sales de metales alcalinotérreos, tales como sales de calcio y magnesio, sales con bases

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orgánicas (por ejemplo, aminas orgánicas) tales como diciclohexilaminas, t-butil aminas, y sales con amino ácidos tales como arginina, lisina, y similares. Los grupos básicos que contienen nitrógeno pueden cuaternizarse con agentes tales como haluros de alquilo inferior (por ejemplo. cloruros, bromuros y ioduros de metilo, etilo y butilo), sulfatos de dialquilo (por ejemplo sulfatos de dimetilo, dietilo y dibutilo), haluros de cadena larga (por ejemplo cloruros, bromuros y ioduros de decilo, laurilo y estearilo), haluros de aralquilo (por ejemplo bromuros de bencilo y fenetilo), y otros.

Todas dichas sales ácidas y sales básicas son sales farmacéuticamente aceptables dentro del alcance de la invención y todas las sales ácidas y básicas se consideran equivalentes a las formas libres de los compuestos correspondientes para los propósitos de la invención.

Los ésteres farmacéuticamente aceptables de los presentes compuestos incluyen los grupos siguientes: (1) ésteres de ácido carboxílico obtenidos por esterificación de los grupos hidroxi, en los cuales la porción no carbonilo de la porción de ácido carboxílico de la agrupación éster está seleccionada entre alquilo de cadena larga o ramificada (por ejemplo, acetilo, n-propilo, t-butilo, o n-butilo), alcoxialquilo (por ejemplo, metoximetilo), aralquilo (por ejemplo, bencilo), ariloxialquilo (por ejemplo fenoximetilo), arilo (por ejemplo fenilo opcionalmente sustituido con por ejemplo halógeno, alquiloC_{1-4}, o alcoxiC_{1-4} o amino); (2) ésteres de sulfato de tales como alquil- o aralquilsulfonilo (por ejemplo, metansulfonilo); (3) ésteres de amino ácido (por ejemplo, L-valilo o L-isoleucilo); (4) ésteres de fosfonato y (5) ésteres de mono-, di- o trifosfato. Los ésteres de fosfato pueden estar adicionalmente esterificados con, por ejemplo, alcohol C_{1-20} o con un derivado reactivo del mismo, o con un 2,3-diacilo(C_{6-24}) glicerol.

Los compuestos de la Fórmula 1, y las sales, solvatos, ésteres y profármacos de los mismos, pueden existir en su forma tautomérica (por ejemplo, en forma de una amida o imino éter). Todas dichas formas tautoméricas están contempladas aquí como parte de la presente invención.

Todos los estereoisómeros (por ejemplo, los isómeros geométricos, los isómeros ópticos y similares) de los presentes compuestos (incluyendo aquellos de las sales, solvatos y profármacos de los compuestos así como también de las sales y solvatos de los profármacos), tal como los que pueden

existir debido a carbonos asimétricos en varios sustituyentes, incluyendo las formas enantioméricas (que pueden existir incluso en ausencia de carbonos asimétricos), las formas rotaméricas, atropisómeros, y las formas diastereoméricas, están contempladas dentro del alcance de esta invención así como también los isómeros posicionales (tales como, por ejemplo, 4-piridilo y 3-piridilo). Los estereoisómeros individuales de los compuestos de la invención pueden, por ejemplo, estar sustancialmente libres de otros isómeros, o pueden mezclarse por ejemplo como racematos o con todos los otros o con otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R tal como ha sido definida por las recomendaciones *IUPAC* 1974. El uso de los términos "sal", "solvato" "profármaco" y similares, se da para aplicarlo igualmente a la sal, el solvato y el profármaco de los enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros posicionales, racematos o profármacos de los compuestos de la invención.

Las formas polimórficas de los compuestos de la Fórmula I, y de las sales, solvatos, ésteres y profármacos de los compuestos de la Fórmula I, se quieren incluir en la presente invención.

Debe entenderse que la utilidad de los compuestos de la Fórmula 1 para las aplicaciones terapéuticas que se discuten aquí, es aplicable a cada compuesto por sí mismo o a la combinación o las combinaciones de uno o más compuestos de la Fórmula 1 tal como se ilustra, por ejemplo, en el párrafo inmediatamente siguiente. La interpretación se aplica también en las composiciones farmacéuticas que comprenden dicho compuesto o compuestos y a los métodos de tratamiento que involucran dicho compuesto o compuestos.

Los compuestos de acuerdo con la invención pueden tener propiedades farmacológicas; en particular, los compuestos de la Fórmula 1 pueden ser inhibidores de la proteasa de HCV, cada compuesto por sí mismo o uno o más compuestos de Fórmula 1 pueden combinarse con uno o más compuestos seleccionados de la Fórmula 1. Los compuestos pueden ser útiles para el tratamiento de enfermedades tales como por ejemplo HCV, HIV, (SIDA, Síndrome de Inmuno Deficiencia Adquirida), y desórdenes relacionados así como también para modular la actividad de la proteasa del

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virus de la hepatitis C (HCV) prevenir el HCV, o mejorar uno o más síntomas de la hepatitis C.

Los compuestos de la Fórmula 1 pueden usarse para la manufactura de un medicamento para tratar desórdenes asociados con la proteasa HCV, por ejemplo el método que comprende poner en contacto íntimo un compuesto de la Fórmula 1 y un portador farmacéuticamente aceptable.

En otra realización, esta invención provee composiciones farmacéuticas que comprenden compuesto o compuestos de la invención como ingrediente activo. Las composiciones farmacéuticas comprenden en general adicionalmente por lo menos un diluyente portador, excipiente o portador farmacéuticamente aceptable (denominados colectivamente aquí materiales portadores). Debido a su actividad inhibidora de HCV, dichas composiciones farmacéuticas poseen utilidad en el tratamiento de la hepatitis C y desórdenes relacionados.

En otra realización más, 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 típicamente se *administrarán en mezcla con materiales portadores apropiados* convenientemente seleccionados con respecto a la forma de administración propuesta es decir, tabletas orales, cápsulas (que pueden ser de relleno sólido, de relleno semi-sólido o de relleno líquido), polvos para ser reconstituidos, geles orales, elixires, gránulos dispersables, jarabes, suspensiones y *similares*, y *coherentes con las prácticas farmacéuticas* convencionales. Por ejemplo, para la administración oral en forma de tabletas o cápsulas, el componente de droga activa puede combinarse con cualquier portador inerte no tóxico, oral, farmacéuticamente aceptable tal como la lactosa, almidón, sucrosa, celulosa, estearato de magnesio, fosfato dicálcico, sulfato dicálcico, talco, *mannitol*, alcohol etílico (*formas líquidas*) y *similares*. Además, cuando se desea o es necesario, pueden incorporarse también a la mezcla aglutinantes, lubricantes, agentes desintegrantes y agentes colorantes apropiados. Los polvos y tabletas pueden estar comprendidos dentro de aproximadamente 5 hasta aproximadamente 95 por ciento en peso de la composición de la invención.

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Los aglutinantes apropiados incluyen almidón, gelatina, azúcares naturales, maíz, edulcorantes, gomas naturales y sintéticas tales como acacia, alginato de sodio, carboximetilcelulosa, polietilen glicol y ceras. Entre los lubricantes pueden mencionarse para ser usados en estas formas de dosificación ácido bórico, benzoato de sodio, acetato de sodio, cloruro de sodio y similares. Los desintegrantes incluyen almidón, metil celulosa, goma guar y similares.

También pueden incluirse cuando es necesario agentes edulcorantes, saborizantes y preservadores. Algunos de los términos indicados anteriormente, es decir desintegrantes, diluyentes, lubricantes, aglutinantes y similares, se discuten en forma más detallada a continuación.

Adicionalmente, las composiciones de la presente invención pueden formularse en formas de liberación sostenida para proveer el régimen de liberación controlada de uno o más de los componentes o ingredientes activos, para optimizar los efectos terapéuticos, es decir la actividad inhibidora de HCV y similares. Las formas de dosificación apropiadas para la liberación sostenida incluyen tabletas en capas que contienen capas de varios regímenes de desintegración o matrices poliméricas de liberación controlada impregnadas con los componentes activos y configurados en forma de tabletas o cápsulas que contienen dichas matrices poliméricas porosas impregnadas o encapsuladas. Las formas de preparación líquida incluyen soluciones, suspensiones y emulsiones. Como ejemplo pueden mencionarse agua o soluciones de agua-propilen glicol para inyecciones parenterales o para adición de edulcorantes y plastificantes para soluciones, suspensiones y emulsiones orales. Las preparaciones de forma líquida pueden incluir también soluciones para administración intranasal.

Las preparaciones en aerosol apropiadas para inhalación pueden incluir soluciones y sólidos en forma de polvos, los cuales pueden estar combinados con un portador farmacéuticamente aceptable tal como gas comprimido inerte, por ejemplo, nitrógeno.

Para preparar supositorios, una cera de bajo punto de fusión tal como una mezcla de glicéridos de ácido graso tales como manteca de cacao se funde primero, y el ingrediente activo se dispersa homogéneamente a diferente agitación o por mezcla similar. La mezcla homogénea fundida se

vierte luego en moldes del tamaño conveniente para permitir que se enfríen y que por lo tanto se solidifiquen.

Asimismo se incluyen las preparaciones de forma sólida que están destinadas a convertirse, poco tiempo antes de uso, a preparaciones de forma líquida para administración oral o parenteral. Dichas formas líquidas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención pueden liberarse transdérmicamente. Las composiciones transdérmicas pueden tener la forma de cremas, lociones, aerosoles y/o emulsiones y pueden incluirse en un parche transdérmico del tipo de matriz o reservorio que son convencionales en el arte para este propósito. Los compuestos de la invención pueden administrarse también por vía oral, intravenosa, intranasal o subcutánea.

Los compuestos de la invención pueden comprender también preparaciones que están en una forma de dosificación unitaria. En tal forma, la preparación se subdivide en dosis unitarias de un tamaño apropiado que contienen las cantidades apropiadas de los componentes activos, por ejemplo una cantidad eficaz para lograr el propósito deseado.

La cantidad de la composición activa de la invención en una dosis unitaria de preparación puede generalmente variar o puede ajustarse desde aproximadamente 1,0 miligramos hasta aproximadamente 1000 miligramos, preferiblemente desde aproximadamente 1,0 hasta aproximadamente 950 miligramos, más preferiblemente desde aproximadamente 1,0 hasta aproximadamente 500 miligramos, y típicamente desde aproximadamente 1 hasta aproximadamente 250 miligramos, de acuerdo con la aplicación particular. La dosis real empleada puede variar dependiendo de la edad del paciente, el sexo, el peso y la gravedad de la afección que se está tratando. Dichas técnicas son bien conocidas por los expertos en la materia.

En general, la forma de dosificación oral humana que contiene los ingredientes activos pueden administrarse 1 o 2 veces por día. La cantidad y frecuencia de la administración se regularán de acuerdo con la opinión del médico de cabecera. Un régimen de dosificación diaria generalmente recomendado para la administración oral puede estar en un rango de aproximadamente 1,0 miligramos hasta aproximadamente 1.000 miligramos por día, en dosis simples o divididas.

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Algunos términos útiles se describen a continuación:

Cápsula – se refiere a un recipiente o contenedor que está hecho de metil celulosa, alcoholes polivinílicos o gelatinas desnaturalizadas o almidón para sostener o contener composiciones que comprenden los ingredientes activos. Las cápsulas de cáscara dura están típicamente hechas a partir de mezclas de gelatinas de piel y hueso de cerdo de alta resistencia gelificante. La cápsula misma puede contener pequeñas cantidades de colorantes, agentes opacantes, plastificantes y preservadores.

Tableta – se refiere a una forma de dosificación sólida comprimida o moldeada que contiene los ingredientes activos con diluyentes apropiados. La tableta puede prepararse por compresión de mezclas o granulaciones obtenidas por granulación en húmedo, granulación en seco o por compactación.

Gel Oral – se refiere a los ingredientes activos dispersados o solubilizados en una matriz semisólido hidrofílica.

Polvo para ser reconstituido se refiere a mezclas de polvo que contienen los ingredientes activos y diluyentes apropiados que pueden estar suspendidos en agua o jugos.

Diluyente – se refiere a sustancias que usualmente constituyen la porción principal de la composición o forma de dosificación. Los diluyentes apropiados incluyen azúcares tales como lactosa, sucrosa, mannitol y sorbitol; almidones derivados de trigo, maíz, arroz y papa; y celulosas tales como celulosa microcristalina. La cantidad de diluyente en la composición puede estar en un rango de desde aproximadamente 10 hasta aproximadamente 90% en peso de la composición total, preferiblemente desde aproximadamente 25 hasta aproximadamente 75%, más preferiblemente desde aproximadamente 30 hasta aproximadamente 60%, y aún más preferiblemente desde aproximadamente 12 hasta aproximadamente 60%.

Desintegrante – se refiere a materiales agregados a la composición para ayudarla a descomponerse (desintegrarse), y liberar los medicamentos. Los desintegrantes apropiados incluyen almidones; almidones modificados "solubles en agua" tales como almidón de carboximetil sodio, gomas naturales y sintéticas tales como de harina de algarrobo, karaya, guar,

tragacanto y agar; derivados de celulosa tales como metilcelulosa y carboximetilcelulosa de sodio; celulosas microcristalinas; y celulosas microcristalinas entrecruzadas tales como croscarmelosa de sodio; alginatos tales como ácido algínico y alginato de sodio; arcillas tales como bentonitas; y mezclas efervescentes.. La cantidad de desintegrante en la composición puede estar en un rango de desde aproximadamente 2 hasta aproximadamente 15% en peso de la composición, más preferiblemente desde aproximadamente 4 hasta aproximadamente 10% en peso.

Aglutinante – se refiere a sustancias que aglutinan o "pegan" polvos entre sí y que los hacen cohesivos mediante la formación de gránulos, por lo cual sirven "adhesivo" en la formulación. Los aglutinantes agregan resistencia cohesiva ya disponible en el agente diluyente o dador de volumen. Los aglutinantes apropiados incluyen azúcares tales como sucrosa; almidones derivados de de trigo, maíz, arroz papa; gomas naturales tales como acacia, gelatina y tragacanto, derivados de algas tales como ácido algínico, alginato de sodio y alginato de amonio calcio; materiales celulósicos tales como metilcelulosa y carboximetilcelulosa de sodio e hidroxipropilmetilcelulosa; polivinilpirrolidona; e inorgánicos tales como silicato de magnesio aluminio. La cantidad de aglutinante en la composición puede estar en un rango de desde aproximadamente 2 hasta aproximadamente 20% en peso de la composición, más preferiblemente de aproximadamente 3 hasta aproximadamente 10% en peso, y aún más preferiblemente de aproximadamente 3 hasta aproximadamente 6% en peso Lubricantes – se refiere a una sustancia agregada a la forma de dosificación para permitir que la tableta gránulos, etc. después de haber sido comprimidos, se liberen del molde o matriz reduciendo la fricción o desgaste. Los lubricantes apropiados incluyen estearatos metálicos, tales como estearato de magnesio, estearato de calcio o estearato de potasio; ácido esteárico; ceras de alto punto de fusión; y lubricantes solubles en agua tales como cloruro de sodio, benzoato de sodio, acetato de sodio, oleato de sodio, polietilen glicoles, y d'l-leucina. Los lubricantes se agregan usualmente en la última etapa antes de la compresión, debido a que deben estar presentes en las superficies de los gránulos y entre las mismas y las partes de la prensa tabletas. La cantidad de lubricante en la composición puede estar en un rango de desde aproximadamente 0.2 hasta

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aproximadamente 5% en peso de la composición, preferiblemente desde aproximadamente 0.5 hasta aproximadamente 2%, más preferiblemente desde aproximadamente 0.3 hasta aproximadamente 1,5% en peso.

Deslizante – material que evita el aterronamiento y que mejora las características de flujo de las granulaciones de manera que el flujo es liso y uniforme. Los deslizantes apropiados incluyen dióxido de silicio y talco. La cantidad de deslizante en la composición puede estar en un rango de desde aproximadamente 0,1% hasta aproximadamente 5% en peso de la composición total, preferiblemente desde aproximadamente 0,5 hasta aproximadamente 2% en peso.

Agentes Colorantes - excipientes que proveen coloración para la composición o la forma de dosificación. Dichos excipientes pueden incluir colorantes de calidad alimenticia y colorantes de calidad alimenticia adsorbidos en un adsorbente apropiado tal como arcilla u óxido de aluminio. La cantidad de agente colorante puede estar comprendida entre desde aproximadamente 0,1 hasta aproximadamente 5% en peso de la composición, preferiblemente desde aproximadamente 0,1 hasta aproximadamente 1%.

Biodisponibilidad – se refiere al régimen y grado hasta el cual se absorbe el ingrediente de droga activa o porción terapéutica dentro de la circulación sistémica a partir de la forma de dosificación administrada, en comparación con un modelo o control.

Los métodos convencionales para preparar tabletas son conocidos. Dichos métodos incluyen métodos en seco tales como compresión directa y compresión de granulación reducida por compactación, o métodos en húmedo u otros procedimientos especiales. Los métodos convencionales para preparar otras formas de administración tales como por ejemplo cápsulas, supositorios y similares son también muy conocidos.

Otra realización de la invención describe el uso de los compuestos de la invención o de las composiciones farmacéuticas descriptas anteriormente para el tratamiento de enfermedades tales como, por ejemplo hepatitis C y similares. El método comprende administrar una cantidad terapéuticamente eficaz del compuesto de la invención o de la composición farmacéutica, a un

paciente que tiene dicha enfermedad o enfermedades y que necesita dicho tratamiento.

En otra realización los compuestos de la invención pueden usarse para el tratamiento de HCV en seres humanos en modo de monoterapia o en una terapia de combinación (por ejemplo., combinación dual, combinación triple etc.), modos tales como por ejemplo, en combinación con agentes antivirales y/o inmunomoduladores. Ejemplos de dichos agentes antivirales y/o inmunomoduladores incluyen Ribavirin (de Schering-Plough Corporation, Madison, New Jersey) y Levovirin™ (de ICN Pharmaceuticals, Costa Mesa, California), VP 50406™ (de Viropharma, Incorporated, Exton, Pennsylvania), ISIS 14803™ (de ISIS Pharmaceuticals, Carlsbad, California), Heptazyme™ (de Ribozyme Pharmaceuticals, Boulder, Colorado), VX 497™ (de Vertex Pharmaceuticals, Cambridge, Massachusetts), Thymosin™ (de SciClone Pharmaceuticals, San Mateo, California), Maxamine™ (Maxim Pharmaceuticals, San Diego, California), micofenolato mofetil (de Hoffman-LaRoche, Nutley, New Jersey), interferon (tales como, por ejemplo, interferon-alfa; conjugados de PEG-interferon alfa) y similares. "Conjugados de PEG-interferon alfa" son moléculas de interferon alfa covalentemente unidas a una molécula de PEG. Entre los conjugados ilustrativos de PEG-interferon alfa se incluyen interferon alfa-2a (Roferon™, de Hoffman La-Roche, Nutley, New Jersey) en forma de interferon alfa-2a pegilado (por ejemplo., tal como el comercializado bajo la denominación Pegasys™), en forma de interferon alfa-2b pegilado (por ejemplo como el comercializado bajo la denominación (Intron™, de Schering-Plough Corporation) en la forma de interferon alfa-2b pegilado (por ejemplo como el comercializado bajo la denominación PEG-Intron™), interferon alfa-2c (Berofor Alpha™ de Boehringer Ingelheim, Ingelheim, Alemania) o interferon de consenso tal como el definido por determinación de una secuencia de consenso de interferon alfa que ocurren en forma natural (Infergen™, de Amgen, Thousand Oaks, California).

Tal como se manifestó anteriormente, la invención incluye también tautómeros, rotámeros, enantiómeros y otros estereoisómeros de los compuestos de la invención. Por lo tanto, tal como un experto en la materia puede apreciar algunos de los compuestos de la invención pueden existir en

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formas isoméricas apropiadas. Dichas variaciones están contempladas dentro del alcance de la invención.

Otra realización de la invención describe un método para preparar los compuestos descriptos aquí. Los compuestos pueden prepararse por varias técnicas conocidas en el arte. Procedimientos ilustrativos son los que se señalan en los siguientes esquemas de reacción. Las ilustraciones no deberían considerarse limitativas del alcance de la invención, la cual se define en las reivindicaciones anexas. Las vías mecánicas alternativas y las estructuras análogas resultarán aparentes para los expertos en la materia.

Debe entenderse que aunque los siguientes esquemas ilustrativos describen la preparación de unos pocos compuestos representativos de la invención, la sustitución apropiada de uno cualquiera de ambos amino ácidos, el natural y el no natural, dará como resultado la formación del compuesto deseado en base a dicha sustitución. Dichas variaciones están contempladas dentro del alcance de la invención.

Para los procedimientos descriptos a continuación, se usan las abreviaturas siguientes:

Abreviaturas

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

THF: Tetrahidrofurano

DMF: N,N-Dimetilformamida

EtOAc: Acetato de etilo

AcOH: Acido 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'-(Azodicarboxil)dipiperidina

DEAD: Dietilazodicarboxilato

MeOH: Metanol

EtOH: Etanol

Et_2O: Dietil éter

DMSO: Dimetilsulfóxido

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HOBt: N-Hidroxibenzotriazol

PyBrOP: Hexafluorfosfato de Bromo-tris-pirrolidinofosfonio

DCM: Diclorometano

DCC: 1,3-Diciclohexilcarbodiimida

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

Phg: Fenilglicina

Chg: Ciclohexilglicina

Bn: Bencilo

Bzl: Bencilo

Et: Etilo

Ph: Fenilo

IBoc: isobutoxicarbonilo

IPr: isopropilo

^{t}Bu o Bu^{t}: ter-Butilo

Boc: ter-Butiloxicarbonilo

Cbz: Benciloxicarbonilo

Cp: Ciclopentildienilo

Ts: p-toluensulfonilo

Me: Metilo

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

DMAP: 4-N,N-Dimetilaminopiridina

BOP: Hexafluorfosfato de Benzotriazol-1-il-oxi-tris(dimetilamino)

PCC: Clorocromato de piridinio

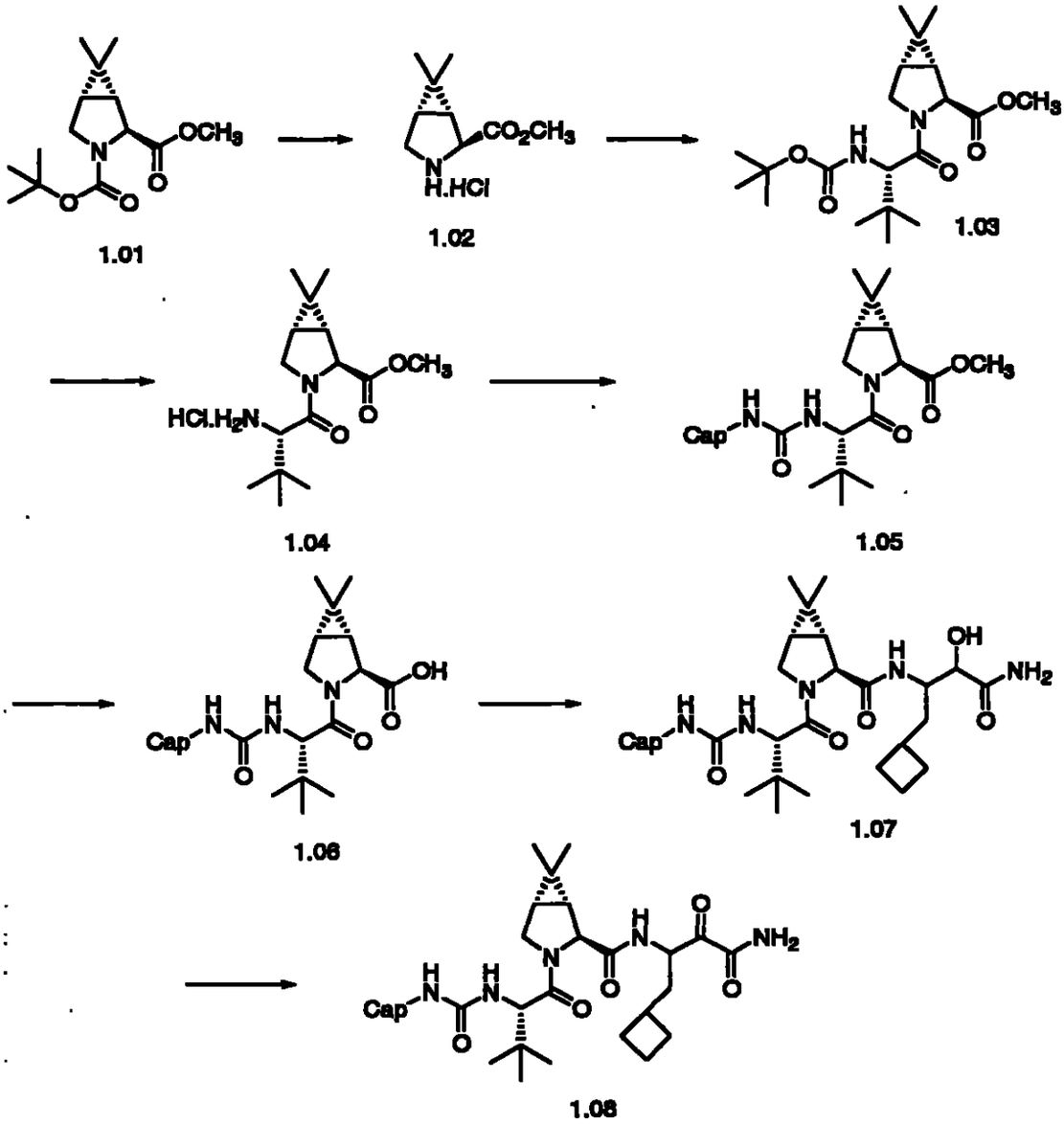
Esquemas Generales para la Preparación de los Compuestos Objetivo

Los compuestos de la presente invención se sintetizaron usando los esquemas generales (Métodos A-E) descriptos a continuación.

Método A:

La desprotección de la funcionalidad N-Boc de 1.01 bajo condiciones ácidas proporcionó la sal de clorhidrato 1.02 la cual se acopló subsguientemente con N-Boc-ter-leucina bajo metodología de acoplamiento peptídico para proporcionar 1.03. La desprotección N-Boc seguida de tratamiento con el isocianato apropiado proporcionó la urea 1.05. La hidrólisis

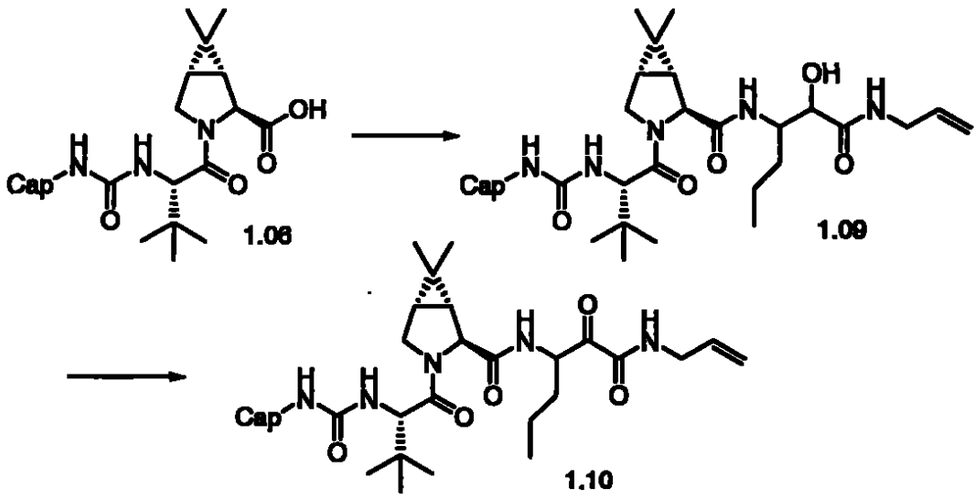
del éster metílico proporcionó el ácido 1.06. El acoplamiento peptídico del ácido 1.06 con la porción amida primaria P_1-P' apropiada, proporcionó la hidroxil amida 1.07. Oxidación (Moffatt o procesos relacionados - T.T.Tidwell, *Synthesis*, **1990**, 857; o Dess-Martin's – *J. Org. Chem.*, **1983**, *48*, 4155) dieron como resultado el compuesto objetivo 1.08.



1.01 1.02 1.03 1.04 1.05 1.06 1.07 1.08

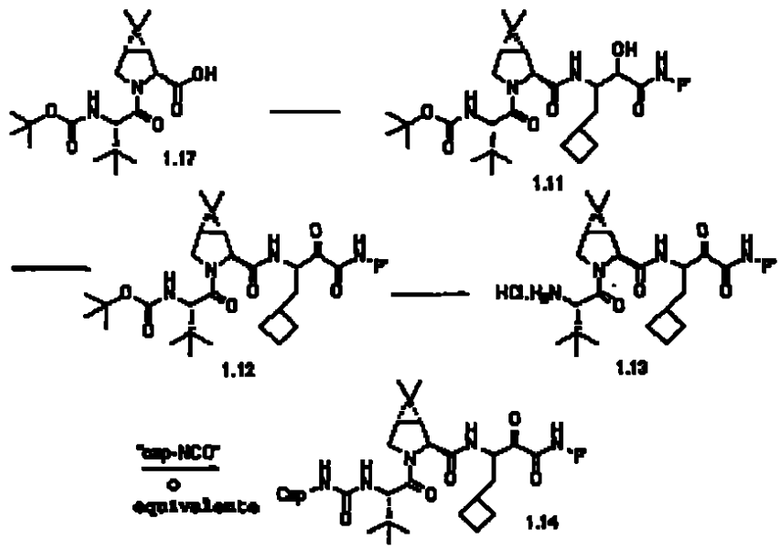
Método B

El acoplamiento peptídico del ácido 1.06 con la porción amida secundaria P_1-P' apropiada proporcionó la hidroxil amida 1.09. La oxidación (Moffatt o Dess-Martin's) dió como resultado el compuesto objetivo 1.10.



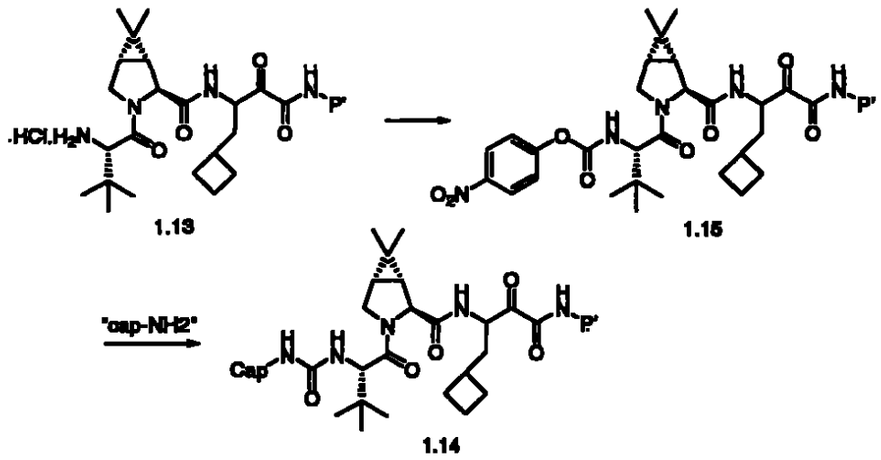
Método C

En otra variación, el acoplamiento peptídico del ácido N-Boc-P2-P3 1.17 con la porción amida P_1-P' apropiada proporcionó la hidroxil amida 1.11. La oxidación (Moffatt o Dess-Martin's) dio como resultado la ceto amida 1.12. La desprotección de la funcionalidad N-Boc proporcionó la sal de clorhidrato 1.13. El tratamiento con un isocianato apropiado (o equivalente de isocianato) dió como resultado el compuesto objetivo 1.14.



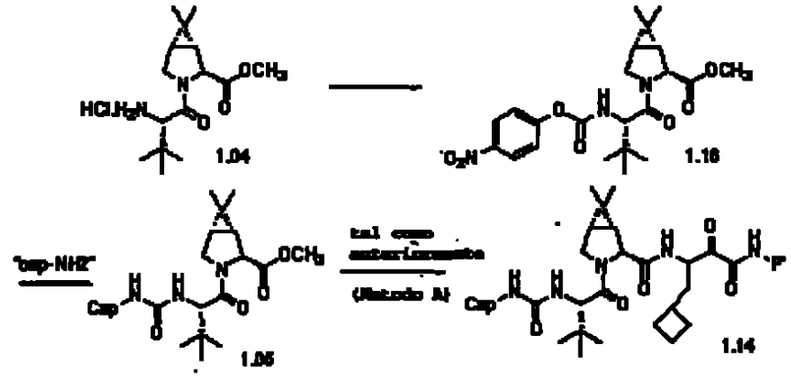
Método D

En una variación más, la sal de clorhidrato 1.13 se convirtió al carbamato de 4-nitrofenilo 1.15 por reacción con cloroformiato de 4-nitrofenilo. El subsiguiente tratamiento con una amina (o sal de clorhidrato de amina) de elección proporcionó el compuesto objetivo 1.14.



Método E

En una variación más, la sal de clorhidrato dipeptídica 1.03 se convirtió al carbamato de 4-nitrofenilo tal como se describió anteriormente. El tratamiento con una amina (o sal de clorhidrato de amina) de elección proporcionó el derivado urea 1.05. La hidrólisis y elaboración adicional descriptas en los Métodos A/B proporcionaron los compuestos objetivo 1.14.

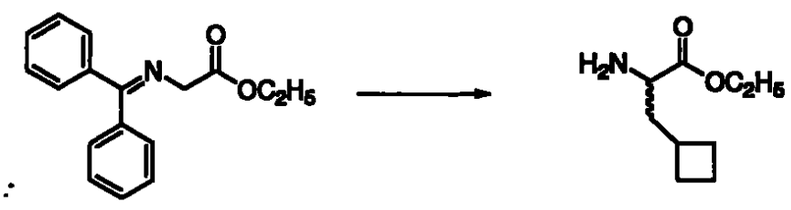


Preparación de Intermediarios:

Preparación de las porciones P_1-P':

Preparación de los Intermediarios 10.11 y 10.12:

Etapa 1:

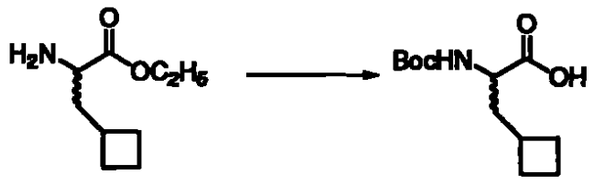


10.01 10.02

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Una solución agitada de cetimina **10.01** (50 g, 187,1 mmoles) bajo N_2 en THF seco (400 mL) se enfrió a –78 °C y se trató con una solución 1 M de K-^{t}BuO (220 mL, 1,5 equiv.) en THF. La mezcla de reacción se calentó a 0 °C y se agitó durante 1 hora y se trató con bromometil ciclobutano (28 mL, 249 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 48 horas 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 5 horas y se extrajo con Et_2O (1 L). La capa acuosa se basificó a 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 proporcionar la amina pura (**10,02**, 18 g) en forma de un aceite incoloro.

Etapa 2

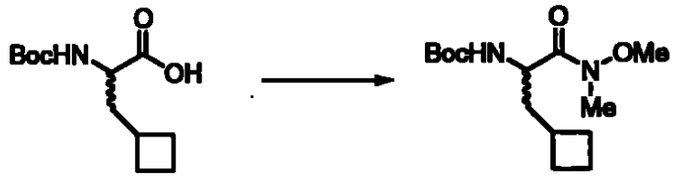


10.02 **10.03**

Una de la amina **10.02** (18 g, 105,2 mmoles) a 0°C en CH_2Cl_2 (350 mL) se trató con dicarbonato de di-*ter*-butilo (23 g, 105,4 mmoles) y se agitó a temperatura ambiente durante 12 horas. Después de completar 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•H_2O (6,5 g, 158,5 mmoles) y se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se concentró y la capa acuosa básica se extrajo con Et_2O. La capa acuosa se acidificó con HCl concentrado a 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 proporcionar **10.03** en forma de un aceite viscoso incoloro, el cual se usó para la etapa siguiente sin ninguna purificación.

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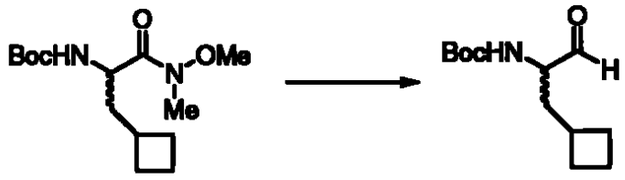
Etapa 3



10.03 10.04

Una solución de ácido **10.03** (15,0 g, 62 mmoles) en CH_2Cl_2 (250 mL) se trató con reactivo BOP (41,1 g, 93 mmoles), N-metil morfolina (27 mL), N,O-clorhidrato de N,O-dimetil hidroxilamina (9,07 g, 93 mmoles) y se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con HCl acuoso 1 N (250 mL), y las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (3 x 300 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 proporcionar la amida **10.04** (15,0 g) en forma de un sólido incoloro.

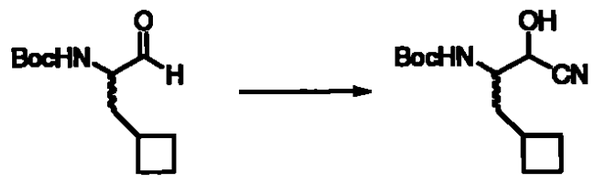
Etapa 4



10.04 10.05

Una solución de la amida **10.04** (15 g, 52,1 mmoles) en THF seco (200 mL) se trató por goteo con una solución de $LiAlH_4$ (1M, 93 mL, 93 mmoles) a 0 °C. La mezcla de reacción se agitó a temperatura ambiente durante 1 hora y se apagó cuidadosamente a 0°C con una solución de $KHSO_4$ (10% acuoso.) y se agitó durante 0.5 horas. La mezcla de reacción se diluyó con HCl acuoso (1 M, 150 mL) y se extrajo con CH_2Cl_2 (3 x 200 mL), Las capas orgánicas combinadas se lavaron con HCl acuoso (1 M), $NaHCO_3$ saturado, salmuera, y se secaron ($MgSO_4$). La mezcla se filtró y se concentró *al* vacío para proporcionar **10.05** en forma de un aceite incoloro viscoso (14 g).

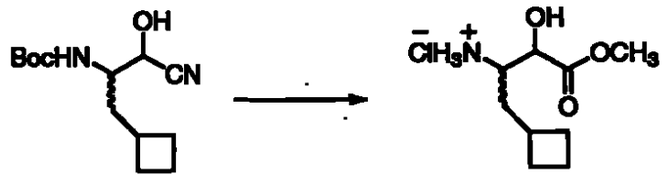
Etapa 5



10.05 **10.06**

Una solución del aldehído **10.05** (14 g, 61,6 mmoles) en CH_2Cl_2 (50 mL), se trataron con Et_3N (10.73 mL, 74., mmoles), y clanohidrina de acetona (10,86 g, 127,57 mmoles) y se agitó a temperatura ambiente durante 24 horas. La mezcla de reacción se concentró *al vacío* y se diluyó con HCl acuoso (1 M, 200 mL) y se extrajo en CH_2Cl_2 (3 x 200 mL). La capa orgánica combinada se lavó con H_2O, salmuera, se secó ($MgSO_4$), se filtró, se concentró *al vacío* y se purificó por cromatografía (SiO_2, EtOAc/Hex 1:4) para proporcionar **10.06** (10.3 g) en forma de un líquido incoloro.

Etapa 6

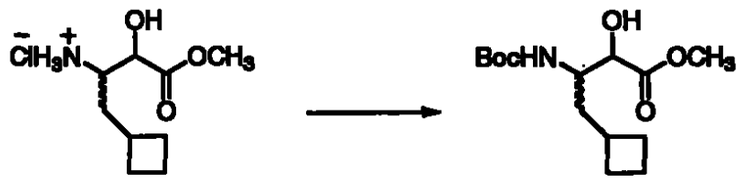


10.06 **10.07**

Metanol saturado con HCl*, preparado por burbujeo de gas HCl a través de CH_3OH (700 ml) a 0°C, se trató con la clanohidrina **10.06** y se calentó a reflujo durante 24 horas. La reacción se concentró *al vacío* para proporcionar **10.07**, que se usó en la etapa siguiente sin purificación.

* Alternativamente, puede usarse también HCl 6M preparado por adición de AcCl a metanol seco.

Etapa 7

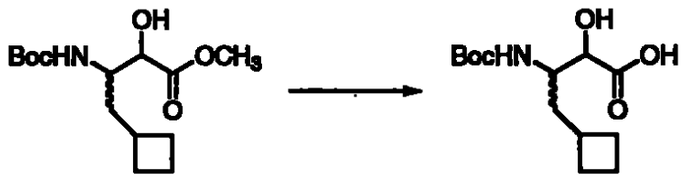


10.07 **10.08**

Una solución del clorhidrato de amina **10.07** en CH_2Cl_2 (200 mL) se trató con Et_3N (45.0 mL, 315 mmoles) y Boc_2O (45.7 g, 209 mmoles) a –78°C. La mezcla de reacción se agitó luego a temperatura ambiente durante la

noche y se diluyó con HCl (2 M, 200 mL) y se extrajo en CH_2Cl_2. Las capas orgánicas combinadas se secaron ($MgSO_4$) se filtraron, se concentraron *al vacío* y se purificaron por cromatografía (EtOAc/Hex 1:4) para proporcionar el hidroxi éster **10.08**.

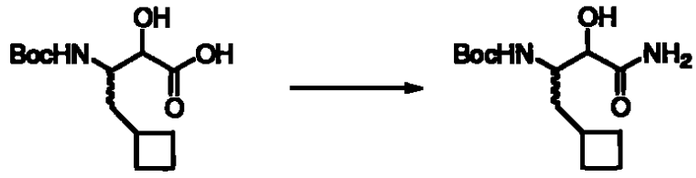
Etapa 8.



10.08 **10.09**

Una solución de éster metílico **10.08** (3 g, 10,5 mmoles) en THF/H_2O (1:1) se trató con LiOH•H_2O (645 mg, 15,75 mmoles) y se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se acidificó con HCl acuoso (1 M, 15 mL) y se concentró *al vacío*. El residuo se secó al vacío para proporcionar **10.09** con un rendimiento cuantitativo.

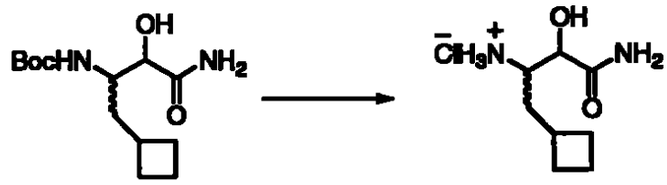
Etapa 9



10.09 **10.10**

La solución del ácido **10.09** (mencionado anteriormente) en CH_2Cl_2 (50 mL) y DMF (25 mL) se trató con NH_4Cl (2,94 g, 55,5 mmoles), EDCI (3,15 g, 16,5 mmoles), HOOBt (2,69 g, 16,5 mmoles), y NMM (4,4 g, 44 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 3 días. Los solventes se extrajeron al 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 se concentraron *al vacío* para obtener **10.10**, que se usó tal cual en las etapas siguientes. (Alternativamente, **10.10** puede obtenerse directamente también por reacción de **10.06** (4,5 g, 17,7 mmoles) con H_2O_2 acuoso (10 mL), LiOH•H_2O (820 mg, 20,8 mmoles) a 0°C en 50 mL de CH_3OH durante 0.5 h.)

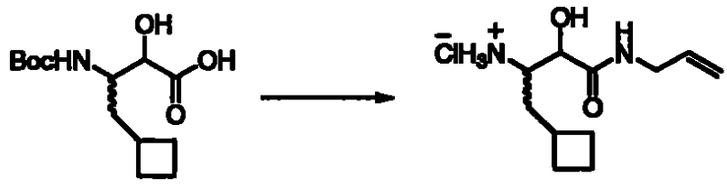
Etapa 10



10.10 10.11

Una solución de **10.10** obtenida en la etapa previa se disolvió en HCl 4N en dioxano y se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se concentró al vacío para proporcionar el intermediario **10.11** en forma de un sólido, que se usó sin purificación adicional.

Etapa 11

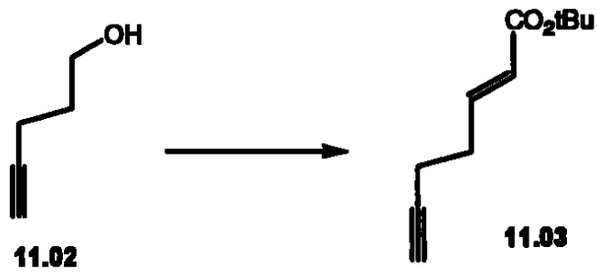


10.09 10.12

El intermediario requerido **10.12** se obtuvo a partir del compuesto **10.09** usando esencialmente los procedimientos descriptos anteriormente en las Etapas 9 y 10 con reactivos apropiados.

Preparación del Intermediario 11.01

Etapa 1



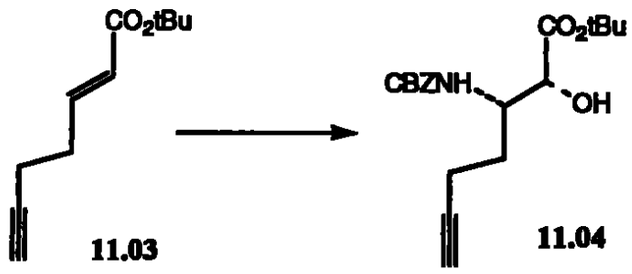
11.02 11.03

A una solución de 4-pentin-1-ol, **11.02** (4,15 g; Aldrich) se le agregó Dess-Martin Periodinano (30,25 g; Aldrich) y la mezcla resultante se agitó durante 45 minutos antes de la adición de (tert-Butoxicarbonilmetilen) trifenilfosforano (26,75 g; Aldrich). La reacción oscura resultante se agitó durante la noche, se diluyó con EtOAc), se lavó con sulfito de sodio saturado,. $NaHCO_3$ acuoso saturado, agua, salmuera y se secó. Los volátiles se extrajeron bajo presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice usando 1% de EtOAc en hexanos como eluyente

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para proporcionar el compuesto deseado **11.03** (3,92 g). Se obtuvieron también algunas fracciones impuras, pero se separaron.

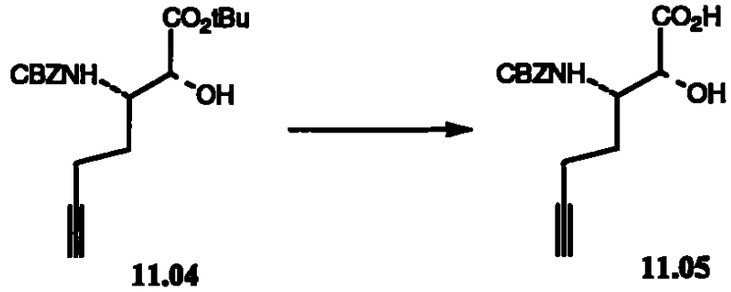
Etapa 2



11.03 **11.04**

Usando el alqueno **11.03** (1,9 g) en n-propanol (20 ml; Aldrich)), carbamato de benzilo (4,95 g; Aldrich) en n-propanol (40 ml), NaOH (1,29 g) en agua (79 ml), hipoclorito de ter-butilo (3,7 ml), (DHQ)2PHAL (0.423g; Aldrich)) en n-propanol (37,5 ml), y osmato de potasio: dehidrato (0,1544 g; Aldrich) y el procedimiento que se indica en Angew. Chem. Int. Ed. Engl (1998), 35, (23/24), pp. 2813-7.se obtuvo el producto crudo, el cual se purificó por cromatografía en columna de gel de sílice usando EtOAc:Hexanos (1:5) para obtener el amino alcohol deseado **11.04** (1,37g, 37%) en forma de un sólido blanco.

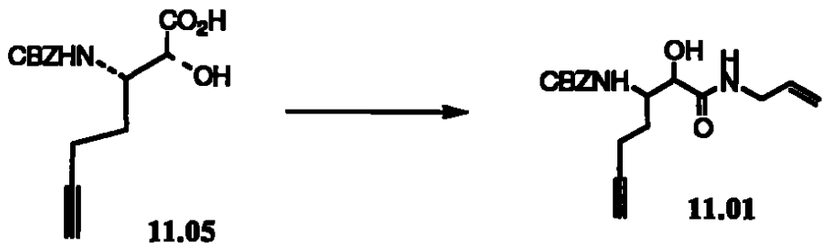
Etapa 3



11.04 **11.05**

Al éster **11.04** (0,700 g) se le agregó HCl 4M en dioxano (20 ml; Aldrich) y la mezcla resultante se dejó reposar a temperatura ambiente durante la noche. Los volátiles se extrajeron bajo presión reducida para proporcionar el ácido **11.05** (0.621 g) en forma de un sólido blanco.

Etapa 4



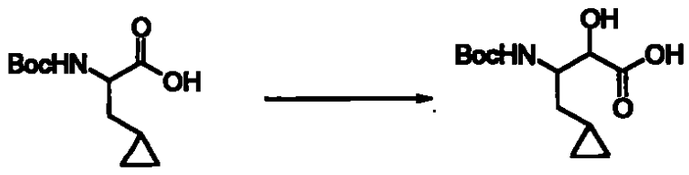
11.05 **11.01**

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Se agregaron reactivos BOP (3,65 g; Sigma) seguido de trietilamina (3,45 ml) a una solución de diclorometano (20 ml) del ácido carboxílico **11.05** (2,00 g) y allí amina (0,616 ml) a temperatura ambiente y la mezcla resultante se agitó durante la noche. La mezcla de reacción se diluyó entre EtOAc y HCl acuoso al 10%. La fase orgánica se separó, se lavó con bicarbonato de sodio acuoso saturado, agua, se secó (sulfato de magnesio). El producto de reacción crudo se purificó por cromatografía en columna de gel de sílice usando (EtOAc:Hexanos; 70:30) como eluyente para proporcionar la amida deseada **11.01** (1,73 g) en forma de un aceite amarillo viscoso.

Preparación de los intermediarios **12.03** y **12.04**

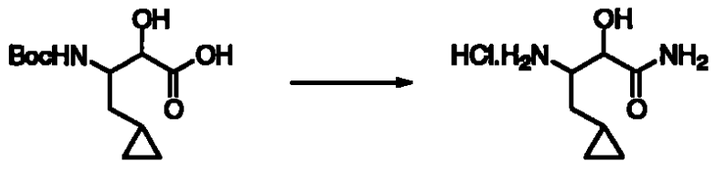
Etapa 1



12.01 **12.02**

El compuesto **12.01** se convirtió al material requerido **12.02** usando esencialmente los procedimientos descriptos para el Intermediario **10.11**, Etapas 3-8.

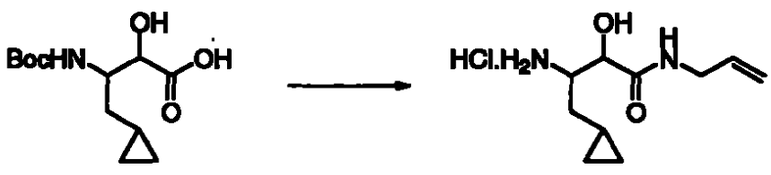
Etapa 2



12.02 **12.03**

El compuesto **12.02** se convirtió al intermediario requerido **12.03** usando esencialmente los procedimientos descriptos para el Intermediario **10.11**, Etapas 9, 10.

Etapa 3

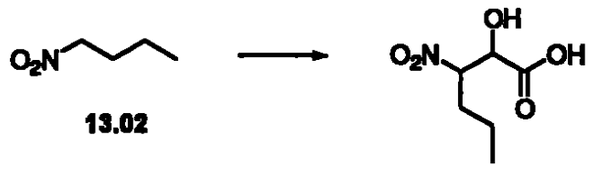


12.02 **12.04**

El compuesto **12.02** se convirtió al intermediario requerido **12.03** usando esencialmente los procedimientos descriptos para el Intermediario **10.12**, Etapa 11.

Preparación del Intermediario **13.01**

Etapa 1



13.02 **13.03**

A una solución agitada de 1-nitrobutano, **13.02** (16,5 g, 0,16 moles) y ácido glioxílico en H_2O (28,1 g, 0,305 moles) y MeOH (122 mL) a 0°C-5°C, se le agregó por goteo trietilamina (93 mL, 0,667 moles) en 2 horas. La solución se calentó a temperatura ambiente, se agitó durante la noche y se concentró hasta sequedad para proporcionar un aceite. Luego el aceite se disolvió en H_2O y se acidificó a pH =1 con 10% de HCl, seguido de extracción con EtOAc. La solución orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró hasta sequedad para proporcionar el producto **13.03** (28,1 g, 99% de rendimiento).

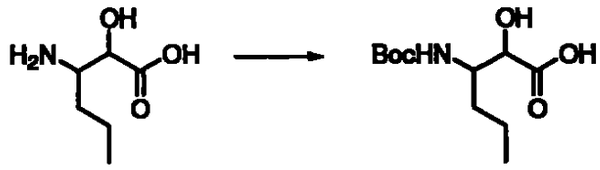
Etapa 2



13.03 **13.04**

A una solución agitada del compuesto **13.03** (240 g, 1,35 moles) en ácido acético (1,25 L) se le agregó 10% de Pd/C (37 g). La solución resultante se hidrogenó a 406,5 kPa (59 psi) durante 3 horas y luego a 413,4 kPa (60 psi) durante la noche. Luego se evaporó el ácido acético y se sometió a azeotropía 3 veces con tolueno, luego se trituró con MeOH y éter. Luego la solución se filtró y se sometió dos veces a azeotropía con tolueno para proporcionar **13.04** en forma de un sólido blancuzco (131 g, 0,891 mol, 66%).

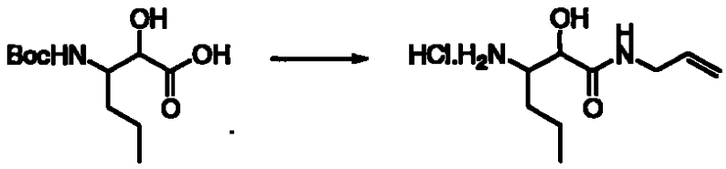
Etapa 3



13.04 13.05

A una solución agitada del amino ácido **13.04** (2,0 g, 13,6 mmoles) en dioxano (10 mL) y H_2O (5 mL) a 0°C, se le agregó una solución de NaOH 1N (4,3 mL, 14,0 mmoles). La solución resultante se agitó durante 10 minutos seguido de adición de dicarbonato de di-*t*-butilo (0,110 g, 14,0 mmoles) y se agitó a 0°C durante 15 minutos. Luego se calentó la solución a temperatura ambiente, se agitó durante 45 minutos y se mantuvo en el refrigerador durante la noche y se concentró hasta sequedad para proporcionar un material crudo. A la solución de este material crudo en EtOAc (100 mL) y hielo, se le agregó $KHSO_4$ (3.36 g) y H_2O (32 mL) y se agitó durante 4-6 minutos. Luego se separó la capa orgánica, y se extrajo dos veces la capa acuosa con EtOAc, y la capa orgánica combinada se lavó con agua, salmuera, se secó sobre Na_2SO_4, se filtró y se concentro hasta sequedad para proporcionar el producto **13.05** en forma de una goma clara (3,0 g, 89% de rendimiento).

Etapa 4

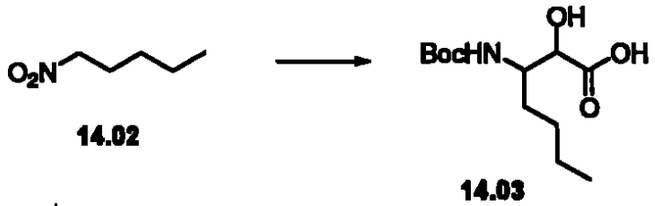


13.05 13.01

El compuesto **13.05** se convirtió al intermediario requerido **13.01** usando esencialmente los procedimientos descritos para el intermediario **10.12** Etapa 11.

Preparación del Intermediario **14.01**

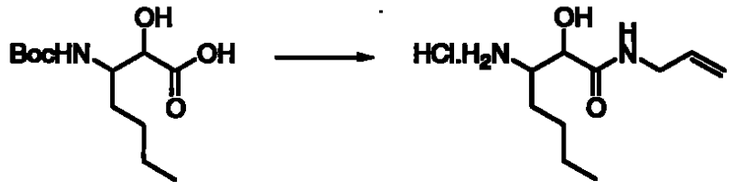
Etapa 1



14.02 14.03

El compuesto **14.02** se convirtió al material requerido **14.03** usando esencialmente los procedimientos descritos para el Intermediario **13.01**, Etapas 1-3.

Etapa 2

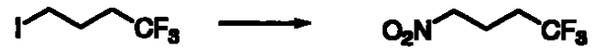


14.03 **14.01**

El compuesto **14.03** se convirtió al intermediario requerido **14.01** usando esencialmente los procedimientos descritos para el Intermediario **10.12**, Etapa 11.

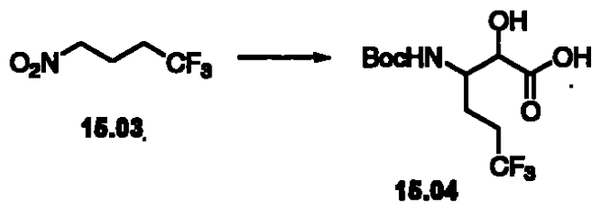
Preparación del Intermediario **15.01**

Etapa 1



15.02 **15.03**

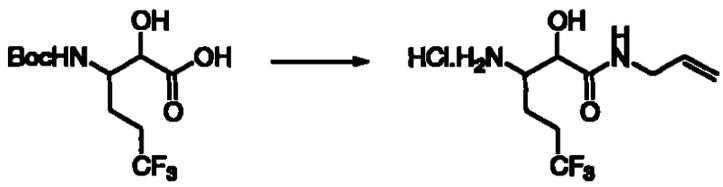
A una suspensión de nitrito de plata (9 g, 58,5 mmoles) en éter dietílico (25 mL) a 0°C se le agregó una solución de 4-iodo-1,1,1-trifluorbutano, **15.02** (10 g, 42,0 mmoles) en éter dietílico (25 mL) lentamente a través de un embudo de adición (aprox. 15 min). La mezcla resultante se agitó vigorosamente a 0°C y se calentó a temperatura ambiente. Después de 50 horas, el material sólido se separó por filtración a través de una almohadilla de celite. La solución de éter dietílico resultante se concentró al vacío para proporcionar **15.03** en forma de un aceite incoloro, que se usó sin purificación adicional. Etapa 2



15.03 **15.04**

El compuesto **15.03** se convirtió al material requerido **15.04** usando esencialmente los procedimientos descritos para el Intermediario **13.01**, Etapas 1-3.

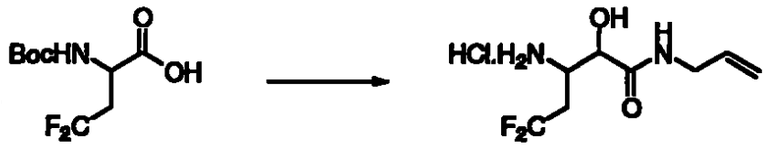
Etapa 3



15.0 15.01

El compuesto **15.04** se convirtió al intermediario requerido **15.01** usando esencialmente los procedimientos descritos para el intermediario **10.12**, Etapa 11.

Preparación del Intermediario **16.01**

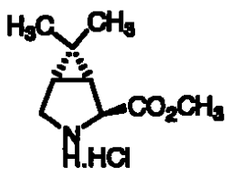


16.02 16.01

El ácido **16.02** (Winkler, D.; Burger, K., *Synthesis*, **1996**, 1419) se procesó tal como se describió anteriormente (preparación del Intermediario **10.12**) para proporcionar el intermediario esperado **16.01.**

PREPARACIÓN DE LAS PORCIONES P_2 / P_3-P_2

Preparación del Intermediario **20.01**



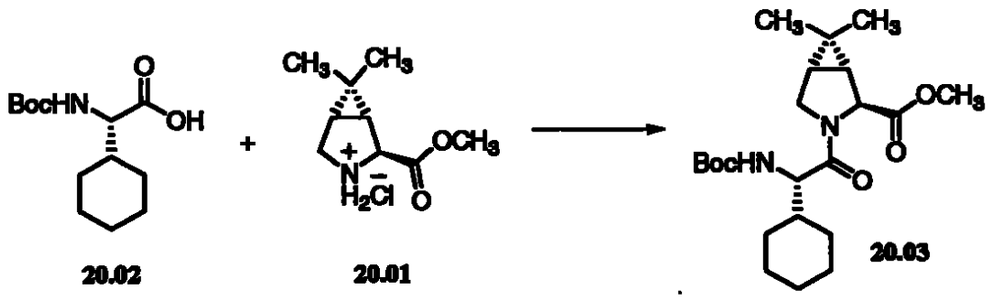
20.01

El amino éster **20.01** se preparó siguiendo el método de R. Zhang and J. S. Madalengoitia (*J. Org. Chem.* **1999**, *64*, 330), con excepción de que el grupo Boc se disoció por reacción del amino ácido Boc-protegido con HCl de metanólico (también se empleó para la desprotección HCl 4M en dioxano).

(Nota: En una variación de la síntesis mencionada, se reemplazó el iluro de sulfonio con el correspondiente iluro de fosfonio).

Preparación de Intermediario **20.04**

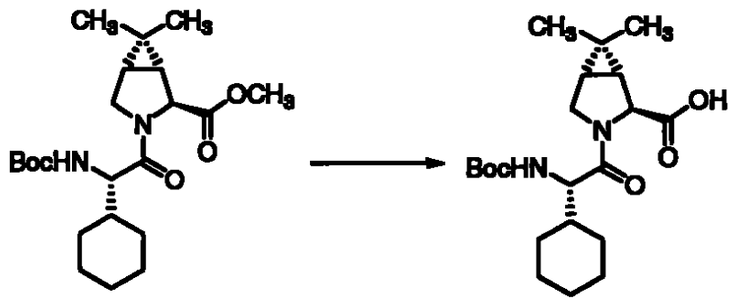
Etapa 1



20.02 20.01 20.03

Una solución del amino ácido comercial Boc-Chg-OH, **20.02** (Senn chemicals, 6,64 g, 24,1 mmoles) y clorhidrato de amina **20.01** (4,5 g, 22 mmoles) en CH_2Cl_2 (100 mL) a 0°C se trató con reactivo BOP y se agitó a temperatura ambiente durante 15 horas. La mezcla de reacción se concentró al vacío y luego se diluyó con HCl 1 M acuoso 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 cromatografiaron (SiO_2, EtOAc/Hex 3:7) para obtener **20.03** (6,0 g) en forma de un sólido incoloro.

Etapa 2

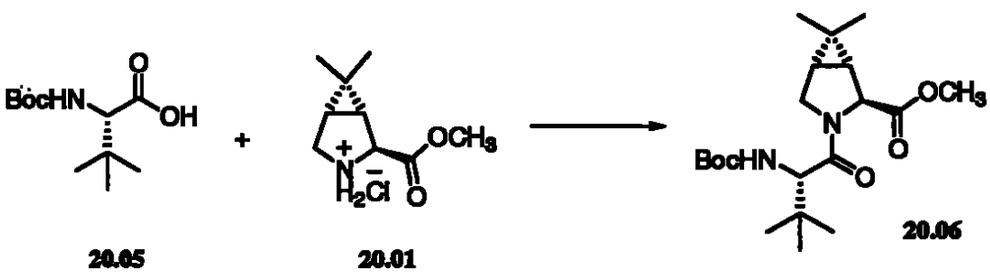


20.03 20.04

Una solución de éster metílico **20.03** (4,0 g, 9,79 mmoles) en THF/H_2O (1:1) se trató con $LiOH \cdot H_2O$ (401 mg, 9,79 mmoles) y se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se acidificó con HCl acuoso y se concentró al vacío el intermediario requerido, ácido libre **20.04**.

Preparación del Intermediario 20.08

Etapa 1

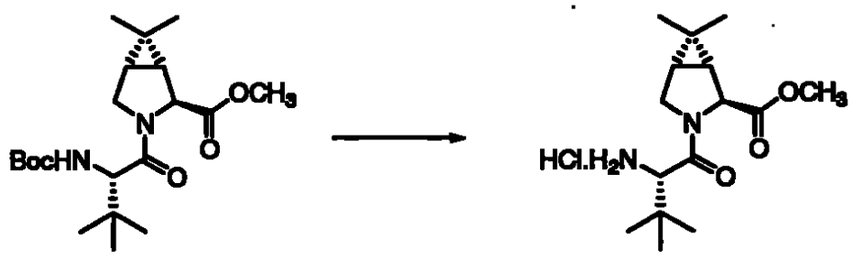


20.05 20.01 20.06

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Una solución de Boc-ter-Leu **20.05** (Fluka, 5,0 g 21,6 mmoles) en CH_2Cl_2/DMF seco (50 mL, 1:1) se enfrió a 0°C y se trató con la sal de amina **20.01** (5,3 g, 25,7 mmol), NMM (6,5 g, 64,8 mmoles) y el reactivo BOP (11,6 g, 25,7 mmoles). La reacción se agitó a temperatura ambiente durante 24 horas, 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 proporcionar **20.06** en forma de un sólido incoloro.

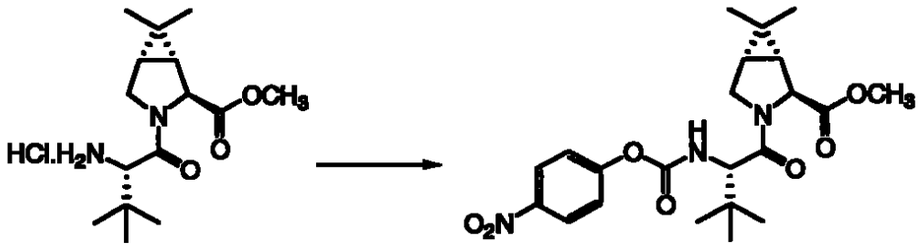
Etapa 2



20.06 **20.07**

Una solución del éster metílico **20.06** (4,0 g, 10,46 mmoles) se disolvió en HCl 4M en dioxano y se agitó a temperatura ambiente durante 3 horas. La mezcla de reacción se concentró al vacío para obtener la sal de clorhidrato de amina **20.07** que se usó sin purificación.

Etapa 3



20.07 **20.08**

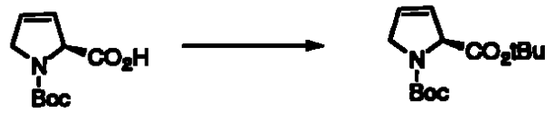
Una solución de la sal de amina **20.07** (840 mg, 2,64 mmoles) en THF (14 mL)/acetonitrilo (2 mL) se enfrió a 0°C. Se agregó cloroformato de 4-Nitrofenilo (800 mg, 3,96 mmoles) seguido de piridina (0,64 mL, 7,92 mmoles). La mezcla de reacción se calentó lentamente a temperatura ambiente durante 3 horas hasta que la TLC indicó el completamiento de la reacción. Se agregó éter dietílico (50 mL) y el precipitado resultante se

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separó por filtración. El filtrado se lavó con solución de cloruro de amonio saturada (1 x), salmuera (1 x), se secó (Na_2SO_4) y se concentró. El residuo se purificó por cromatografía evaporativa usando 20/80 de EtOAc/hexanos lo cual proporcionó 1,15 g del intermediario requerido **20.08**.

Preparación del Intermediario **21.01**

Etapa 1



21.02 **21.03**

A una solución agitada de *N*-Boc-3,4-dehidroprolina **21.02** (5,0 g, 23,5 mmoles), dicarbonato de di-*ter*-butil (7,5 g, 34,4 mmoles), y 4-*N,N*-dimetilaminopiridina (0,40 g, 3,33 mmoles) en acetonitrilo (100 mL) a temperatura ambiente se le agregó trietilamina (5,0 mL, 35,6 mmoles). La solución resultante se agitó a esta temperatura durante 18 horas antes de concentrarla al vacío. El residuo de color castaño oscuro se purificó por cromatografía en columna evaporativa eluyendo con 10-25% EtOAc/hexano para proporcionar el producto **21.03** en forma de un aceite de color amarillo pálido (5,29 g, 84%).

Etapa 2

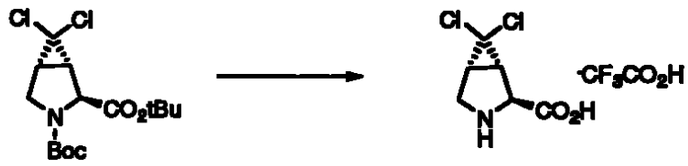


21.03 **21.04**

A una solución agitada del derivado dehidroprolina **21.03** (10,1 g, 37,4 mmoles), cloruro de benciltrietilamonio (1,60 g, 7,02 mmoles) en cloroformo (120 mL) a temperatura ambiente, se le agregó hidróxido de sodio acuoso al 50% (120 g). Después de agitar vigorosamente a esta temperatura durante 24 horas, la mezcla oscura se diluyó con CH_2Cl_2 (200 mL) y éter dietílico (600 mL). Después de separar las capas, se extrajo la solución acuosa con CH_2Cl_2/Et_2O (1:2, 3x600 mL). La solución orgánica se secó ($MgSO_4$) y se concentró. El residuo se purificó por cromatografía en columna evaporativa usando 5-20% EtOAc/hexano para proporcionar 9,34 g (71%) de **21.04** en forma de un sólido blancuzco.

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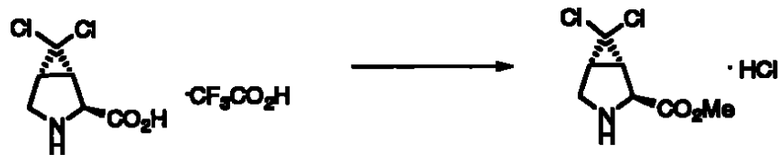
Etapa 3



21.04 21.05

La solución de **21.04** (9,34 g, 26,5 mmoles) en CH_2Cl_2 (25 mL) y CF_3CO_2H (50 mL) se agitó a temperatura ambiente durante 4,5 horas antes de concentrarla al vacío para proporcionar un residuo de color castaño **21.05** que se usó en la Etapa 4 sin purificación adicional.

Etapa 4

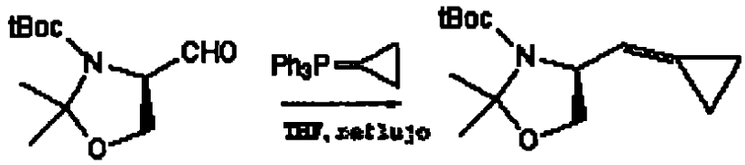


21.05 21.01

Se agregó ácido clorhídrico concentrado (4,5 mL) a una solución del residuo **21.05** de la Etapa 3 en metanol (70 mL) la mezcla resultante se calentó a 65°C en un baño de aceite. Después de 18 horas la mezcla se concentró al vacío para proporcionar un aceite de color castaño **21.01**, que se usó adicionalmente sin purificación.

Preparación del Intermediario **22.01**

Etapa 1

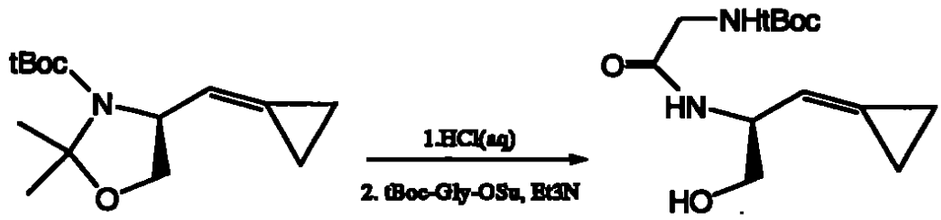


22.02 22.03

Se agregó bis(trimetilsilil)amida de potasio (158 ml de una solución 0,5M en tolueno; 79 mmoles) a una suspensión agitada de bromuro de ciclopropiltrifenilfosfonio (33,12g; 86,4 mmoles) en tetrahidrofurano anhidro (130 ml) y la mezcla de color naranja resultante se agitó bajo atmósfera de nitrógeno a temperatura ambiente por un período 1 hora, antes de la adición del aldehído **22.02** (9,68 g; 42,2 mmoles) en THF (8ml). La reacción se reflujó bajo atmósfera de nitrógeno por un período de 2 horas. Después del

enfriamiento, se agregaron metanol, éter dietílico y sal Rochelles. La fase orgánica, se separó, se lavó con salmuera, se secó y se concentró bajo presión reducida. El producto de reacción crudo se purificó por cromatografía en columna de gel de sílice usando EtOAc-hexano (1:99) a EtOAc-hexano (5:95) para proporcionar el alqueno **22.03** (8,47g) en forma de un aceite amarillo.

Etapa 2



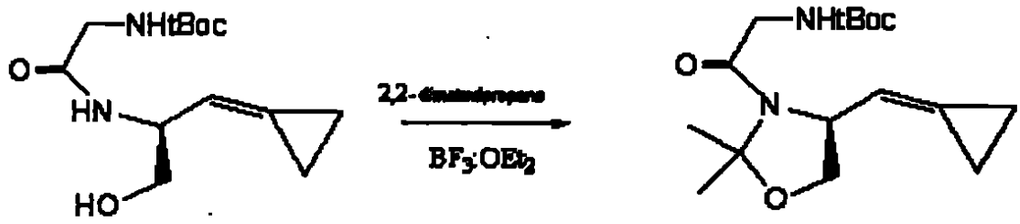
22.03 **22.04**

Se preparó una solución de HCl 1M en MeOH/MeOAc, mediante adición de 14,2ml de cloruro de acetilo por goteo a metal frío, y se diluyó a la solución resultante hasta 200ml a temperatura ambiente.

El carbamato **22.03** (9,49 g; 37,5 mmoles) se disolvió en metanol (12ml) y se agregó a HCl 1M en MeOH/MeOAc (150 ml) mientras se enfriaba en un baño de hielo. La mezcla resultante se mantuvo a esta temperatura durante 1 hora, y luego se extrajo el baño de hielo y se continuó la agitación durante la noche a temperatura ambiente. Se extrajeron los volátiles bajo presión reducida para proporcionar un aceite amarillo que se usó en la etapa siguiente sin purificación.

El aceite de color amarillo se disolvió en una mezcla de THF (30 ml) y MeOH (20 ml) y se trató con trietilamina (15 ml; 108 mmoles) hasta que la solución fue de pH=9-10. Después de colocaría en un baño de hielo, la mezcla se trató con N-Boc-Gly-OSu (11,22 g; 41 mmoles). El baño de hielo se extrajo y la reacción se agitó a temperatura ambiente durante 1 hora. Se extrajeron los volátiles bajo presión reducida y el residuo se purificó por cromatografía en columna de gel de sílice usando metanol (1-3%) en diclorometano lo cual proporcionó la amida deseada **22.04** (9,09g).

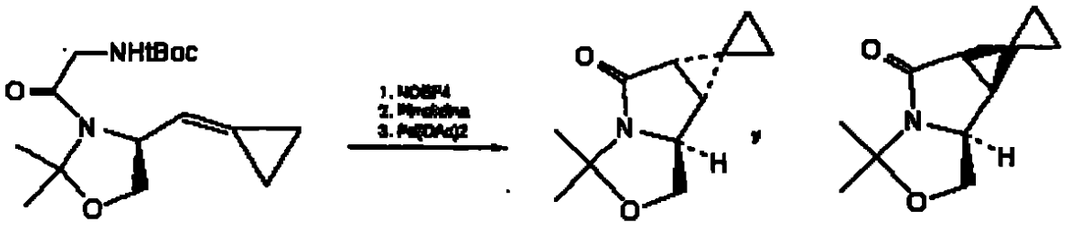
Etapa 3



22.04 22.05

El alcohol **22.04** (9,09 g; 33,6 mmoles) se disolvió en acetona (118,5 ml) y se trató con 2,2-dimetoxipropano (37,4 ml; 304 mmoles) y BF_3:Et_2O (0,32 ml; 2,6 mmoles) y la mezcla resultante se agitó a temperatura ambiente por un período de 5,5 horas. La solución de reacción se trató con unas pocas gotas de trietilamina y los volátiles se extrajeron bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice usando 5-25% de EtOAc en hexanos para proporcionar el N,O-acetal **22.05** (8,85g).

Etapa 4



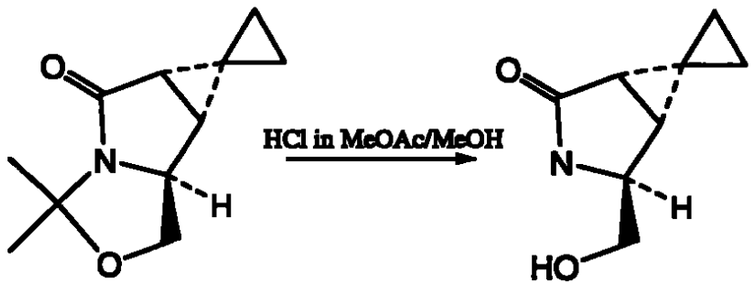
22.05 22.06 22.07

El carbamato **22.05** (8,81g; 28,4 mmoles) se disolvió en acetonitrilo (45 ml) y la solución se enfrió a –40°C bajo atmósfera de nitrógeno. Se agregaron piridina (6,9ml; 85,3 mmoles) seguido de tetrafluorborato de nitrosio (6,63 g; 56,8 mmoles) y la mezcla de reacción resultante se mantuvo por debajo de 0°C hasta que la TLC indicó que no quedaba material de partida (aprox. 2,25 horas). Se agregaron pirrolidina (20 ml; 240 mmoles) y el baño refrigerante se extrajo y la agitación se continuó a temperatura ambiente durante 1 hora y luego se extrajeron los volátiles bajo presión reducida. El residuo se hizo pasar rápidamente a través de una almohadilla de gel de sílice para proporcionar un aceite de color amarillo.

El aceite amarillo se disolvió en benceno anhidro (220ml) y se agregó acetato de paladio (0,317g; 1,41mmoles) antes de calentar la mezcla resultante a reflujo, bajo atmósfera de nitrógeno por un período de 1,5 hora. Después del enfriamiento los volátiles se extrajeron bajo presión reducida, y el residuo oscuro se purificó por cromatografía en columna de gel de sílice,

usando EtOAc-hexano (1:4) para proporcionar la I) trans-pirrolidinona **22.06** (1,94 g) seguido de il) cis-pirrolidinona **22.07** (1,97g).

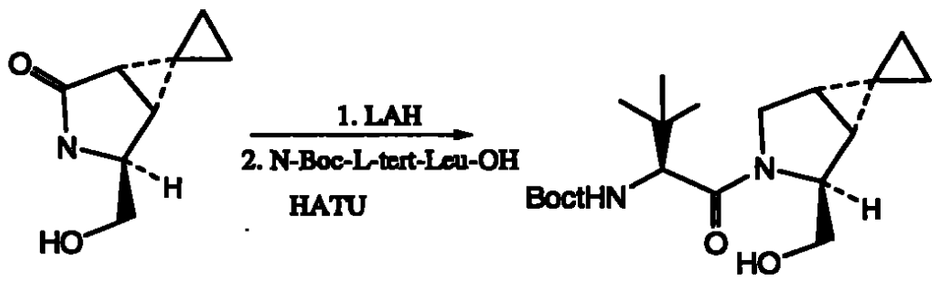
Etapa 5



22.06 **22.08**

HCl 1M en MeOAc/MeOH (10 ml; tal como se describió anteriormente) recientemente preparado, se agregó al N,O-acetal **22.06** y se agitó a temperatura ambiente durante 1 hora. El solvente se extrajo bajo presión reducida y el residuo se purificó por cromatografía en columna evaporativa usando 0-4% de MeOH en diclorometano como eluyente para proporcionar el alcohol deseado **22.08** (1,42 g), en forma de un aceite amarillo.

Etapa 6



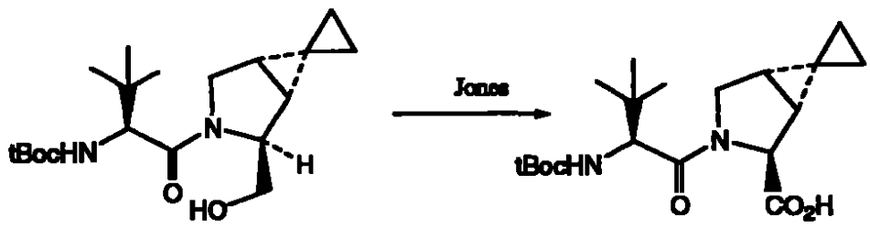
22.08 **22.09**

Una solución de la lactama **22.08** (1,29 g; 8,44 mmoles) en tetrahidrofurano anhidro (55 ml) se agregó hidruro de litio aluminio (2,40 g; 63,2 mmoles) y la mezcla resultante se reflujó durante 8 horas. Después de enfriar agua, seguido de NaOH acuosa al 15%, y la mezcla resultante se filtró a través de celite y el sólido se lavó cuidadosamente con THF y MeOH. El solvente se extrajo bajo presión reducida, y el residuo se redisolvió en diclorometano, se secó y se concentró bajo presión reducida para proporcionar la pirrolidina, que se usó sin purificación.

Se agregó base de Hunigs (4,5 ml; 25,8 mmoles) a una mezcla de N-Boc-L-ter-Leu-OH (1,76 g; 7,6 mmoles), pirrolidina cruda HATU (2,89 g; 7,6

mmoles) en diclorometano anhidro (50 ml) a –60°C, bajo atmósfera de nitrógeno. La reacción resultante se dejó llegar hasta temperatura ambiente lentamente, durante la noche. Se agregó ETOc y la solución de cloro amarillo se lavó con HCl acuoso diluido, bicarbonato de sodio acuoso saturado, agua, salmuera. La capa orgánica se secó, y se concentró bajo presión reducida. El residuo se purificó por cromatografía en columna de gel de sílice usando EtOAc:hexanos (1:3) para proporcionar la amida deseada **22.09** (2,00 g).

Etapa 7

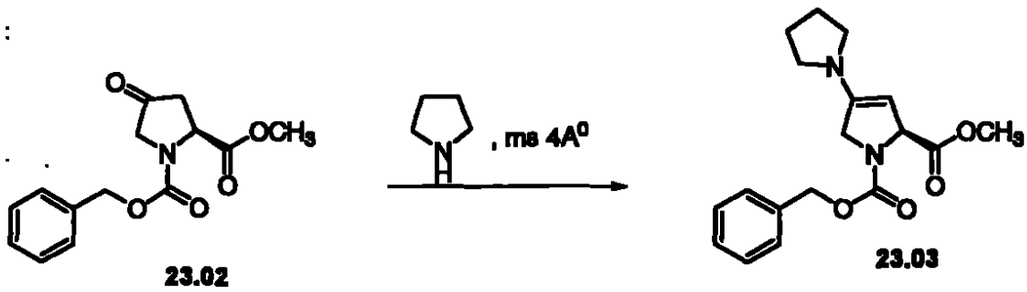


22.09 **22.01**

Se disolvió el alcohol **22.09** (2,00 g; 5,67 mmoles) en acetona (116 ml) y se enfrió en un baño de hielo durante 10 minutos. La solución se agregó luego a un reactivo Jones enfriado (14,2 ml; aprox 2 mmoles/ml) y la mezcla resultante se agitó a 5°C durante 0,5 horas, y se extrajo el baño refrigerante. La reacción se agitó durante 2 horas más a temperatura ambiente, antes de agregar sulfato de sodio (28,54 g), celite (15 g) en EtOAc (100 ml). Isopropanol (15ml) después de 1 minuto y luego se agitó durante 10 minutos más y se filtró. El filtrado se concentró bajo presión reducida, lo cual proporcionó un aceite de color castaño que se disolvió en EtOAc. Esta solución se lavó con agua, ácido cítrico acuoso al 3%, salmuera, se secó y se concentró para proporcionar el ácido carboxílico deseado **22.01** (1,64 g) en forma de un sólido blanco.

Preparación del Intermediario **23.01**

Etapa 1

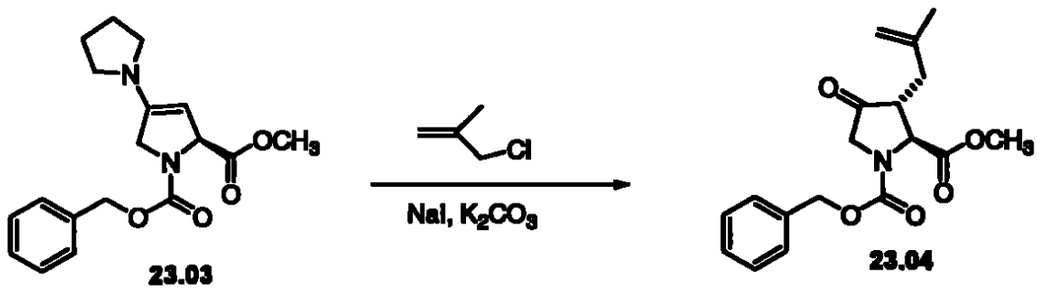


23.02 **23.03**

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A la mezcla del éster **23.02** (6,0 g) y tamices moleculares (5,2 g) en cloruro de metileno anhidro (35 mL) se le agregó pirrolidina (5,7 mL, 66,36 mmoles). La suspensión de color castaño resultante se agitó a temperatura ambiente bajo N_2 durante 24 horas, se filtró y se lavó con CH_3CN anhidro. El filtrado combinado se concentró para proporcionar el producto deseado **23.03.**

Etapa 2



23.03 **23.04**

A una solución del producto **23.03** de la etapa precedente en CH_3CN (35 mL) se le agregó K_2CO_3 anhidro, cloruro de metalilo (2,77 g, 30,5 mmoles), NaI (1,07 g, 6,7 mmoles). La suspensión resultante se agitó a temperatura ambiente bajo N_2 durante 24 horas. Se agregaron 50 mL de agua enfriada con hielo, seguido de solución de $KHSO_4$ 2N hasta que el pH fue de 1.Se agregó EtOAc (100 mL) y la mezcla se agitó durante 0,75 horas. La capa orgánica combinada se recogió y lavó con salmuera, se secó sobre $MgSO_4$, y se evaporó para proporcionar el producto deseado, **23.04.**

Etapa 3



23.04 **23.05**

El producto **23.04** de la etapa precedente (2,7 g, 8,16 mmoles) se disolvió en dioxano (20 mL) y se trató con LiOH 1N recientemente preparado (9 mL). La mezcla de reacción se agitó a temperatura ambiente bajo N_2 durante 20 horas. La mezcla de reacción se recogió en EtOAc y se lavó con H_2O. La fase acuosa combinada se enfrió a 0ºC y se acidificó a pH 1,65 usando HCl 1N. La mezcla turbia se extrajo con EtOAc (2 x 100 mL). La capa

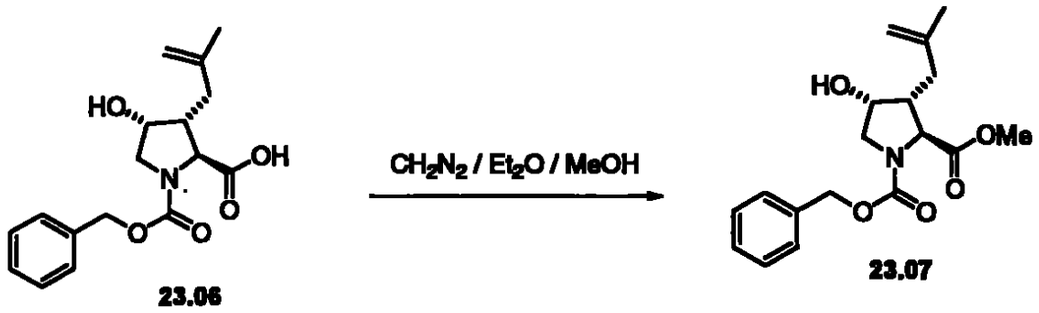
orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, y se concentró para proporcionar el ácido deseado **23.05** (3,40 g).

Etapa 4



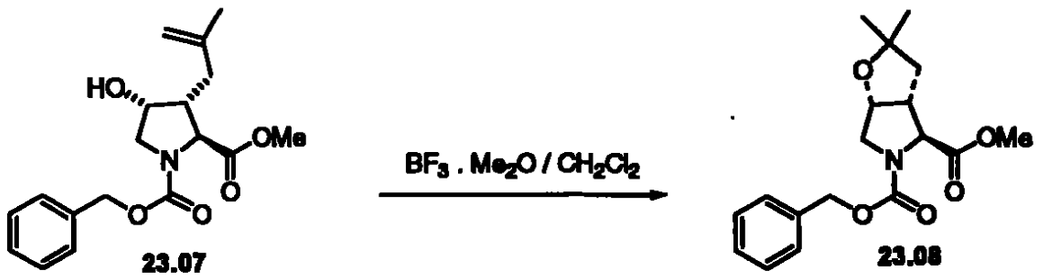
A una suspensión de $NaBH(OAc)_3$ (3,93g, 18,5 mmoles) en CH_2Cl_2 (55 mL) se le agregó una solución del producto **23.05** de la etapa precedente en CH_2Cl_2 anhidro (20 mL) ácido acético (2 mL). La suspensión se agitó a temperatura ambiente durante 20 horas. Se agregó agua helada (100 mL) a la suspensión y se agitó durante 1/2 hora. La capa orgánica se separó, se filtró, se secó y se evaporó para proporcionar el producto deseado, **23.06**.

Etapa 5



Una solución del producto **23.06** de la etapa precedente (1,9g) en MeOH (40 mL) se trató con un exceso de una solución de CH_2N_2 / Et_2O y se agitó durante la noche. La mezcla de reacción se concentró hasta sequedad para proporcionar un residuo crudo. El residuo se cromatografió sobre gel de sílice eluyendo con un gradiente de EtOAc / hexano para proporcionar 1,07 g del producto puro deseado, **23.07**.

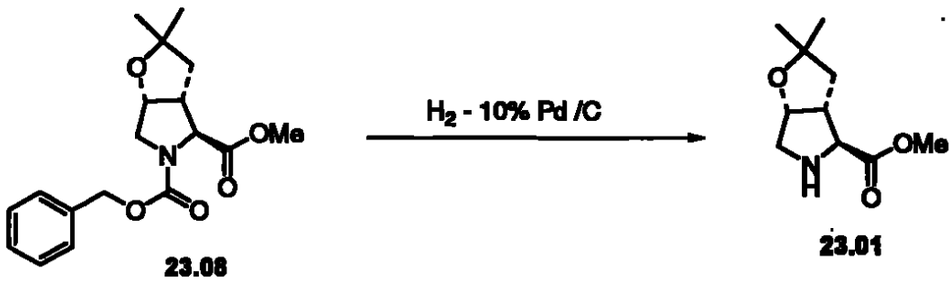
Etapa 6



23.07 23.08

Una solución del producto **23.07** de la etapa 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 horas y se apagó con $NaHCO_3$ saturado (30 mL) y se agitó durante 1/2 hora. La capa orgánica se separó y la capa orgánica combinada se lavó con salmuera, se secó sobre $MgSO_4$, se concentró para proporcionar el residuo crudo. El residuo se cromatografió sobre gel de sílice eluyendo con un gradiente de EtOAc / hexano para proporcionar 0,88 g del compuesto deseado, **23.08**.

Etapa 7



23.08 23.01

A una solución del producto **23.08** (0,92 g) de la etapa precedente en MeOH (30 mL) se le agregó 10% Pd/C (0,16 g) a temperatura ambiente y se hidrogenó a temperatura ambiente bajo una atmósfera de presión. La mezcla de reacción se agitó durante 4 horas y se concentró hasta sequedad para proporcionar el compuesto deseado, **23.01**.

PREPARACIÓN DE LAS PORCIONES P_3

Preparación del Intermediario 50.01

Etapa 1



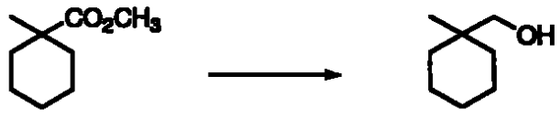
50.02 50.03

A una solución de **50.02** (15 g) en MeOH (150 mL) se le agregó HCl concentrado (3-4 mL) y la mezcla se reflujó durante 16 horas. La mezcla de

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reacción se enfrió a temperatura ambiente y se concentró. El residuo se recogió en éter dietílico (250 mL) y se lavó con solución fría saturada de bicarbonato de sodio, y salmuera. La capa orgánica se secó (Na_2SO_4) y se concentró para proporcionar el éster metílico **50.03** (12,98 g) el cual se llevó a cabo sin purificación adicional.

Etapa 2



50.03 **50.04**

El éster metílico **50.03** anterior se disolvió en cloruro de metileno (100 mL) y se enfrió a -78°C, bajo atmósfera de nitrógeno. Se agregó por goteo en un período de 2 horas, DIBAL (solución 1,0 M en cloruro de metileno, 200 mL). La mezcla de reacción se calentó a temperatura ambiente durante 16 horas. La mezcla de reacción se enfrió a 0ºC y se agregó por goteo MeOH (5-8 mL). Se agregó lentamente con agitación una solución de tartrato de potasio de sodio acuoso al 10% (200 mL) con agitación. Se diluyó con cloruro de metileno (100 mL) y se separó la capa orgánica (junto con un poco de precipitado blanco). La capa orgánica se lavó con HCl 1 N (250 mL), salmuera (200 mL), se secó (Na_2SO_4) y se concentró para proporcionar el alcohol **50.04** (11,00 g) en forma de un aceite claro.

Etapa 3

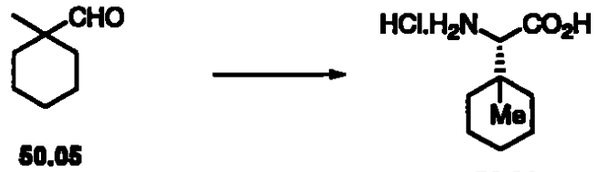


50.04 **50.05**

El alcohol **50.04** anterior se disolvió en cloruro de metileno (400 mL) y se enfrió a 0°C bajo atmósfera de nitrógeno. Se agregó PCC (22,2 g) en porciones y la mezcla de reacción se calentó lentamente a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con éter dietílico (500 mL) y se filtró a través de una almohadilla de (500 mL). Esto se hizo pasar a través de una almohadilla de gel de sílice, y el filtrado se concentró para proveer el aldehído **50.05** que se llevó a cabo sin purificación adicional.

Etapa 4

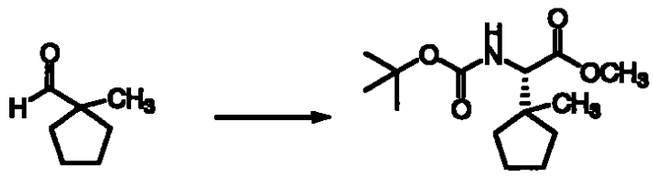
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50.05 50.01

El aldehído **50.05** anterior se convirtió al material deseado **50.01** usando esencialmente el método de Chakraborty *et. al* (Tetrahedron, **1995**, 51(33), 9179-90).

Preparación del Intermediario **51.01**

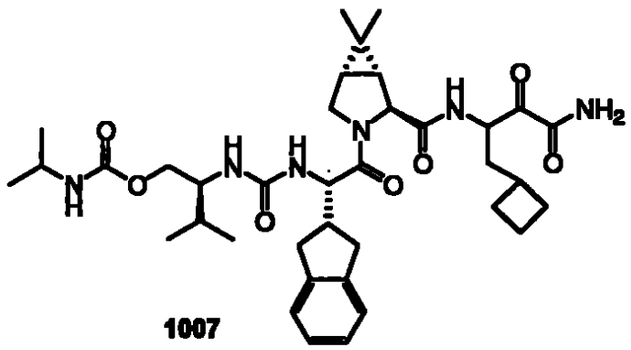


51.02 51.01

El intermediario requerido **51.01** se obtuvo a partir del aldehído **51.02** usando el procedimiento descrito en la literatura (T. K. Chakraborty et al., *Tetrahedron*, **1995**, 51 (33), 9179-90).

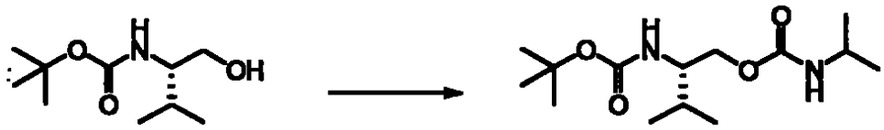
PREPARACIÓN DE LOS EJEMPLOS ESPECIFICOS

Preparación del Ejemplo 1007



1007

Etapa 1



1007a 1007b

El compuesto **1007a** comercialmente obtenible (Aldrich Chemical Co., Milwaukee, Wisconsin, USA) se convirtió a **1007b** de acuerdo con el procedimiento de la literatura (M. E. Duggan, J. S. Imagire *Synthesis* **1989**, 131-2) con un rendimiento del 90%. LC-EM: 289 (M+H).

Etapa 2

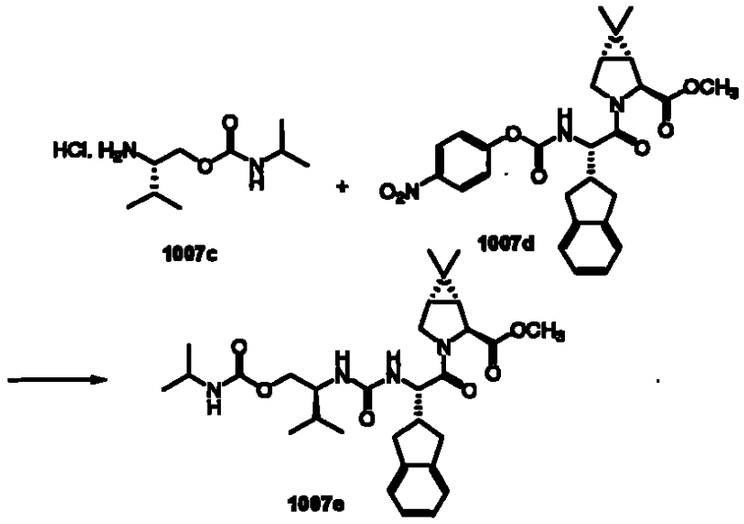
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1007b 1007c

La desprotección de **1007b** usando HCl 4M en dioxano a temperatura ambiente durante 3 horas proporcionó **1007c** un rendimiento cuantitativo. Este material se usó sin purificación adicional.

Etapa 3



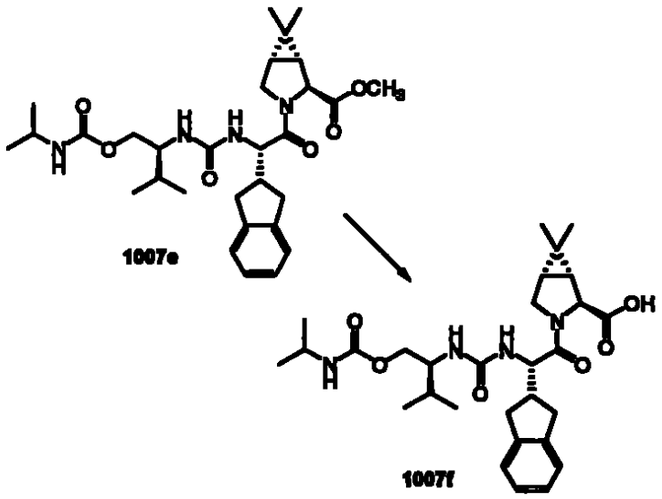
1007c 1007d 1007e

El compuesto **1007d** se obtuvo a partir de los materiales/reactivos de partida apropiados usando los procedimientos previamente descritos (Ver preparación del Intermediario **20.08**).

A una solución de **1007d** (200 mg, 0,394 mmoles) en diclorometano (10 mL) a 0ºC, bajo atmósfera de nitrógeno, se agregó **1007c** (115 mg, 0,512 mmoles) seguido de DIPEA (0,22 mL, 1,182 mmoles). La reacción se mantuvo a esta temperatura durante 30 minutos y se almacenó en el congelador (-20ºC) durante 48 horas. La mezcla de reacción se apagó con una solución saturada de cloruro de amonio y el producto se extrajo en diclorometano (3 x). Las capas orgánicas combinadas se lavaron con salmuera (1 x), se secaron (Na_2SO_4), se filtraron y se concentraron. El residuo crudo se purificó por cromatografía evaporativa usando 30/70 de acetona/hexanos lo cual proporcionó el compuesto requerido **1007e** con un rendimiento del 69%. LC-EM: 557 (M+H).

Etapa 4

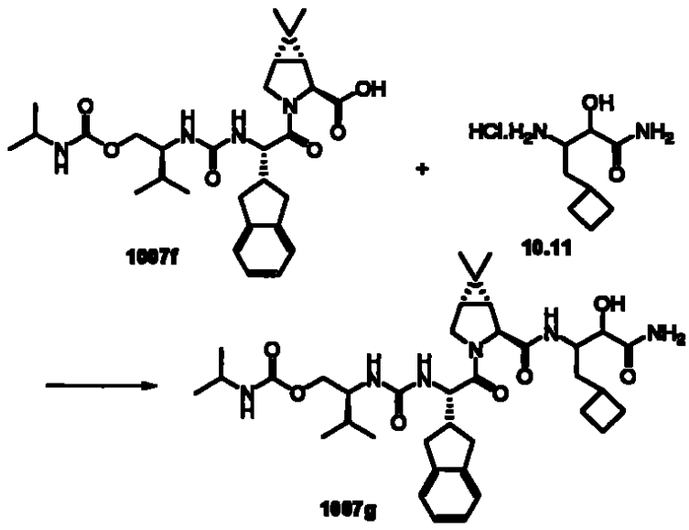
~~215~~
218



1007e 1007f

La hidrólisis del éster metílico de **1007e** para proveer el ácido requerido **1007f** se llevó a cabo tal como se describió anteriormente (ver preparación del Intermediario **20.04**, Etapa 2) con las modificaciones apropiadas.

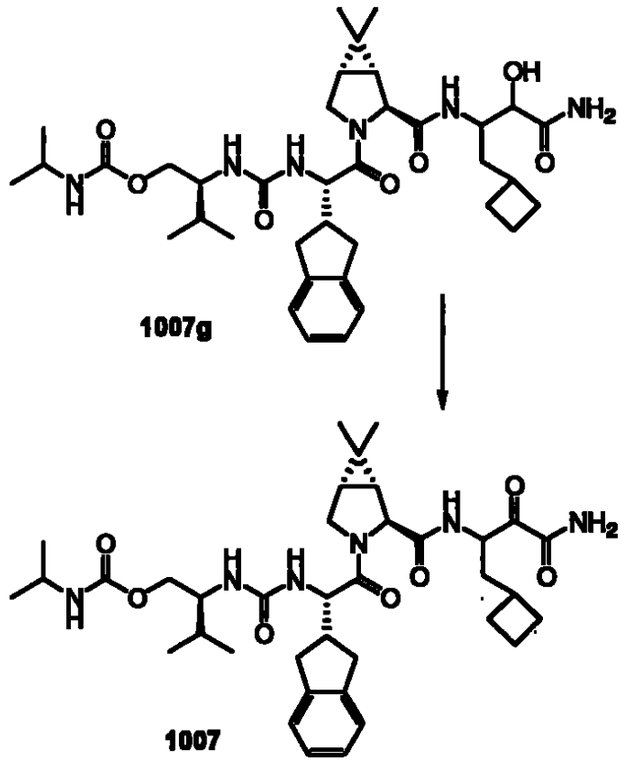
Etapa 5



1007f 10.11 1007g

La reacción de acoplamiento del ácido **1007f** (0,125 mmoles) con la sal de amina **10.11** se llevó a cabo tal como se describió anteriormente (ver preparación del Intermediario **20.08**, Etapa 1) con modificaciones (HATU en lugar de BOP, DIPEA en lugar de NMM; la reacción se llevó a cabo a 0ºC durante 15 minutos y se calentó a 10ºC durante 24 horas), y cantidades apropiadas de los reactivos. El material crudo obtenido después de la elaboración, **1007g** se llevó a cabo sin purificación. LC-EM: 697,2 (M+H).

Etapa 6



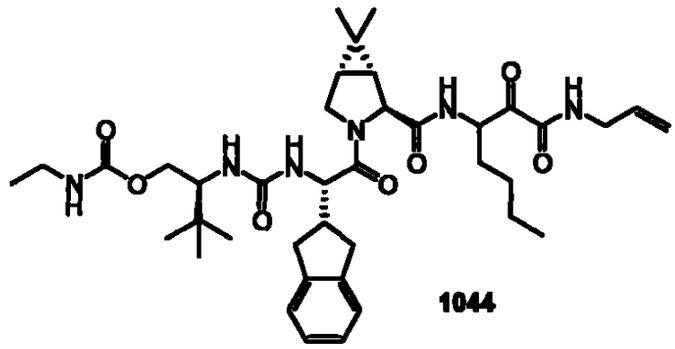
1007g

1007

A una solución fría (0ºC) del material anterior, **1007g** (0,125 mmoles) en DMSO/tolueno (3 mL de cada uno) se le agregó EDCI (240 mg, 1,25 mmoles) seguido de ácido dicloroacético (0,52 mL, 0,625 mmoles). Después de 15 minutos, se extrajo el baño frío y la mezcla de reacción se calentó a temperatura ambiente durante 16 horas. La mezcla de reacción se diluyó con EtOAc (20 mL) y se lavó con $NaHSO_4$ 1N acuoso (20 mL). La capa acuosa se separó y se extrajo con EtOAc (20 mL). Las capas orgánicas combinas se lavaron con $NaHSO_4$ 1N acuoso (20 mL), $NaHCO_3$ saturado (20 mL), salmuera (20 mL), se secaron (Na_2SO_4), se filtraron y se concentraron al vacío. El residuo crudo se purificó por cromatografía en columna evaporativa usando 40/60 de acetona/hexanos para proveer el compuesto efectivo requerido **1007** (57 mg, 0,082 mmoles, rendimiento 66%). LC-EM: 695,2 (M+H).

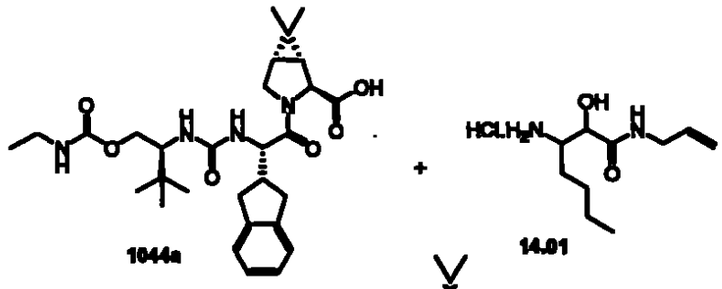
Preparación del Ejemplo 1044

220



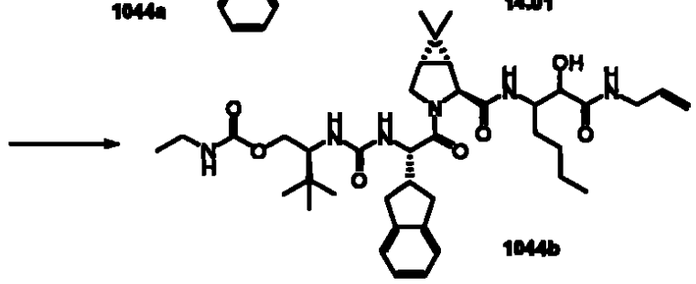
1044

Etapa 1



1044a

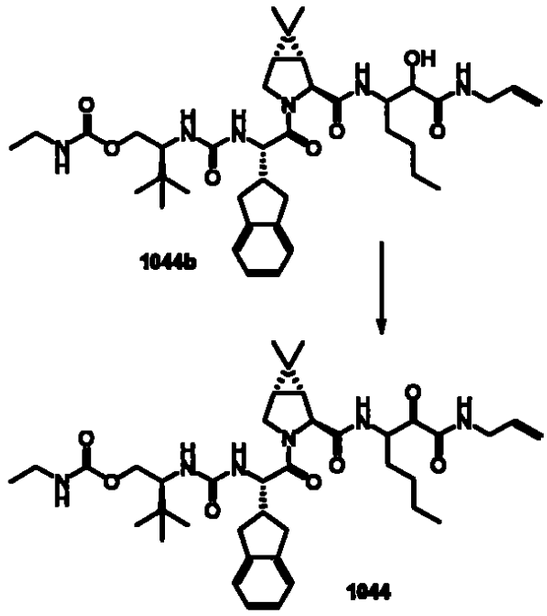
14.01



1044b

La reacción de acoplamiento del ácido **1044a**, obtenido de manera similar a la descrita para **1007f** (ver preparación del ejemplo **1007**), con la sal de amina **14.01** se llevó a cabo tal como se describió anteriormente (ver preparación del ejemplo **1007**, Etapa 5). El material crudo obtenido después de la elaboración, **1044b** se llevó a cabo sin purificación. LC-EM: 725,2 (M+H).

Etapa 2:



1044b

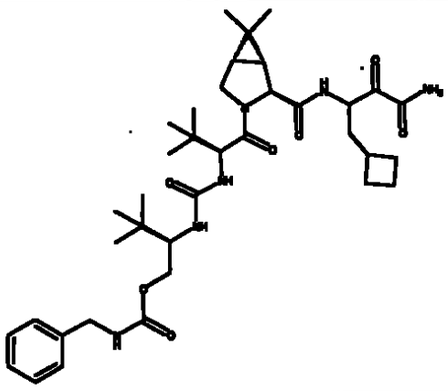
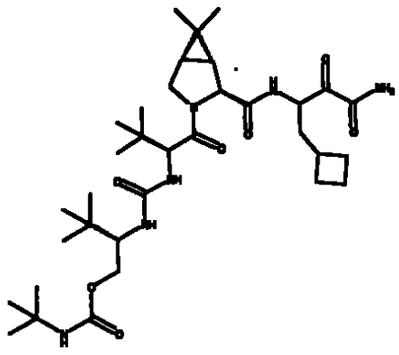
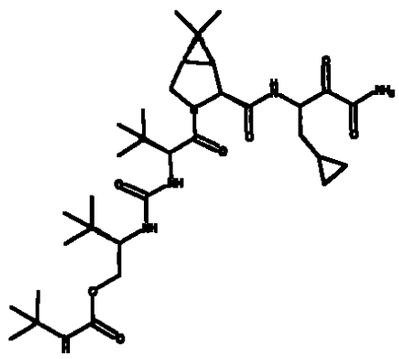
1044

A una solución del material anterior, **1044b** (0,054 mmoles) en diclorometano (5 mL) se le agregó periodinado de Dess-Martin (68 mg, 0,16 mmoles). La mezcla de reacción se agitó a temperatura ambiente, bajo atmósfera de nitrógeno, durante 4,5 horas. La mezcla de reacción se diluyó con diclorometano (10 mL) y se lavó con $Na_2S_2O_3$ acuoso al 10% (30 mL), $NaHCO_3$ saturado (30 mL), salmuera (30 mL), se secó (Na_2SO_4), se filtró y se concentró al vacío. El residuo crudo se purificó por cromatografía en columna evaporativa usando 35/65 de acetona/hexanos para proveer el compuesto objetivo requerido **1044** (23 mg, 0,032 mmoles, rendimiento 59%). LC-EM: 723,2 (M+H).

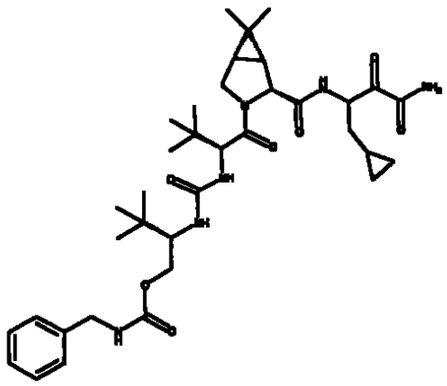
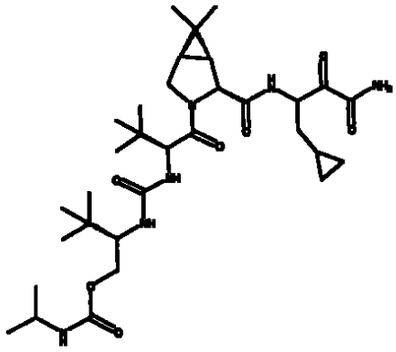
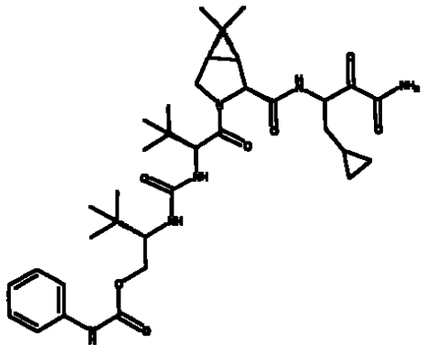
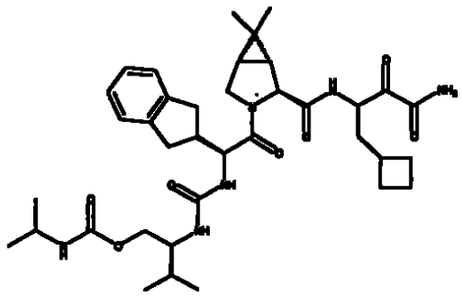
Los compuestos de la siguiente **Tabla 1** y **Tabla 1A** se prepararon esencialmente usando los procedimientos antes descritos (Preparación de los ejemplos **1007** y **1044**) con los reactivos apropiados y las modificaciones descritas en los Esquemas Generales para la Preparación de los Compuestos Objetivo, Métodos A-E.

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222

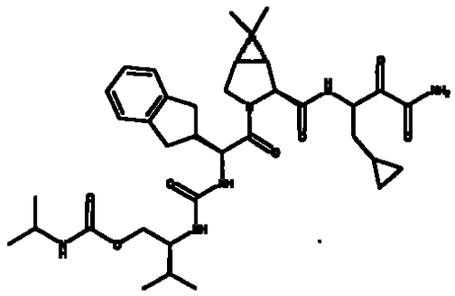
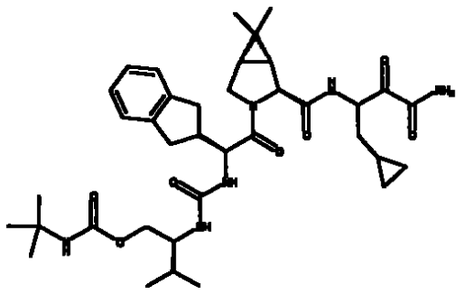
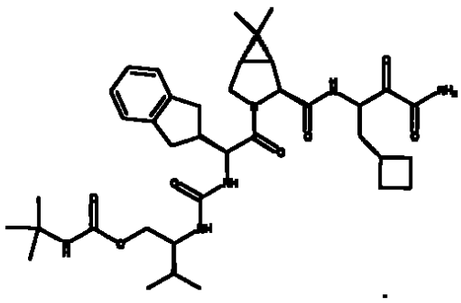
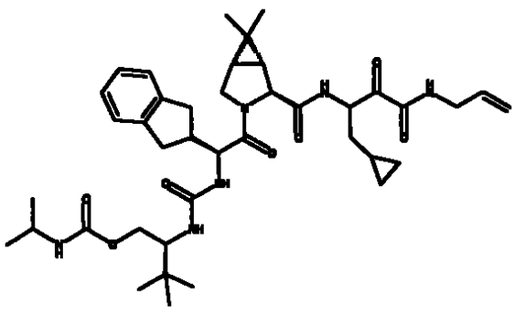
Tabla 1

Ejemplo #	Estructura	KI* (nM)	Peso Molar
1001		A	696.885
1002		A	662.868
1003		A	648.841

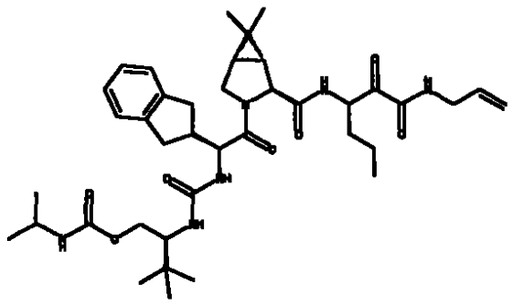
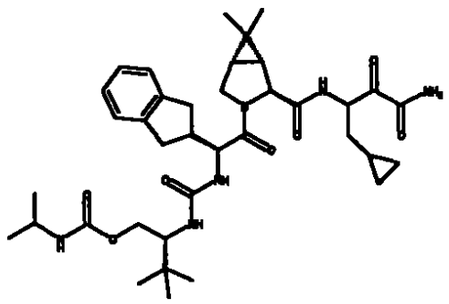
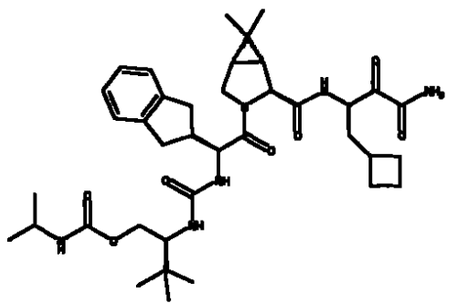
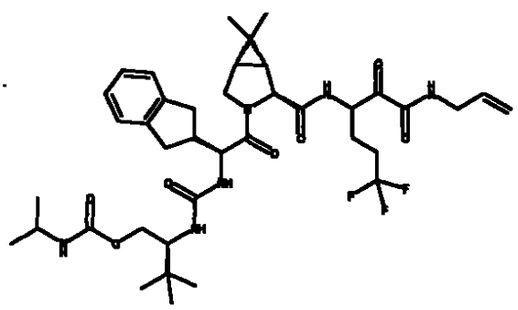
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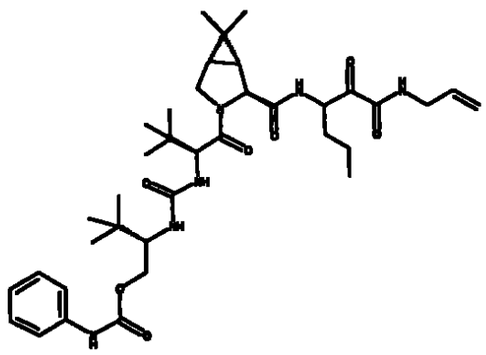
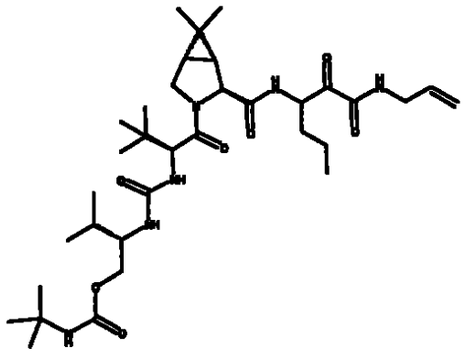
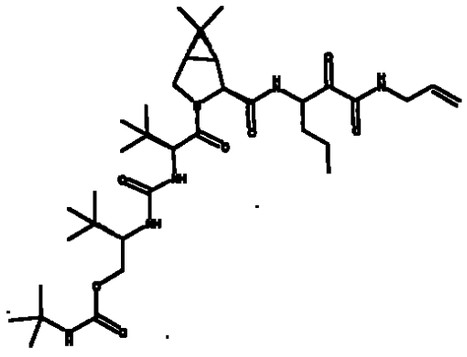
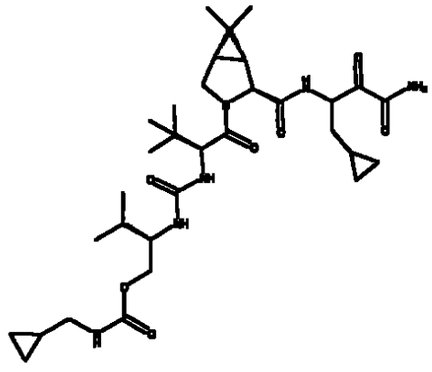
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1005		A	634.815
1006		A	668.832
1007		A	694.87

224
224

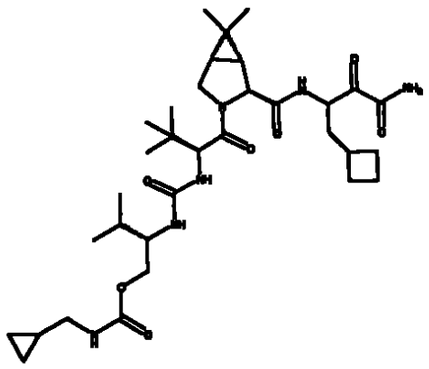
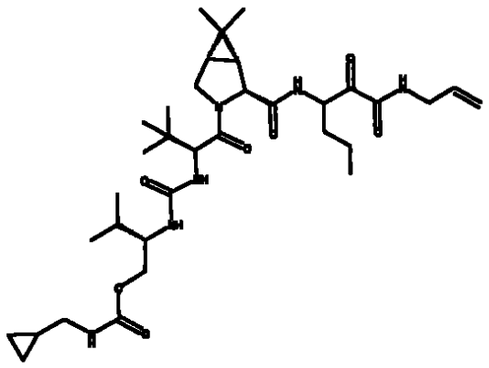
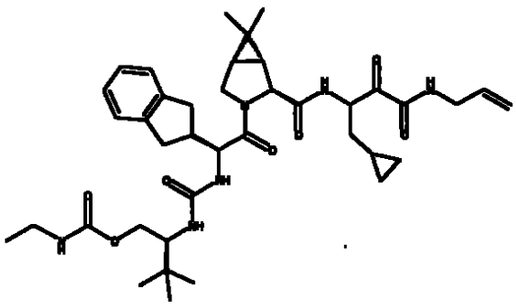
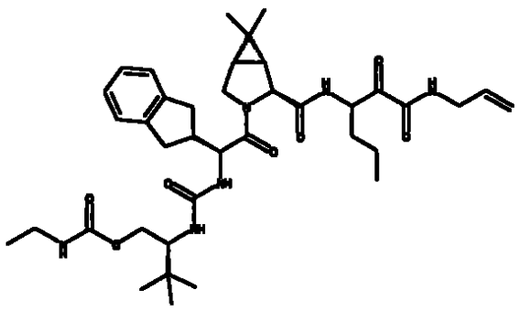
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1009		A	694.87
1010		A	708.896
1011		A	734.934

~~225~~
225

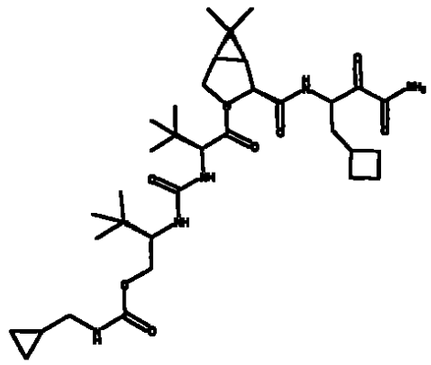
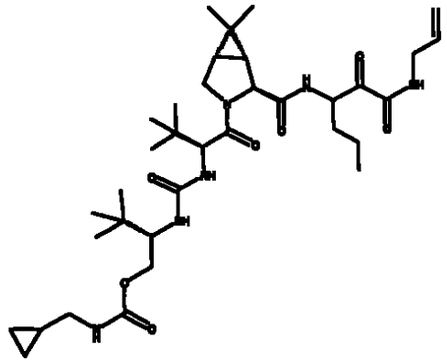
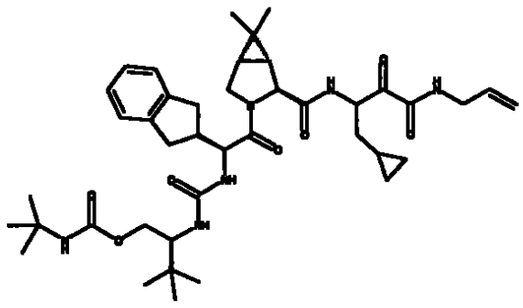
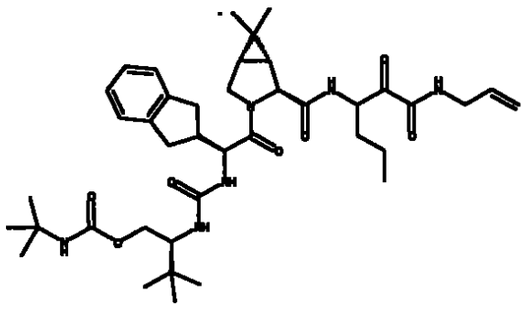
1012		A	722.923
1013		A	694.87
1014		A	708.896
1015		A	776.895

1016		A	696.885
1017		A	662.868
1018		A	676.895
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227
227

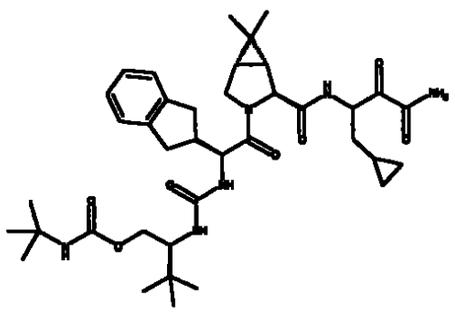
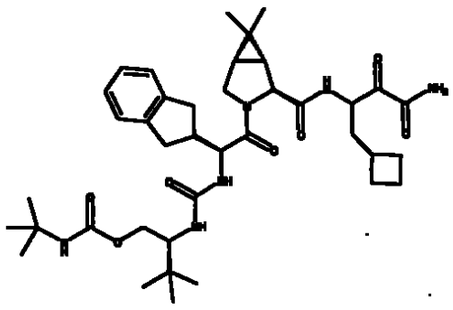
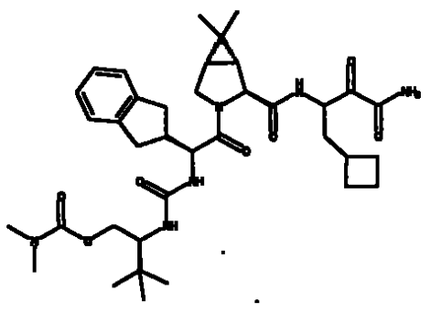
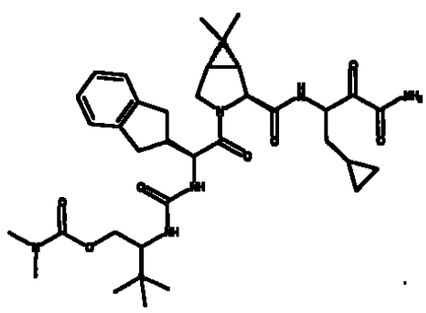
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1021		A	660.852
1022		A	720.907
1023		A	708.896

~~228~~
228

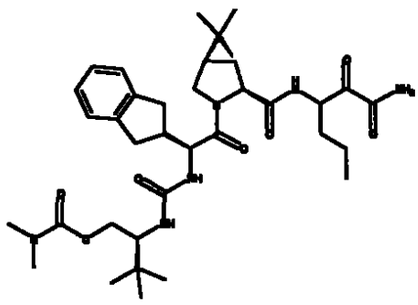
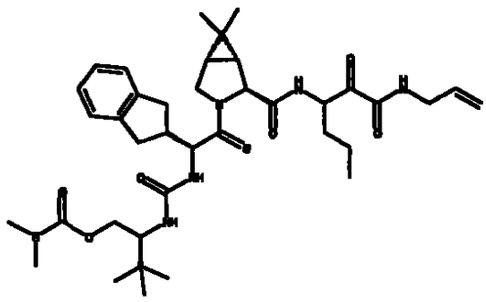
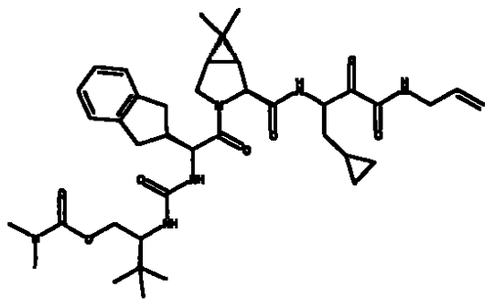
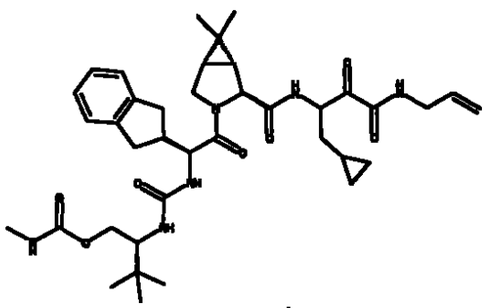
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1030		A	748.961
1031		A	736.95

229

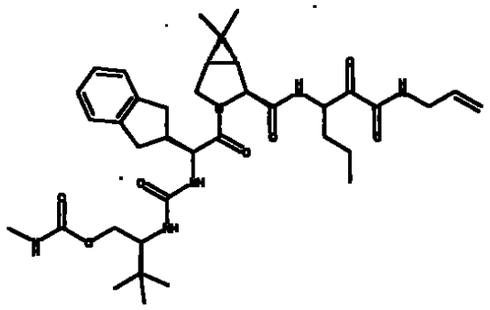
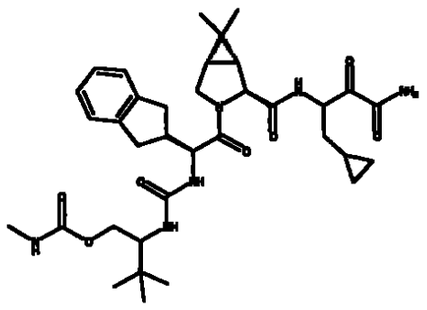
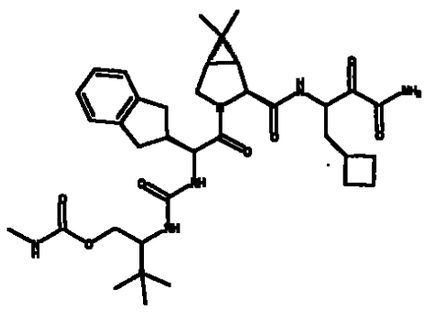
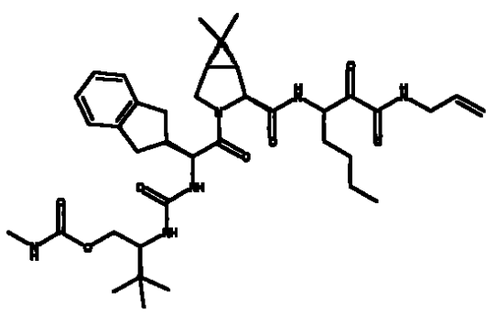
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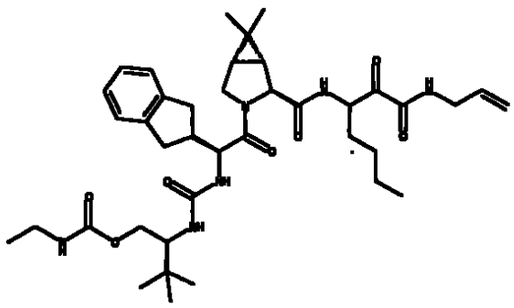
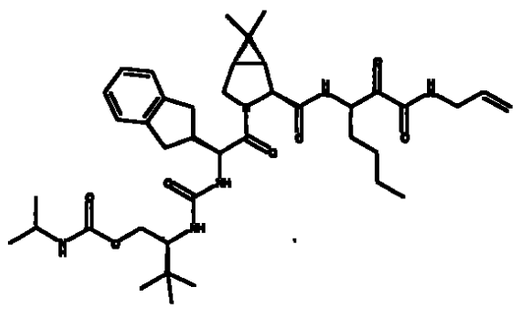
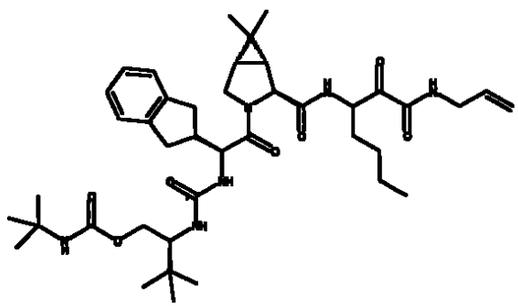
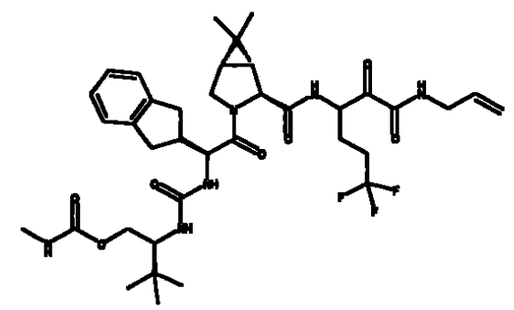
1032		A	708.896
1033		A	722.923
1034		A	694.87
1035		A	680.843

~~283~~ 230

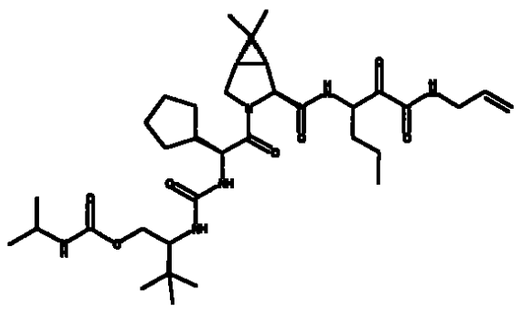
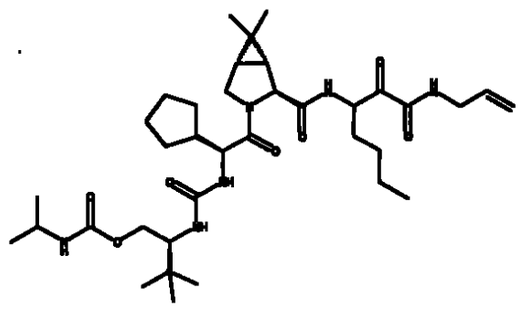
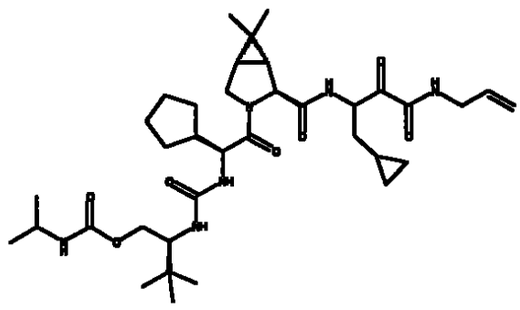
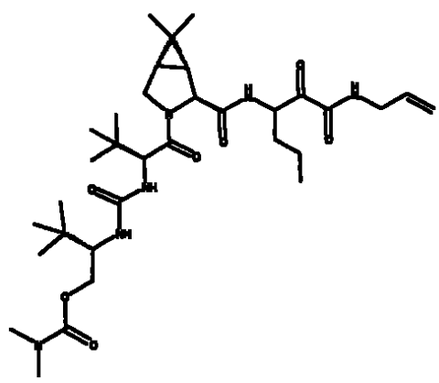
1036		A	668.832
1037		B	708.896
1038		B	720.907
1039		A	706.881

234
231

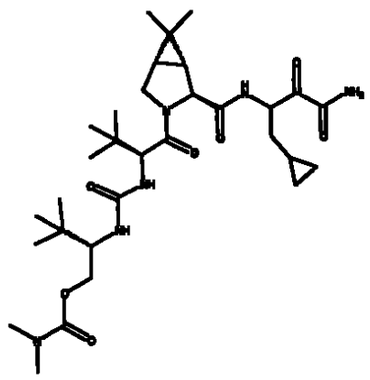
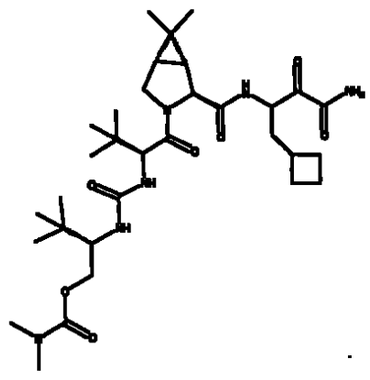
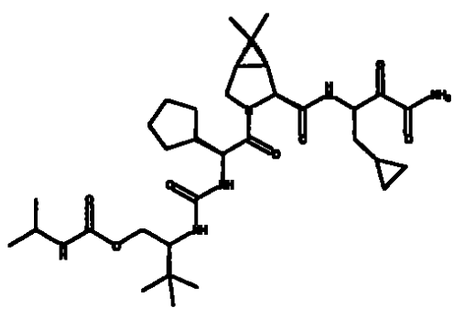
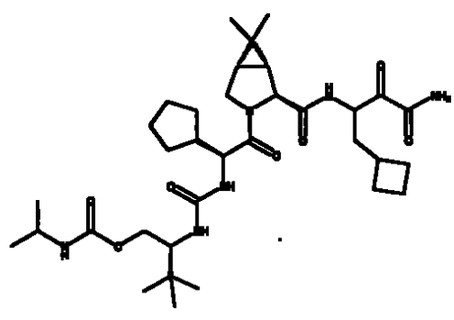
1040		A	694.87
1041		A	666.816
1042		A	680.843
1043		A	708.896

1044		A	722.923
1045		A	736.95
1046		A	750.977
1047		A	748.841

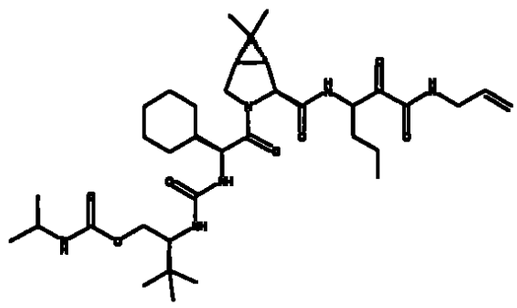
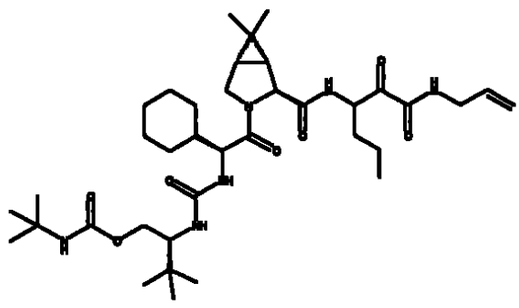
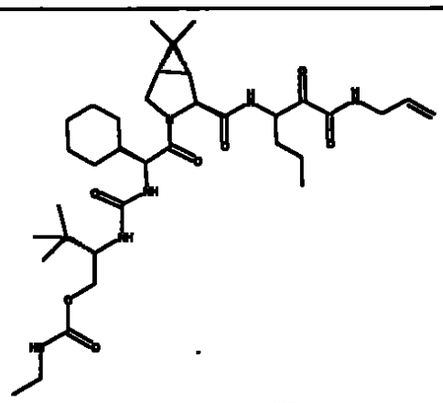
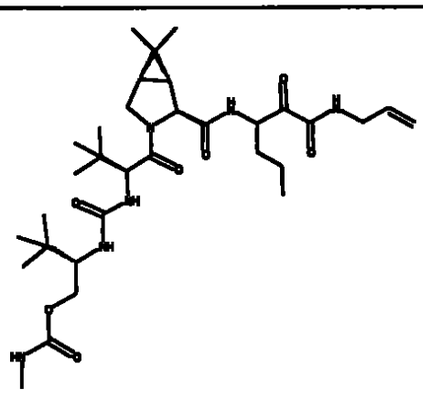
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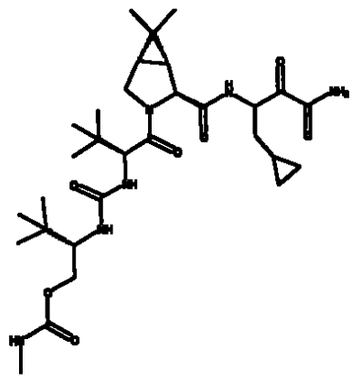
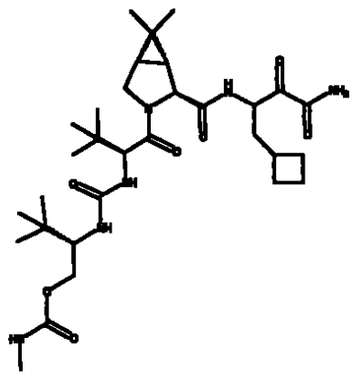
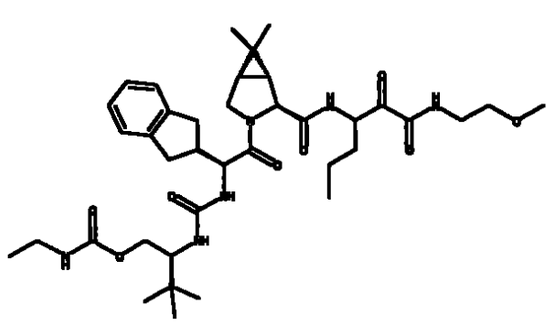
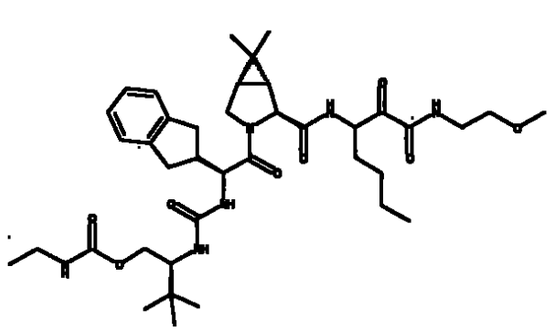
1048		A	674.879
1049		A	688.906
1050		B	686.89
1051		A	648.841

~~234~~
234

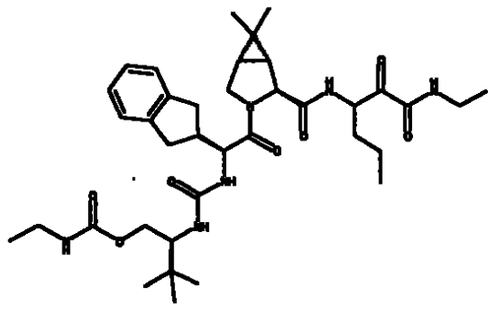
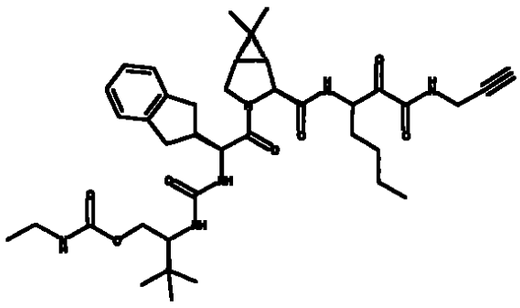
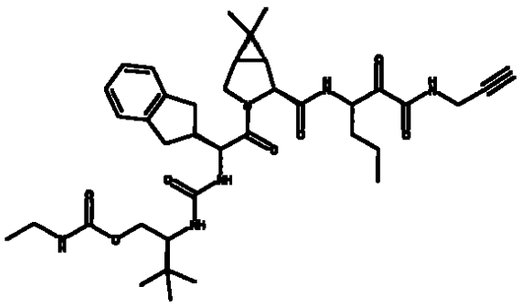
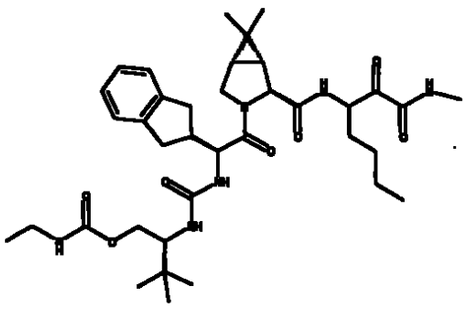
1052		A	620.788
1053		A	634.815
1054		A	646.826
1055		A	660.852

235

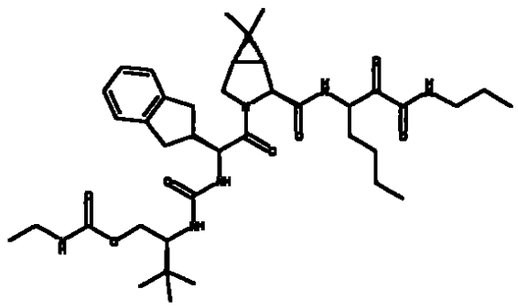
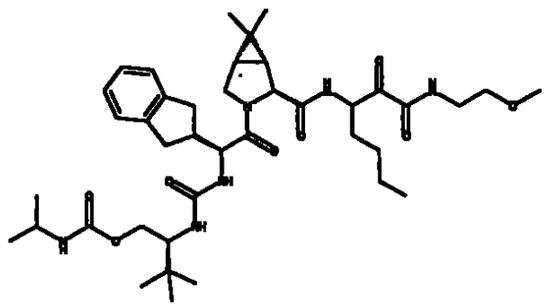
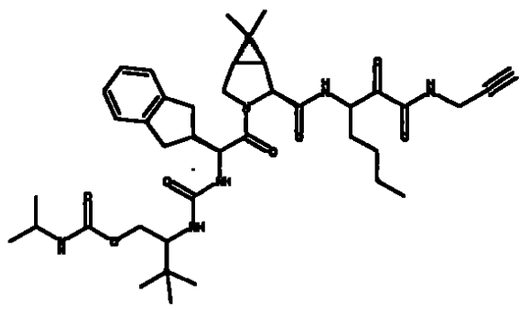
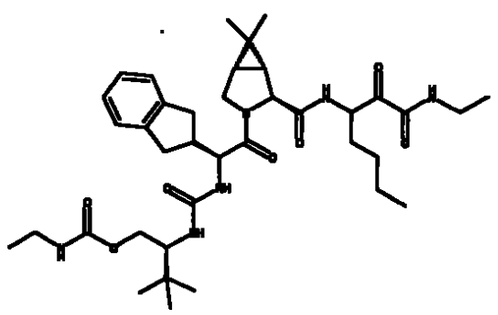
1056		A	688.906
1057		A	702.933
1058		A	674.879
1059		A	634.815

1060		A	606.761
1061		A	620.788
1062		B	726.912
1063		B	740.938

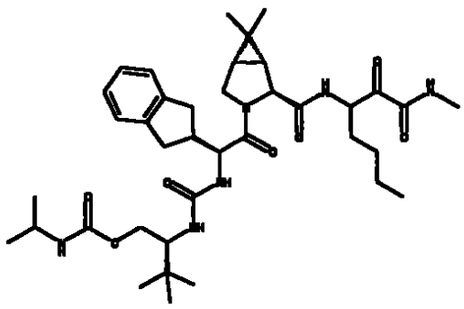
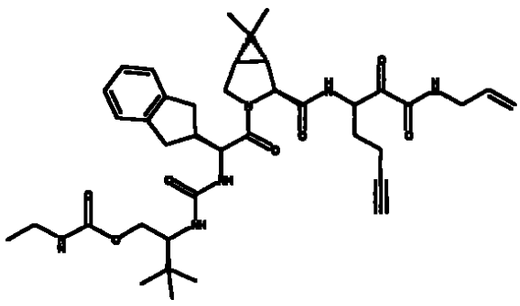
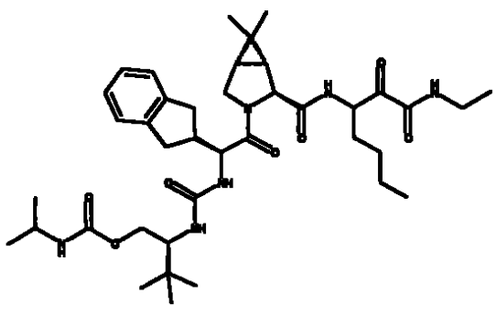
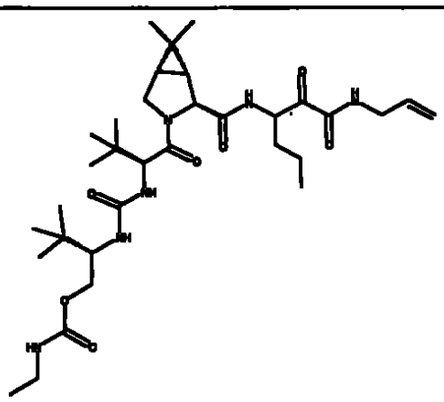
237
237

1064		B	696.885
1065		A	720.907
1066		A	706.881
1067		A	696.885

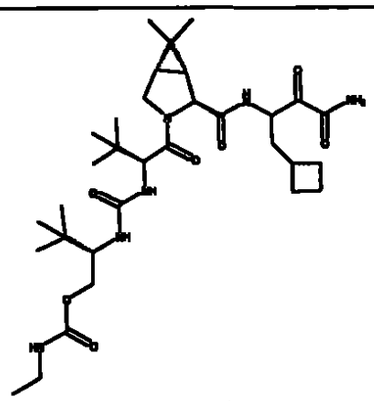
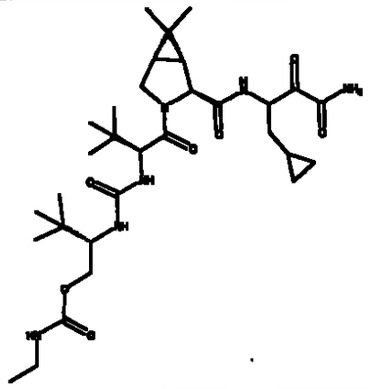
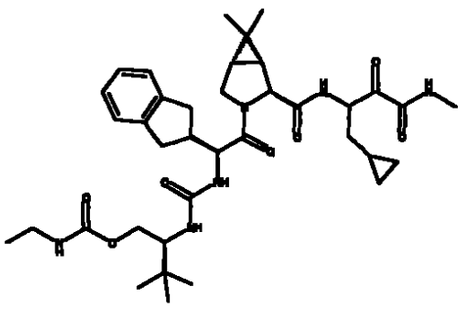
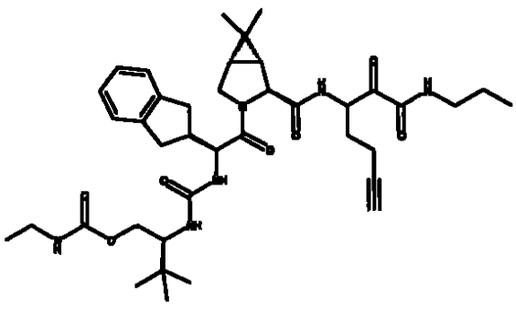
~~238~~
238

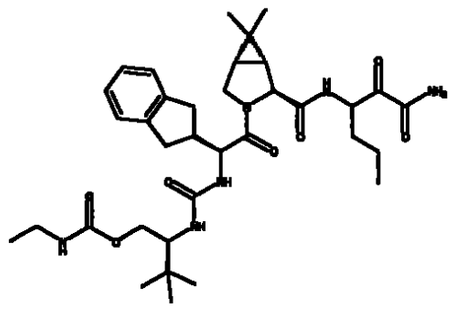
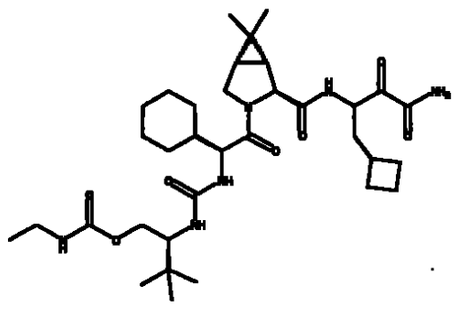
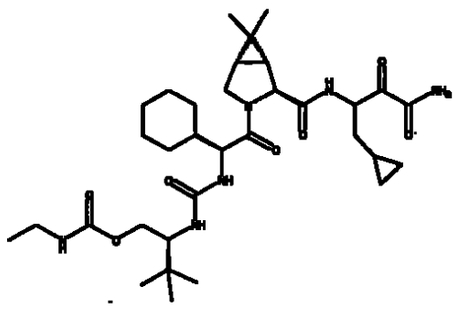
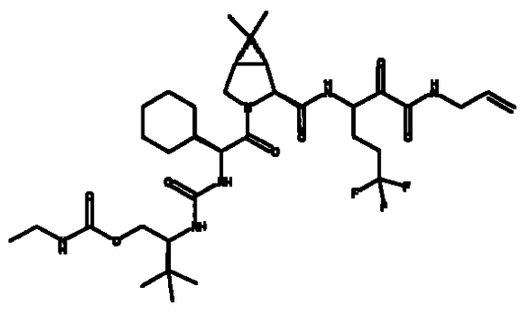
1068		B	724.939
1069		B	754.965
1070		A	734.934
1071		A	710.912

239
239

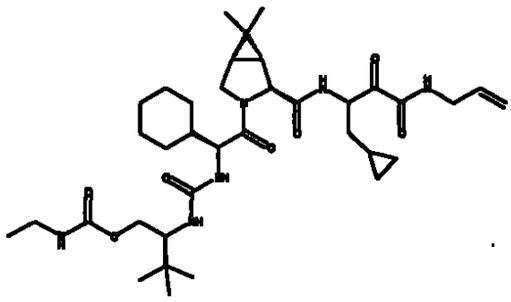
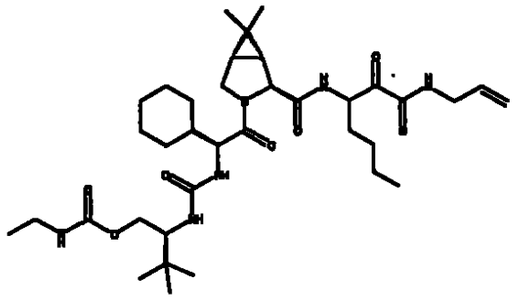
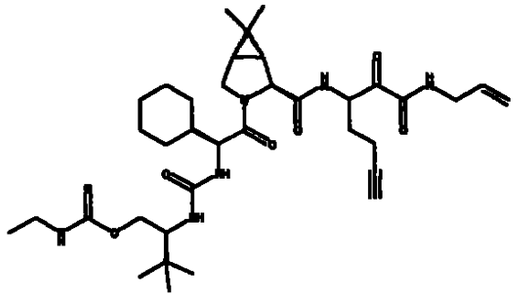
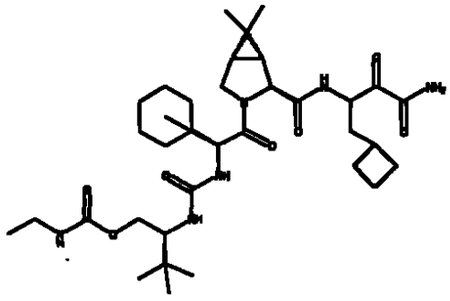
1072		A	710.912
1073		A	718.892
1074		B	724.939
1075		A	648.841

240
240

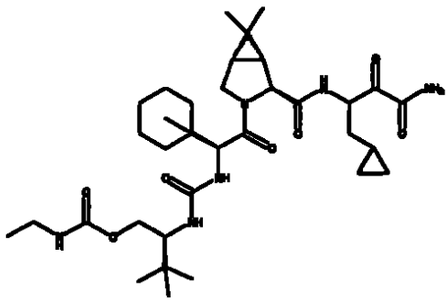
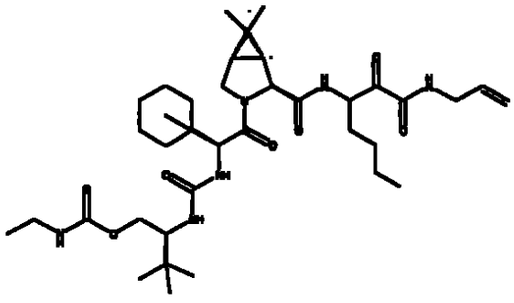
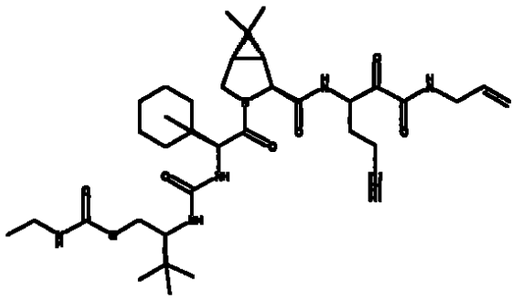
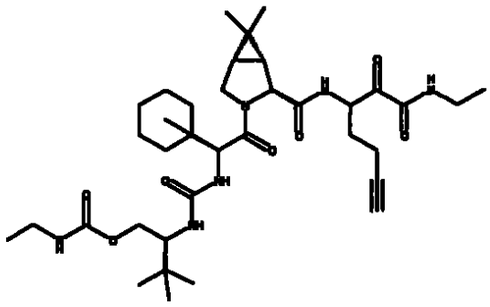
1076		A	634.815
1077		A	620.788
1078		B	694.87
1079		A	720.907

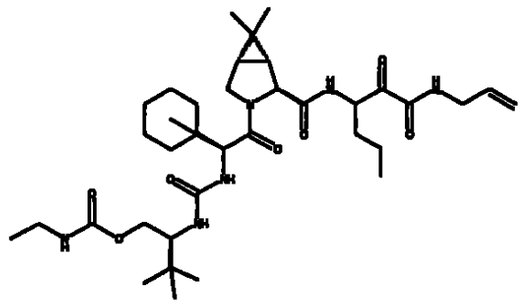
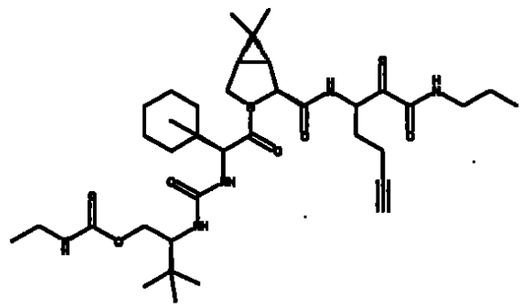
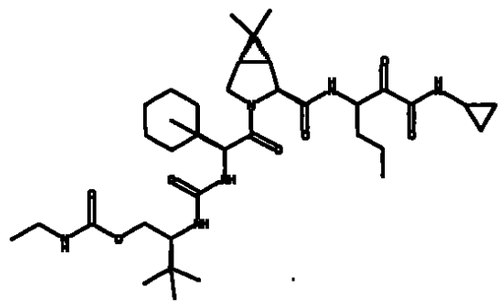
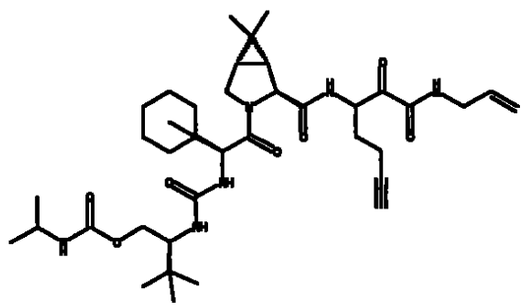
1080		A	668.832
1081		A	660.852
1082		A	646.826
1083		A	728.851

242

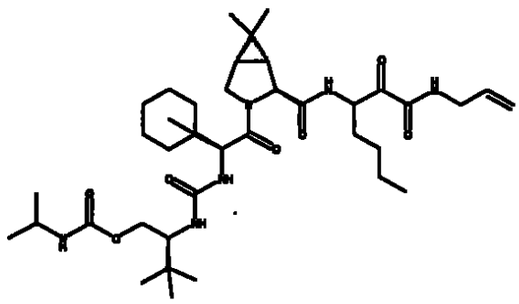
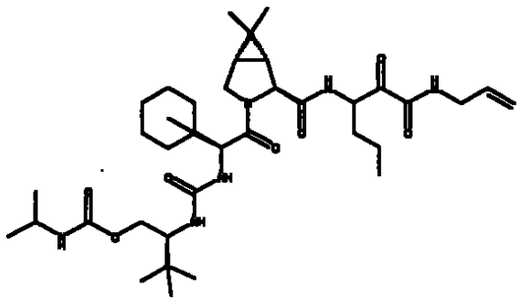
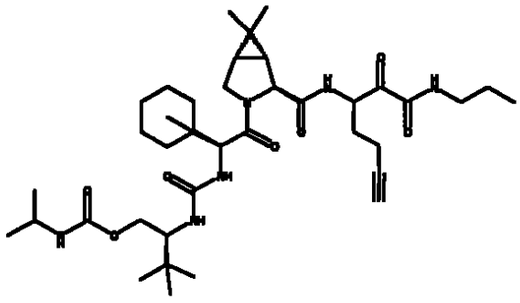
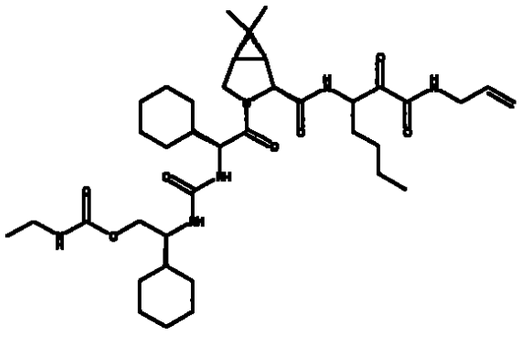
1084		A	686.89
1085		A	688.906
1086		A	684.874
1087		A	674.871

243
243

1088		A	660.844
1089		A	702.924
1090		A	698.892
1091		A	686.882

1092		A	688.898
1093		A	700.908
1094		A	688.898
1095		A	712.919

245
245

1096		A	716.951
1097		A	702.924
1098		A	714.935
1099		A	714.935

2446
2446

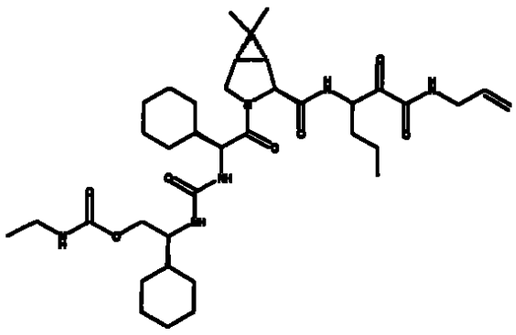
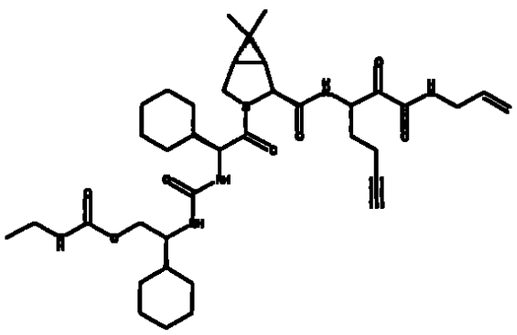
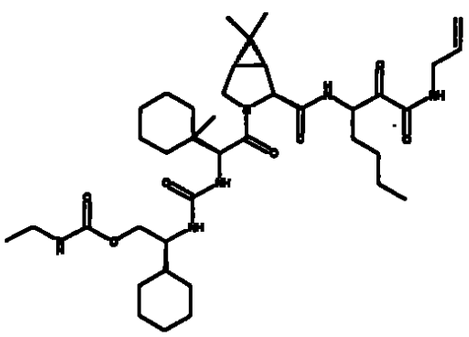
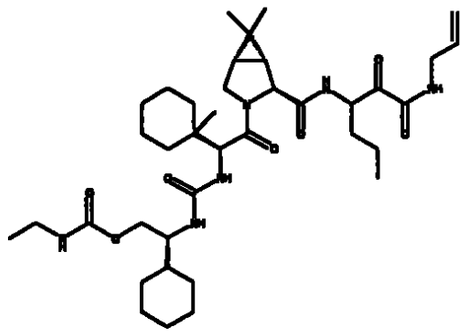
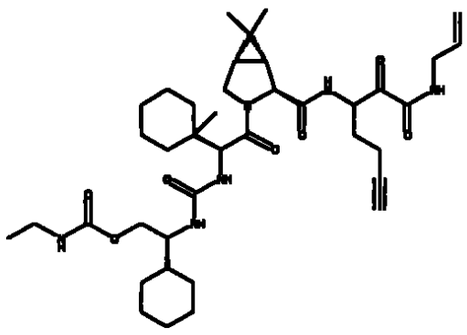
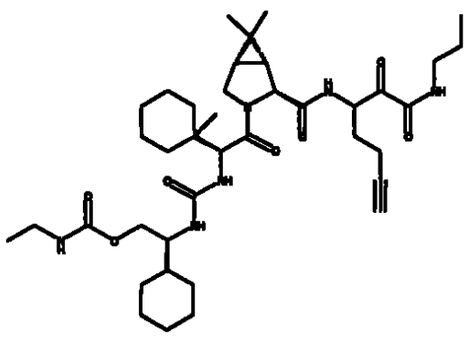
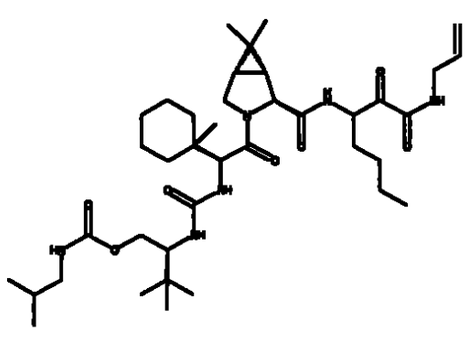
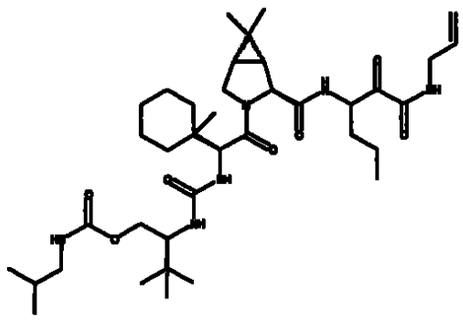
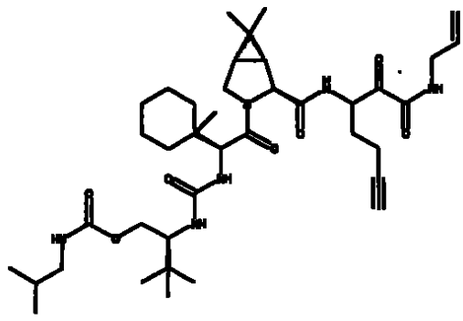
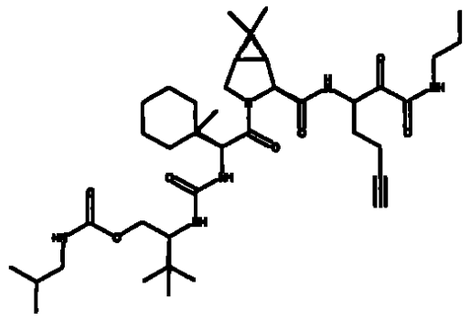
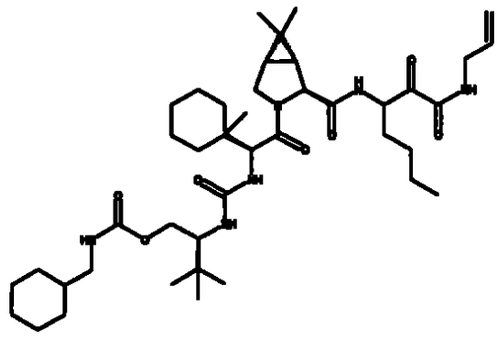
1100		A	700.908
1101		A	710.903

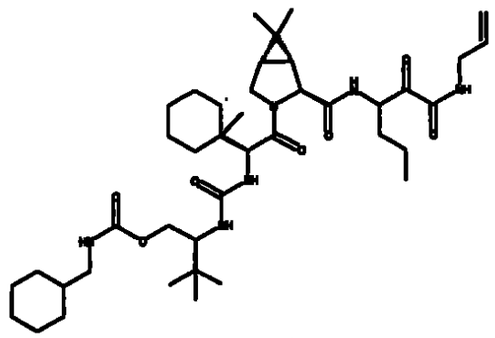
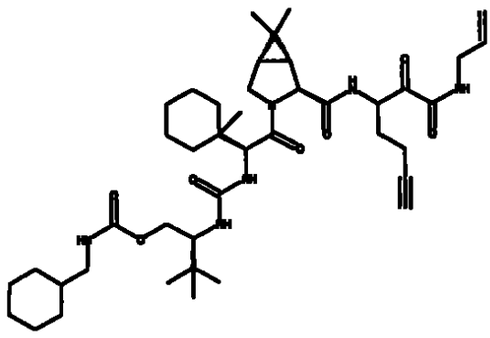
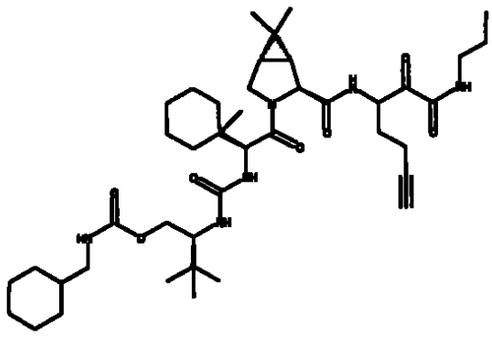
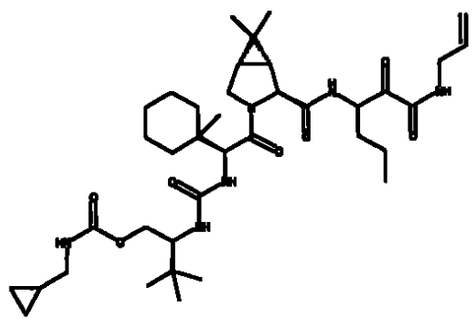
Tabla 1A

Ejemplo #	Estructura	Ki* (nM)	LC-EM (M+H)
1102		A	729.2

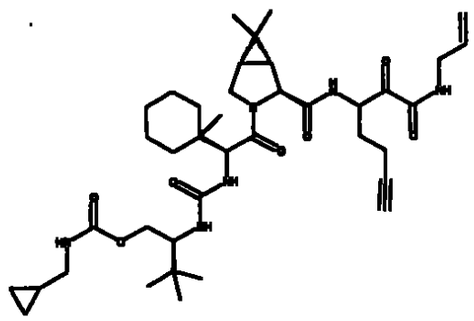
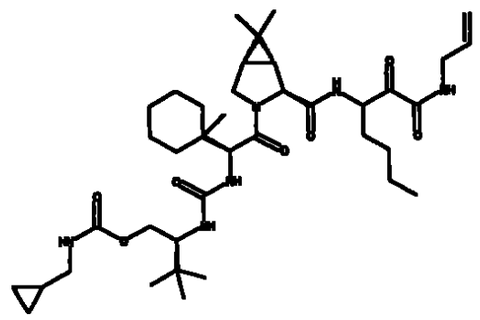
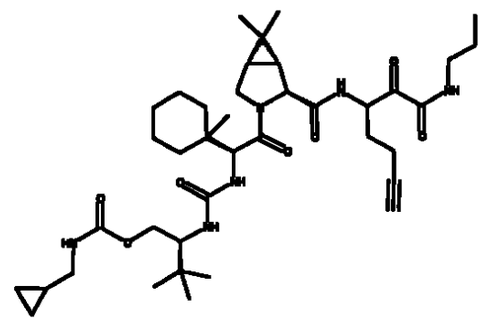
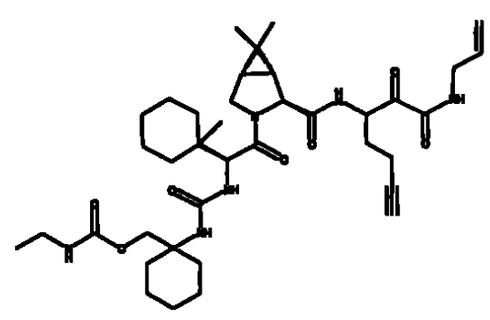
247
247

1103		B	715.2
1104		A	725.2
1105		A	727.2
1106		A	731.2

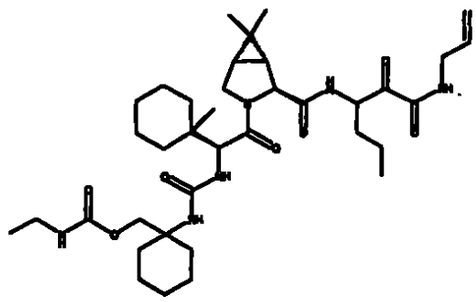
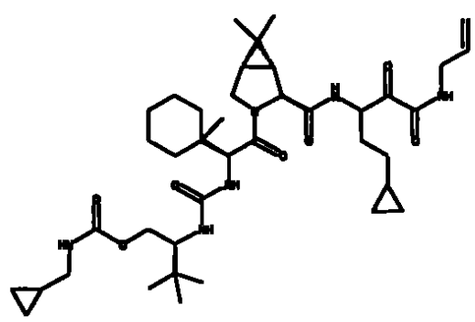
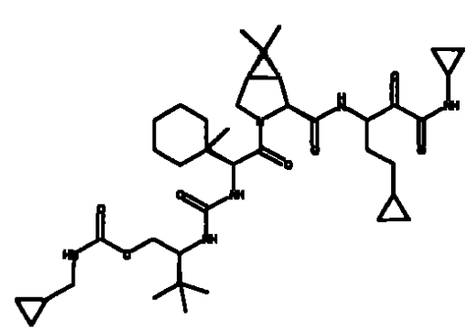
1107		A	717.2
1108		A	727.2
1109		A	729.2
1110		B	772.2

1111		B	757.2
1112		A	767.2
1113		B	769.4
1114		A	715.2

250
250

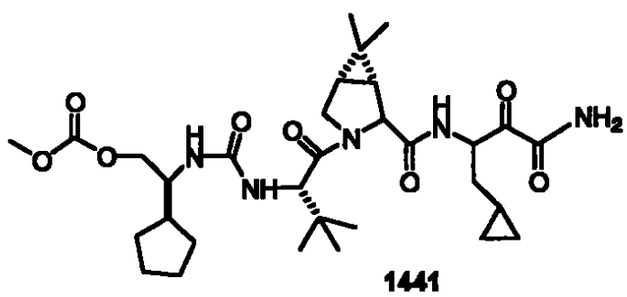
1115		A	724.939
1116		A	729.2
1117		A	727.2
1118		A	711.2

254
251

1119		B	701.2
1120		A	741.2
1121		A	741.4

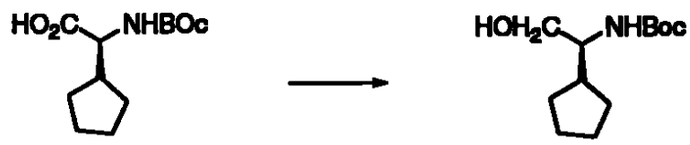
Rango de Ki*: A = <75 nM, B = 75-250 nM; C = > 250 nM

Preparación del Ejemplo 1441:



1441

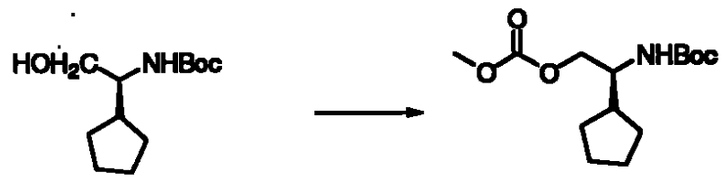
Etapa 1



1441a 1441b

A una solución enfriada con hielo de **1441a** (4,28 g, 10,08 mmoles) en éter anhidro (100 mL) se le agregó LAH (1,53 g, 40,32 mmoles) y la mezcla de reacción se dejó calentar a temperatura ambiente durante la noche. La mezcla de reacción se enfrió a 0ºC y se agregó a la misma EtOAc (3 mL), seguido de $KHSO_4$ acuoso (10 g en 25 mL de H_2O). El residuo gomoso se extrajo con éter (300 mL) y la capa orgánica se lavó con $NaHCO_3$ saturado, seguido de KH_2PO_4 acuoso al 10%, salmuera, se secó sobre $MgSO_4$, se filtró y se concentró. El residuo crudo se purificó por cromatografía evaporativa sobre SiO_2, usando acetato de etilo/DCM (1:4) para proporcionar **1441b** (2,14 g, 92%).

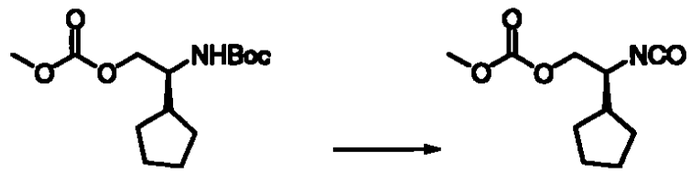
Etapa2



1441b 1441c

A una solución enfriada con hielo **1441b** (743 mg, 3,24 mmoles) en piridina anhidra (10 mL) se le agregó cloroformiato de metilo (1 mL, 13 mmoles), seguido de DMAP (1,6 g, 13 mmoles) y la mezcla de reacción se dejó calentar a temperatura ambiente durante 2 días. La mezcla de reacción se concentró y se agregó a la misma EtOAc (100 mL) seguido de 100 mL de KH_2PO_4 (al 5% que contenía 0,05 volúmenes H_3PO_4 1M) helado. La capa orgánica se lavó con salmuera y se secó sobre $MgSO_4$, se filtró y se concentró. El crudo se purificó por cromatografía evaporativa sobre SiO_2 usando acetato de etilo/DCM (1:4) para proporcionar **1441c** (931 mg, 100% rendimiento).

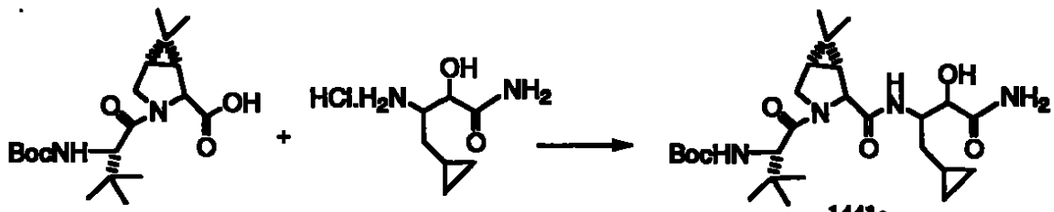
Etapa 3



1441c 1441d

Se disolvió **1441c** en HCl 4M en dioxano (10 mL) y se concentró después de 30 minutos. Se agregó $NaHCO_3$ saturado (25 mL) a una solución enfriada con hielo de la sal de clorhidrato cruda (194 mg, 1 mmol) en CH_2Cl_2 (25 mL). La mezcla de reacción se agitó vigorosamente durante 10 minutos, y se le agregó $COCl_2$ (solución 1,85 M en PhMe, 4 mL) y se continuó la agitación a temperatura ambiente durante 1 hora. La capa orgánica se separó, se secó sobre $MgSO_4$, se filtró y se concentró hasta mitad de volumen para proporcionar **1441d** en forma de una solución 0,05 M en CH_2Cl_2.

Etapa 4



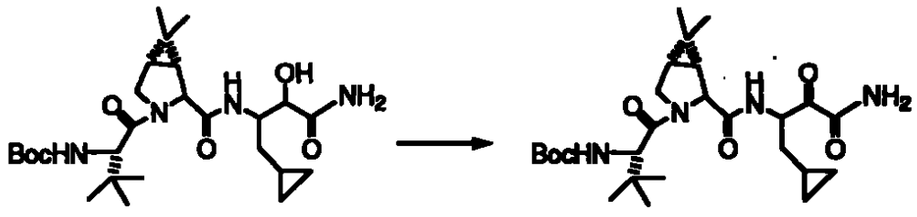
1.17 12.03 1441e

A una solución **1.17** a -20°C (10,4 g, 28 mmoles; obtenida por hidrólisis de **20.06** usando el procedimiento descrito para el intermediario **20.04**, Etapa 2) en DCM (300 mL) se le agregó HATU (1,05 equiv, 29,4 mmoles, 11,2g), sal de amina, Intermediario **12.03** (1,0 equiv, 28 mmoles, 5,48 g). Después de 10 mín a -20°C, se agregaron DIPEA (3,6 equiv, 100 mmoles, 17,4 mL). La reacción se agitó a esta temperatura durante 16 horas. Después de 16 horas, la reacción se diluyó con EtOAc y se lavó sucesivamente con $NaHCO_3$, ácido cítrico (10% p/p) y salmuera. La capa orgánica se secó sobre $MgSO_4$, se filtró y se concentró al vacío para proporcionar 14 g del Intermediario requerido **1441e**.

Etapa 5

254

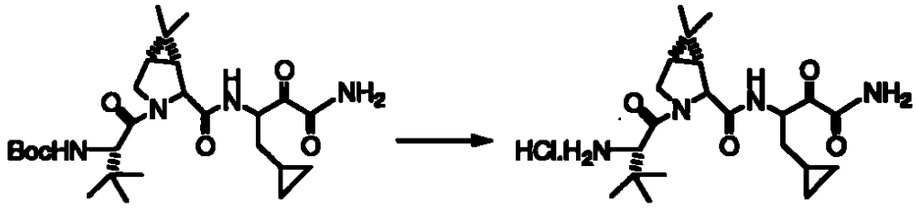
254



1441e 1441f

Se oxidó la hidroxiamida **1441e** a la cetoamida requerida **1441f** en la manera descrita para el ejemplo **1007**, Etapa 6. LC-EM = 507 $(M+H)^+$

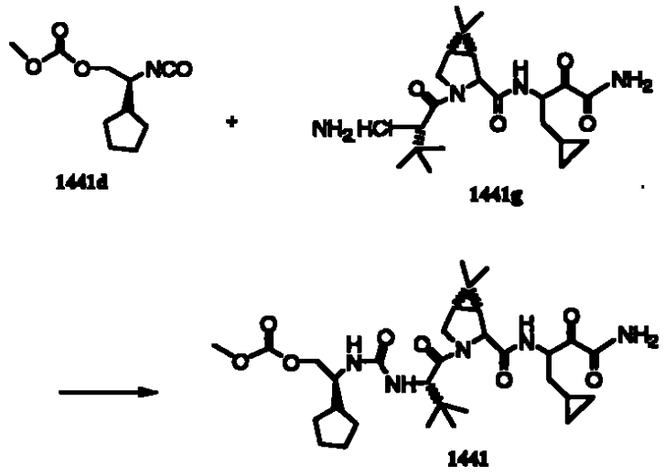
Etapa 6



1441f 1441g

La desprotección de la funcionalidad t-Boc de **1441f** para proporcionar el material requerido **1441g** se llevó a cabo tal como se describió para el ejemplo **1007**, Etapa 2.

Etapa 7



1441d 1441g

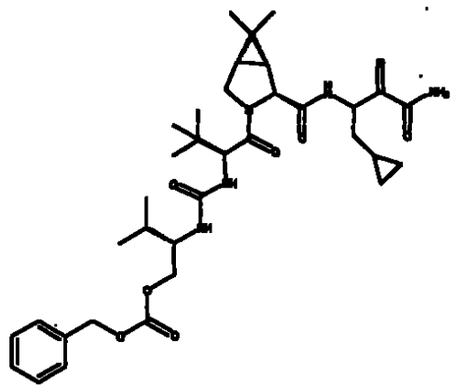
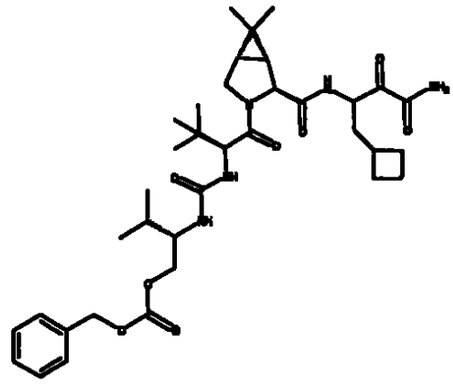
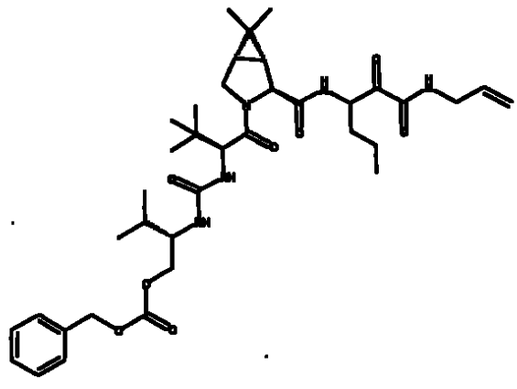
1441

A una solución enfriada (0°C) del clorhidrato de amina **1441g** (20 mg, 0,045 mmoles) en CH_2Cl_2 (2,0 mL) se le agregó **1441d** (1,35 mL, 0,135 mmoles), seguido de DIPEA (63 µL, 0,4 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 1,2 horas, se diluyó con acetato de etilo (20 mL), se lavó con ácido cítrico al 3%, salmuera, se secó sobre $MgSO_4$, se filtró, se concentró y se purificó sobre SiO_2 usando EtOAc/DCM (1:9 a 9:1) para proporcionar **1441** (23 mg). LCEM = 620,3 $(M+H)^+$.

255
255

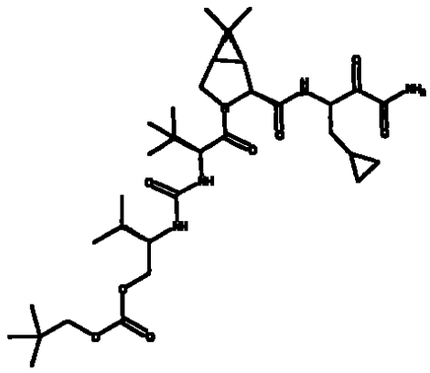
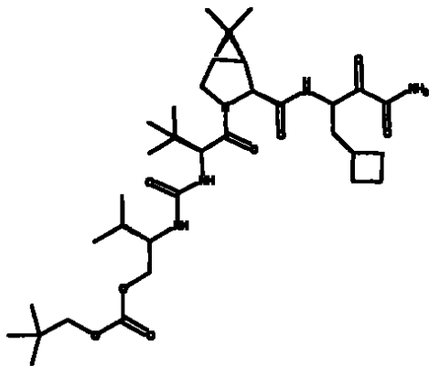
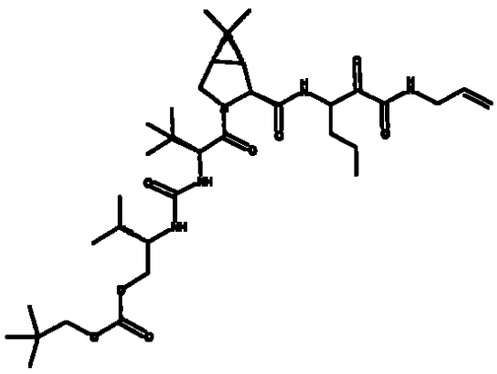
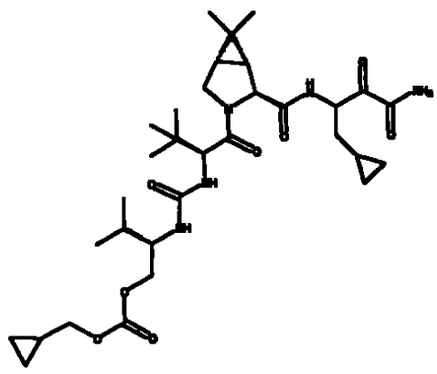
Los compuestos de la tabla siguiente (**Tabla 2**) se prepararon esencialmente usando los procedimientos descritos anteriormente (Preparación del ejemplo **1441**) con los reactivos apropiados y las modificaciones descritas en los Esquemas Generales para la Preparación de los Compuestos Objetivos, Métodos A-E.

Tabla 2

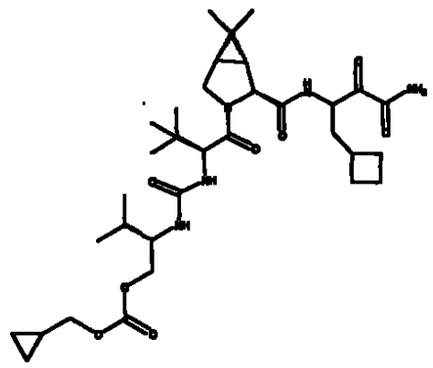
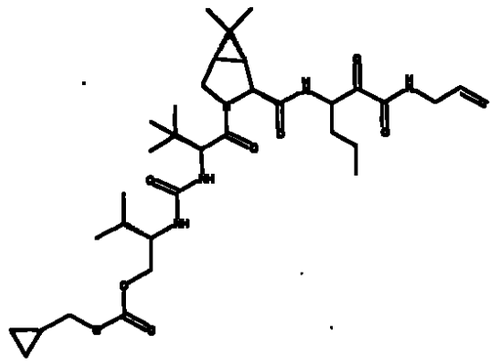
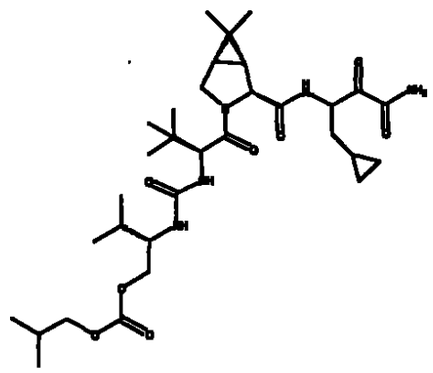
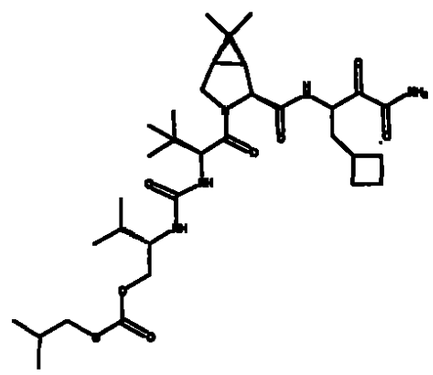
Ejemplo #	Estructura	Ki* (nM)	Peso Molar
1401		A	669.817
1402		A	683.843
1403		B	697.87

256

256

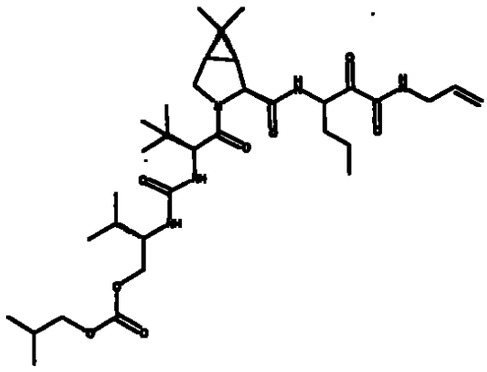
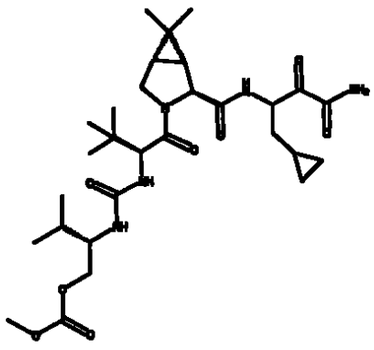
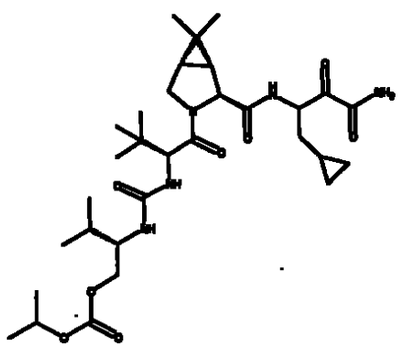
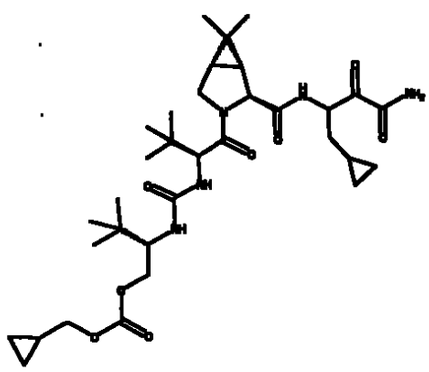
1404		A	649.826
1405		A	663.853
1406		B	677.88
1407		A	633.784

~~252~~
257

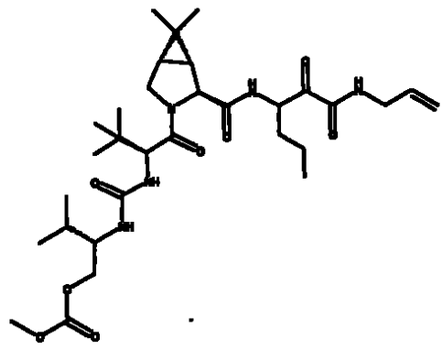
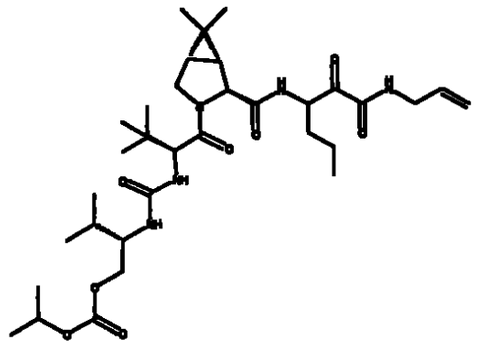
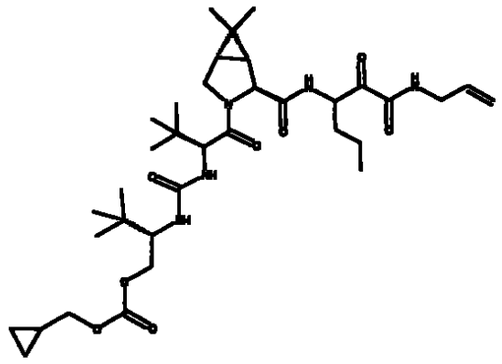
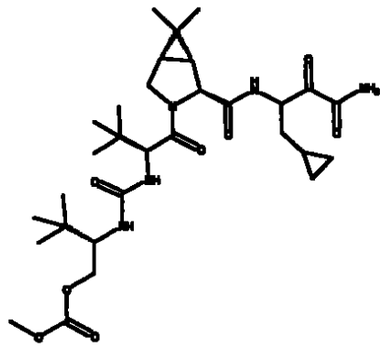
1408		A	647.81
1409		B	661.837
1410		A	635.799
1411		A	649.826

258

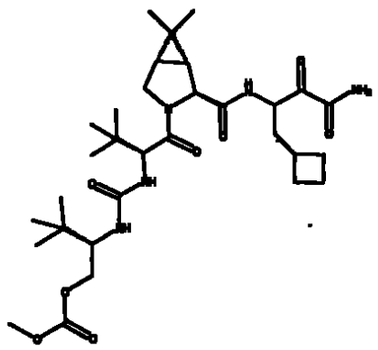
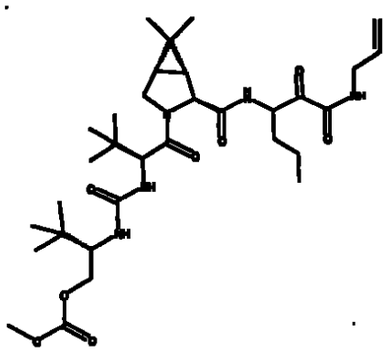
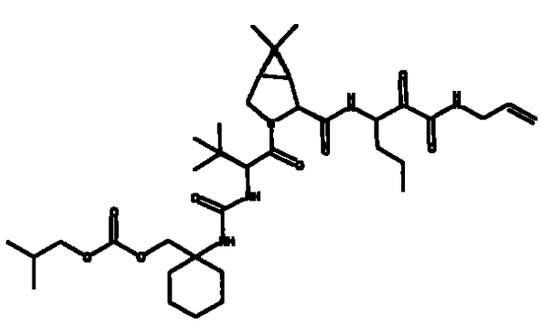
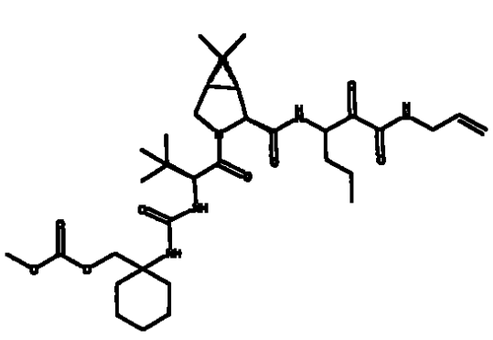
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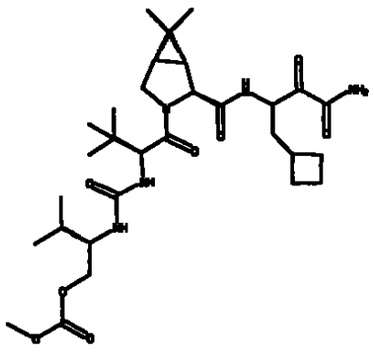
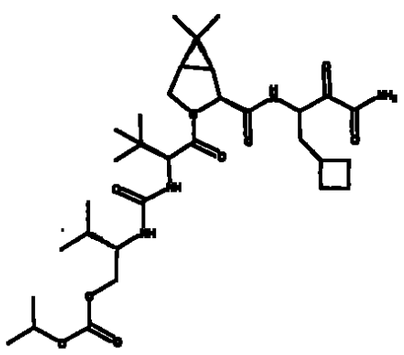
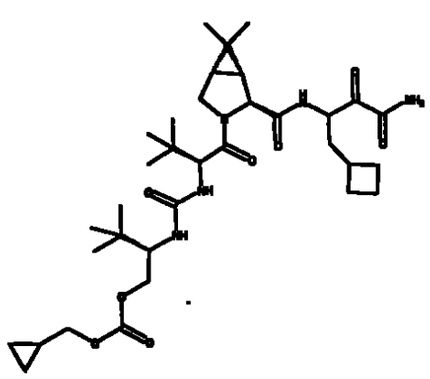
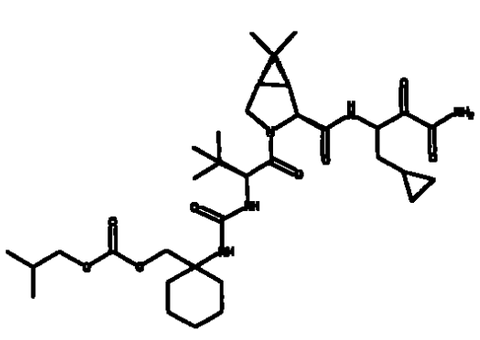
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1413		A	593.719
1414		A	621.773
1415		A	647.81

259

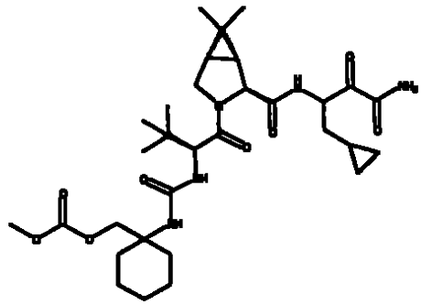
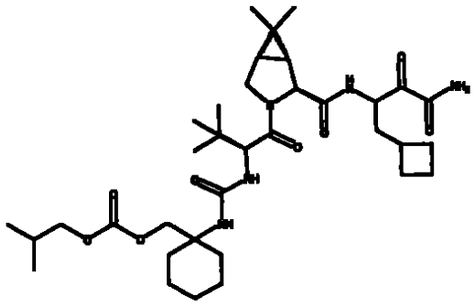
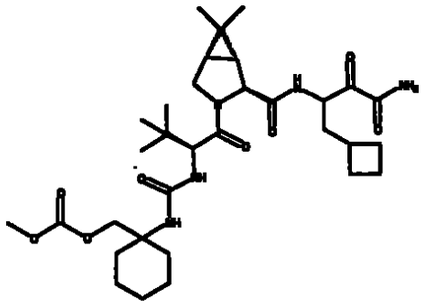
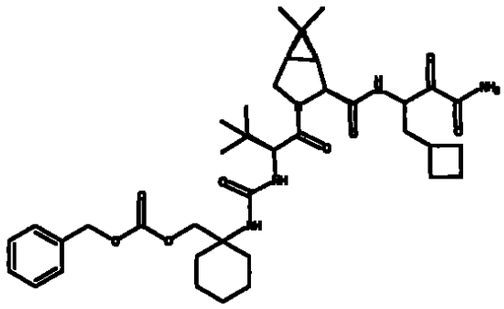
1416		A	621.773
1417		A	649.826
1418		A	675.864
1419		A	607.746

260

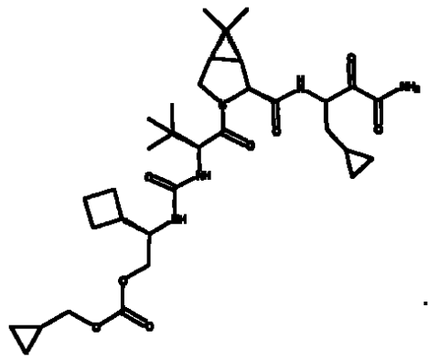
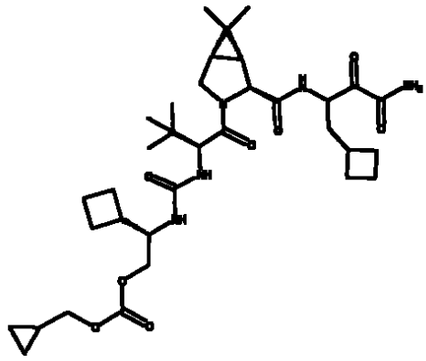
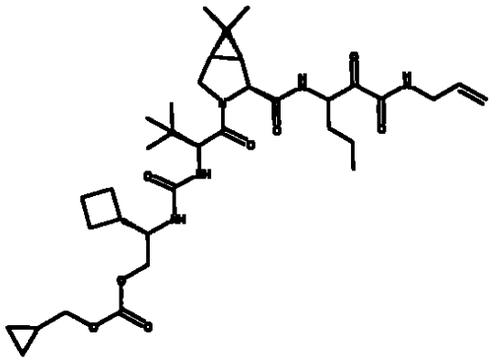
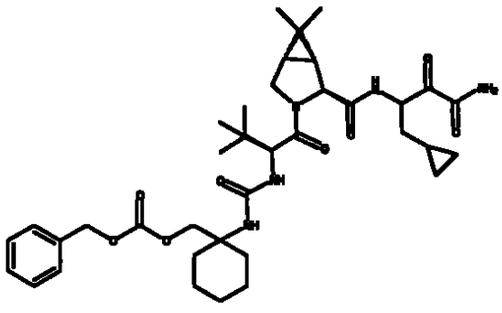
1420		A	621.773
1421		A	635.799
1422		C	689.891
1423		B	647.81

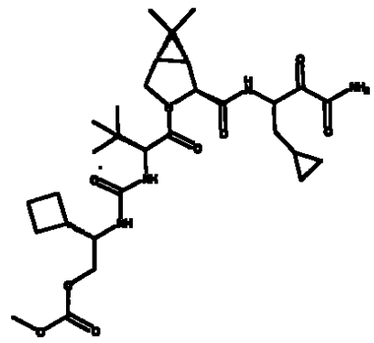
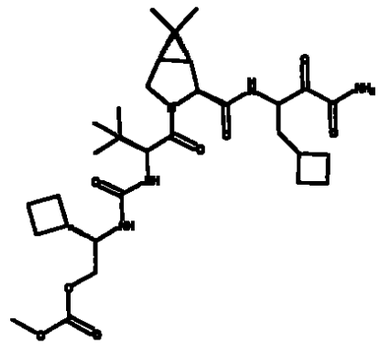
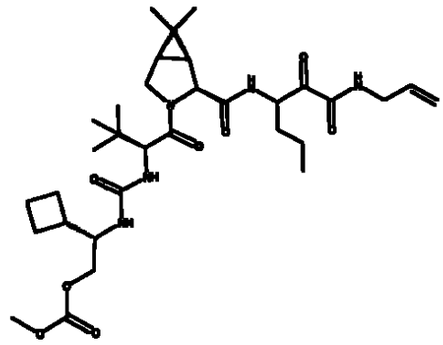
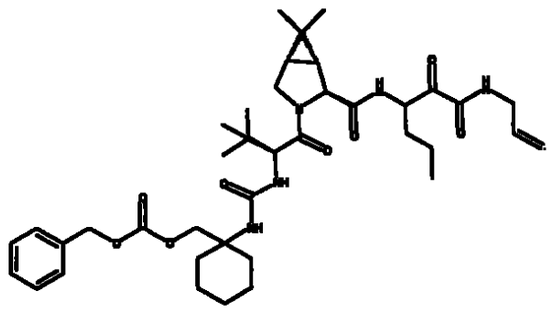
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1426		A	661.837
1427		A	661.837

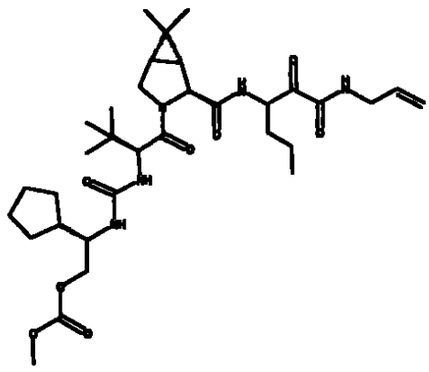
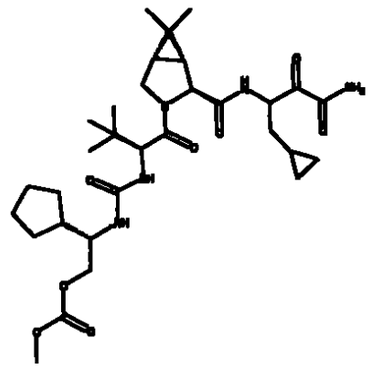
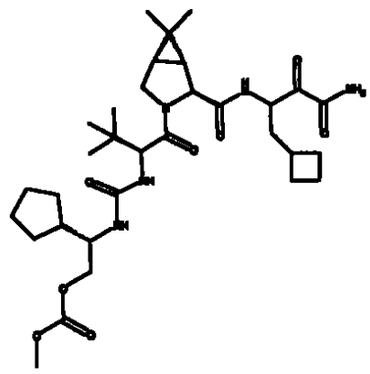
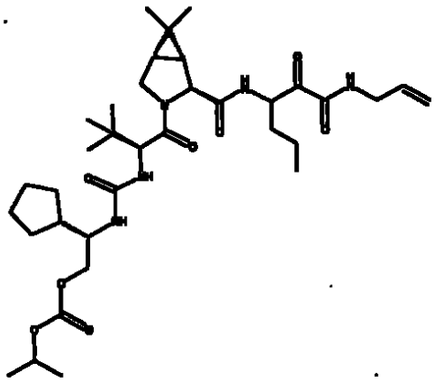
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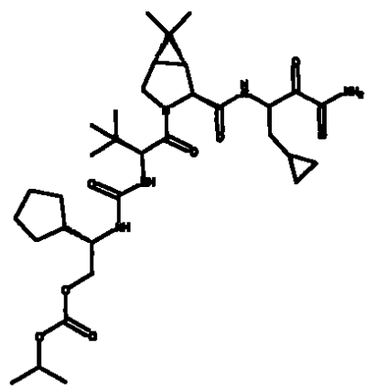
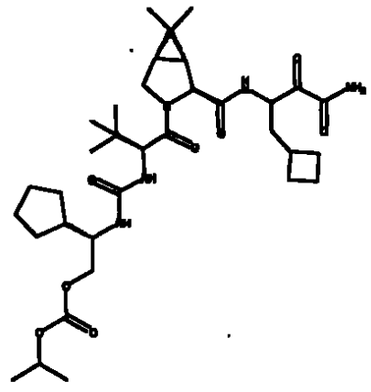
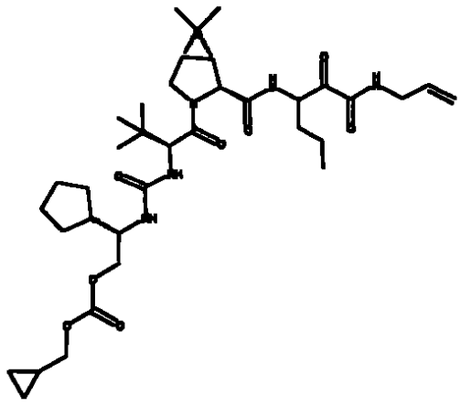
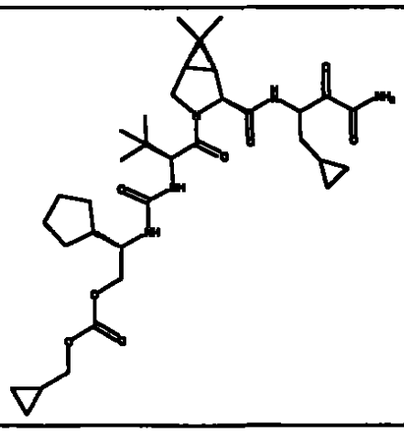
1428		A	619.757
1429		A	675.864
1430		A	633.784
1431		B	709.881

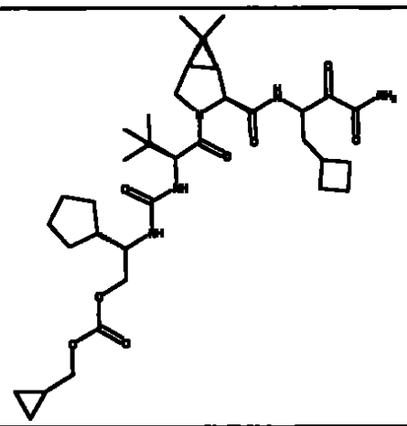
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263

1432		A	645.795
1433		A	659.821
1434		B	673.848
1435		B	695.854

1436		A	605.73
1437		A	619.757
1438		B	633.784
1439		B	723.908

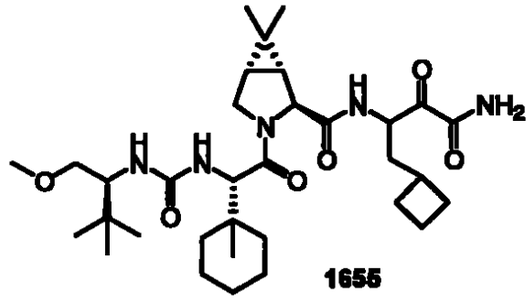
1440		B	647.81
1441		A	619.757
1442		A	633.784
1443		B	675.864

1444		A	647.81
1445		A	661.837
1446		B	687.875
1447		A	659.821

1448		A	673.848

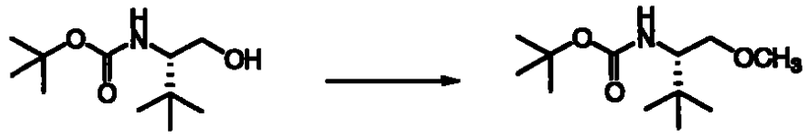
Rango de Ki* A = <75 nM; B = 75-250 nM; C = >250 nM

Preparación del Ejemplo 1655



1655

Etapa 1



1655a 1655b

A una solución del compuesto comercialmente obtenible **1655a** (Aldrich Chemical Co., Milwaukee, Wisconsin, USA, 950 mg, 4,38 mmoles) en acetonitrilo (40 mL) a temperatura ambiente se le agregó yoduro de metilo (4,63 mL, 74,42 mmoles). Luego se agregó óxido de plata (I) (1,62 g, 7,01 mmoles) bajo atmósfera de nitrógeno, y la mezcla de reacción se reflujó durante aproximadamente 16 horas. (Nota: El frasco de reacción se cubrió con una hoja de aluminio). En este momento, la mezcla de reacción se enfrió a temperatura ambiente y se filtró a través de una almohadilla de celite. La torta filtrada se enjuagó con acetato de etilo varias veces. El filtrado combinado se concentró y se purificó por cromatografía en columna evaporativa usando 20/80 a 40/60 de acetato de etilo/hexanos para proporcionar 720 mg del producto esperado **1655b**.

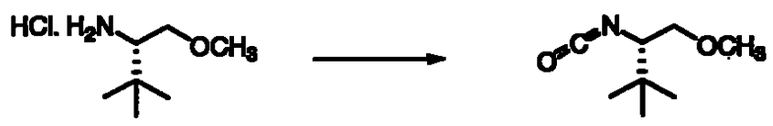
Etapa 2



1655b 1655c

La conversión de **1655b** al compuesto **1655c** prosiguió con un rendimiento cuantitivo usando previamente el procedimiento descrito (Etapa 2, Ejemplo **1007**).

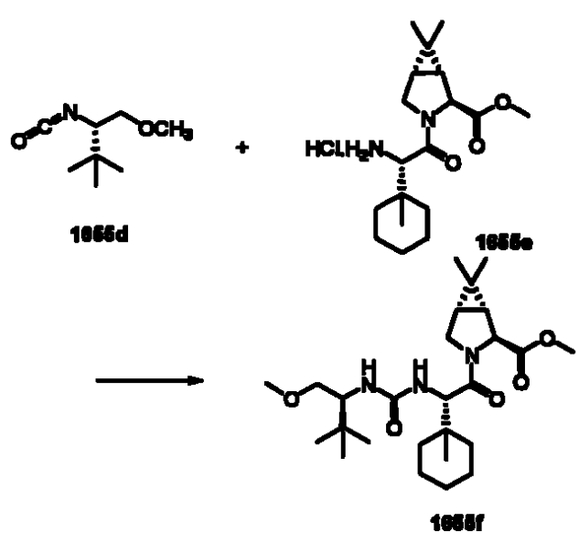
Etapa 3



1655c 1655d

A una soluciónd el compuesto **1655c** (514 mg, 3,08 mmoles) en diclorometano (20 mL) se le agregó una solución saturada de bicarbonato de sodio (20 mL). Esta mezcla se agitó vigorosamente, se enfrió a 0ºC. Se agregó por goteo fosgena (20% en peso en tolueno, 6,5 mL). La mezcla de reacción se agitó vigorosamente durante 4,5 horas mientras se mantenía la temperatura por debajo de 5ºC. Al cabo de este período de tiempo la mezcla de reacción se vertió en un embudo separador y se separó la capa orgánica. La capa orgánica se lavó con solución saturada de cloruro de amonio (1 x), aguá (1 x), se secó (Na_2SO_4) y se concentró. El residuo, **1655d**, se diluyó con diclorometano (10 mL) y se usó adicionalmente como una solución 0,308M.

Etapa 4

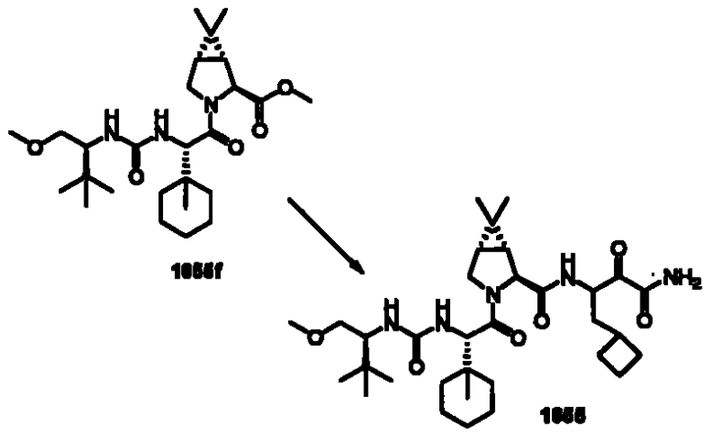


1655d 1655e

1655f

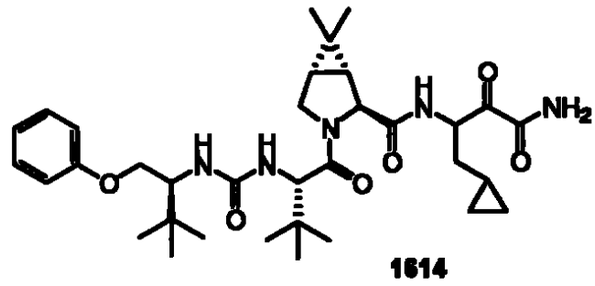
A una solución fría (0ºC) de **1655e** (176 mg, 0,5 mmoles; **1655e** preparada tal como se describió para el intermediario **20.08**, Etapas 1 y 2 usando los materiales de partida apropiados) en diclorometano (4 mL) se le agregó **1655d** (solución 0,308 M, 4,87 mL, 1,5 mmoles) seguido de DIPEA (0,276 mL, 1,5 mmoles). La mezcla de reacción se mantuvo a 10ºC durante 16 horas. La reacción se apagó con una solución saturada de cloruro de amonio, y la capa acuosa se extrajo con diclorometano (3 x). La capa orgánica combinada se lavó salmuera, se secó (Na_2SO_4), se filtró y se concentró al vacío. El residuo crudo se purificó por cromatografía en columna evaporativa usando 20/80 de acetona/hexanos para proveer el compuesto requerido **1655f** (240 mg, rendimiento 100%). LC-EM: 480.1 (M+H).

Etapa 5



El compuesto **1655f** se convirtió al compuesto objetivo requerido **1655** usando el intermediario **10.11** y los procedimientos descritos anteriormente (Etapas 4 - 6, Ejemplo **1007**). LC-EM de **1655** = 618,1 (M+H).

Preparación del Ejemplo 1614



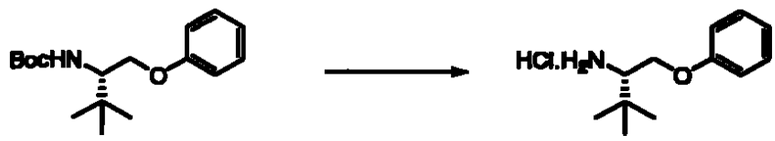
Etapa 1



1655a 1614a

A una solución agitada de *N*-Boc-*ter*-leucinol **1655a** (2,0 g, 9,22 mmoles), fenol (1,0 g, 10,6 mmoles) y ADDP (3,8 g, 15,1 mmoles) en CH_2Cl_2 (80 mL) a temperatura ambiente se le hizo burbujear gas argon durante 15 minutos. Luego se agregó trifenilfosfina en una sola porción. La solución resultante se agitó a temperatura ambiente durante 18 horas. El precipitado se separó por filtración y se lavó con éter dietílico (2 X 30 mL). El filtrado se concentró al vacío. El residuo se purificó por cromatografía en columna evaporativa eluyendo con 2-10% de EtOAc/hexano para proporcionar el producto deseado **1614a** (0,33 g, 12%).

Etapa 2



1614a 1614b

Se disolvió el compuesto **1614a** (0,32 g, 1,13 mmoles) en una solución de cloruro de hidrógeno 4 M en *p*-dioxano (20 mL) y se agitó a temperatura ambiente durante 3 horas. Se concentró al vacío para proporcionar el compuesto **1614b**, el cual se usó sin purificación alguna.

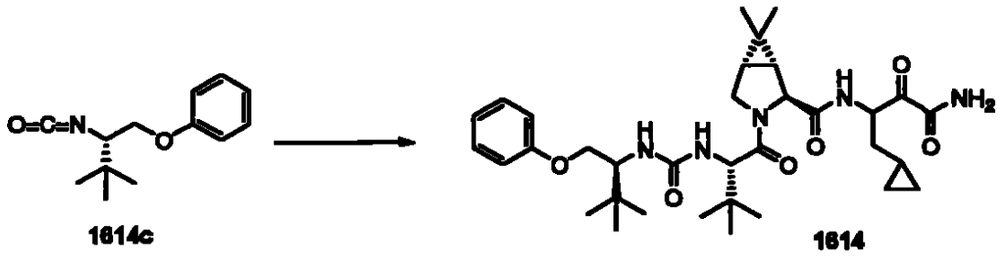
Etapa 3



1614b 1614c

El compuesto **1614c** se preparó a partir de **1614b** de acuerdo con los procedimientos descritos en el ejemplo **1655**, Etapa 3.

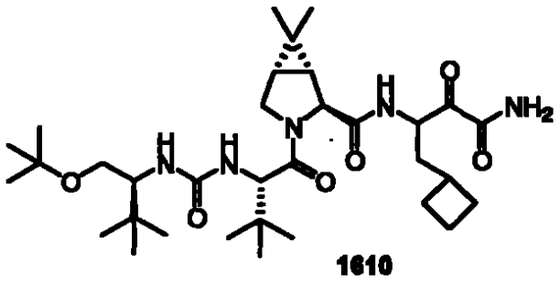
Etapa 4



1614c 1614

El isocianato **1614c** se convirtió al compuesto objetivo **1614** tal como se describió en los Esquemas Generales, Métodos C usando los reactivos e intermediarios apropiados.

Preparación del Ejemplo 1610



1610

Etapa 1



1610a 1610b

A una suspensión agitada de sulfato de magnesio anhidro en CH_2Cl_2 anhidro (40 mL) a temperatura ambiente se le agregó ácido sulfúrico concentrado (0,32 mL, 5,76 mmoles). La mezcla se agitó vigorosamente durante 30 minutos antes de agregar una solución de **1610a** (2,0 g, 7,90 mmoles) en CH_2Cl_2 anhidro (15 mL). La mezcla se agitó luego vigorosamente a temperatura ambiente durante 68 horas. Se agregó cuidadosamente una solución satura de $NaHCO_3$ (50 mL), junto con CH_2Cl_2 (100 mL) y agua (50 mL). Se separaron dos fases, y la capa acuosa se extrajo con CH_2Cl_2 (2 X 100 mL). La solución orgánica combinada se secó ($MgSO_4$), se filtró y concentró al vacío para obtener **1610b**.

Etapa 2

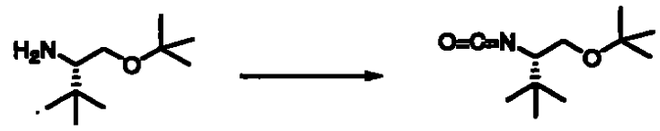


1610b 1610c

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272

Una suspensión del compuesto **1610b** y el 10% de Pd-C en etanol absoluto se agitó vigorosamente bajo atmósfera de hidrógeno durante 4 horas. El catalizador se separó por filtración a través de una almohadilla de celite. El filtrado se concentró al vacío para proporcionar **1610c** que se usó sin purificación adicional.

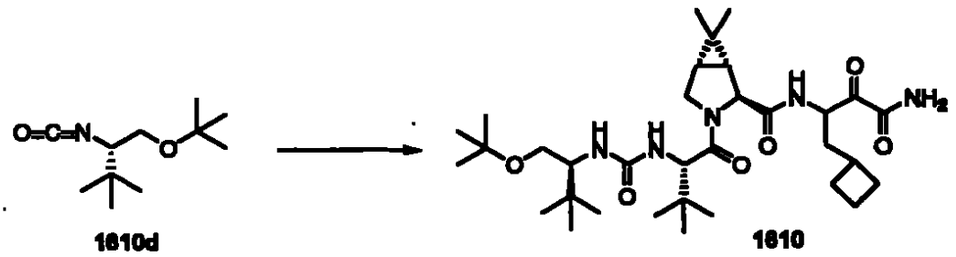
Etapa 3



1610c **1610d**

El compuesto **1610d** se preparó a partir de **1610c**, de acuerdo con los procedimientos descritos para el ejemplo **1655**, Etapa 3.

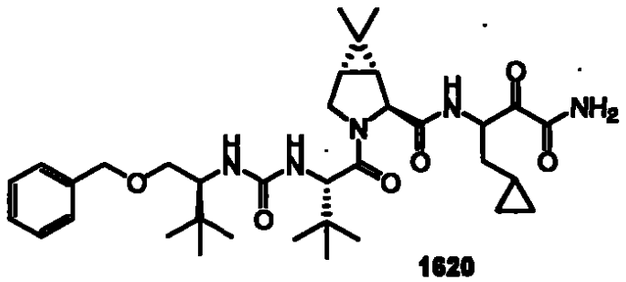
Etapa 4



1610d **1610**

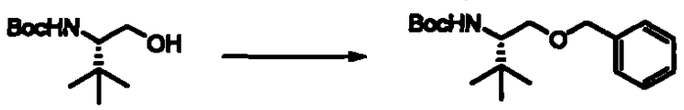
El isocianato **1610d** se convirtió al compuesto objetivo **1610** tal como se describió en los Esquemas Generales, Método C usado los reactivos e intermediarios apropiados.

Preparación del Ejemplo 1620



1620

Etapa 1

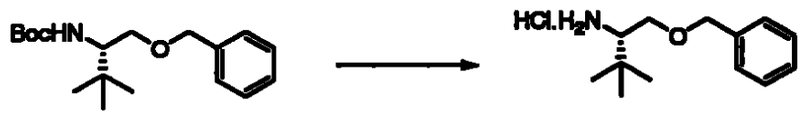


1655a **1620a**

Suspensión del alcohol **1655a** (3,46 g, 12,8 mmoles), bromuro de bencilo (10 mL, 84,2 mmoles) y óxido de plata (I) (5,0 g, 21,6 mmoles) en

acetonitrilo, se agitó vigorosamente a 76ºC en un baño de aceit durante la noche (18 h). El material sólido se separó por filtración y la solución se concentró al vacío. El producto se purificó por cromatografía en columna evaporativa eluyendo con 5-40% de EtOAc/hexano para proporcionar el producto deseado **1620a** (0,78 g, 20%).

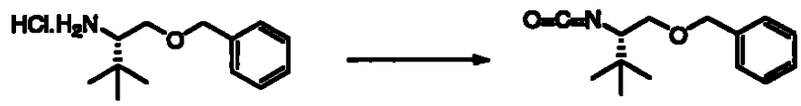
Etapa 2



1620a **1620b**

Se preparó el compuesto **16120b** a partir de **1620a** de acuerdo con los procedimientos descritos para el ejemplo **1614**, Etapa 2.

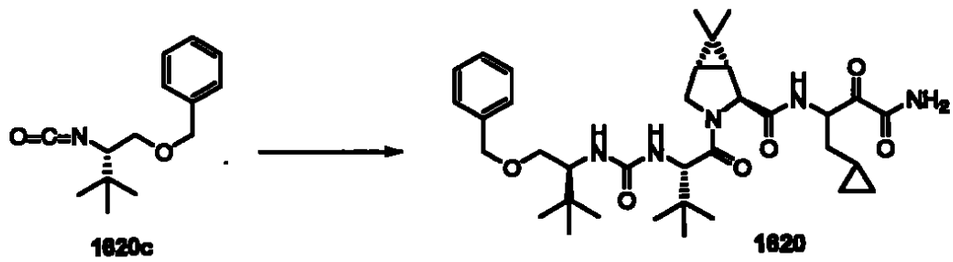
Etapa 3



1620b **1620c**

Se preparó el compuesto **1620c** a partir de **1620b** de acuerdo a los procedimientos descritos en el ejemplo **1655**, Etapa 3.

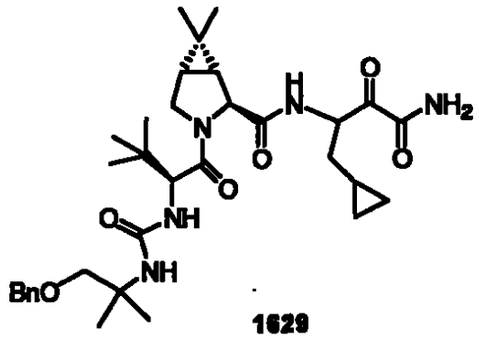
Etapa 4



1620c **1620**

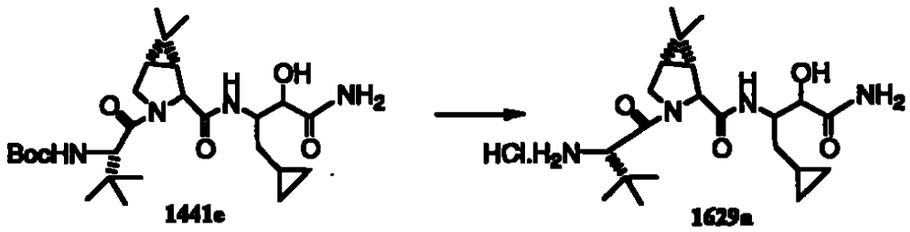
El isocianato **1620c** se convirtió al compuesto objetivo **1620** tal como se describió en los Esquemas Generales, Método C usando los reactivos e Intermediarios apropiados.

Preparación del Ejemplo 1629



1629

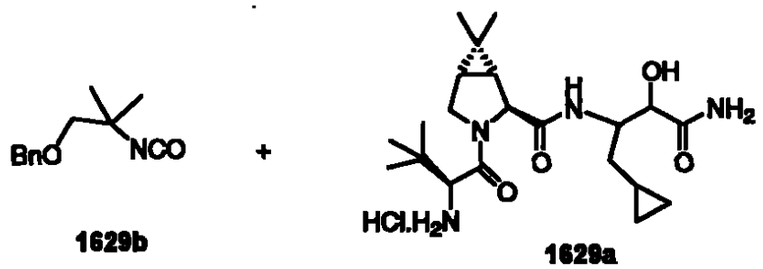
Etapa 1



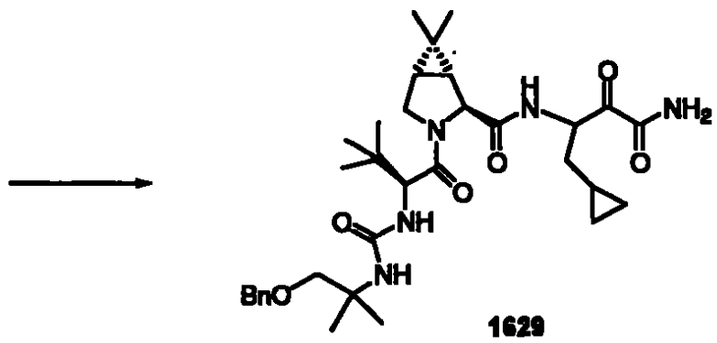
1441e **1629a**

A **1441e** (600 mg) se le agregó HCl 4 M en dioxano (25 mL). La reacción se agitó a temperatura ambiente durante 30 minutos y se concentró para proporcionar un sólido blanco, **1629a** (490 mg), que se llevó a cabo sin purificación.

Etapa 2



1629b **1629a**



1629

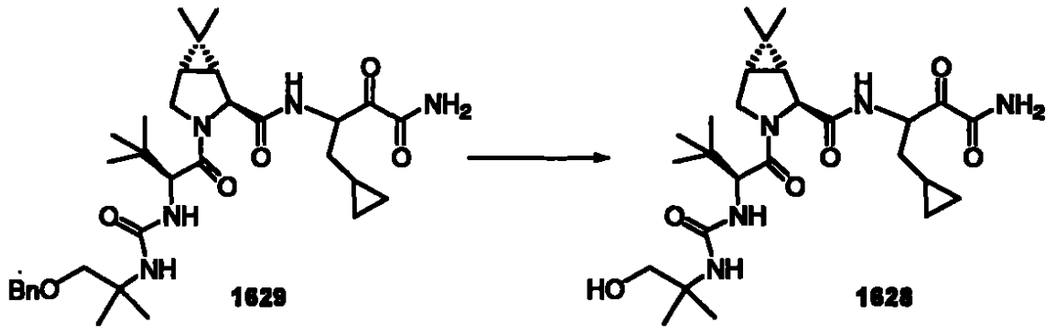
A una solución enfriada (0°C) del compuesto **1629a** (395 mg) en CH_2Cl_2 (25 mL) se le agregó Et_3N (0,57 mL), seguido del isocianato **1629b**

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(Robenson, Ralph P.; Marfat, Anthony. *Eur. Pat. Appl.* (1991), EP 436333 A2 19910710, 53 pp) de la manera descripta anteriormente (Ejemplo **1655**, Etapa 4). La hidroxiamida cruda obtenida se usó sin purificación.

Una solución de la hidroxiamida cruda en tolueno-DMSO (2,0 mL cada una) se enfrió a 0°C. A la mezcla de reacción se le agregó EDCI.HCl (410,0 mg), seguido de ácido dicloracético (0,087 mL), después de agitar durante 2 horas a temperatura ambiente y se diluyó con EtOAc, se lavó con HCl 1N, con $NaHCO_3$ saturado, salmuera, se secó sobre $MgSO_4$, se filtró, se concentró para proporcionar un sólido blanco que se purificó por cromatografía sobre gel de sílice usando acetona-hexano (40:60) para proporcionar el compuesto del título **1629** (280,0 mg) en forma de un sólido blanco: Espectro de masa para C33H49N5O6 (611.77); hallado FAB $(M+H)^+$ = 612,5

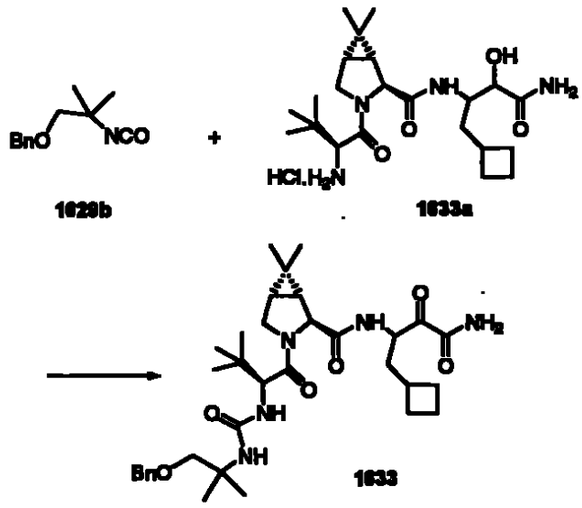
Preparación del Ejemplo 1628



A una solución del compuesto **1629** (37,0 mg) en MeOH (2,0 mL) se le agregó Pd-C (10 % p/v, 5,0 mg) y la reacción se agitó bajo atmósfera de hidrógeno durante 1 hora, se filtró a través de una almohadilla de celite, se concentró y purificó por cromatografía sobre gel de sílice usando acetona-hexano (4:6) para proporcionar el compuesto requerido **1628** (22,0 mg) en forma de un sólido blanco. Espectro de masa para C26H43N5O6 (521,65); hallado FAB $(M+H)^+$ = 522,6.

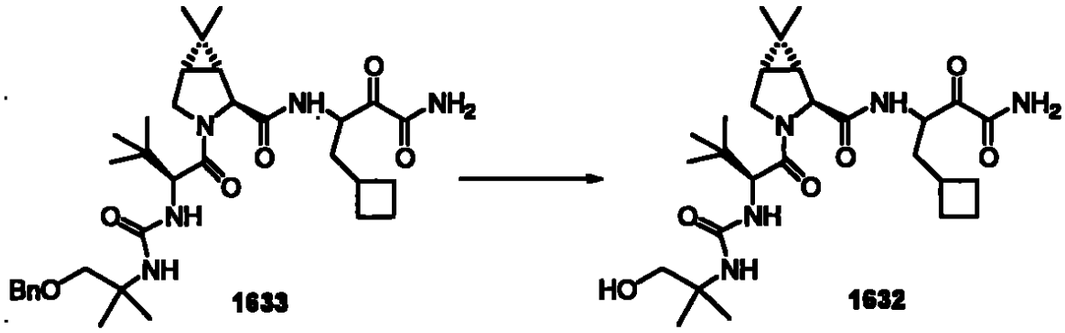
Preparación del Ejemplo 1633

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276



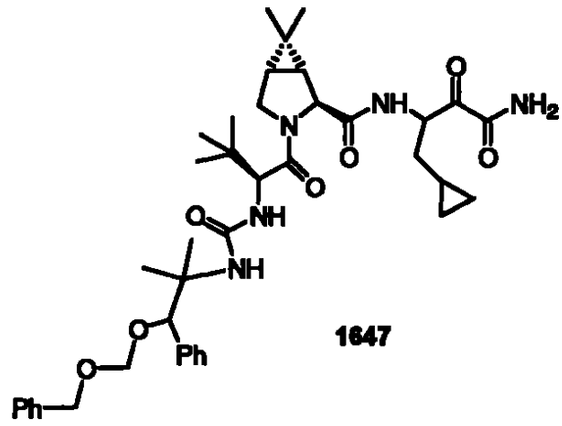
El compuesto del título requerido **1633** se obtuvo a partir del isocianato **1629b** y el compuesto **1633a** (preparado a partir de **1.17** y **10.11**) usando procedimientos descriptos para el Ejemplo **1629**. Espectro de masa para C34H51N5O6 (625.80); hallado FAB $(M+H)^+$ = 626,8.

Preparación del Ejemplo 1632



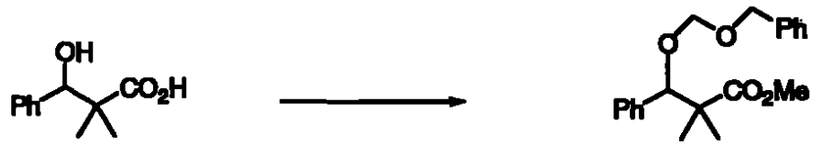
A una solución del compuesto **1633** (10,0 mg) en MeOH (2,0 mL) se le agregó Pd-C (10 % p/v, 2,0 mg) y la reacción se agitó bajo atmósfera de hidrógeno durante 1 hora, se filtró a través de una almohadilla de celite, se concentró y se purificó por cromatografía sobre gel de sílice usando acetona-hexano (4:6) para proporcionar el compuesto del título **1632** en forma de un sólido blanco (4,2 mg). Espectro de masa para C27H45N5O6 (535,68); hallado FAB $(M+H)^+$ = 536,7.

Preparación del Ejemplo 1647



1647

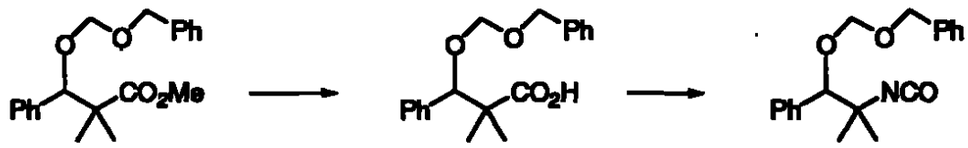
Etapa 1



1647a 1647b

A una solución agitada del compuesto comercialmente obtenible **1647a** (Aldrich Chemical Co., Milwaukee, Wisconsen, USA, 250,0 mg) en MeOH se le agregó trimetilsilil diazometano (2,0 mL, solución 2M en PhMe). Después de 20 minutos el solvente se extrajo y el crudo se redisolvió en CH_2Cl_2 (2,0 mL) y se agregó cloruro de benciloximetilo (1,5 equivalentes) junto con Et_3N (1,5 equivalente). La mezcla de reacción se agitó durante la noche, se diluyó con EtOAc, se lavó sucesivamente con 5% de $Na_2S_2O_3$, $NaHCO_3$ saturado, HCl 1N, salmuera, se secó sobre $MgSO_4$, se filtró, se concentró para proporcionar un sólido blanco el cual se purificó por cromatografía sobre gel de sílice usando EtOAc-hexano (1:3) para proporcionar el compuesto **1647b** (413 mg) en forma de un sólido blanco: Espectro de masa para C20H24O4 (328,40); hallado FAB $(M+H)^+$ = 329,4.

Etapa 2



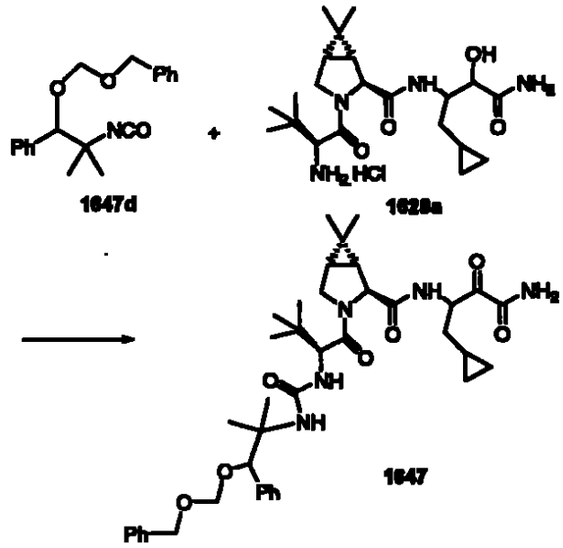
1647b 1647c 1647d

A una solución de 0,413 g del compuesto **1647b** en MeOH/H_2O (5,0/0,5 mL) se le agregó 0,735 g de KOH. La mezcla de reacción se reflujó durante la noche, se enfrió a temperatura ambiente y se concentró. El crudo

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se redisolvió en H_2O (10,0 mL) y se acidificó con HCl acuoso al 10% y se extrajo con CH_2Cl_2, se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar el correspondiente ácido carboxílico **1647c** (392 mg). El crudo se usó directamente en la etapa siguiente. A una solución de 123,2 mg del ácido **1647c** en tolueno (5,0 mL) se le agregó DPPA (0,09 mL) y Et_3N (0,055 mL). La mezcla de reacción se calentó a 110°C durante 40 minutos, se enfrió y se lavó con $NaHCO_3$ saturado, se secó sobre $MgSO_4$, se filtró y se concentró para proporcionar el isocianato **1647d**. El crudo obtenido se usó sin purificación.

Etapa 3

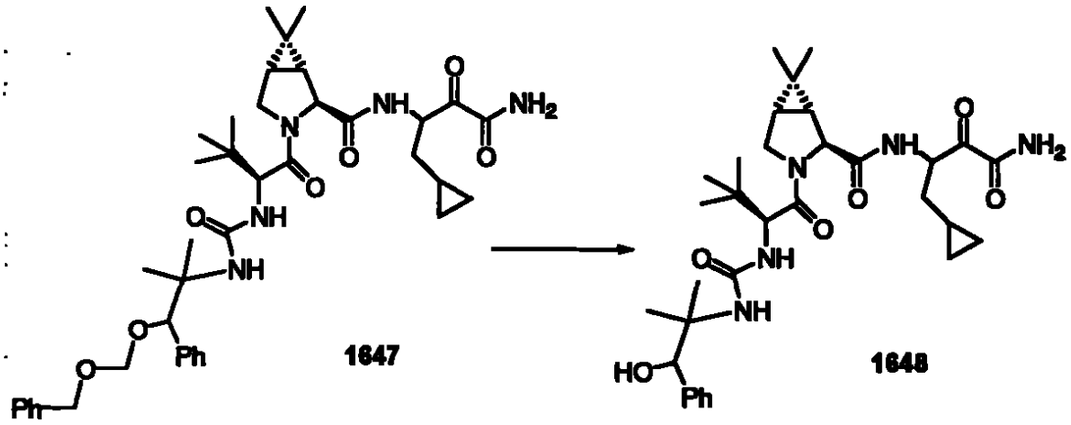


1647d **1629a**

1647

El isocianato **1647d** tratado con el compuesto **1629a** (90,0 mg) en la manera descripta en el Ejemplo **1629** proporcionó el compuesto del título **1647**. Espectro de masa para C40H55N5O7 (717,89); hallado FAB $(M+H)^+$ = 718,8.

Preparación del Ejemplo 1648



1647 **1648**

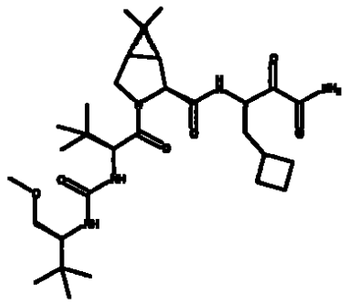
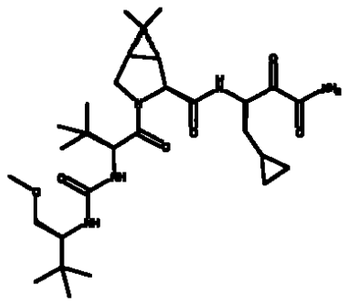
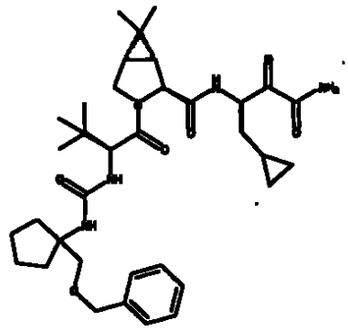
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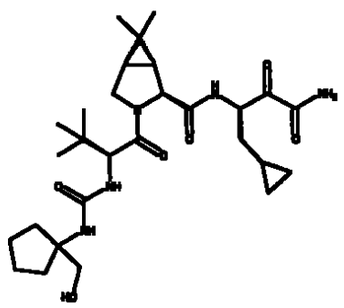
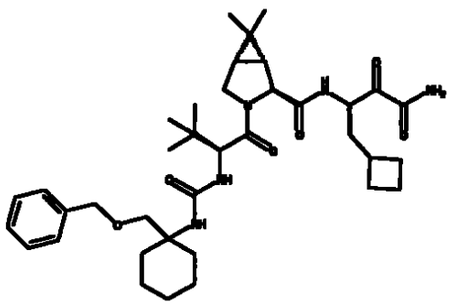
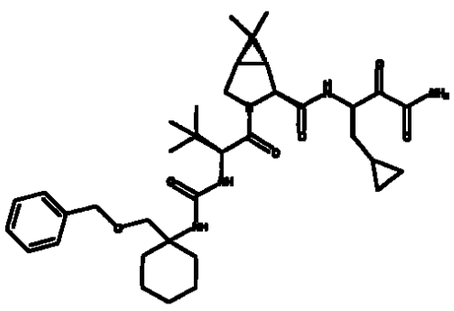
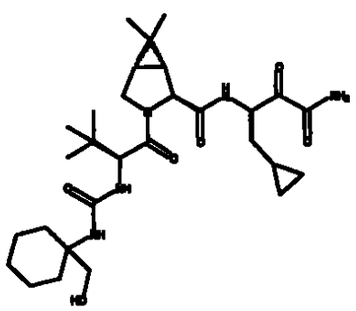
A una solución del compuesto **1647** en MeOH se le agregó HCl 6N después de 30 minutos, se extrajo el MeOH y el crudo se redisolvió en acetato de etilo y se lavó con $NaHCO_3$ saturado. El crudo se purificó p r cromatografía sobre gel de sílice usando acetona-hexano (40:60) para proporcionar el compuesto del título **1648** (25,0 mg) en forma de un sólido blanco. Espectro de masa para C32H47N5O6 (597,75); hallado FAB $(M+H)^+$ = 598,7.

Los compuestos en la tabla siguiente (**Tabla 3**) se prepararon esencialmente usando los procedimientos descriptos anteriormente (Preparación de los Ejemplos **1610, 1614, 1620, 1628, 1629, 1632, 1633, 1647, 1648, 1655**) con reactivos apropiados y modificaciones tal como las descriptas en los Esquemas Generales para la Preparación de los Compuestos Objetivo, Métodos A-E.

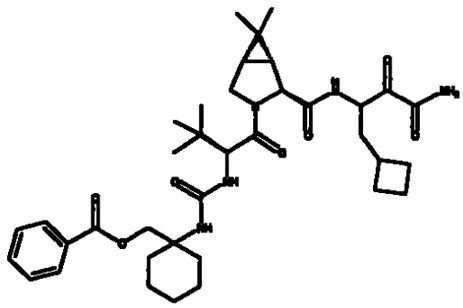
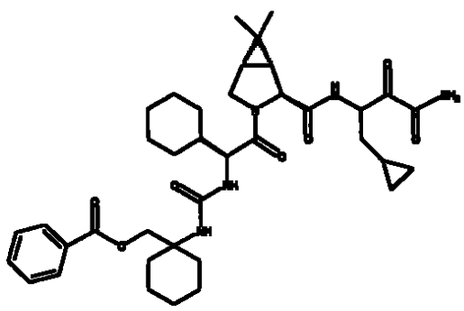
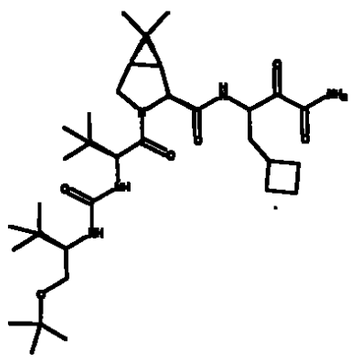
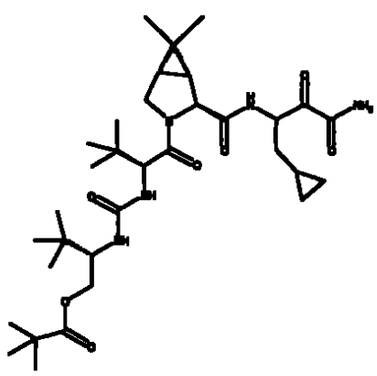
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280

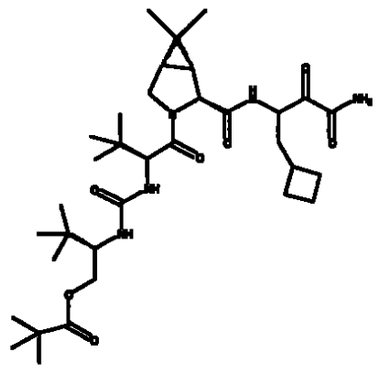
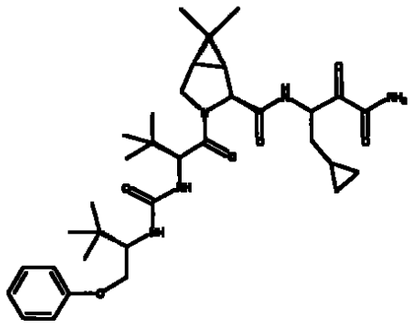
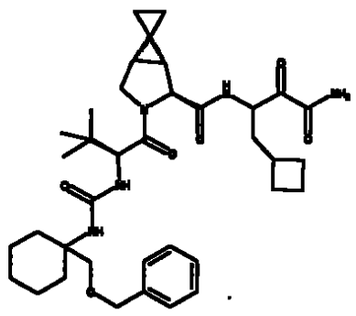
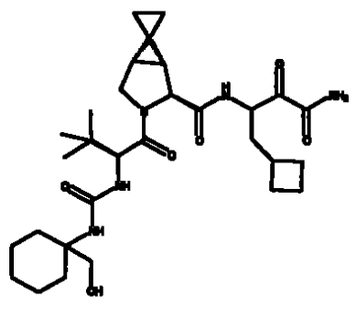
Tabla 3

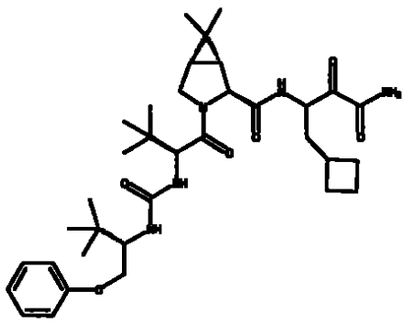
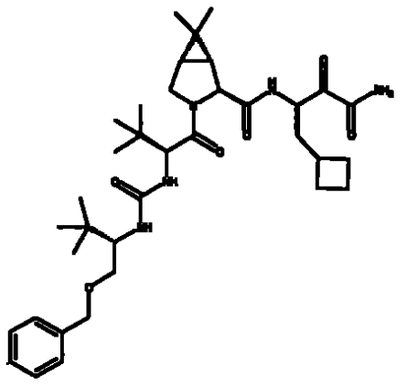
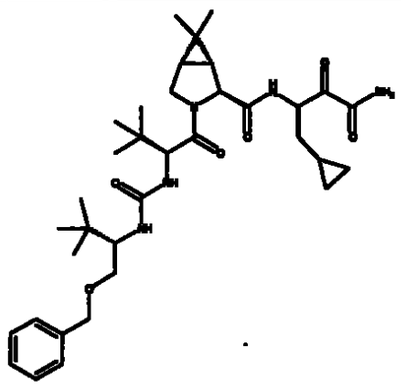
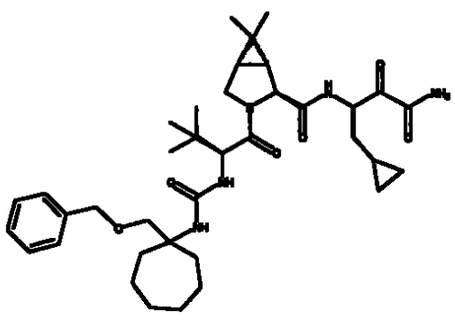
Ejemplo #	Estructura	Ki* (nM)	PM
1601		B	577.763
1602		B	563.736
1603		A	637.818

1604		A	547.693
1605		A	665.871
1606		A	651.845
1607		A	561.72

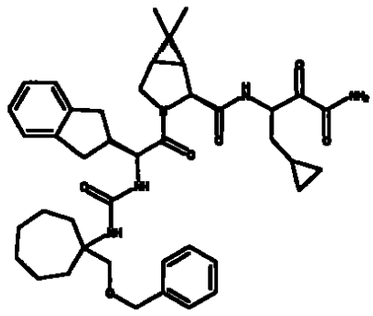
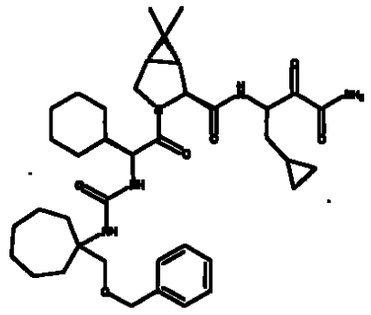
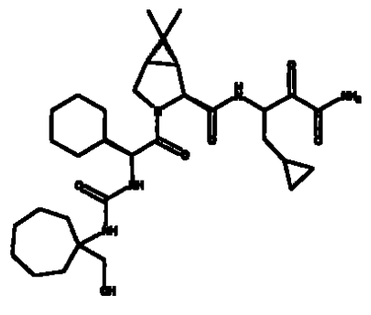
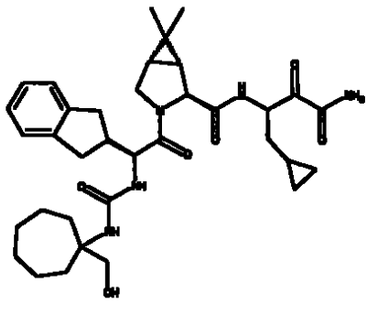
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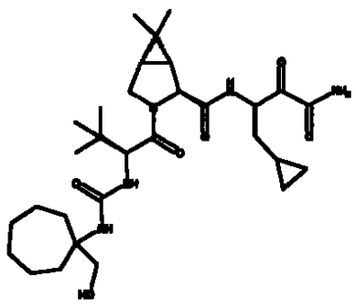
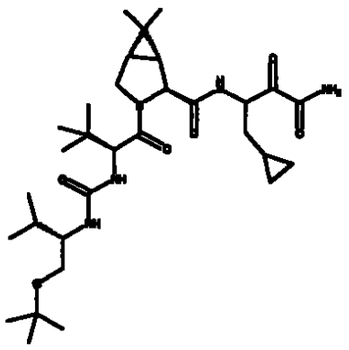
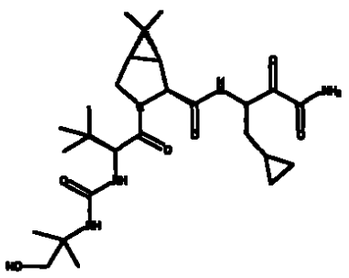
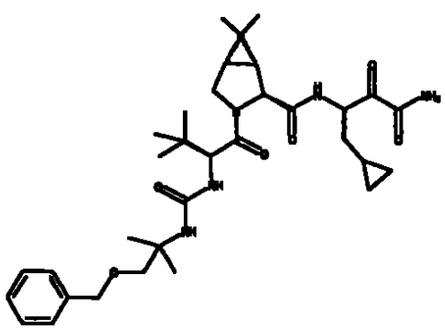
1608		B	679.855
1609		B	691.866
1610		A	619.843
1611		A	633.827

1612		A	647.854
1614		B	625.807
1616		C	663.856
1617		B	573.731

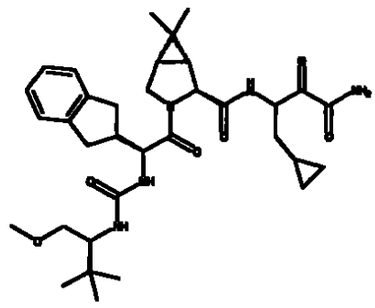
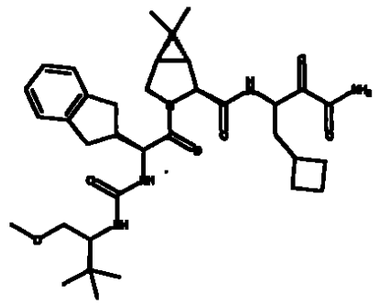
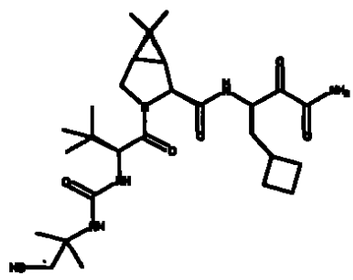
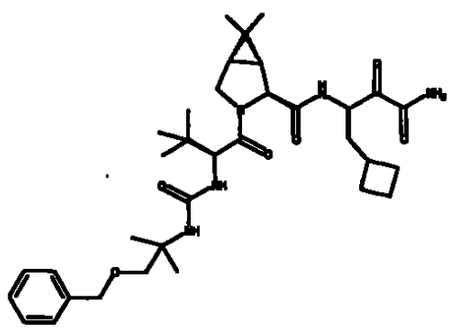
1618		B	639.834
1619		B	653.86
1620		B	639.834
1621		A	665.871

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285

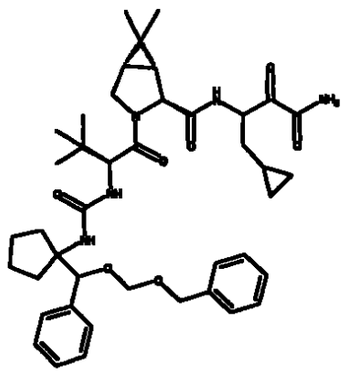
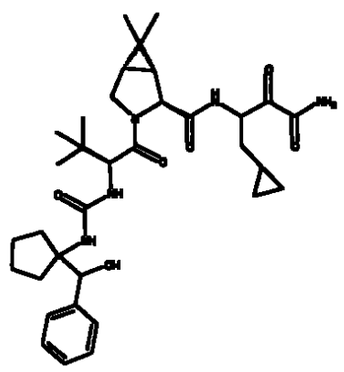
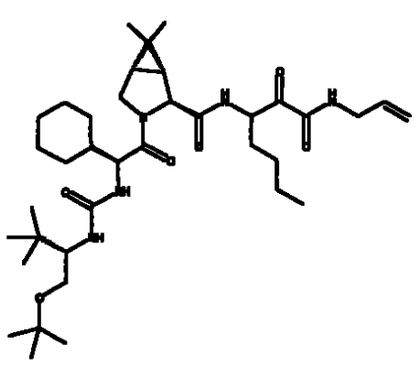
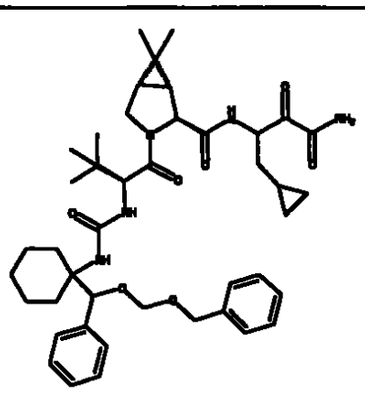
1622		C	725.926
1623		B	691.909
1624		A	601.785
1625		B	635.802

1626		A	575.747
1627		A	591.79
1628		A	521.656
1629		B	611.78

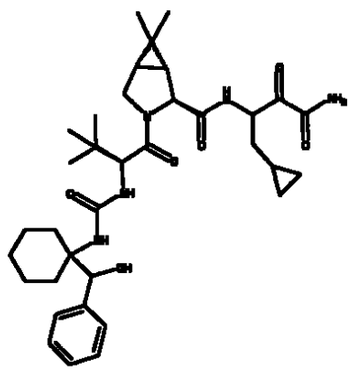
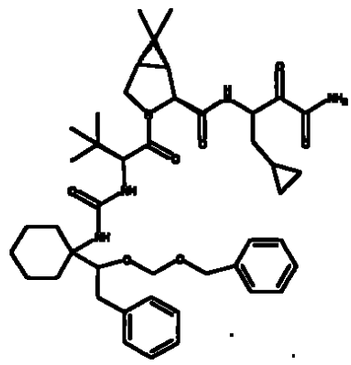
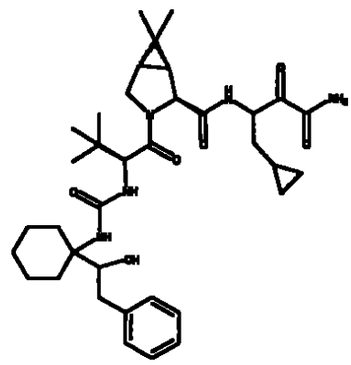
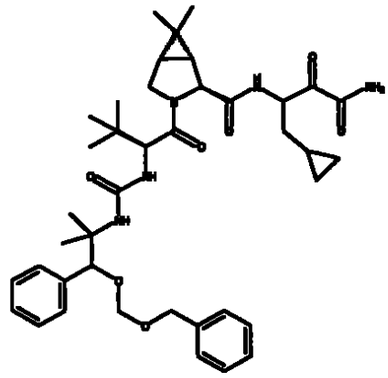
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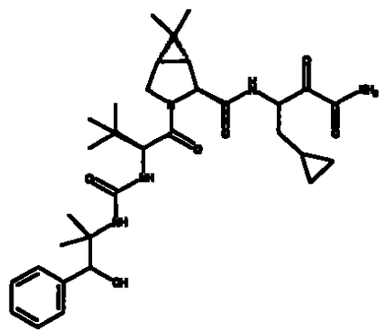
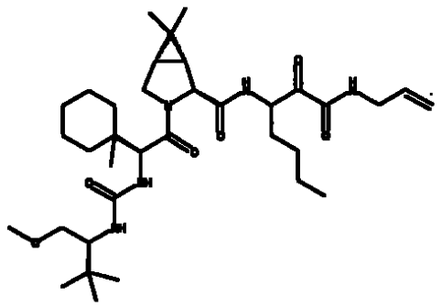
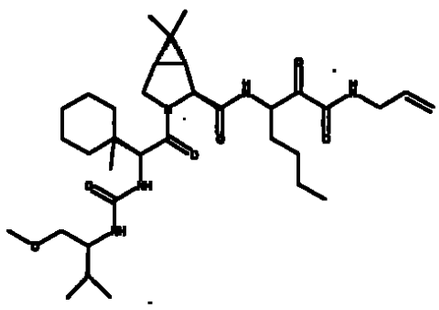
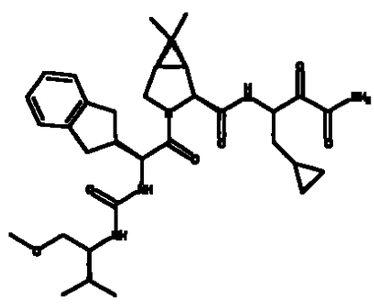
1630		A	623.791
1631		A	637.818
1632		A	535.682
1633		B	625.807

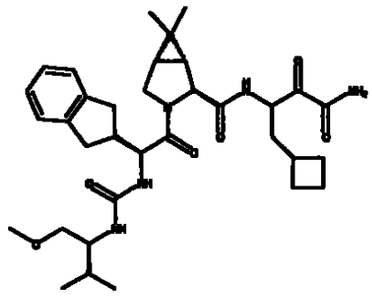
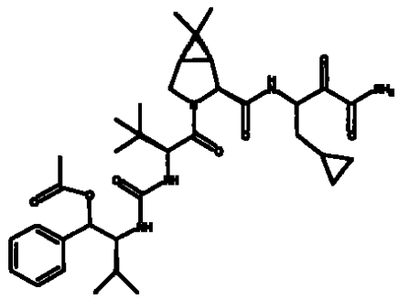
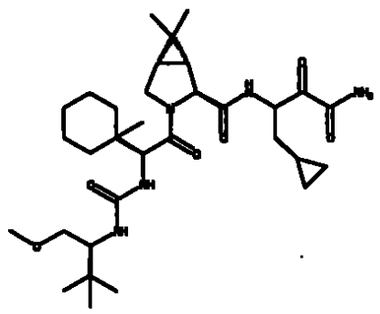
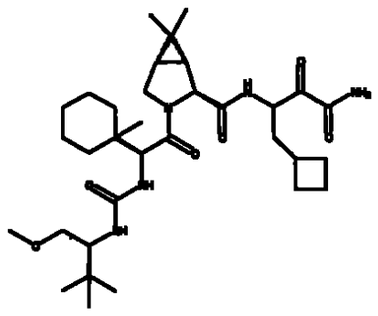
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287

1634		B	743.942
1635		A	623.791
1636		B	673.935
1641		A	757.968

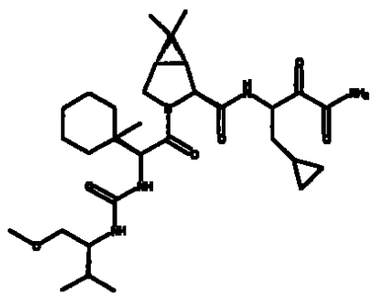
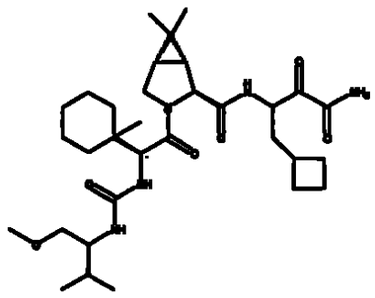
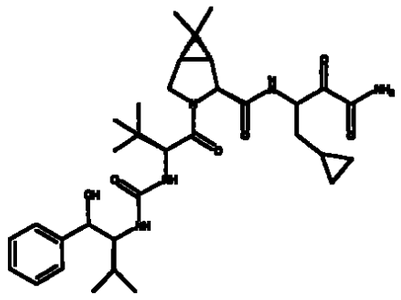
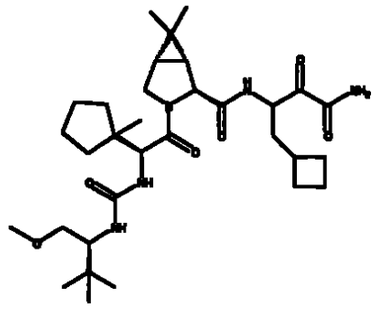
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1642		A	637.818
1643		B	771.995
1644		A	651.845
1647		B	717.904

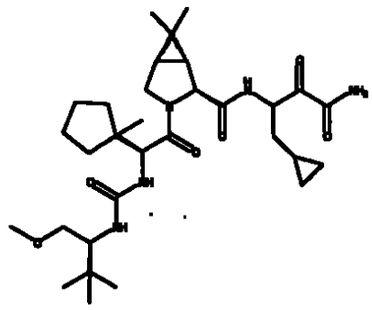
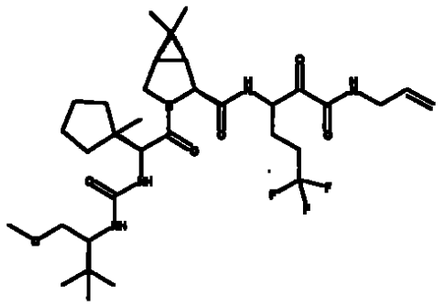
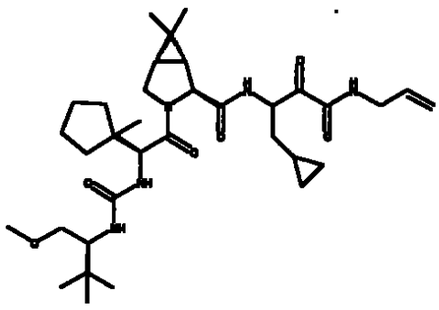
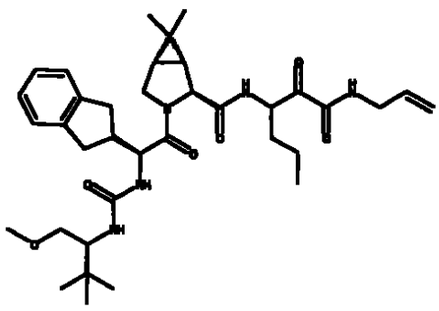
1648		B	597.753
1649		A	645.881
1650		B	631.854
1651		A	609.764

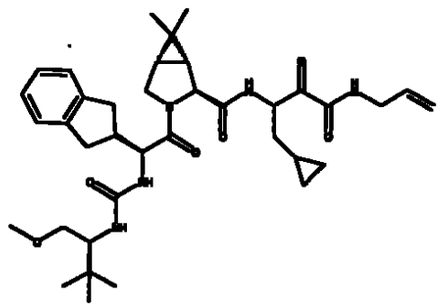
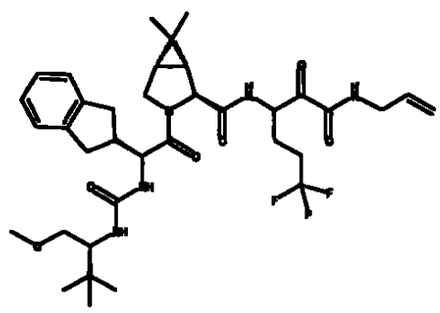
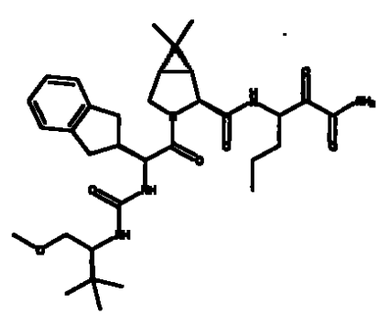
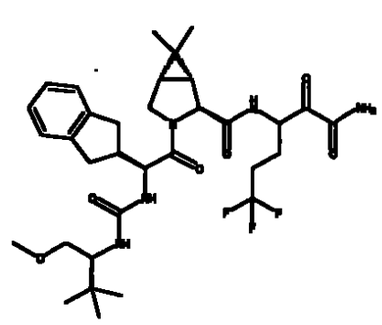
1652		A	623.791
1653		B	653.817
1654		A	603.801
1655		A	617.827

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292

1656		A	589.774
1657		A	603.801
1658		B	611.78
1659		A	603.801

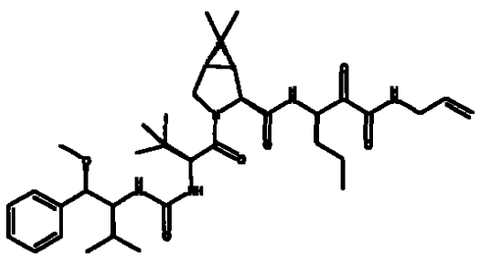
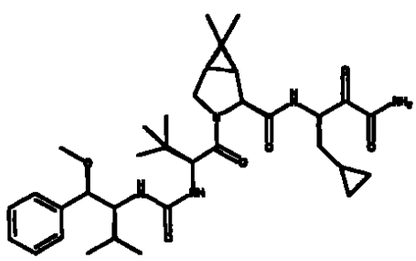
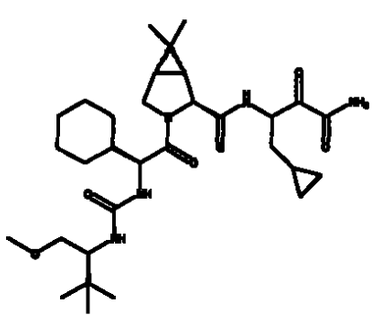
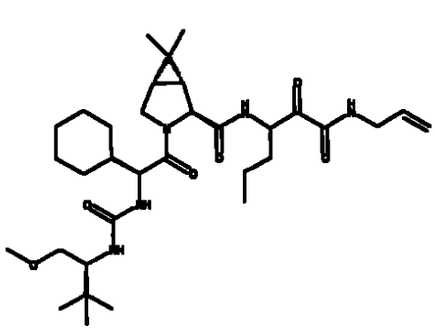
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293

1660		A	589.774
1661		B	671.799
1662		B	629.838
1663		B	651.845

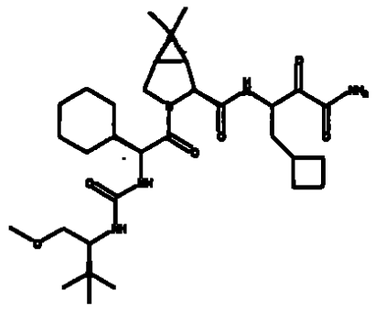
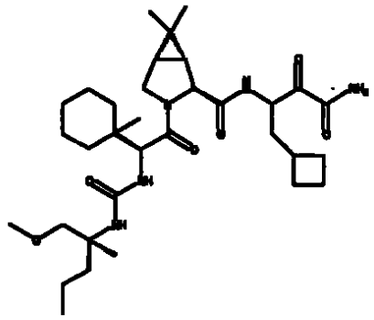
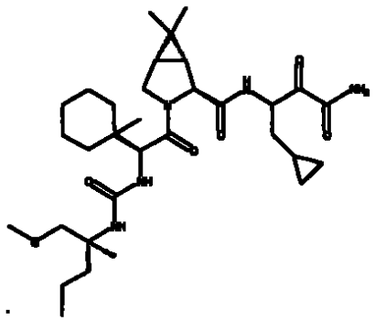
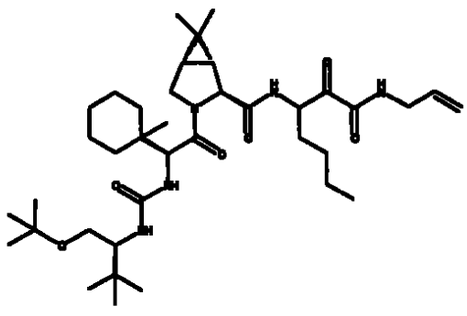
1664		B	663.856
1665		B	705.816
1666		A	611.78
1667		A	665.751

295

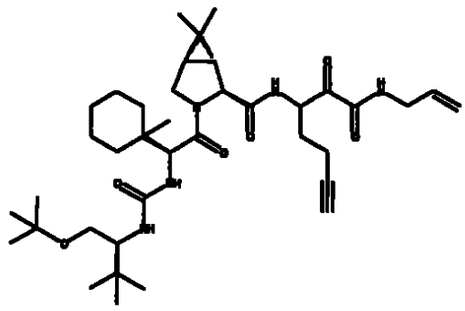
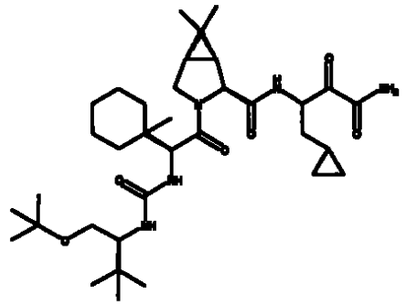
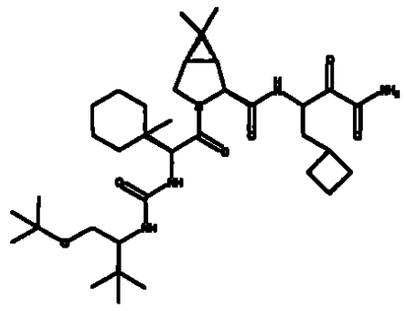
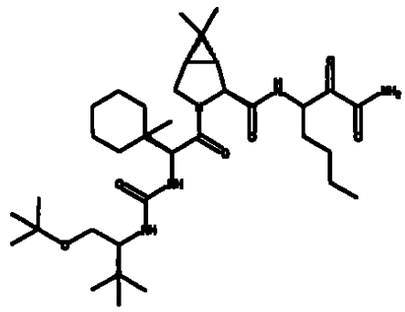
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1668		B	653.86
1669		A	625.807
1670		A	589.774
1671		B	617.827

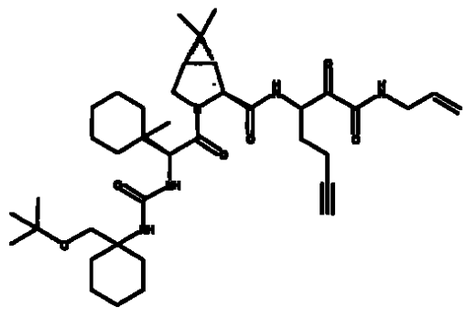
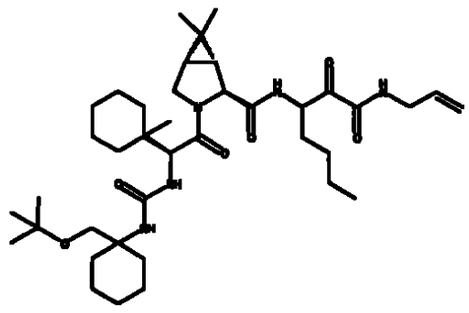
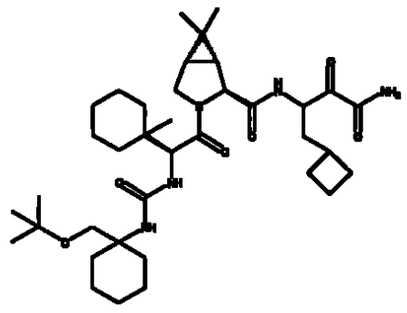
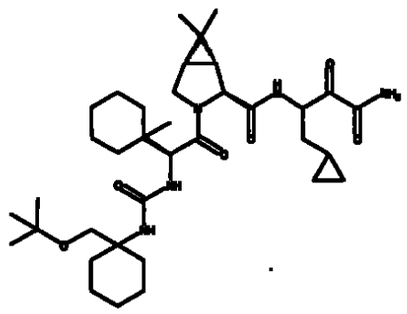
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1672		A	603.801
1673		B	617.827
1674		B	603.801
1675		C	687.953

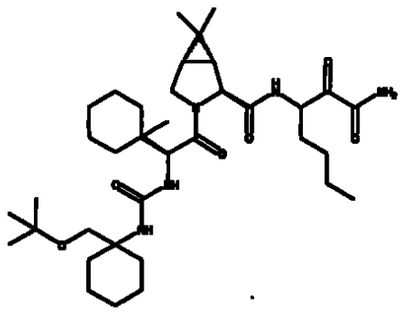
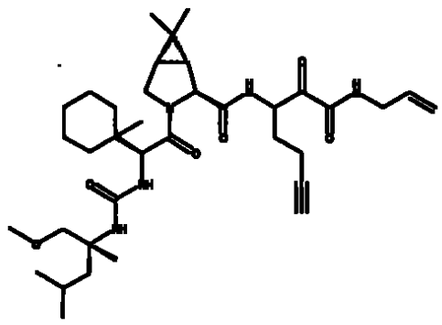
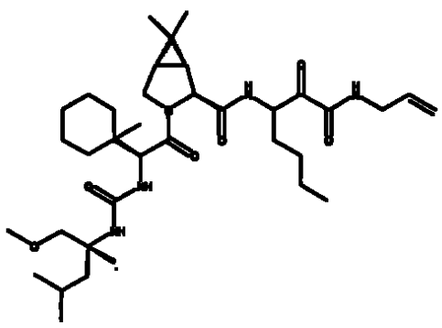
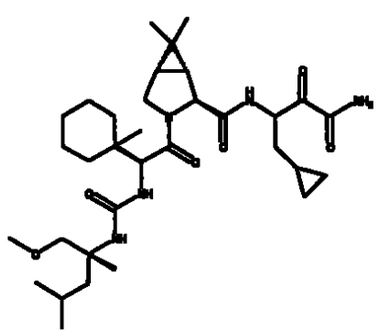
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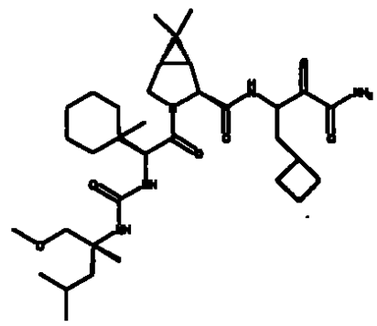
1676		B	683.921
1677		A	645.873
1678		B	659.899
1679		B	647.889

298
298

1680		A	695.932
1681		C	699.963
1682		B	671.910
1683		A	657.884

299
299

1684		B	659.899
1685		B	655.868
1686		C	659.899
1687		A	617.820

1688		A	631.846

Rango de Ki* A = <75 nM; B = 75-250 nM; C = >250 nM

La presente invención se refiere a nuevos inhibidores de proteasa HCV. Esta utilidad puede manifestarse por su capacidad para inhibir la serina proteasa NS2/NS4a de HCV. Un procedimiento general para dicha demostración se ilustra mediante el siguiente ensayo *in vitro*.

Ensayo para la Actividad Inhibidora de Proteasa HCV:

Ensayo Espectrofotométrico: El ensayo espectrofotométrico para la serina proteasa de HCV puede llevarse a cabo en los compuestos de la invención siguiendo el procedimiento descripto por R. Zhang *et al*, *Analytical Biochemistry*, 270 (1999) 268-275, cuya descripción se incorpora aquí como referencia. El ensayo basado en la proteólisis de sustratos de éster cromogénico es apropiado para el monitoreo continuo de la actividad de la proteasa NS3 de HCV. Los sustratos derivan del lado P de la secuencia de unión NS5A-NS5B (Ac-DTEDVVX(Nva), donde X = A o P) cuyos grupos carboxilo C-terminales se esterifican con uno de cuatro alcoholes cromofóricos diferentes (3- o 4-nitrofenol, 7-hidroxi-4-metil-cumarina o 4-fenilazofenol). A continuación se ilustran la síntesis, la caracterización y la aplicación de estos nuevos sustratos de éster espectrofotométricos para un rastreo de alto rendimiento y para una evaluación cinética detallada de los inhibidores de proteasa NS3 de HCV.

Materiales y Métodos:

Materiales: Los reactivos químicos para el ensayo de los buffers relacionados se obtuvieron en Sigma Chemical Company (St. Louis, Missouri). Los reactivos para la síntesis peptídico fueron de Aldrich Chemicals, Novabiochem (San Diego, California), Applied Biosystems (Foster City, California) y Perseptive Biosystems (Framingham, Massachusetts). Los

péptidos se sintetizaron manualmente o en un sintetizador automático ABI modelo 431A (de Applied Biosystems). El espectrómetro UV/VIS modelo LAMBDA 12 fue de Perkin Elmer (Norwalk, Connecticut) y las placas de UV de 96 receptáculos se obtuvieron en Corning (Corning, New York). El bloque de precalentamiento puede ser de USA Scientific (Ocala, Florida) y la placa de remolino de 96 receptáculos es de Labline Instruments (Melrose Park, Illinois). El lector de placa microevaluadora Spectramax Plus con monocrómetro se obtiene en Molecular Devices (Sunnyvale, California).

Preparación de Enzimas: Se preparó proteasa NS3/NS4A de HCV (cepa 1a) heterodimérica recombinante usando los procedimientos publicados previamente (D. L. Sali *et al*, *Biochemistry*, 37 (1998) 3392-3401). Las concentraciones de proteína se determinaron mediante el método de tinción Biorad usando modelos de proteasa de HCV recombinantes cuantificados por análisis de aminoácido. Antes de la iniciación del ensayo, el buffer de almacenamiento enzimático (50 mM de fosfato de sodio a pH 8,0, 300 mM de NaCl, 10% de glicerol, 0,05% de lauril maltosida y 10 mM de DTT), se intercambiaron para el buffer de ensayo (25 mM MOPS a pH 6,5, 300 mM de NaCl, 10% de glicerol, 0,05% de lauril maltosida, 5 µM de EDTA y 5 µM de DTT) utilizando una columna precargada Biorad Bio-Spin P-6.

Síntesis y Purificación del Sustrato: La síntesis de los sustratos de acuerdo a lo informado por R. Zhang *et al*, (*ibid.*) y se inicia anclando la resina del cloruro Fmoc-Nva-OH a 2-clorotritilo usando un protocolo convencional (K. Barlos *et al*, *Int. J. Pept. Protein Res.*, 37 (1991), 513-520). Los péptidos fueron subsiguientemente ensamblados, usando química Fmoc, en forma manual o automática en un sintetizador de péptidos ABI modelo 431. Los fragmentos peptídicos N-acetilados y totalmente protegidos se disociaron de la resina con 10% de ácido acético (HOAc) y 10% de trifluoretanol (TFE) en diclorometano (DCM) durante 30 minutos, o bien con 2% de ácido trifluoracético (TFA) en DCM durante 10 minutos. El filtrado combinado y la lavaza de DCM se evaporó azeotrópicamente (o se extrajo repetidamente por solución acuosa de Na_2CO_3) para remover el ácido usado en la disociación. La fase de DCM se secó sobre Na_2SO_4 y se evaporó.

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Los sustratos de éster se reunieron usando procedimientos de acoplamiento convencionales de ácido-alcohol (K. Holmber *et al, Acta Chem. Scand.*, B33 (1979) 410-412). Los fragmentos peptídicos se disolvieron en piridina anhidra (30-60 mg/ml) a la cual se habían agregado 10 equivalentes molares de cromóforo y una cantidad catalítica (0,1 eq.) de ácido para-toluensulfónico (pTSA). Se agregó diciclohexilcarbodiimida (DCC, 3 eq.) para iniciar las reacciones de acoplamiento. La formación de producto se monitoreó por HPLC y puede hallarse que está completa después de 12-72 horas de reacción a temperatura ambiente. El solvente piridina se evaporó al vacío y se removió adicionalmente por evaporación azeotrópica con tolueno. El éster peptídico se desprotegió con 95% de TFA en DCM durante dos horas y se extrajo tres veces con éter etílico anhidro para remover el exceso de cromóforo. El sustrato desprotegido se purificó por HPLC de fase inversa sobre una columna C3 o C8 con un gradiente de acetonitrilo al 30% hasta 60% (usando volúmenes de seis columnas). El rendimiento general después de la purificación de HPLC puede ser de aproximadamente 20-30%. La masa molecular puede confirmarse por espectroscopia de masa de ionización por electro-rocío. Los sustratos se almacenaron en forma de polvo seco por desecación.

Espectro de Sustratos y Productos: Los espectros de sustratos y los correspondientes productos cromofóricos se obtienen en el buffer de ensayo a pH 6,5. Los coeficientes de extinción se determinaron en la longitud de onda óptima fuera de pico en cubetas de 1 cm (340 nm para 3-Np y HMC, 370 nm para PAP y 400 nm para 4-Np) usando múltiples diluciones. La longitud de onda óptima fuera de pico se define como la longitud de onda que proporciona la diferencia fraccional máxima de absorbancia entre el sustrato y el producto (producto OD-sustrato OD)/sustrato OD).

Ensayo de Proteasa: Los ensayos de proteasa HCV se llevaron a cabo a 30°C usando una mezcla de reacción de 200 µl en una placa microevaluadora de 96 receptáculos. Las condiciones del buffer de ensayo (25 mM de MOPS a pH 6,5, 300 mM de NaCl, 10% de glicerol, 0,05% de lauril maltosida, 5 µM de EDTA y 5 µM de DTT) se optimizaron para el heterodímero NS3/NS4A (D. L. Sali *et al, ibid.*)). Típicamente, se colocaron en los receptáculos mezclas de 150 µl de buffer, sustrato e inhibidor

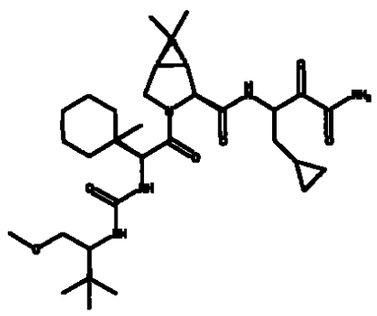
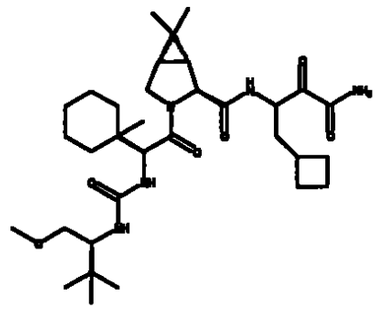
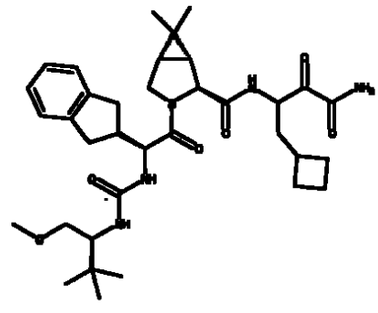
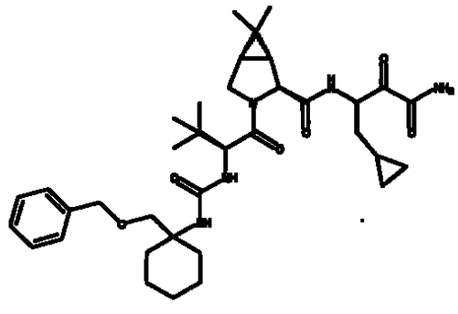
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(concentración final de DMSO ≤ 4% v/v) y se dejaron preincubar hasta 30°C durante aproximadamente 3 minutos. Luego se usaron 50 µls de proteasa precalentada (12 nM, 30°C) en buffer de ensayo, para iniciar la reacción (volumen final 200 µl). Las placas se monitorearon durante toda la duración del ensayo (60 minutos) para determinar la absorbancia en la longitud de onda apropiada (340 nm para 3-Np y HMC, 370 nm para PAP, y 400 nm para 4-Np) usando un lector de placa microevaluadora Spectromax Plus equipado con un monocrómetro (pueden obtenerse resultados aceptables con lectores de placas que utilizan filtros de corte). La disociación proteolítica del enlace éster entre el Nva y el cromóforo se monitoreó a la longitud de onda apropiada contra un blanco no enzimático como control para la hidrólisis no enzimática. La evaluación de los parámetros cinéticos del sustrato se llevó a cabo en un rango de concentración del sustrato de 30 veces (~6-200 µM). Las velocidades iniciales se determinaron usando regresión lineal y las constantes cinéticas se obtuvieron ajustando los datos a la ecuación de Michaelis-Menten usando análisis de regresión no lineal (Mac Curve Fit 1.1, K. Raner). Los números de cambio (k_{cat}) se calcularon asumiendo que la enzima es totalmente activa.

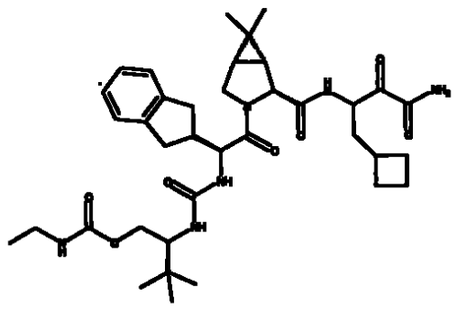
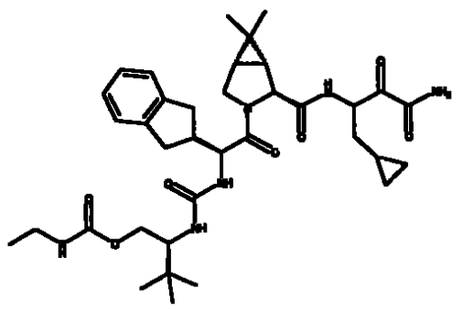
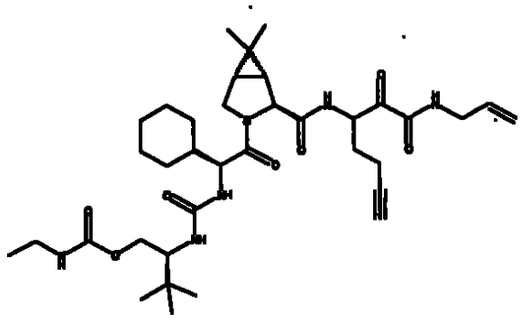
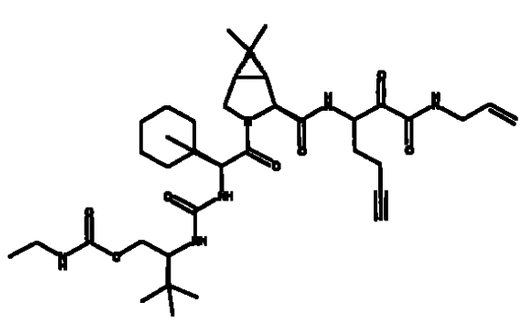
Evaluación de los Inhibidores e Inactivadores: Las constantes de inhibición (K_i) para los inhibidores competitivos Ac-D-(D-Gla)-L-I-(Cha)-C-OH (27), Ac-DTEDVVA(Nva)-OH y Ac-DTEDVVP(Nva)-OH se determinaron experimentalmente en concentraciones fijas de enzima y sustrato graficando v_o/v_i vs. concentración de inhibidor ($[I]_o$) de acuerdo con la ecuación reordenada Michaelis-Menten para la cinética de inhibición competitiva: $v_o/v_i = 1 + [I]_o/(K_i (1 + [S]_o/K_m))$, donde v_o es la velocidad inicial no inhibida, v_i es la velocidad inicial en presencia de inhibidor en cualquier concentración de inhibidor determinada ($[I]_o$) y $[S]_o$ es la concentración de sustrato usada. Los datos resultantes se ajustaron usando regresión lineal y la pendiente resultante, $1/(K_i(1+[S]_o/K_m)$, se usó para calcular el valor de K_i. Valores de K_i^* de algunos de los compuestos de la invención se muestran en la Tabla 6 y en la Tabla 6A siguiente:

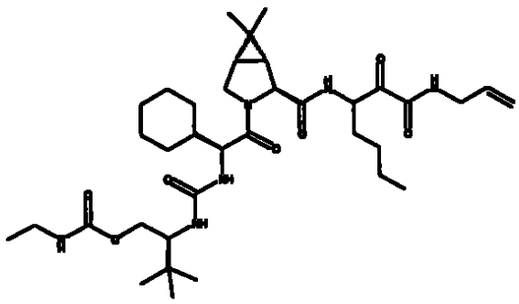
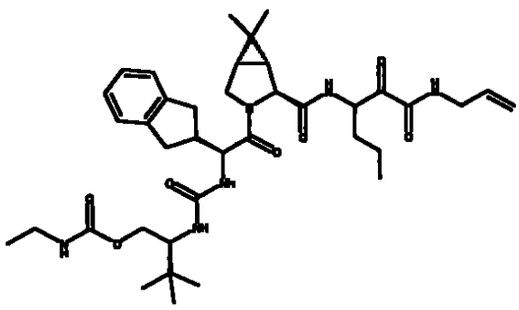
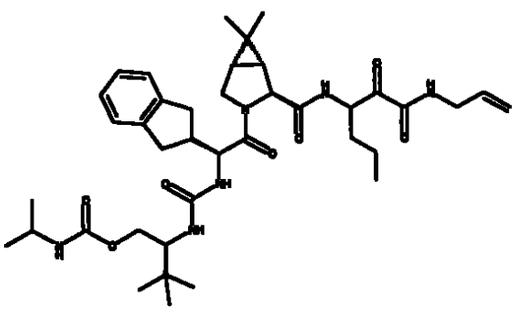
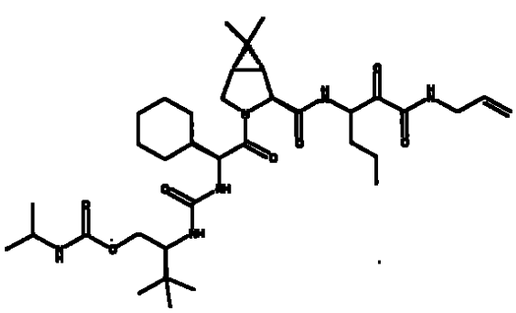
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Tabla 6

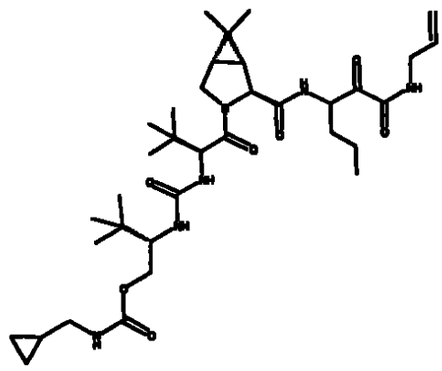
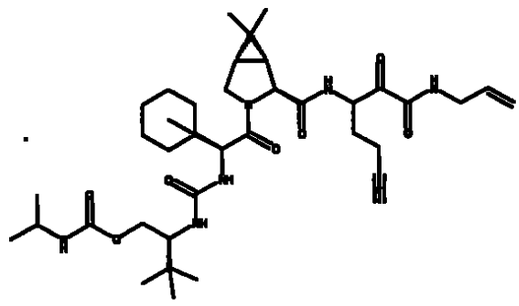
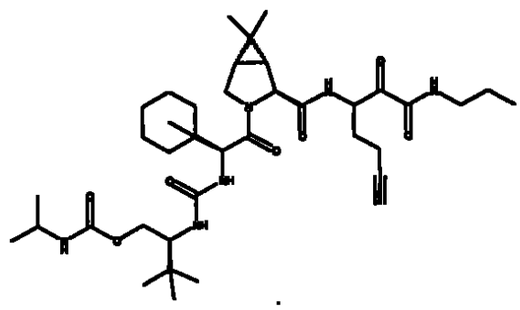
Ejemplo #	Estructura	KI* (nM)
1654		12
1655		24
1631		15
1606		16

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1025		6.7
1024		7.3
1086		8
1090		9

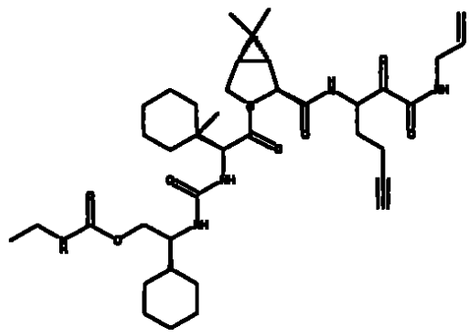
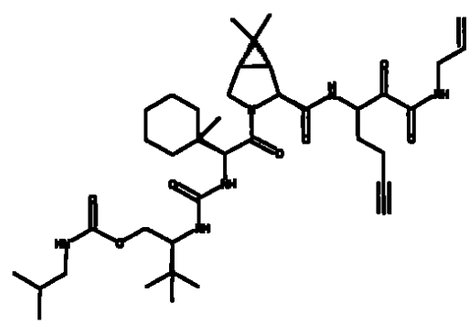
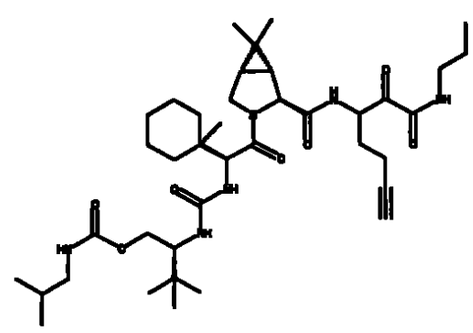
1085		11
1023		33
1012		40
1056		30

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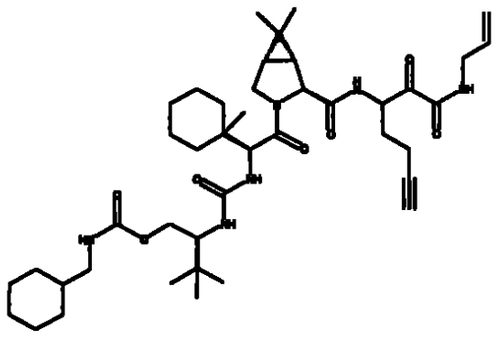
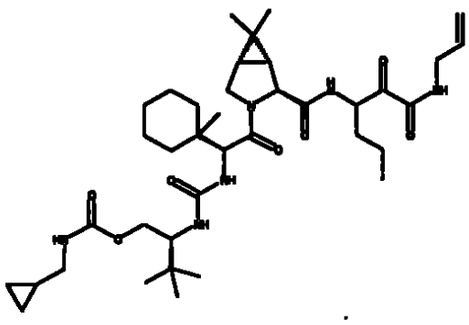
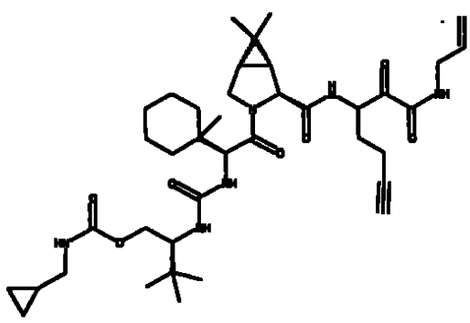
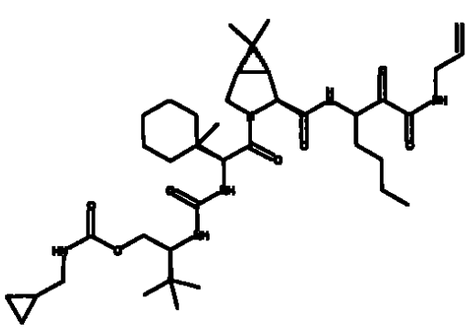
1029		14
1095		8
1098		15

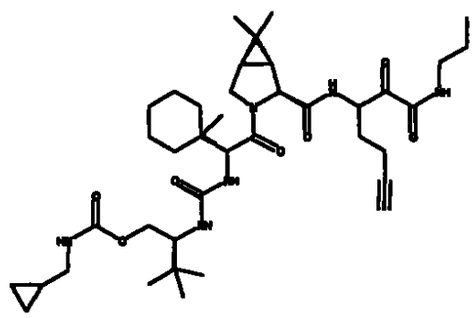
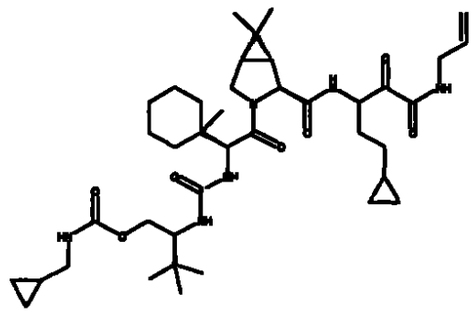
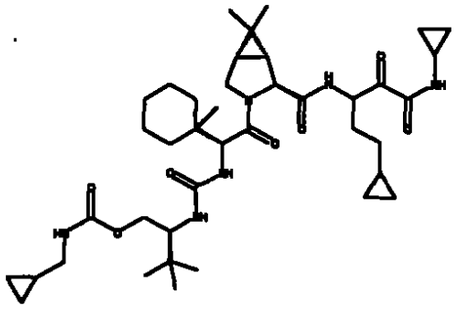
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Tabla 6A

Ejemplo #	Estructura	Ki* (nM)
1104		13
1108		9
1109		27

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1112		20
1114		32
1115		7.4
1116		34

1117		19
1120		30
1121		22

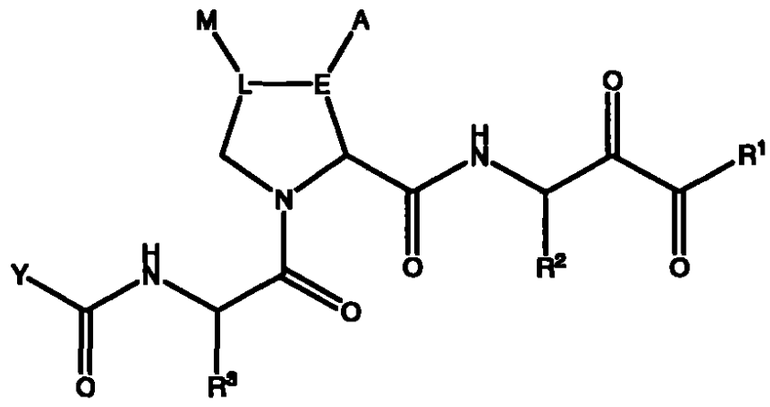
Aunque la presente invención ha sido descripta conjuntamente con las realizaciones específicas indicadas anteriormente, muchas alternativas, modificaciones y otras variaciones de las mismas resultarán aparentes para los expertos en la materia. Todas dichas alternativas, modificaciones y variaciones entran dentro del espíritu y alcance de la presente invención.

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REIVINDICACIORNES

Habiendo así especialmente descripto y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

1. Un compuesto, o enantiómeros, estereoisómeros, rotámeros, tautómeros o racematos de dicho compuesto, o una sal, solvato o éster farmacéuticamente aceptable de dicho compuesto, donde dicho compuesto tiene la estructura general que se muestra en la Fórmula I:

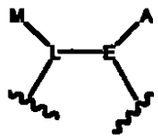


Fórmula I

en la cual:

R^1 es H, OR^8, NR^9R^{10}, o CHR^9R^{10}, donde R^8, R^9 y R^{10} pueden ser iguales o diferentes, y cada uno está independientemente seleccionado del grupo que consiste en H, alquil-, alquenil-, alquinil-, aril-, heteroalquil-, heteroaril-, cicloalquil-, heterociclil-, arilalquil- y heteroarilalquilo;

A y M pueden ser iguales o diferentes, y cada uno independientemente seleccionado de R, OR, NHR, NRR', SR, SO_2R, y halo; o A y M están conectados uno al otro de manera que la porción:



que se muestra anteriormente en la Fórmula I forma un cicloalquilo de tres, cuatro, seis, siete u ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros, o un heteroarilo de cinco a diez miembros;

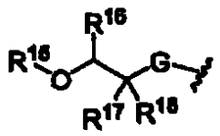
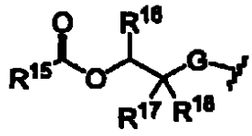
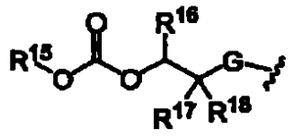
E es C(H) o C(R);

L es C(H), C(R), $CH_2C(R)$, o $C(R)CH_2$;

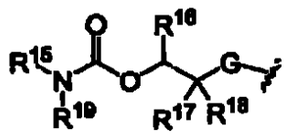
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R, R', R^2 y R^3 pueden ser iguales o diferentes y cada uno está independientemente seleccionado del grupo que consiste en H, alquil-, alquenil-, alquinil-, cicloalquil-, heteroalquil-, heterociclil-, aril-, heteroaril-, (cicloalquil)alquil-, (heterociclil)alquil-, aril-alquil- y heteroaril-alquil-; o alternativamente R y R' en NRR' están conectados uno al otro de manera que NRR' forma un heterociclilo de cuatro a ocho miembros;

e Y está seleccionado de las siguientes porciones:

o



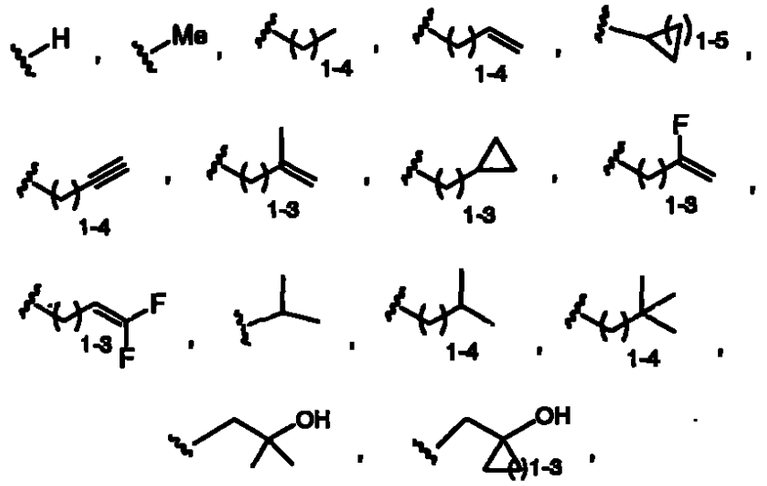
en las cuales G es NH u O; y R^{15}, R^{16}, R^{17}, R^{18} y R^{19} pueden ser iguales o diferentes, y cada una está independientemente seleccionado del grupo que consiste en H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo y heteroarilalquilo, o alternativamente, (i) cualquiera de R^{15} y R^{16} están conectados uno al otro para formar una estructura cíclica de cuatro a ocho miembros, o R^{15} y R^{19} están conectados uno al otro para formar una estructura cíclica de cuatro a ocho miembros, y (ii) asimismo, independientemente, R^{17} y R^{18} están conectados uno al otro para formar un cicloalquilo o heterociclilo de tres a ocho miembros;

donde cada uno de dichos alquilo, arilo, heteroarilo, cicloalquilo o heterociclilo pueden estar no sustituidos u opcionalmente independientemente sustituidos con una o más porciones seleccionadas del grupo que consiste en: hidroxi, alcoxi, ariloxi, tio, alquiltio, ariltio, amino, amido, alquilamino, arilamino, alquilsulfonilo, arilsulfonilo, sulfonamido, alquilsulfonamido, arilsulfonamido, alquilo, arilo, heteroarilo, ceto, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halo, ciano y nitro.

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2. El compuesto de la reivindicación 1, en el cual R^1 es NR^9R^{10} y R^9 es H, R^{10} es H o R^{14} donde R^{14} es H, alquilo, arilo, heteroalquilo, heteroarilo, cicloalquilo, alquil-arilo, alquil-heteroarilo, aril-alquilo, alquenilo, alquinilo o heteroaril-alquilo.

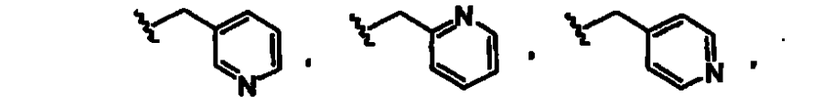
3. El compuesto de la reivindicación 2, en el cual R^{14} está seleccionado del grupo que consiste en:









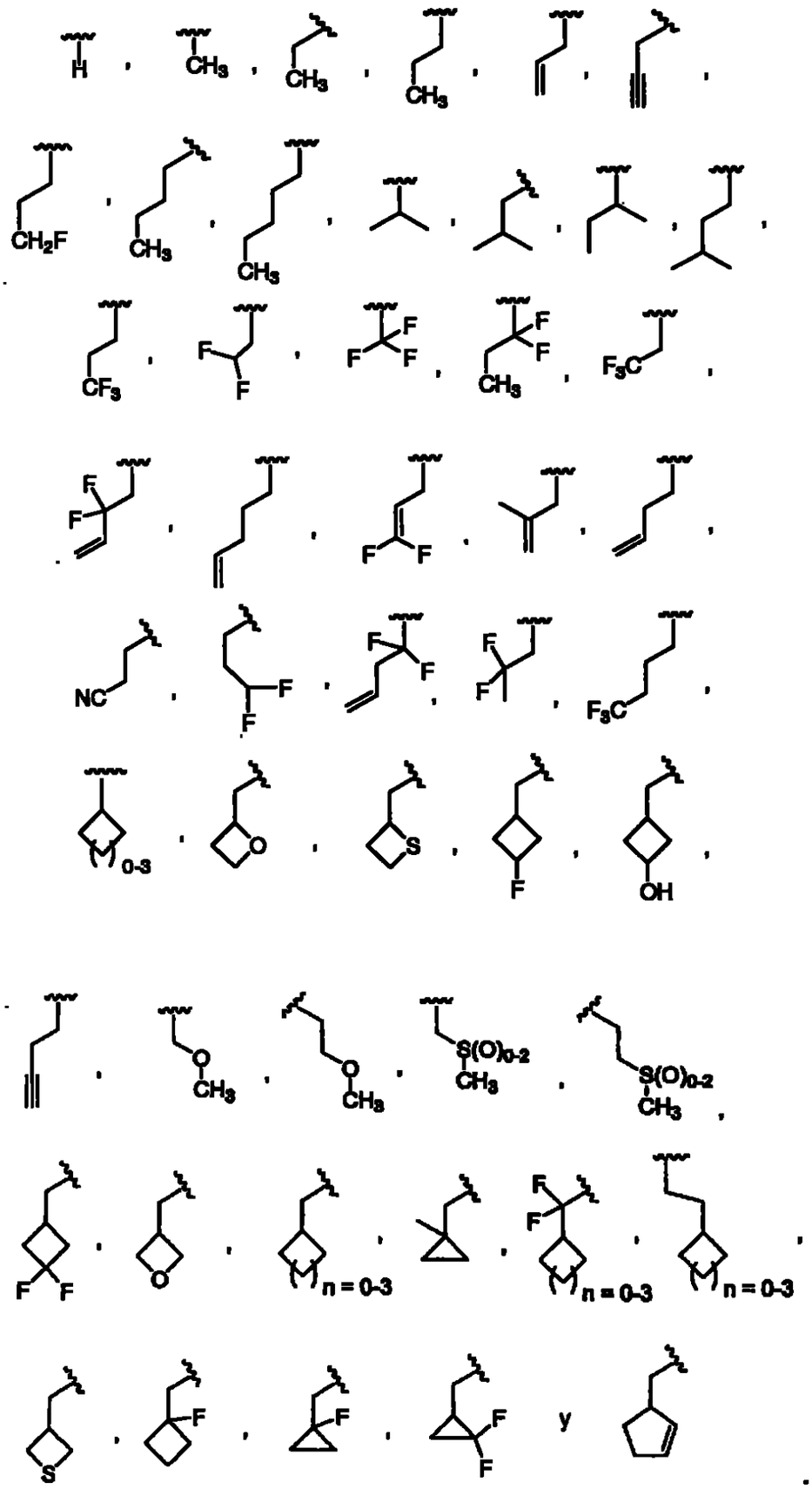






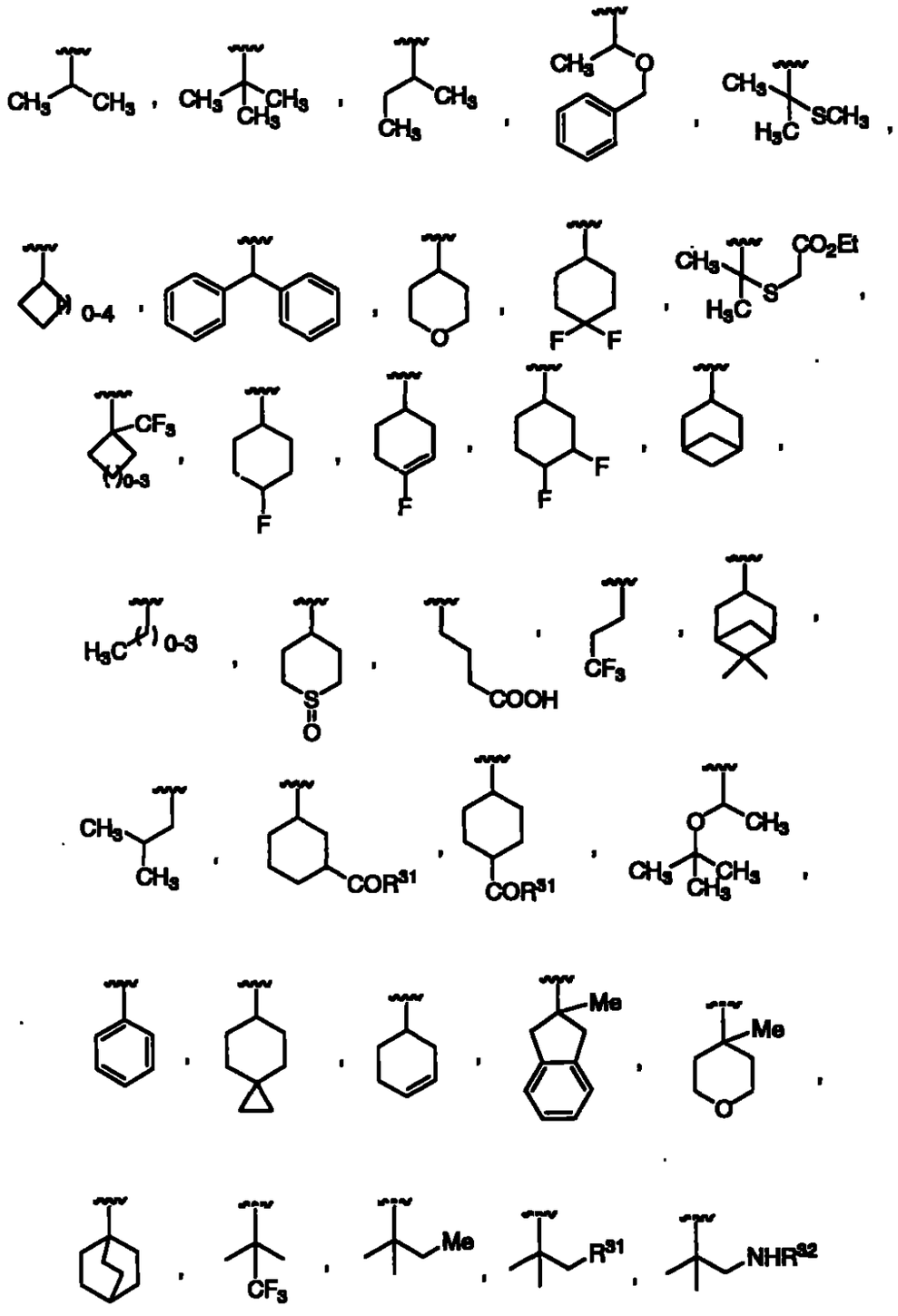


4. El compuesto de la reivindicación 1, en el cual R^2 está seleccionado del grupo que consiste en las siguientes porciones:

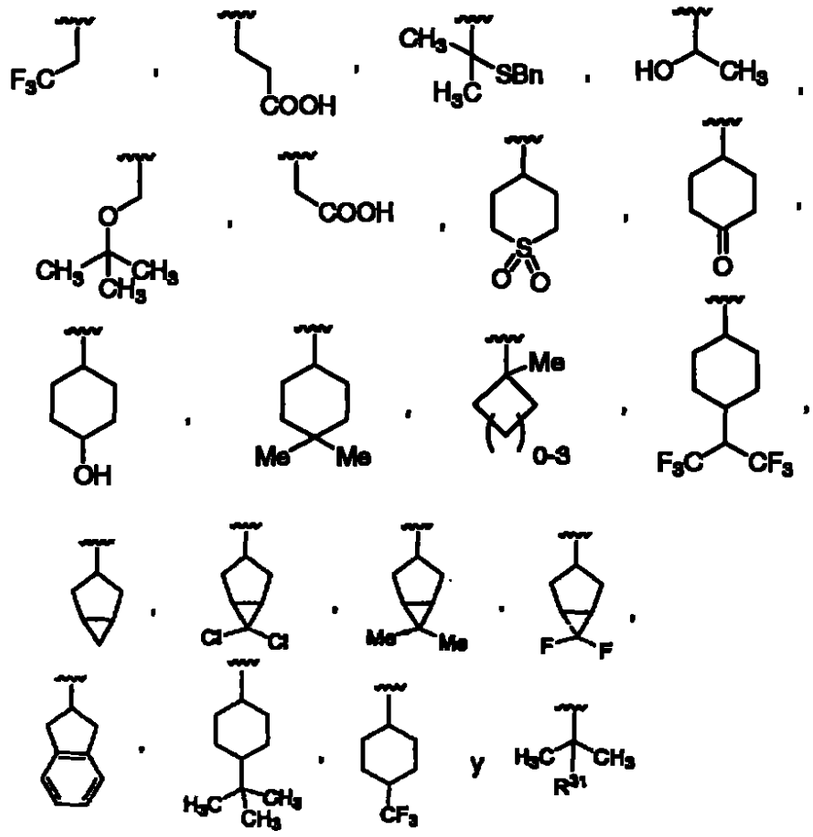

H
CH3
CH3
CH3
CH2F
CH3
CH3
CF3
F
F
F
F
F
CH3
F3C
F
F
F
F
NC
F
F
F
F
F3C
0-3
O
S
F
OH
O
CH3
O
CH3
S(O)0-2
CH3
S(O)0-2
CH3
F
F
O
n = 0-3
F
F
n = 0-3
n = 0-3
S
F
F
F
F
y

345
315

5. El compuesto de la reivindicación 1, en el cual R^3 está seleccionado del grupo que consiste en:



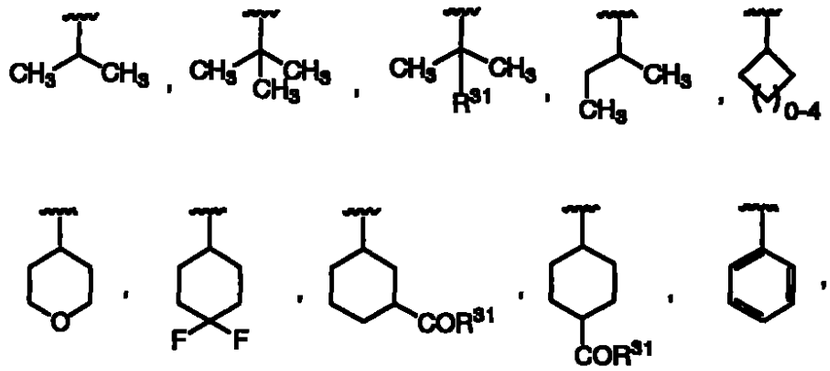
346
316



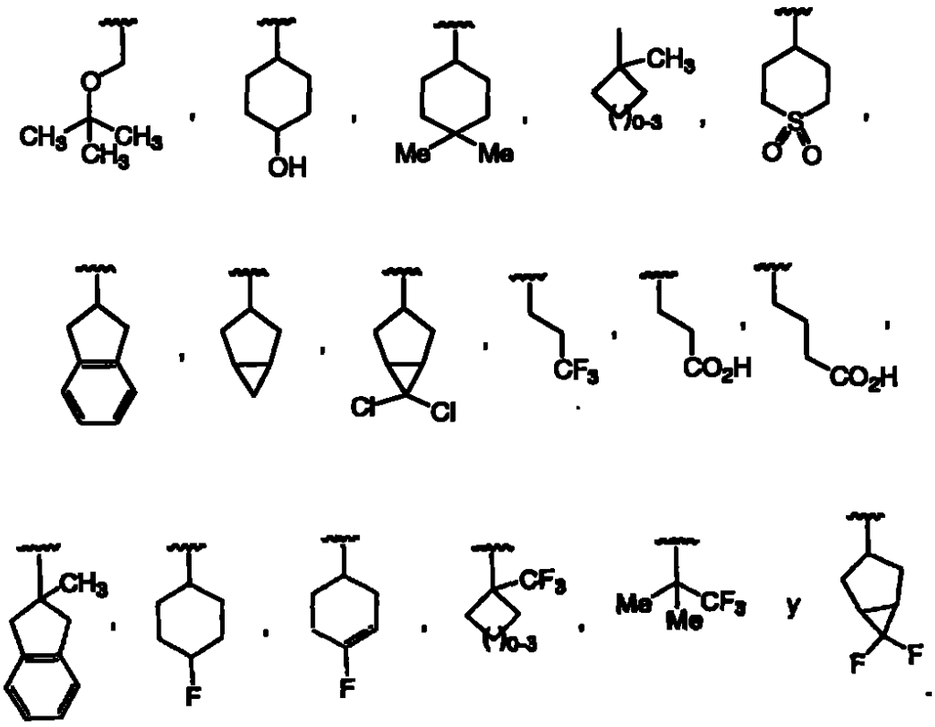
en las cuales R^{31} es OH u O-alquilo; y

R^{32} es H, $C(O)CH_3$, C(O)OtBu o C(O)N(H)tBu.

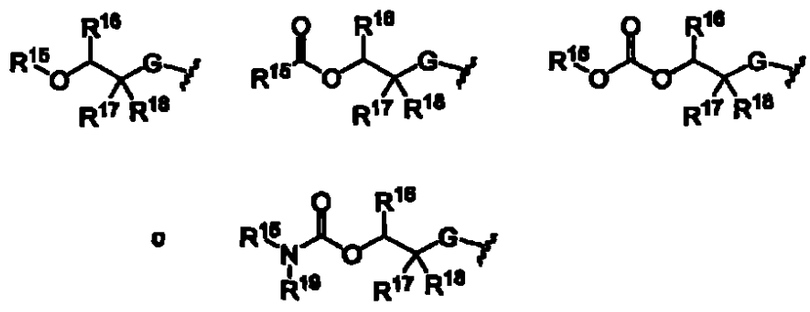
6. El compuesto de la reivindicación 5, en el cual R^3 está seleccionado del grupo que consiste en las siguientes porciones:



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7. El compuesto de la reivindicación 1, en el cual Y está seleccionado de las siguientes porciones:



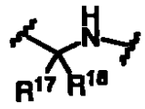
en las cuales G = NH u O; y

R^{15}, R^{16}, R^{17}, R^{18} y R^{19} pueden ser iguales o diferentes, y cada uno está independientemente seleccionado del grupo que consiste en H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo y heteroarilo, o alternativamente, (i) R^{15} y R^{16} están directamente conectados para formar una estructura cíclica de cuatro a ocho miembros o R^{15} y R^{19} están directamente conectados para formar una estructura cíclica de cuatro a ocho miembros, y (ii) asimismo, independientemente, R^{17} y R^{18} están directamente conectados para formar un cicloalquilo o heterociclilo de tres a ocho miembros;

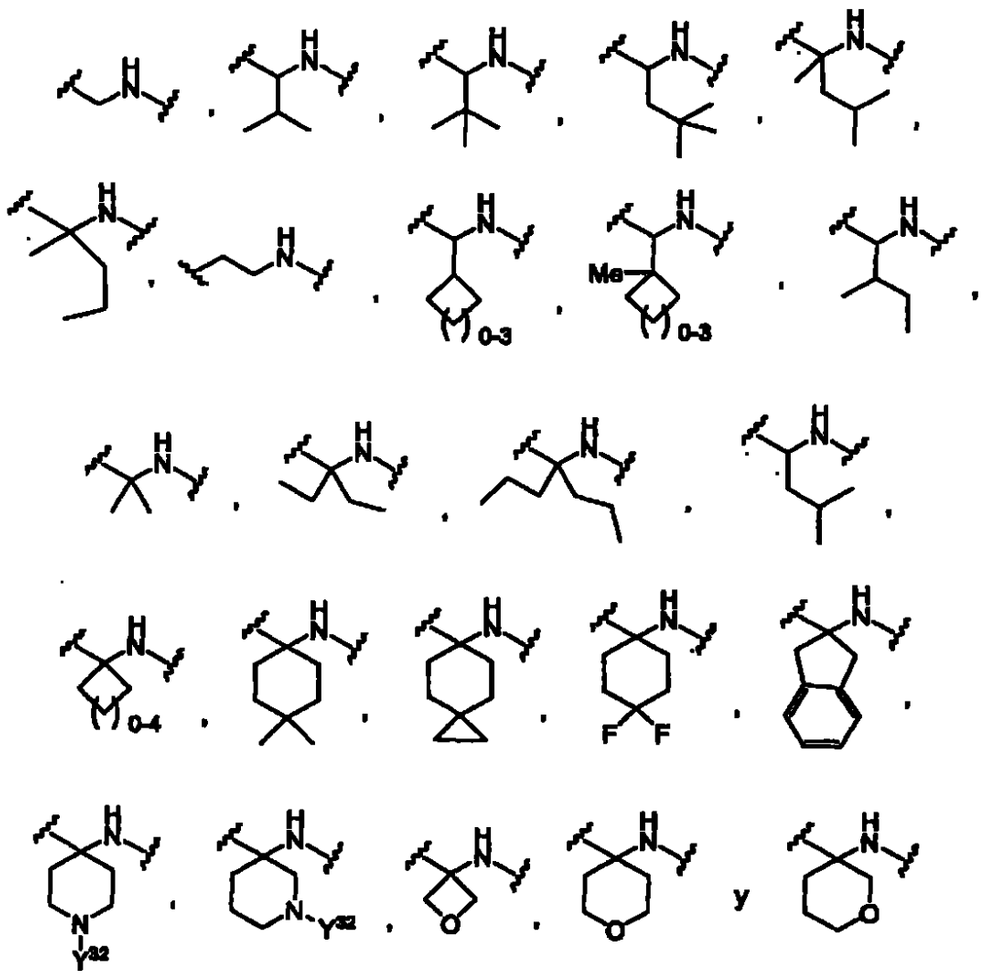
donde cada uno de dichos alquilo, arilo, heteroarilo, cicloalquilo o heterocicilo pueden estar no sustituidos u opcionalmente independientemente sustituidos con una o más porciones seleccionadas del grupo que consiste en: hidroxi, alcoxi, ariloxi, tio, alquiltio, ariltio, amino, amido, alquilamino, arilamino, alquilsulfonilo, arilsulfonilo, sulfonamido, alquilsulfonamido, arilsulfonamido, ceto, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halo, ciano y nitro.

8. El compuesto de la reivindicación 7, en el cual G es NH.

9. El compuesto de la reivindicación 8, en el cual

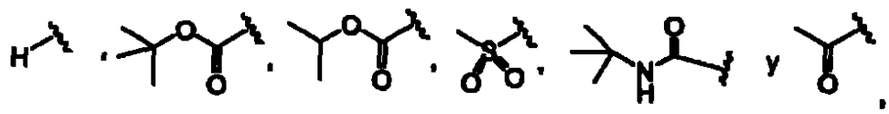


está seleccionado del grupo que consiste en:



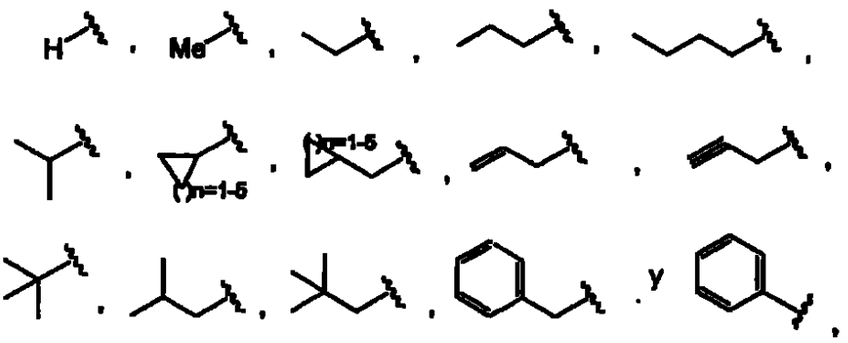
donde Y^{32} está seleccionado del grupo que consiste en:

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R^{18} está seleccionado de H, metilo, fenilo, bencilo; y

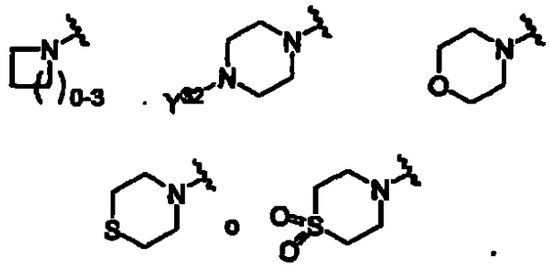
R^{15} y R^{19} pueden ser iguales o diferentes, y cada uno está independientemente seleccionado entre los siguientes:



o alternativamente, la porción:

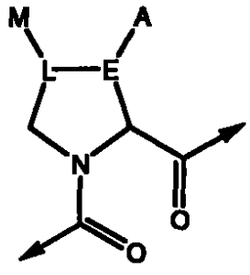


está seleccionada de las siguientes porciones:

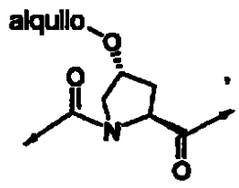


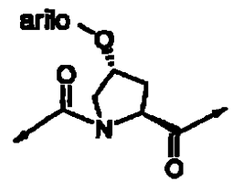
10. El compuesto de la reivindicación 9, en el cual R^{18} es H.

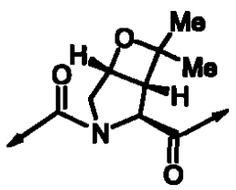
11. El compuesto de la reivindicación 1, en el cual la porción:

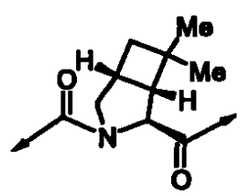


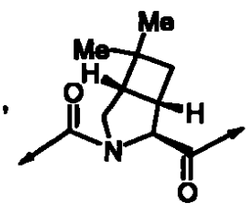
está seleccionada de las siguientes estructuras:

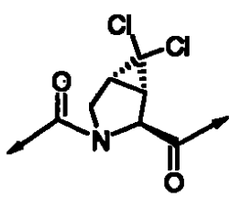


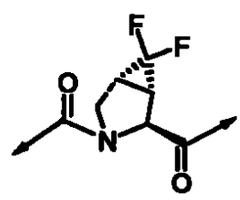


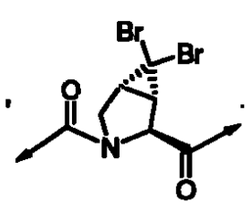


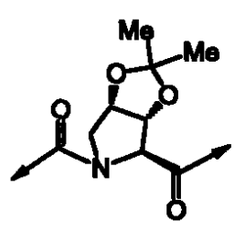


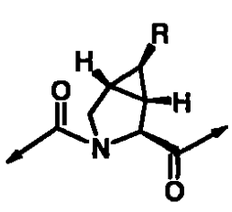


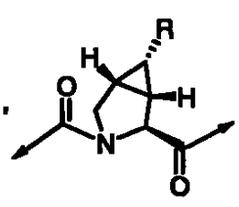


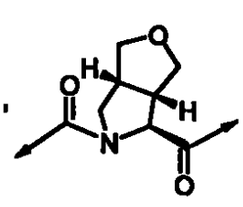


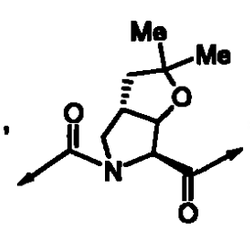


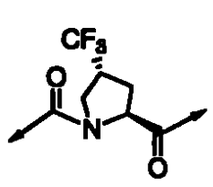


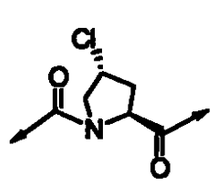


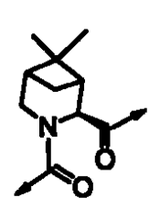






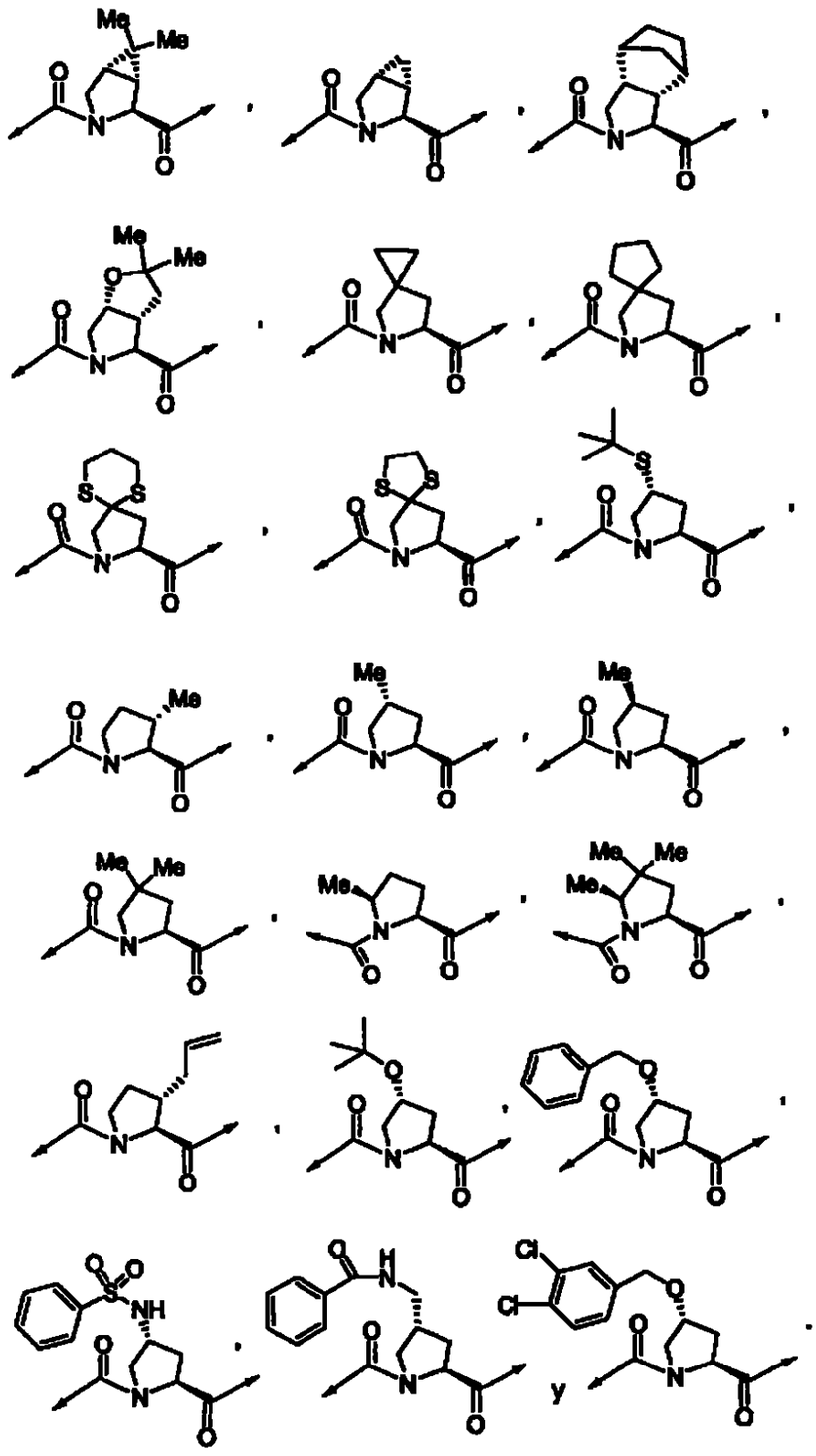




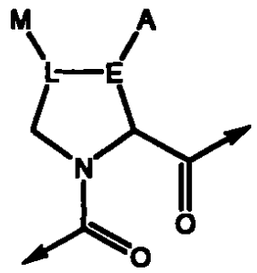




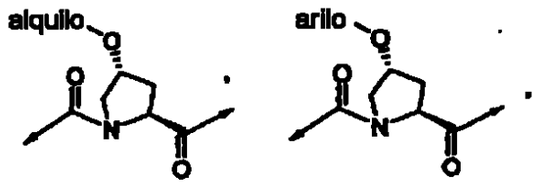
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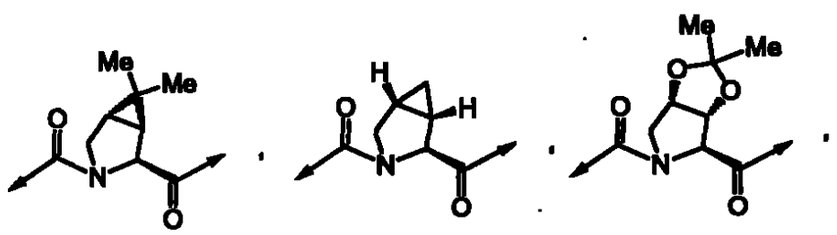


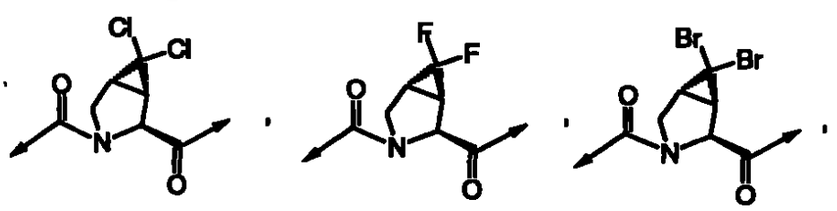
12. El compuesto de la reivindicación 11, en el cual la porción:

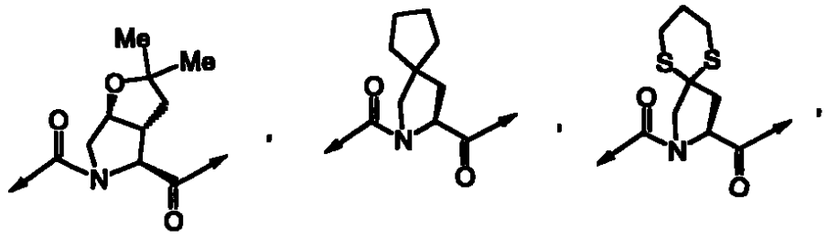


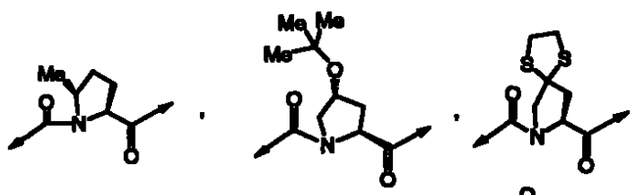
está seleccionada entre las siguientes estructuras:

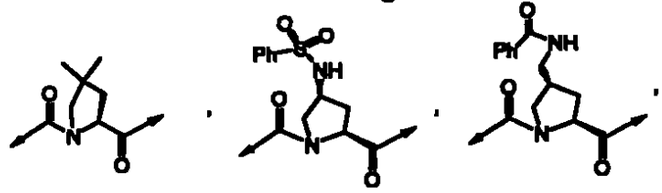




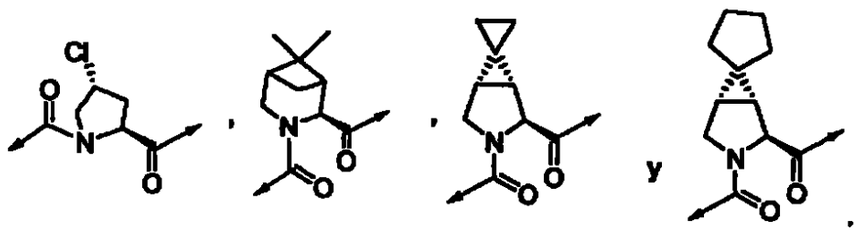




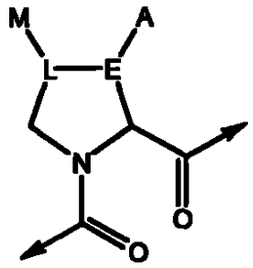




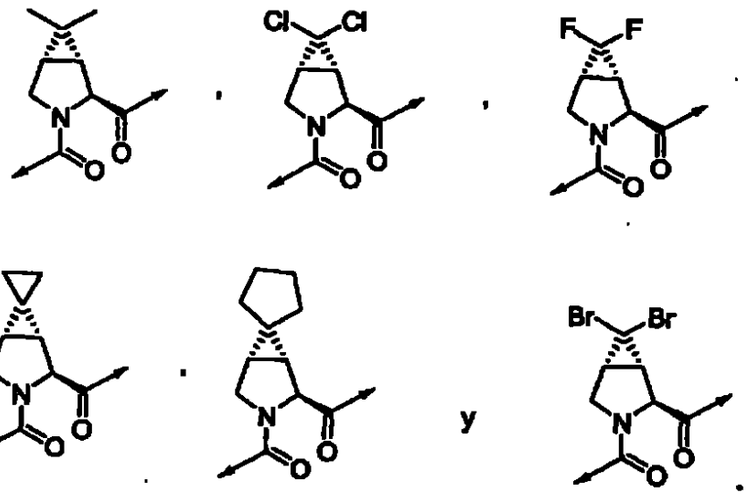
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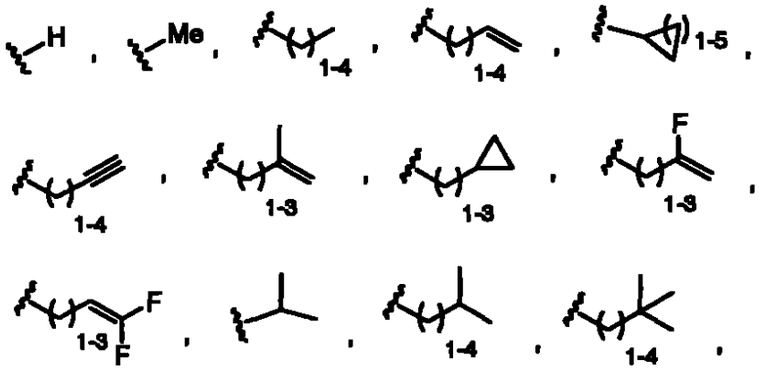
13. El compuesto de la reivindicación 12, en el cual la porción:



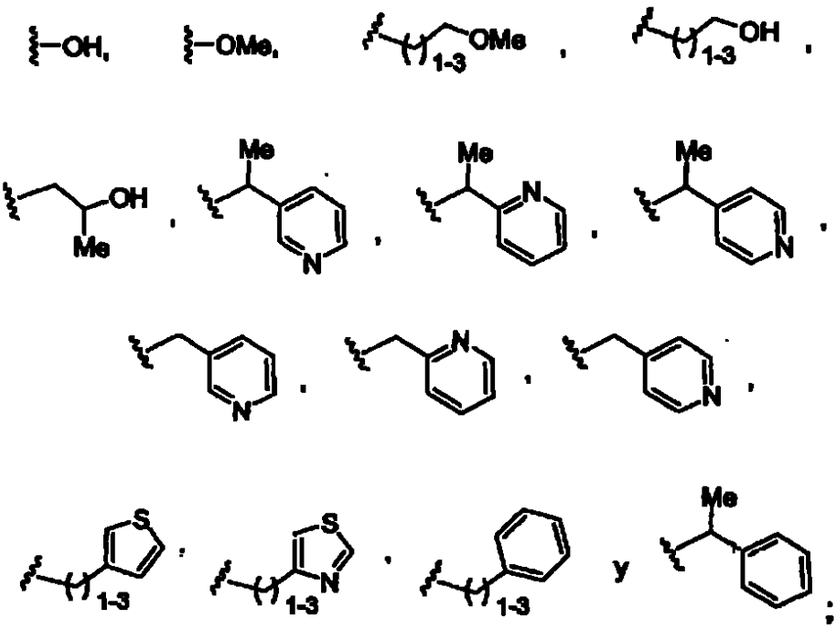
está seleccionada de las siguientes estructuras:



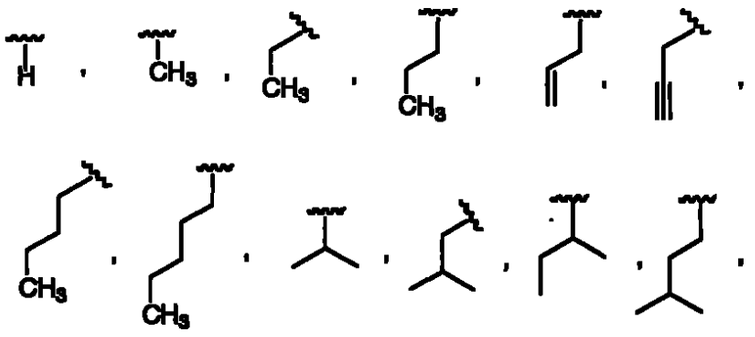
14. El compuesto de la reivindicación 1, en el cual R^{14} está seleccionado del grupo que consiste en:

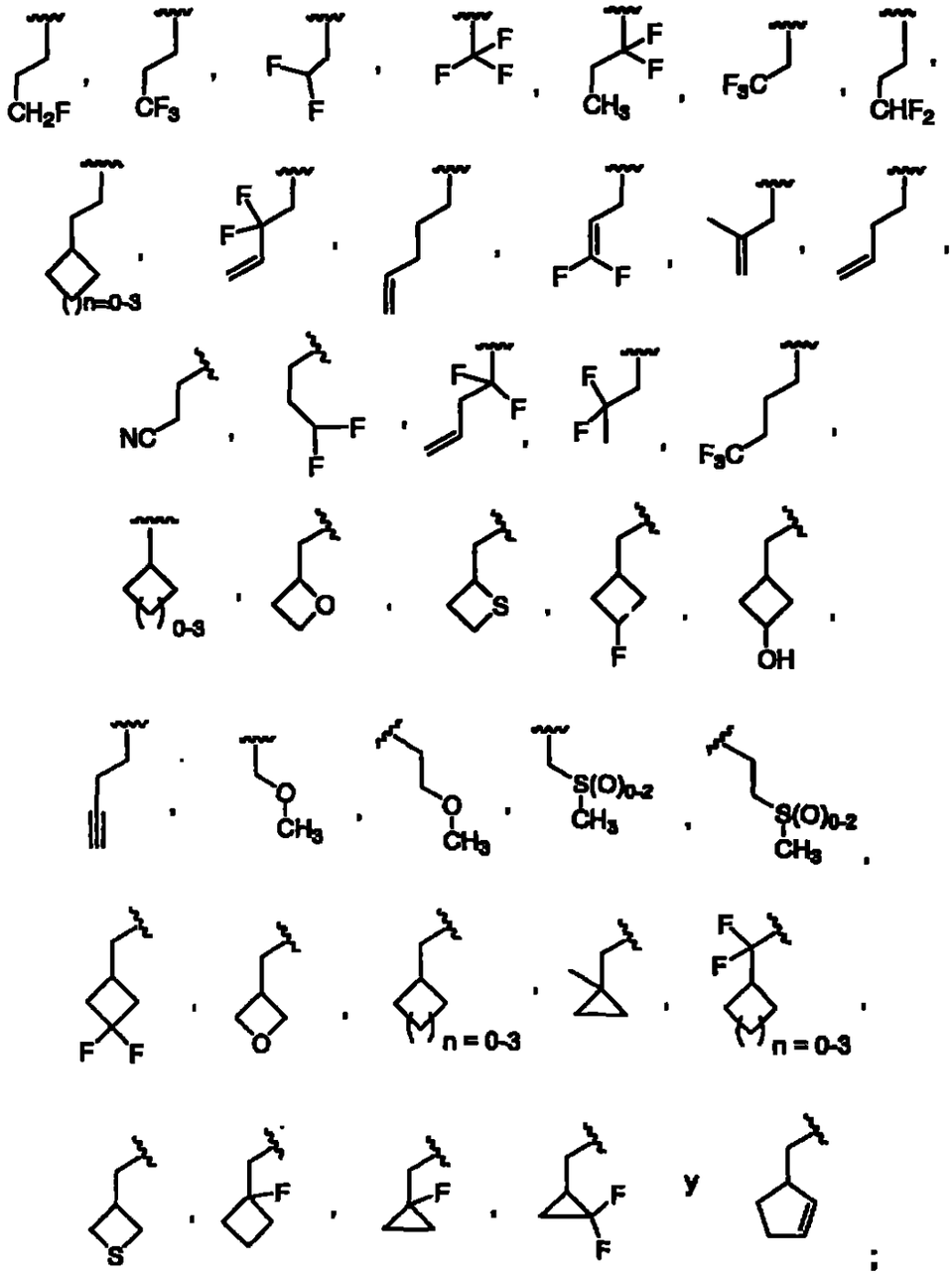


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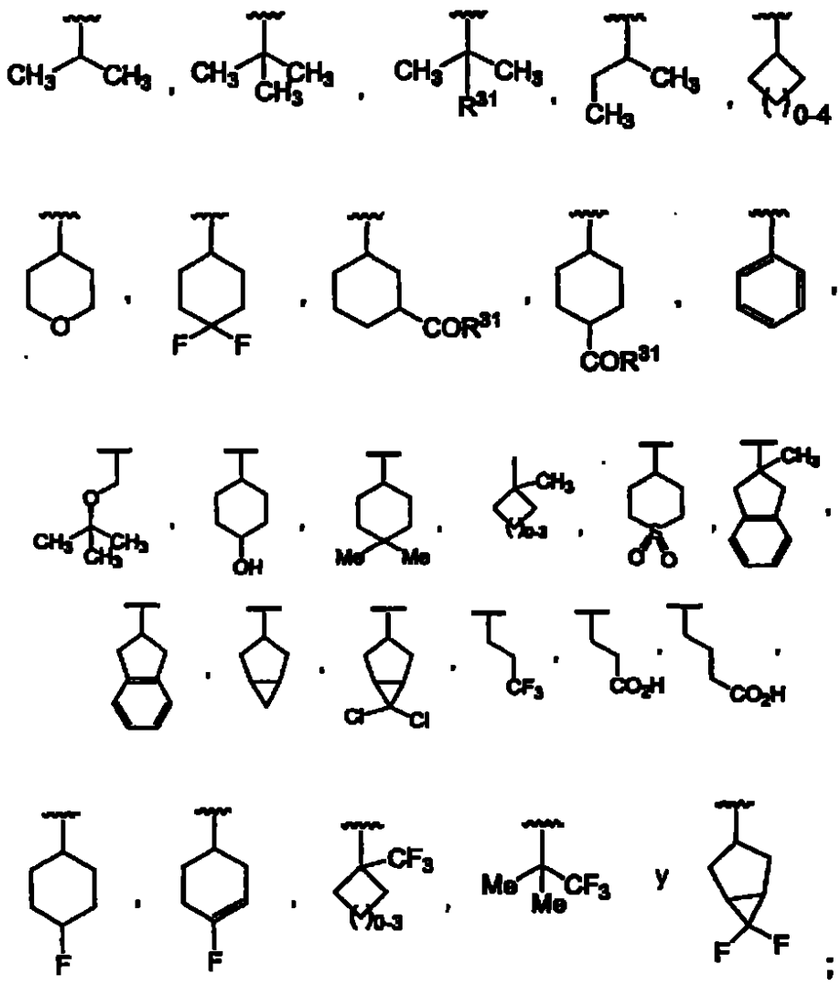
R^2 está seleccionado del grupo que consiste en las siguientes porciones:



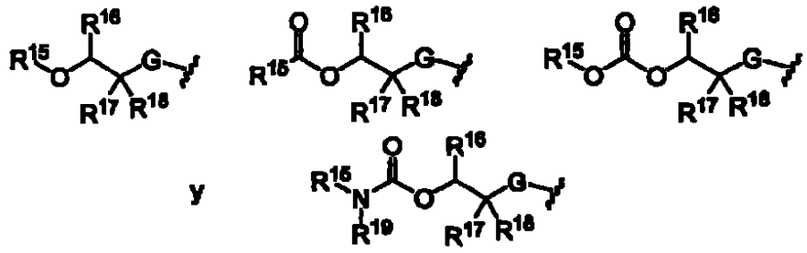


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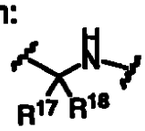
R^3 está seleccionado del grupo que consiste en las siguientes porciones:



Y está seleccionado del grupo que consiste en:



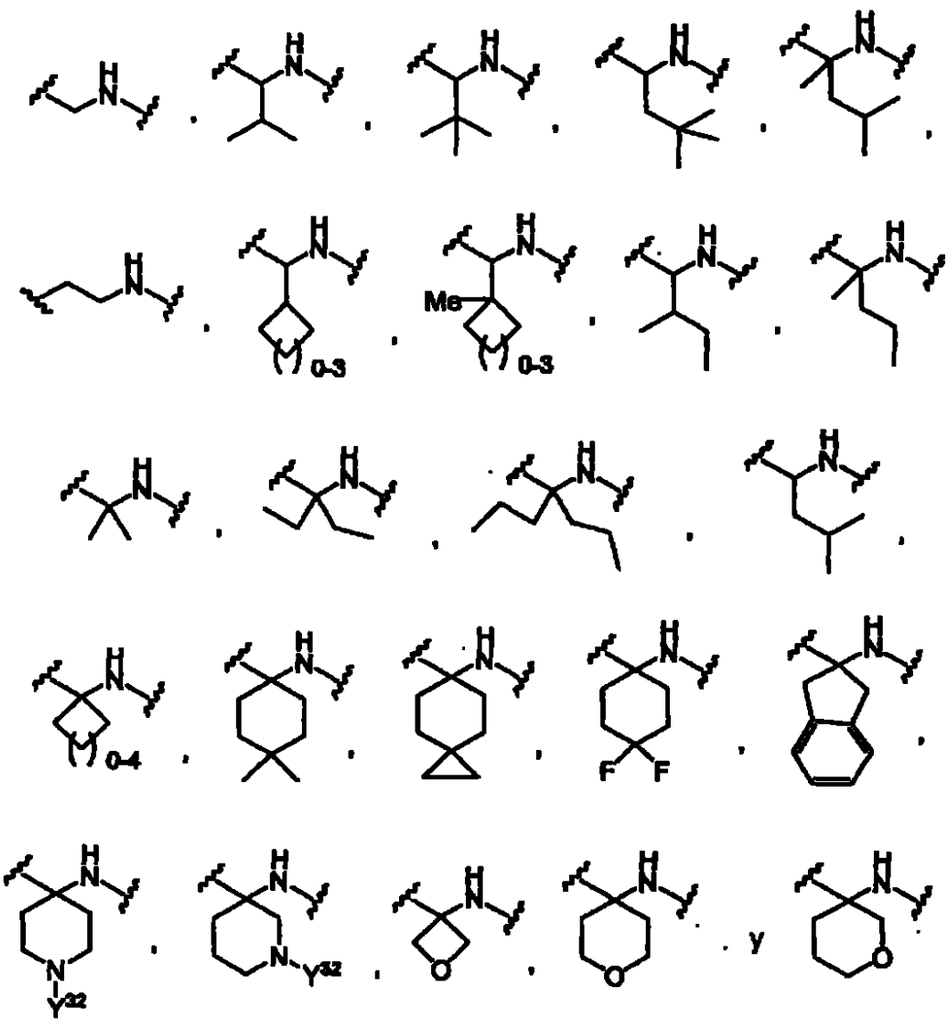
donde G = NH; y la porción:



está seleccionada del grupo que consiste en:

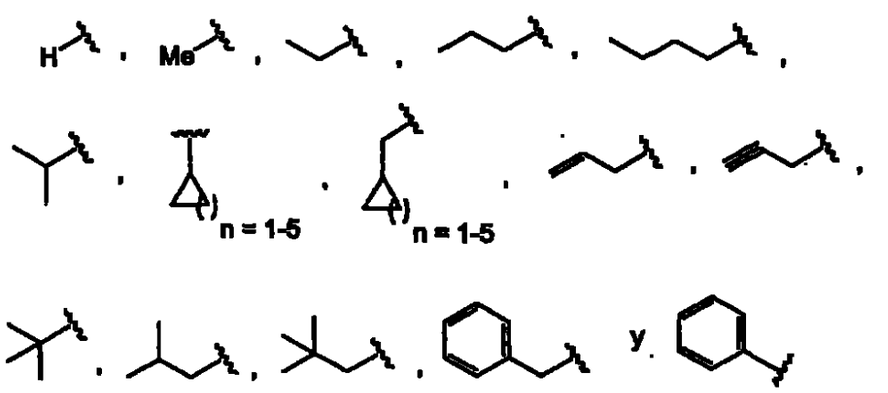
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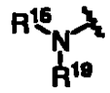


R^{16} = H; y

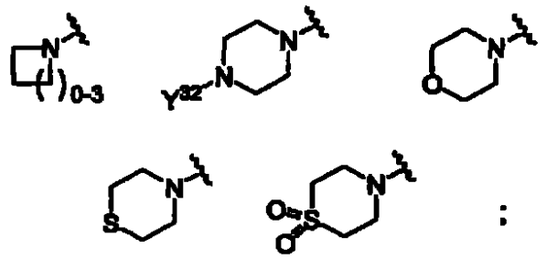
R^{15} y R^{19} pueden ser iguales o diferentes, y están seleccionados entre uno de los siguientes:



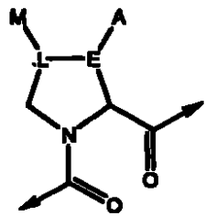
o alternativamente, la porción:



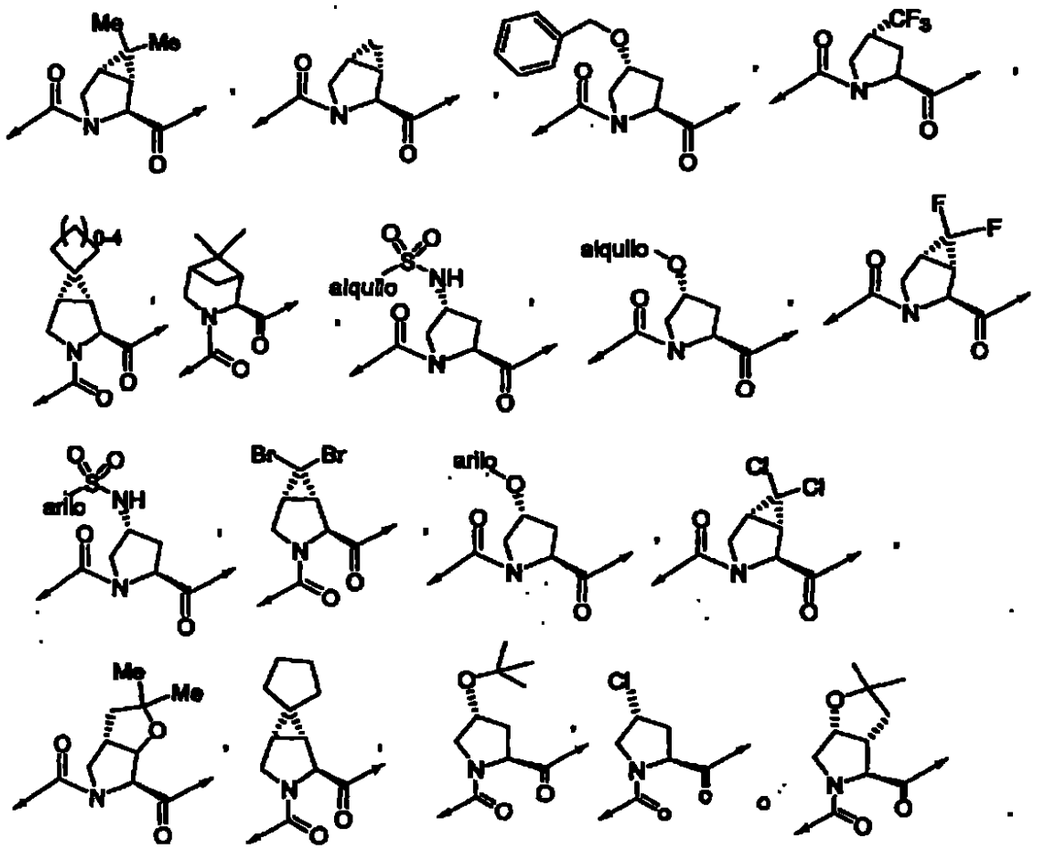
está representada por una de las siguientes porciones,



y la porción:



es:



15. Una composición farmacéutica que comprende como ingrediente activo por lo menos un compuesto de la reivindicación 1.

16. La composición farmacéutica de la reivindicación 15 para ser usada en el tratamiento de desórdenes asociados con HCV.

17. La composición farmacéutica de la reivindicación 16 que comprende adicionalmente por lo menos un portador farmacéuticamente aceptable.

18. La composición farmacéutica de la reivindicación 17, que contiene adicionalmente por lo menos un agente antiviral.

19. La composición farmacéutica de la reivindicación 18, que contiene adicionalmente por lo menos un interferón.

20. La composición farmacéutica de la reivindicación 19, donde dicho por lo menos un agente antiviral es ribavirina y dicho por lo menos un interferón es α-interferón o interferón pegilado.

21. Un método para el tratamiento de desórdenes asociados con el HCV, donde dicho método comprende administrar a un paciente que necesita dicho tratamiento una composición farmacéutica que comprende cantidades terapéuticamente eficaces de por lo menos un compuesto de la reivindicación 1.

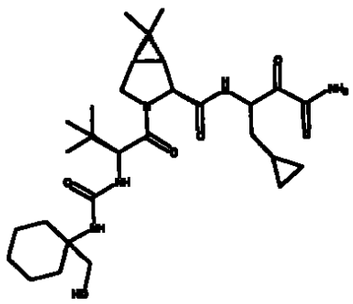
22. El método de la reivindicación 21, en el cual dicha administración es oral o subcutánea.

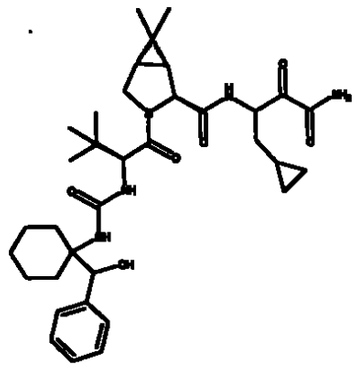
23. El uso de un compuesto de la reivindicación 1 para la manufactura de un medicamento para tratar desórdenes asociados con el HCV.

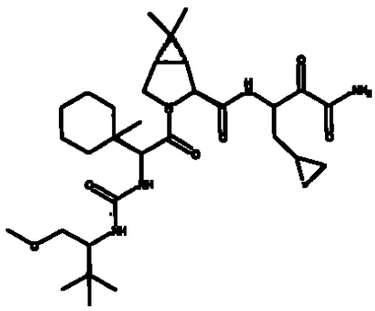
24. Un método para preparar una composición farmacéutica para el tratamiento de desórdenes asociados con el HCV, donde dicho método comprende poner en íntimo contacto físico por lo menos un compuesto de la reivindicación 1 y por lo menos un portador farmacéuticamente aceptable.

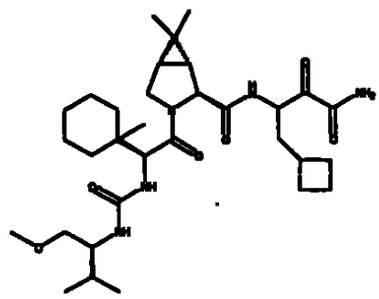
25. Un compuesto que exhibe actividad inhibidora de proteasa HCV, o enantiómeros, estereoisómeros, rotámeros, tautómeros, diastereómeros o racematos de dicho compuesto, o una sal, solvato o éster farmacéuticamente aceptable de dicho compuesto, donde dicho compuesto está seleccionado entre los compuestos de las estructuras enumeradas a continuación:

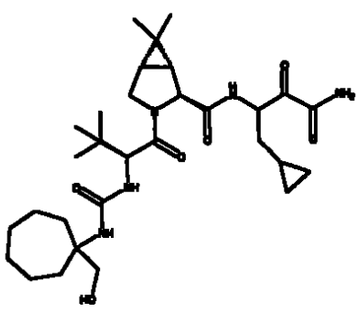
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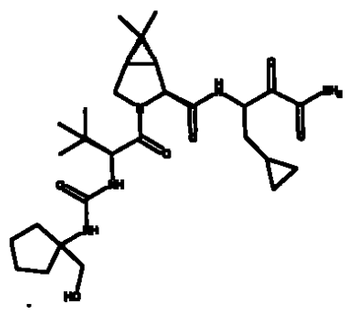


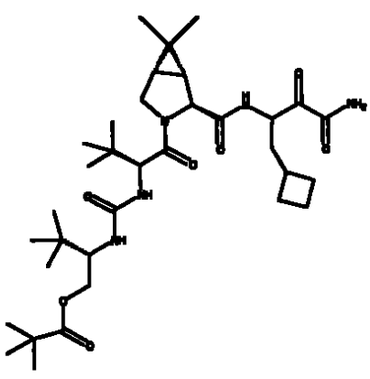


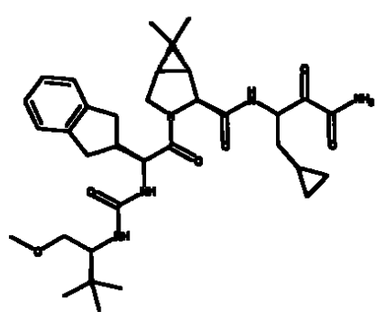




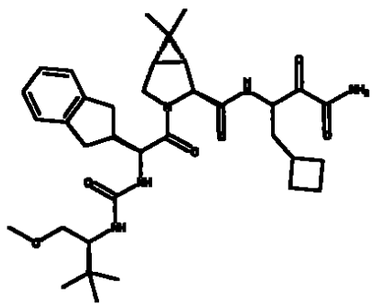


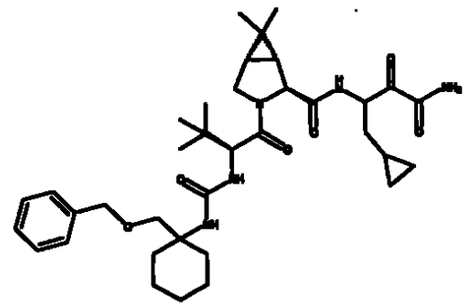


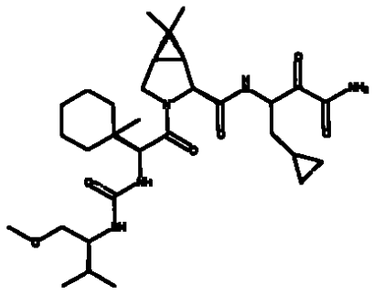


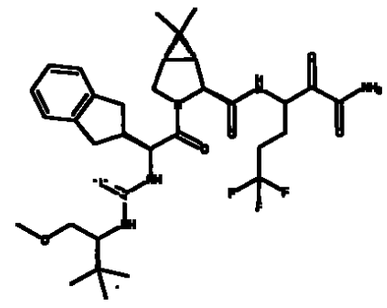


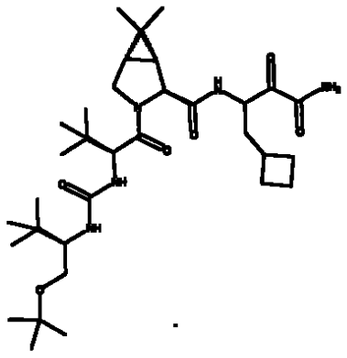
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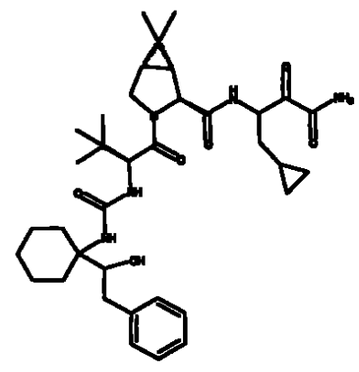


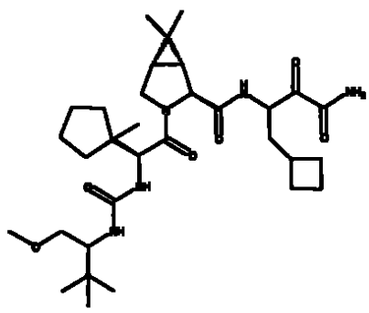


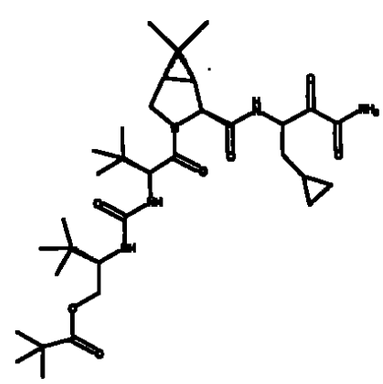




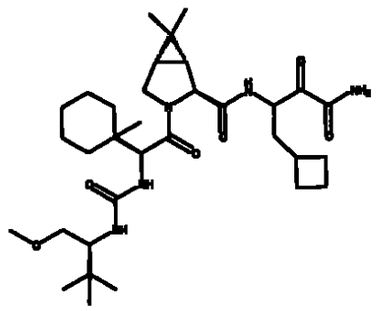


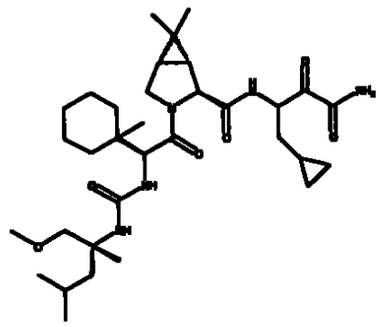


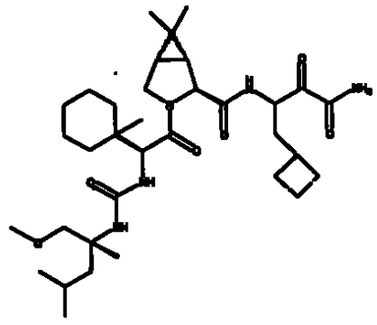


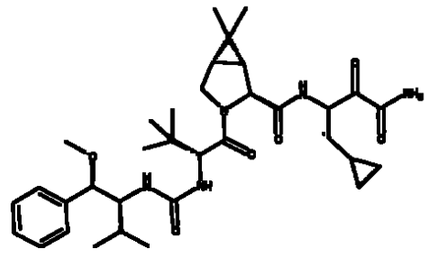


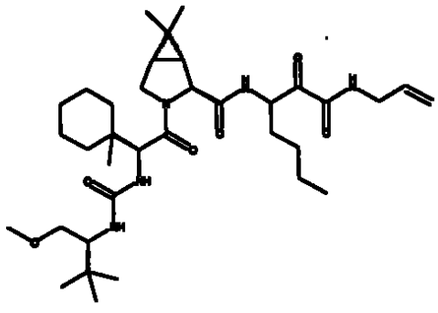
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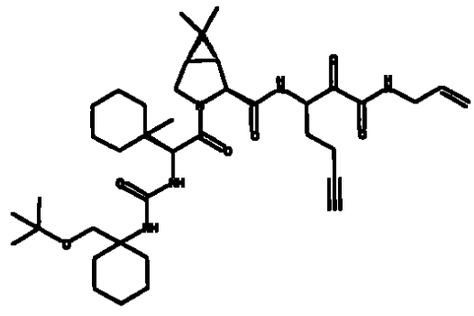


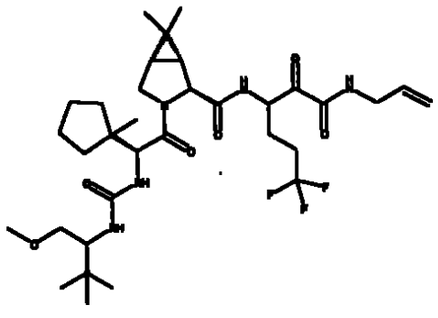


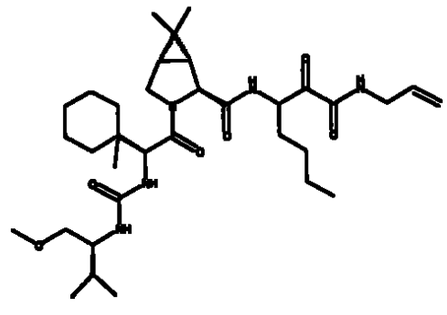




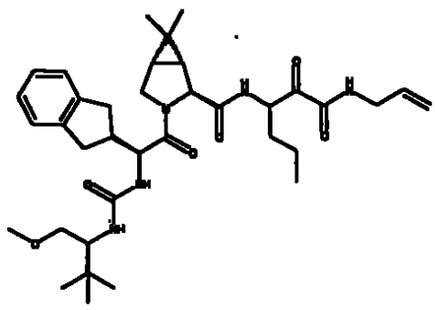


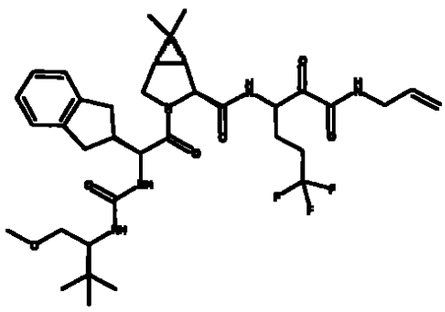


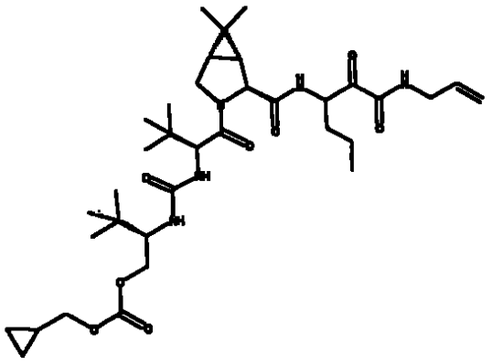


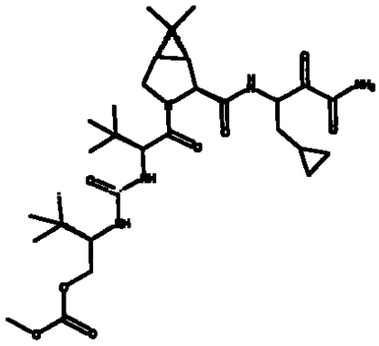


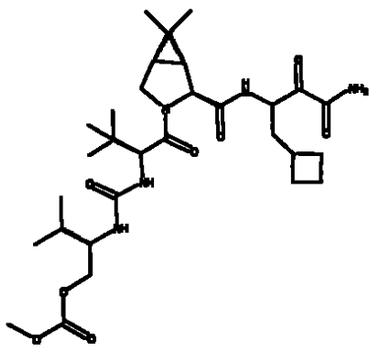
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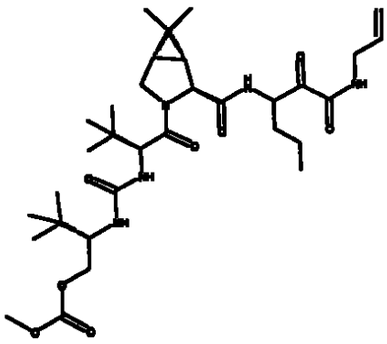


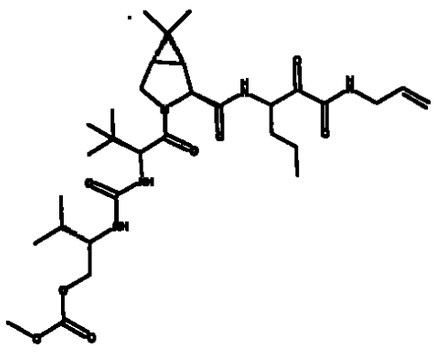




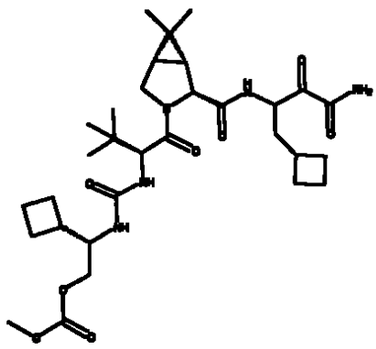


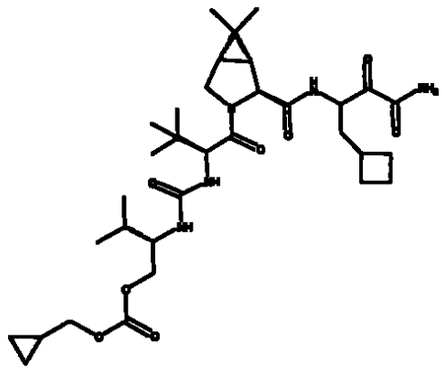


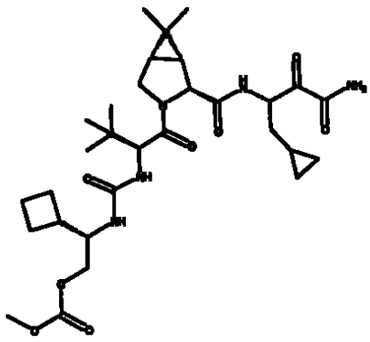


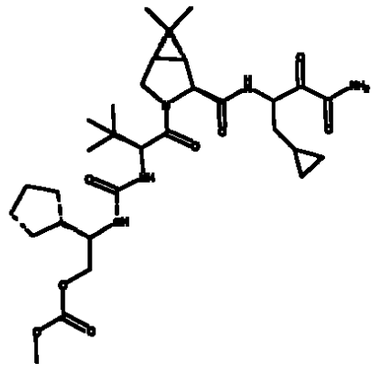


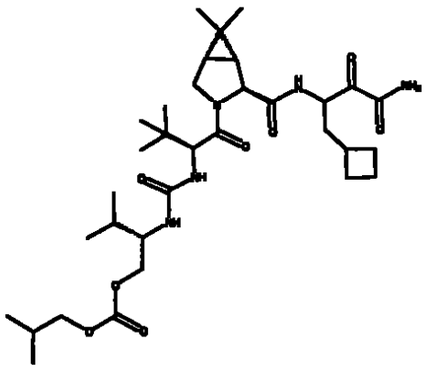
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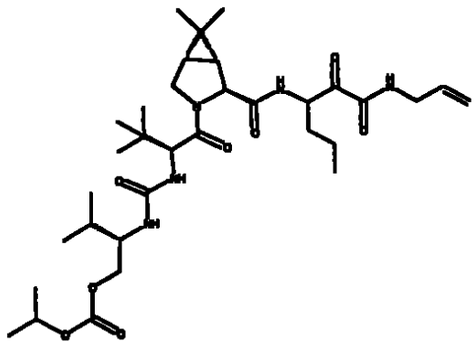


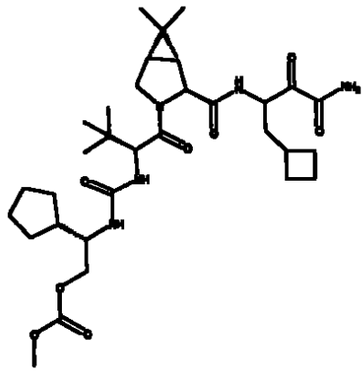


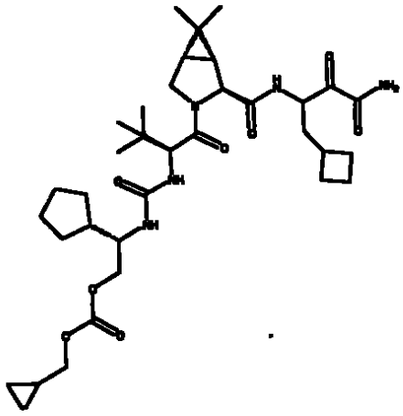




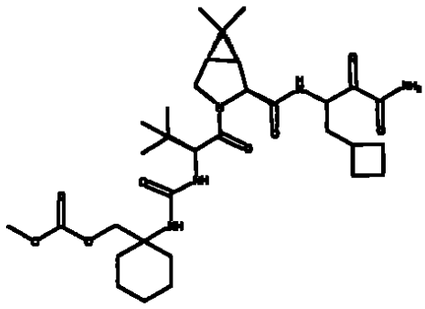


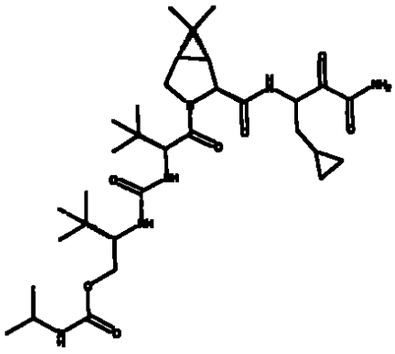


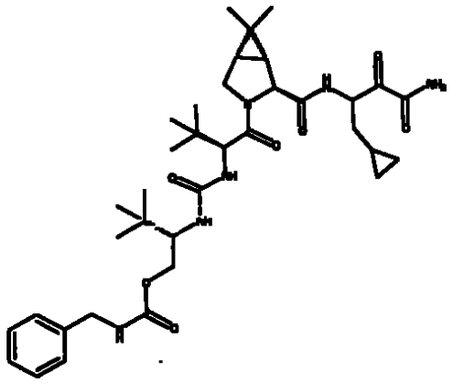


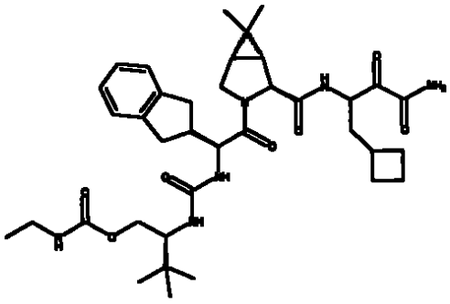


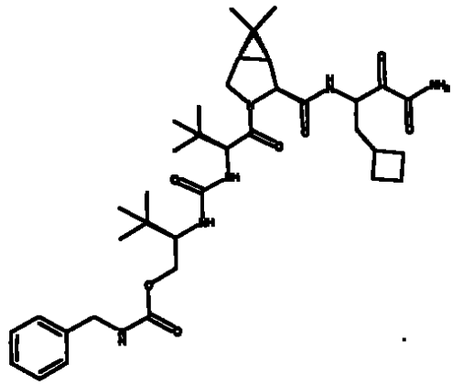
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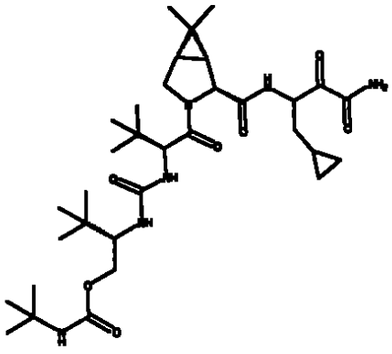


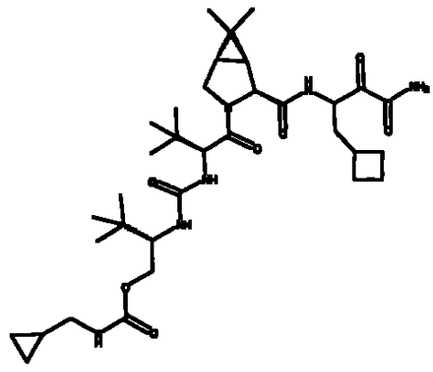






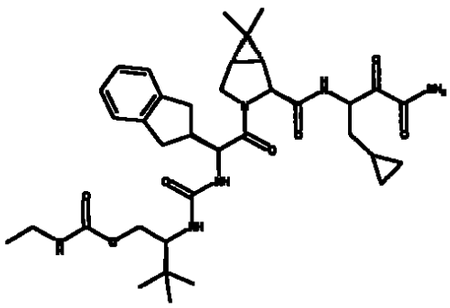


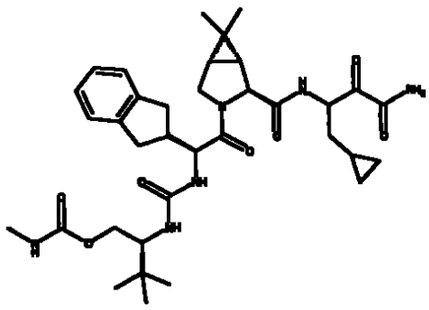


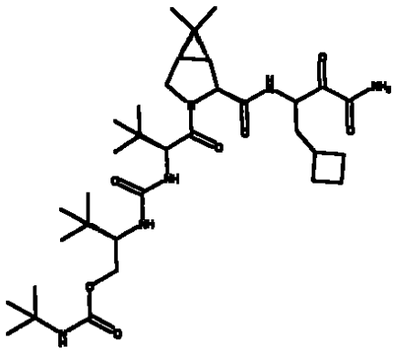


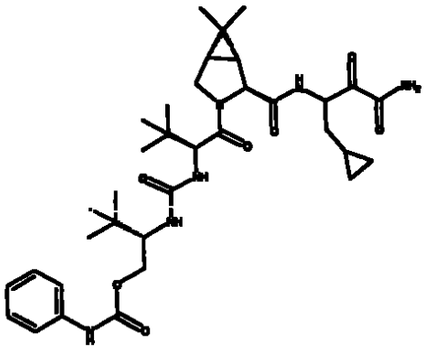
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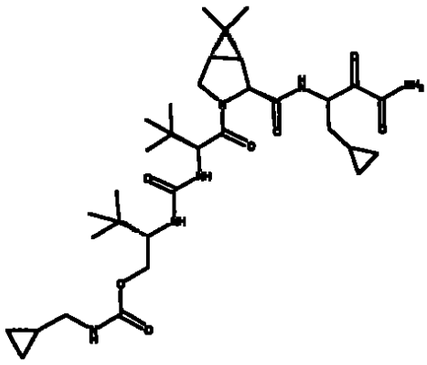
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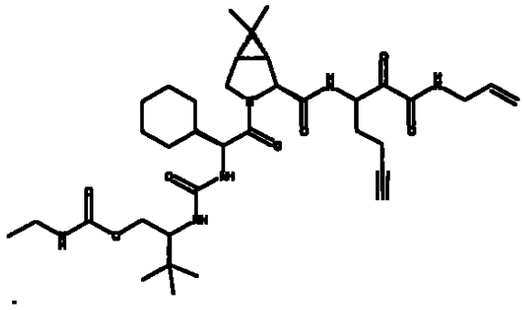


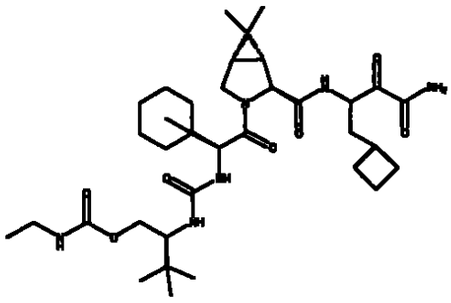


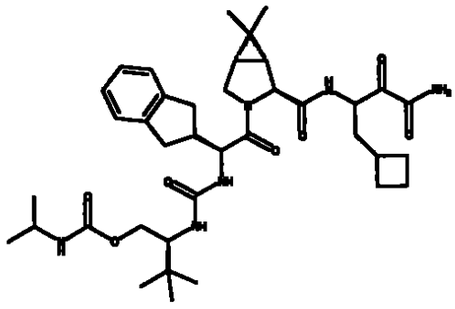




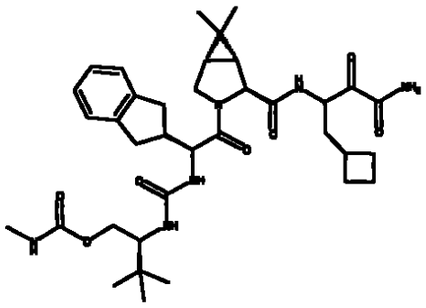


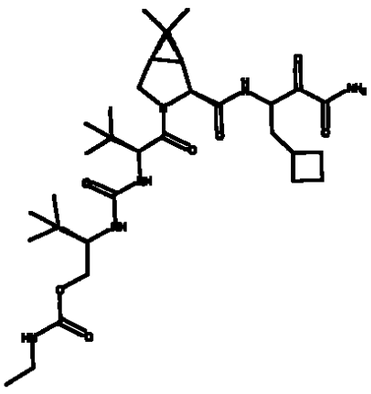


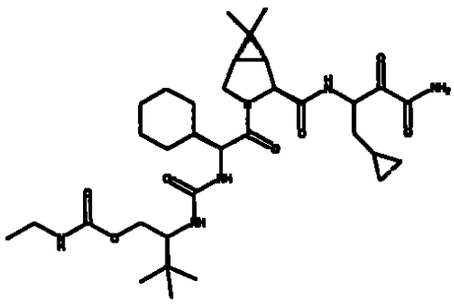


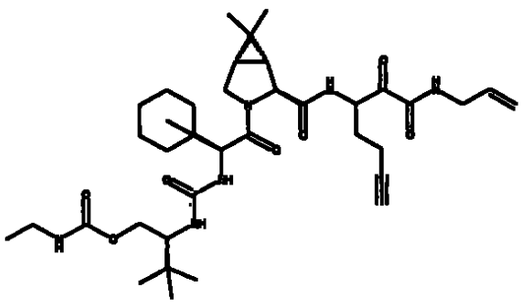


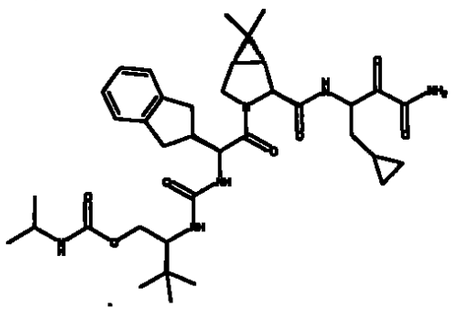
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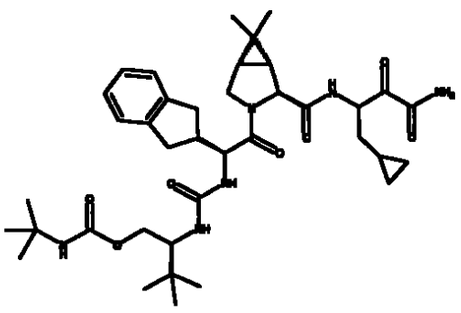


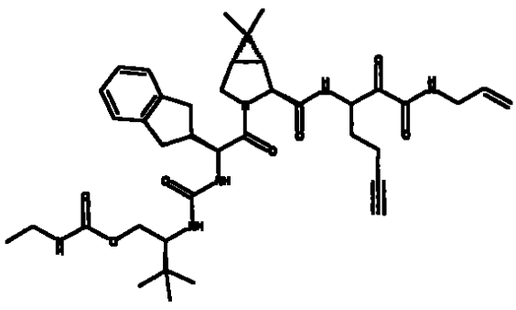


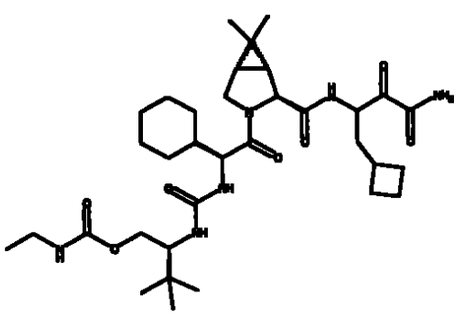




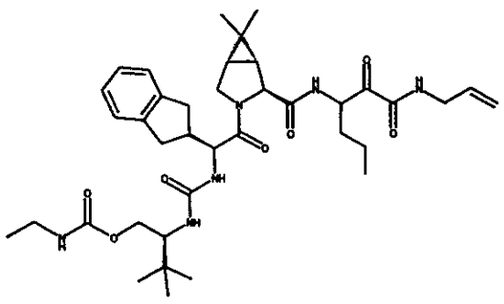


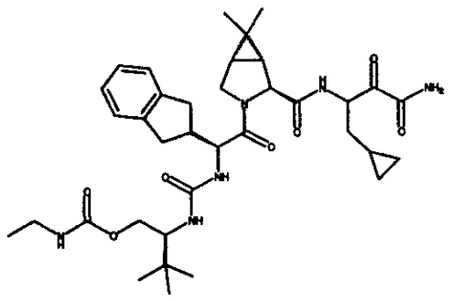


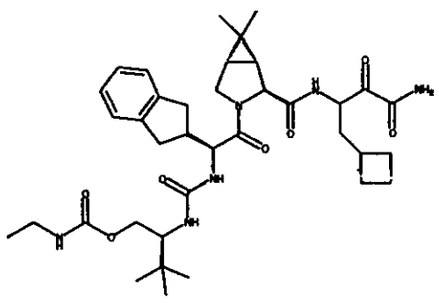


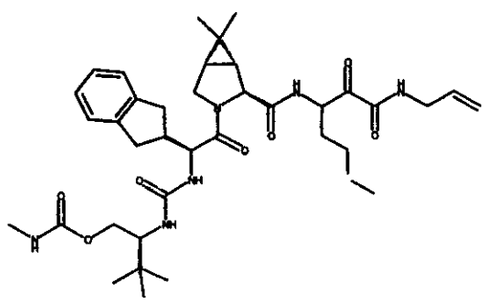


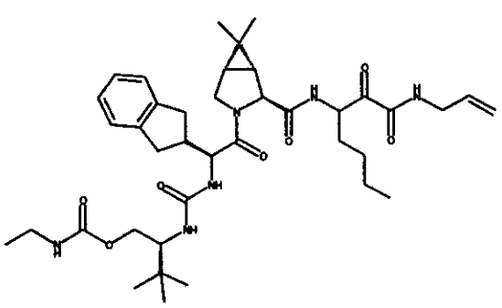
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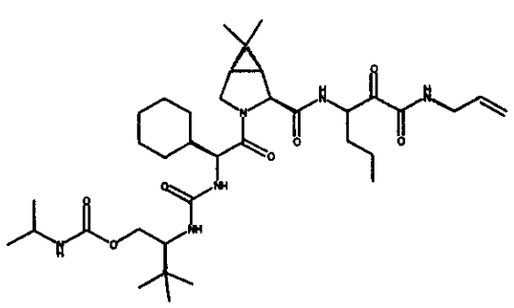


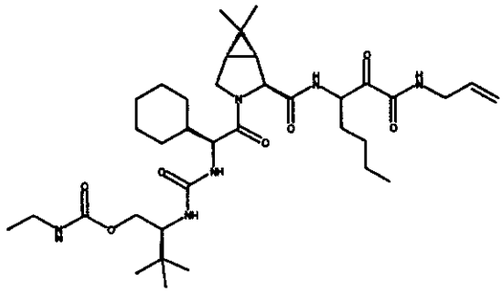


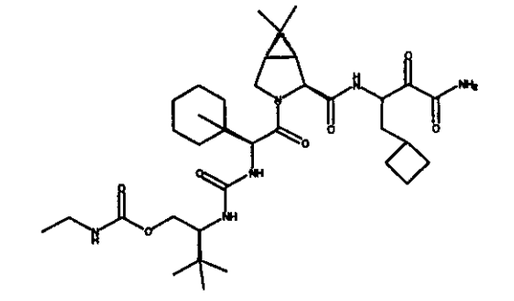




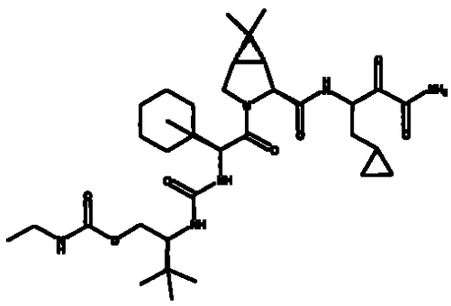


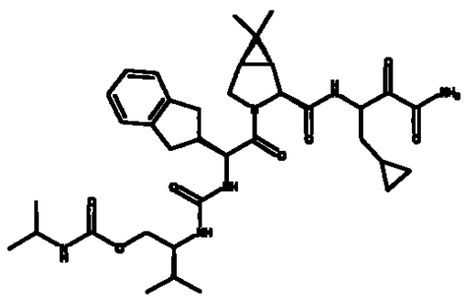


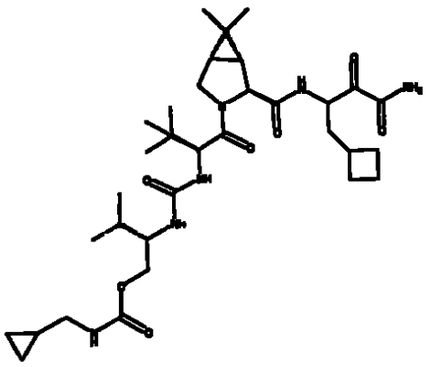


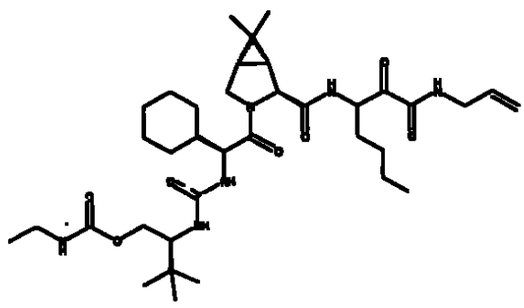


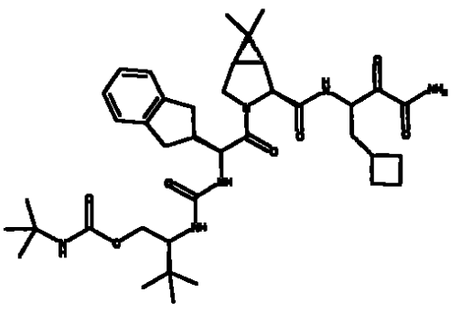
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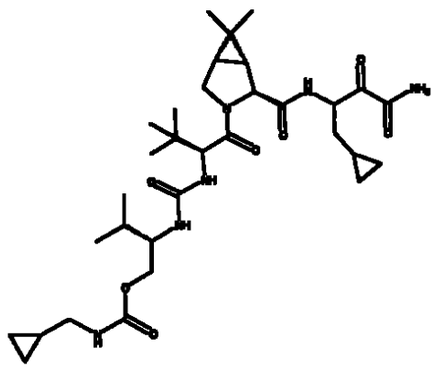


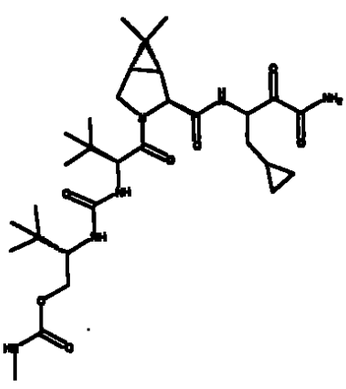


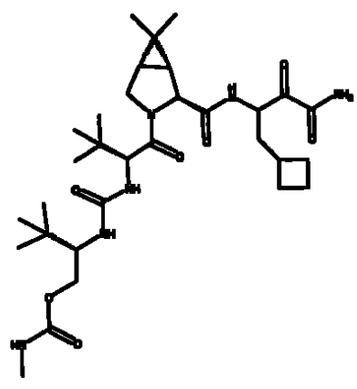






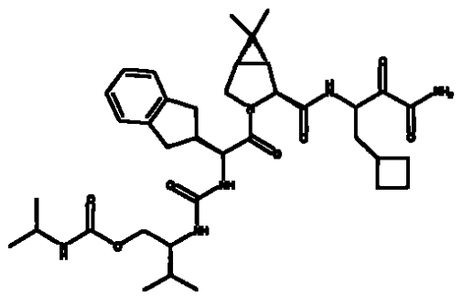


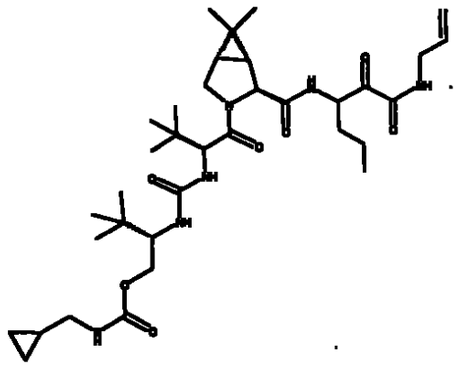


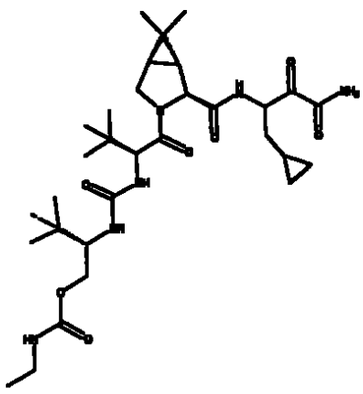


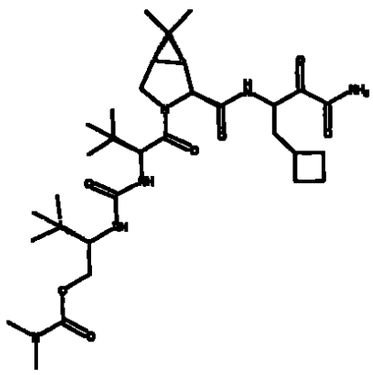
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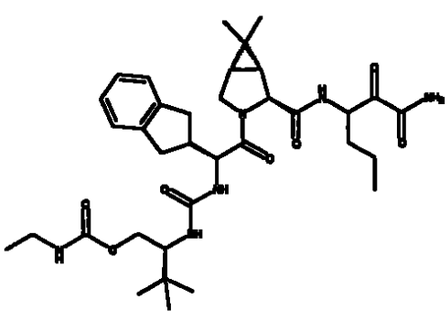
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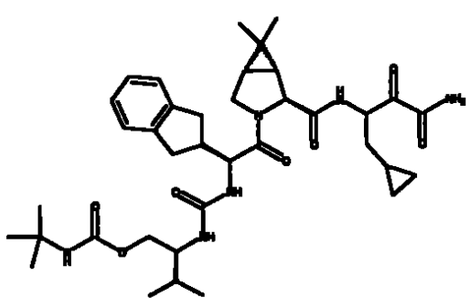


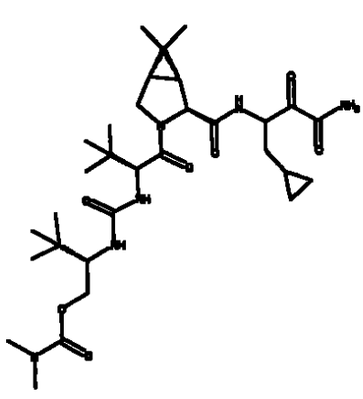


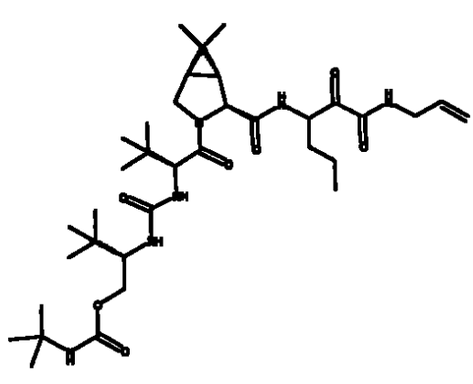






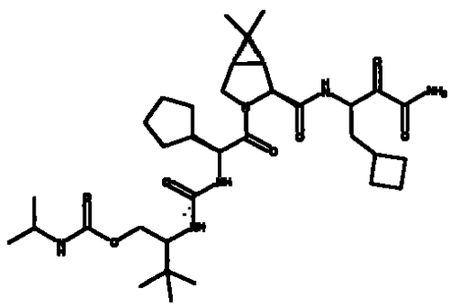


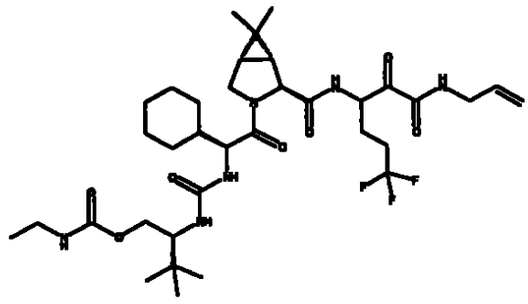


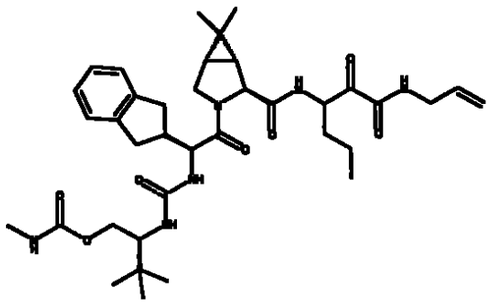


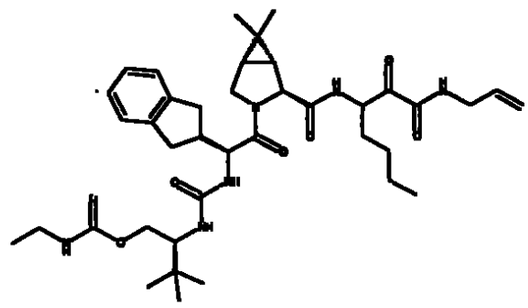
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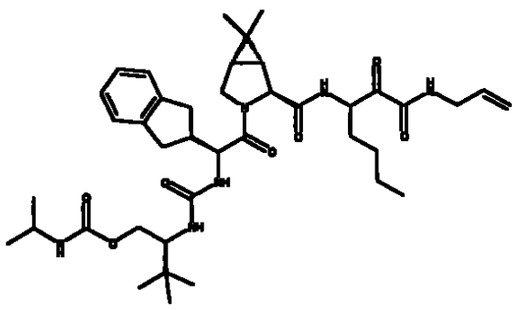
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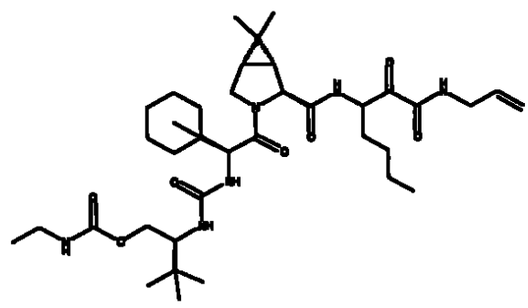


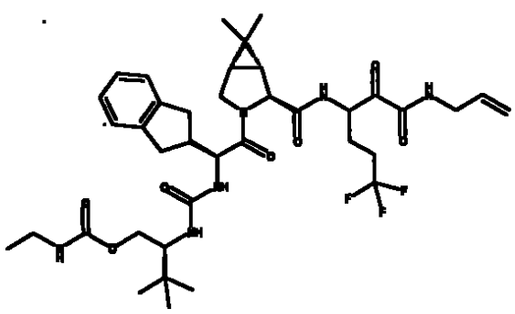


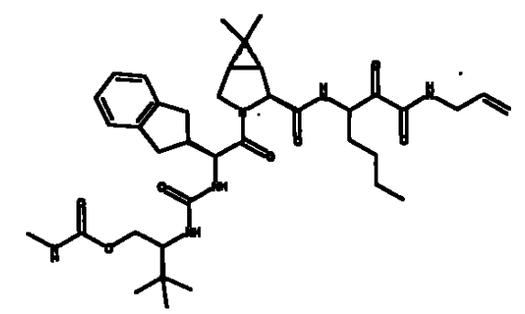


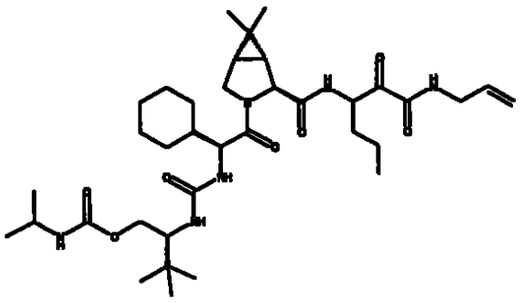


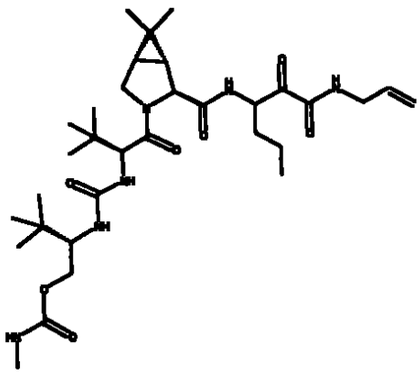


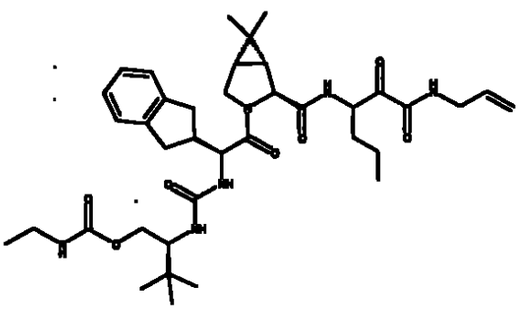


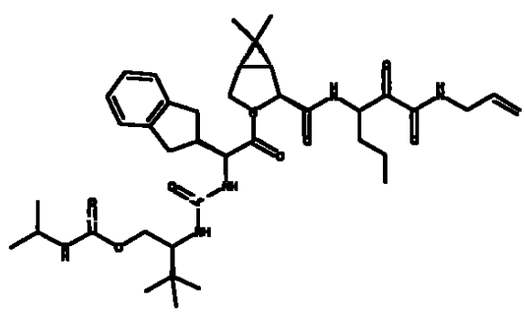


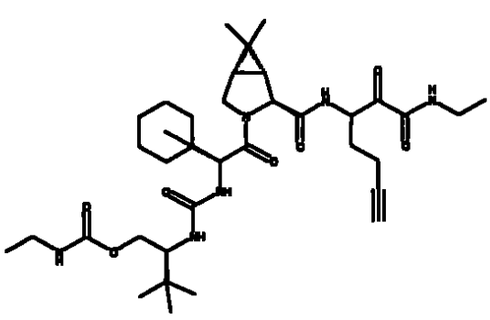


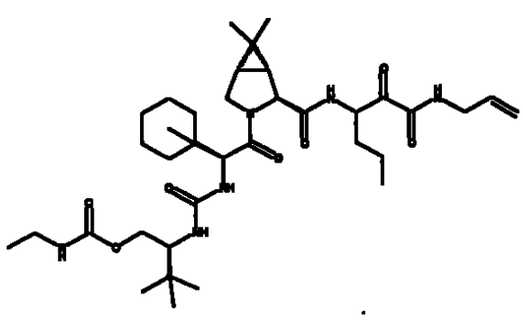


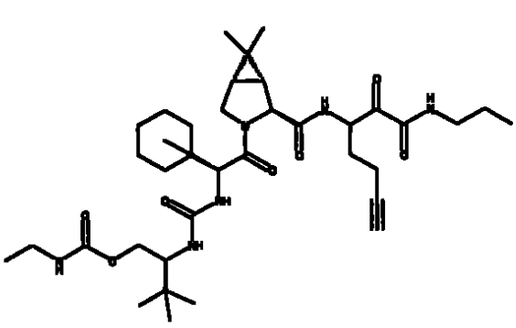


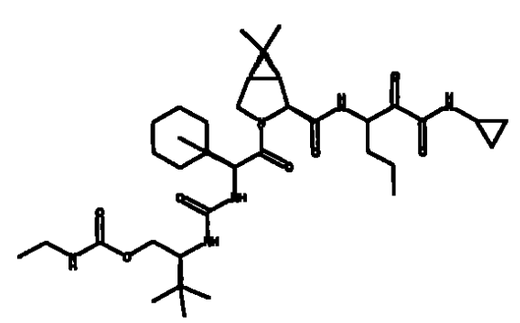




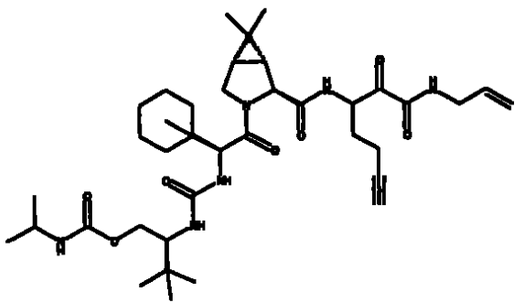


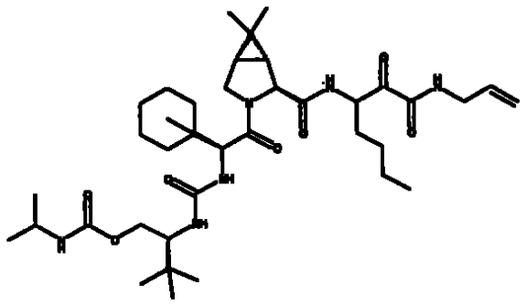


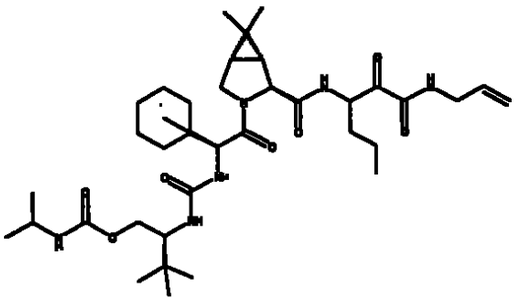


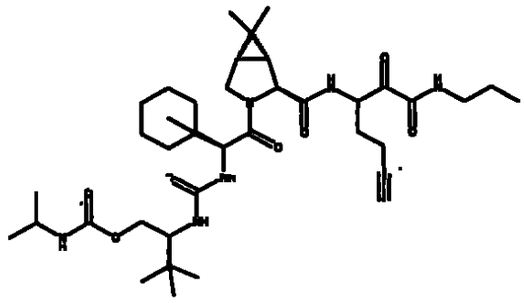


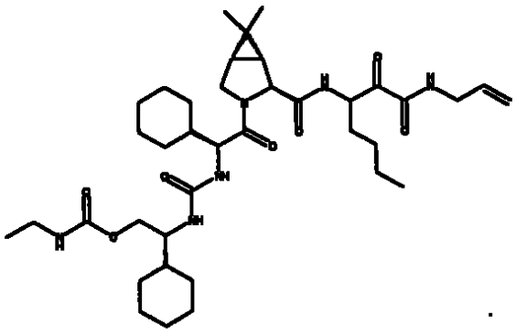
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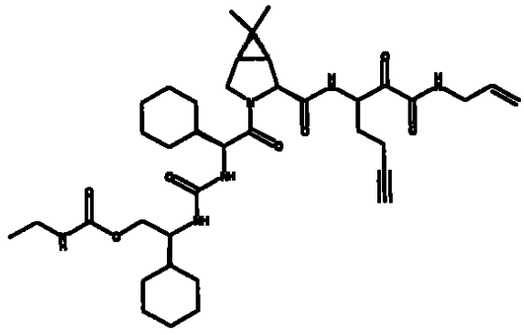


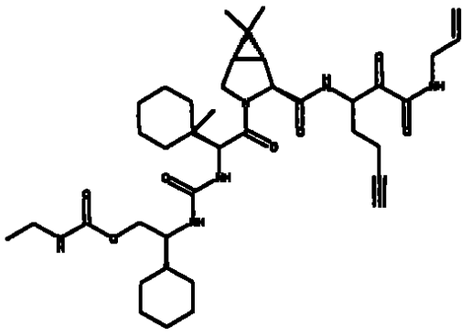


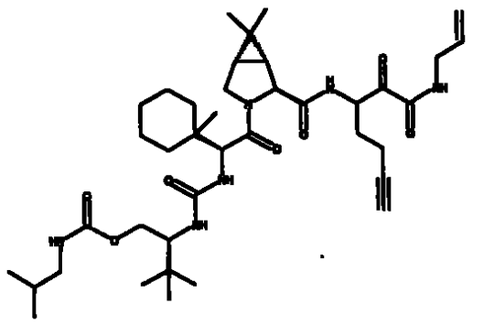


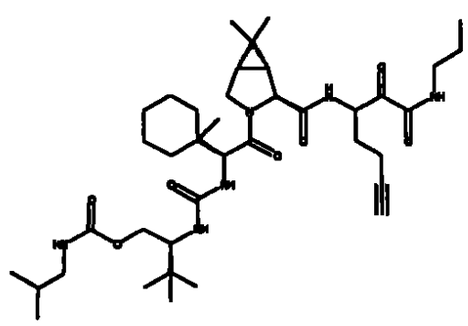


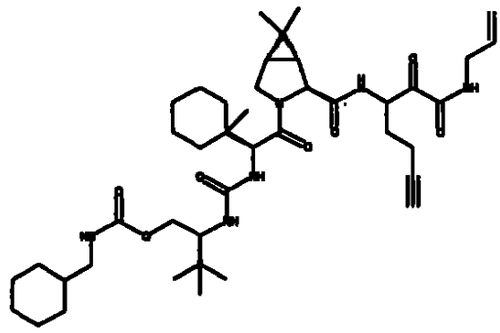


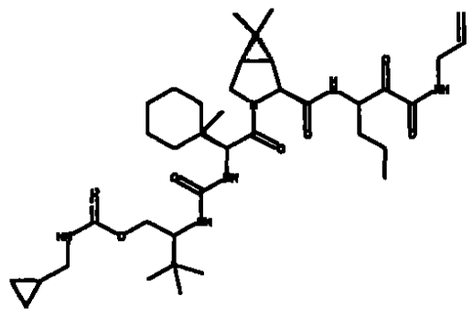


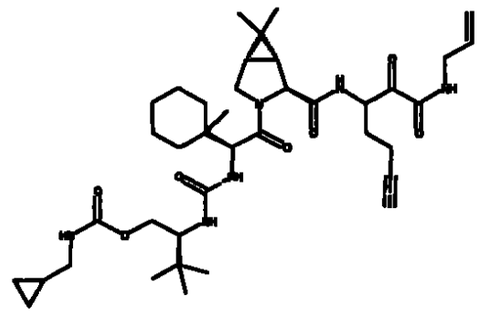


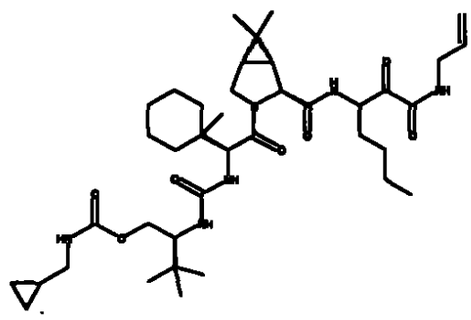


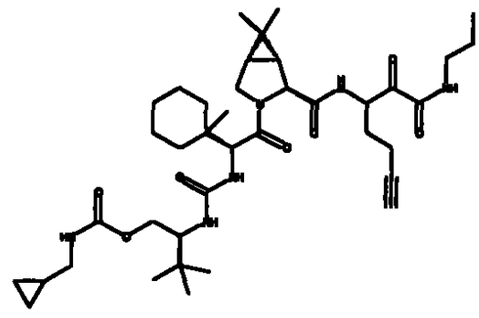


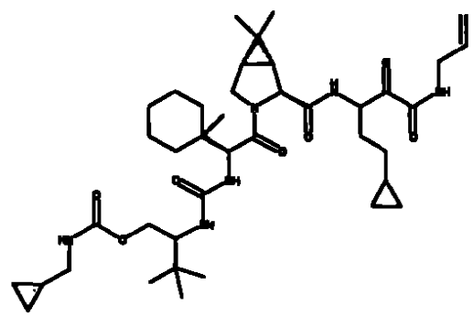


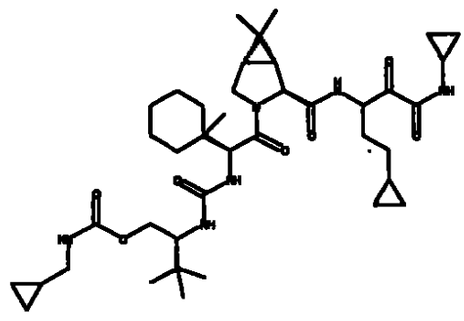












26. Una composición farmacéutica para el tratamiento de desórdenes asociados con HCV, donde dicha composición comprende una cantidad

terapéuticamente eficaz de uno o más compuestos de la reivindicación 25 y un portador farmacéuticamente aceptable.

27. La composición farmacéutica de la reivindicación 26, que contiene adicionalmente por lo menos un agente antiviral.

28. La composición farmacéutica de la reivindicación 27, que contiene adicionalmente por lo menos un interferón o un conjugado de PEG-interferón alfa.

29. La composición farmacéutica de la reivindicación 28, donde dicho por lo menos un agente antiviral es ribavirina y dicho por lo menos un interferón es α-interferón o interferón pegilado.

30. Un método para el tratamiento de un desorden asociado con un virus de la hepatitis C, que comprende administrar una cantidad eficaz de uno o más compuestos de la reivindicación 25.

31. Un método para modular la actividad de la proteasa del virus de hepatitis C (HCV), que comprende poner en contacto la proteasa de HCV con uno o más compuestos de la reivindicación 25.

32. Un método para el tratamiento, prevención o mejoramiento de uno o más síntomas de la hepatitis C, que comprende administrar una cantidad terapéuticamente eficaz de uno o más compuestos de la reivindicación 25.

33. El método de la reivindicación 32, en el cual la proteasa de HCV es la proteasa de NS3/NS4a.

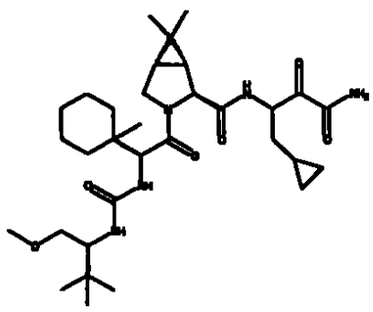
34. El método de la reivindicación 33, en el cual el compuesto o compuestos inhiben la proteasa NS3/NS4a de HCV.

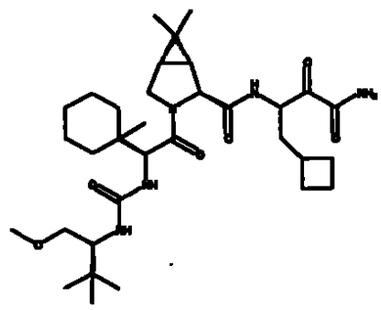
35. Un método para modular el procesamiento del polipéptido del virus de la hepatitis C (HCV) que comprende poner en contacto una composición que contiene el polipéptido HCV bajo condiciones en las cuales dicho polipéptido es procesado con uno o más compuestos de la reivindicación 25.

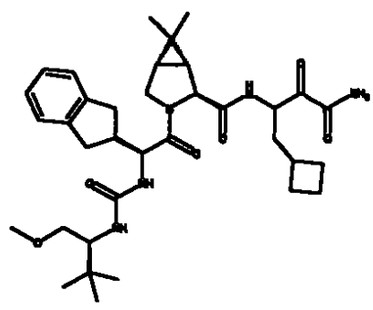
36. Un método para el tratamiento de desórdenes asociados con el HCV, donde dicho método comprende administrar a un paciente que necesita dicho tratamiento una composición farmacéutica que comprende cantidades terapéuticamente eficaces de por lo menos un compuesto, o enantiómeros, estereoisómeros, rotámeros, tautómeros, diastereómeros o racematos de dicho compuesto, o una sal, solvato o éster de dicho compuesto

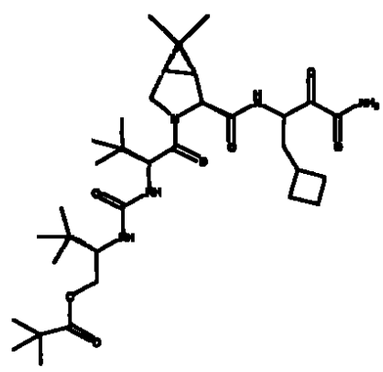
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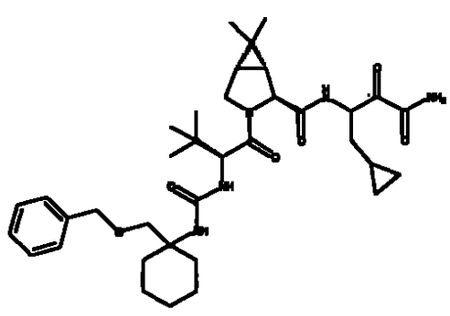
farmacéuticamente aceptable donde dicho compuesto está seleccionado entre los siguientes:

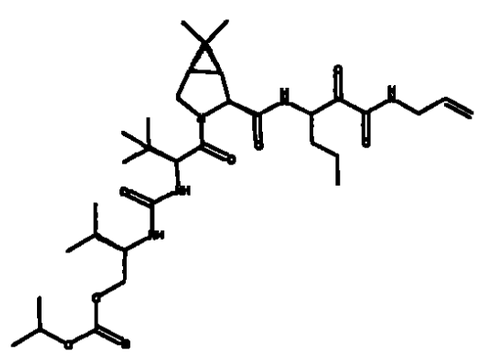


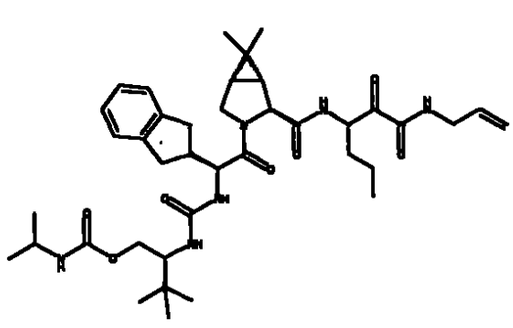


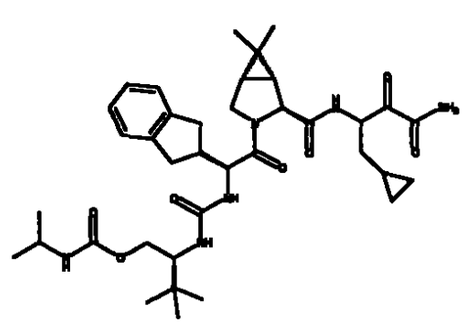




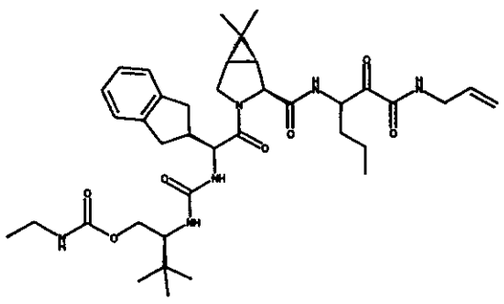


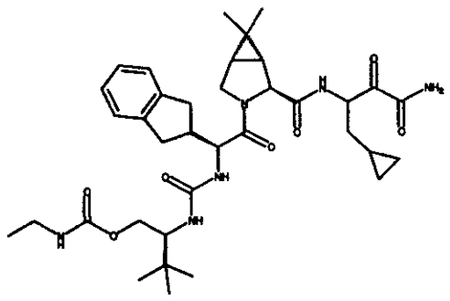


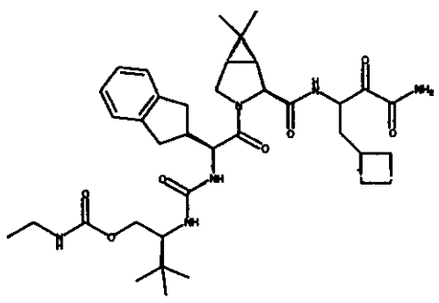


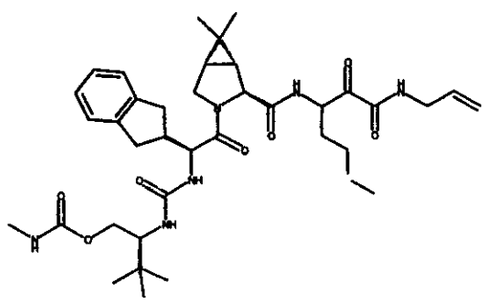


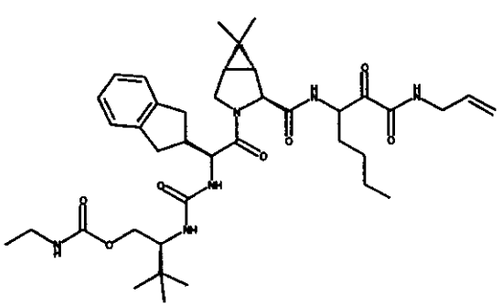
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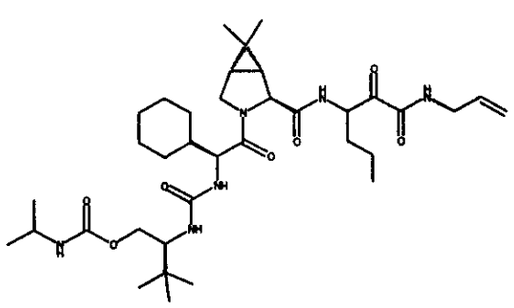


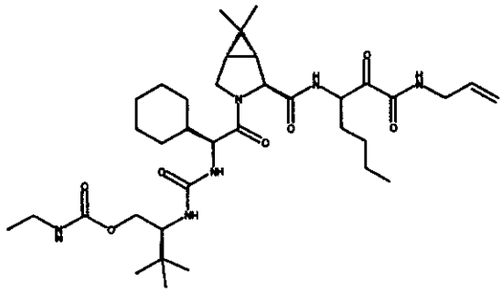


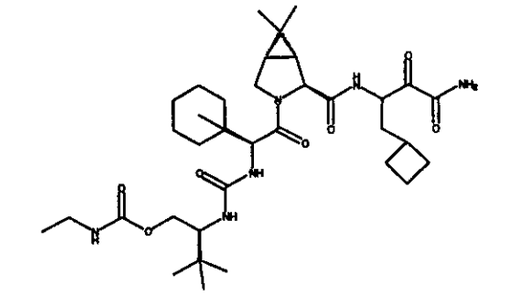




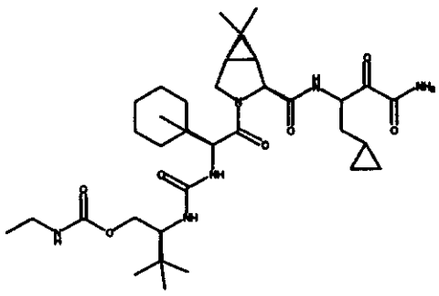


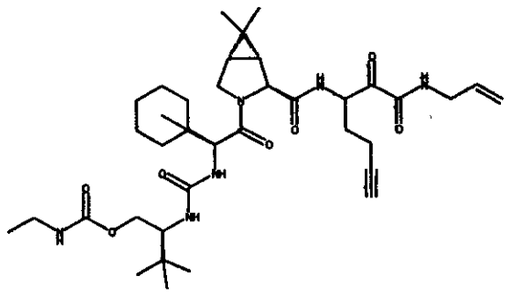


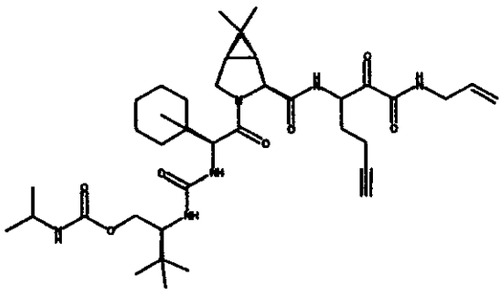


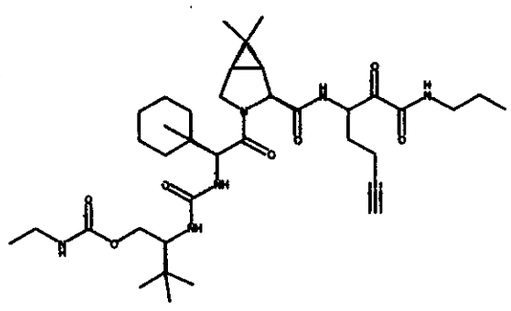


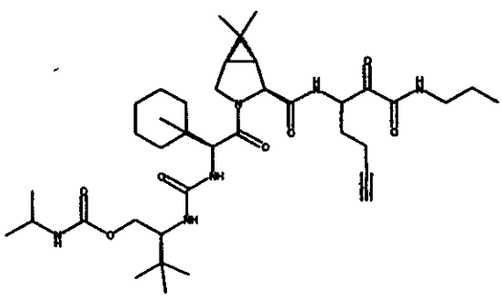
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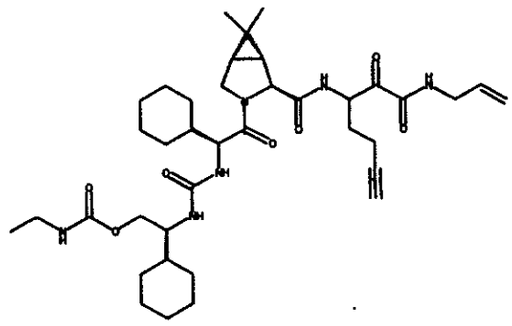


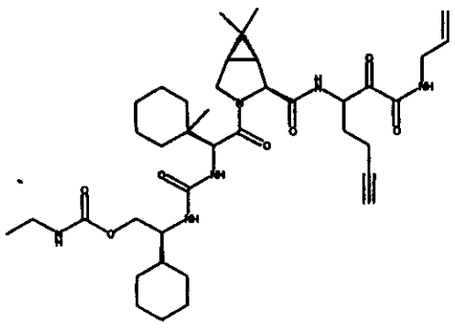


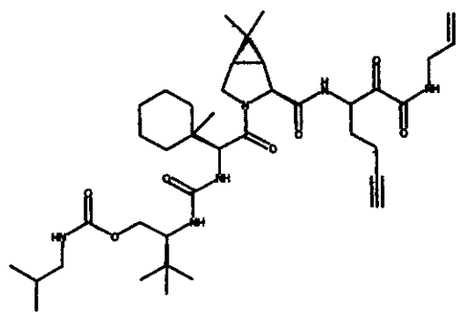




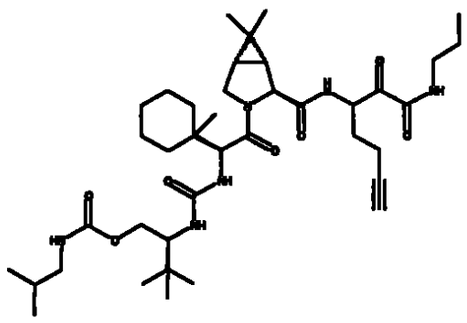


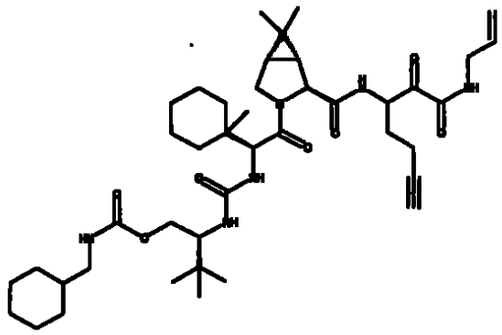


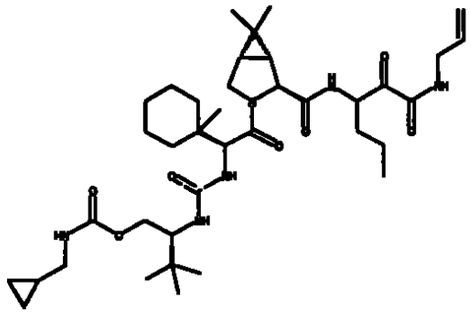


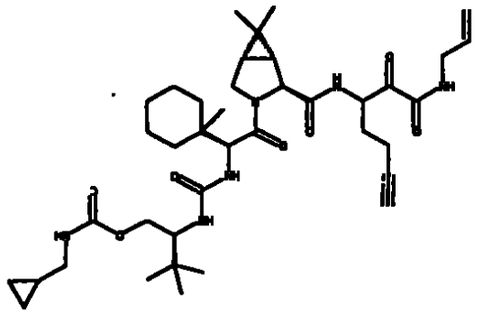


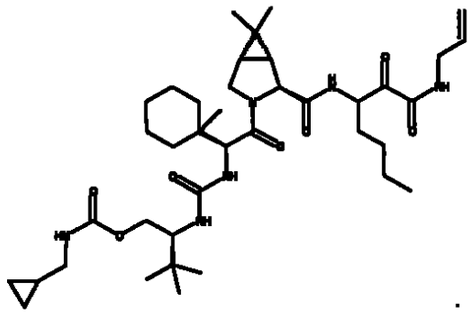
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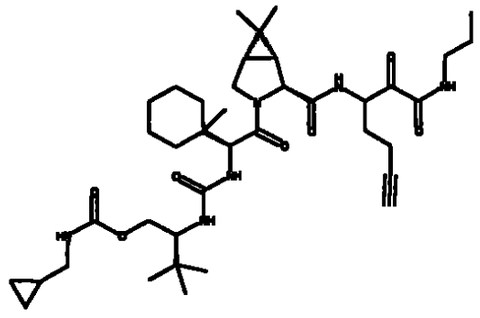


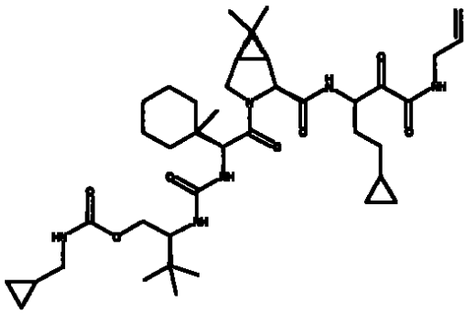


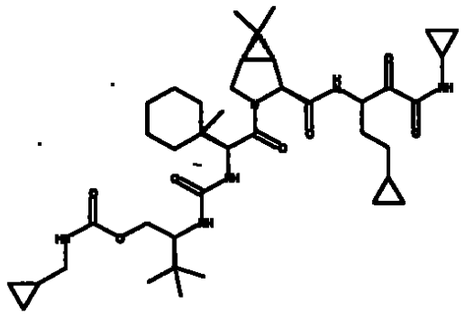












38. Un compuesto la reivindicación 1 en forma purificada.

p.: SCHERING CORPORATION

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RESUMEN

La presente invención describe nuevos compuestos que tienen actividad inhibidora de la proteasa de HCV, así como también métodos para preparar dichos compuestos. En otra realización, la invención describe composiciones farmacéuticas que comprenden dichos compuestos así como también métodos de uso de los mismos para tratar desórdenes asociados con la proteasa de HCV.

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TRATADO DE COOPERACIÓN DE PATENTES
PCT
NOTIFICACIÓN DE TRANSMISIÓN DEL REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL
(PCT Regla 71.1)
De: AUTORIDAD DE REVISION PRELIMINAR INTERNACIONAL

Para:
Schering-Plough Corporation
Patent Department, K-6-1 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
Estados Unidos de América.

Sello de recibido de fecha 20 de enero de 2006.

Fecha de expedición: 18.01.2006
Referencia del expediente del solicitante o mandatario: IN06133
Solicitud Internacional No.: PCT/US2005/005773
Fecha de presentación internacional: 24.02.2005
Fecha de prioridad: 27.02.2004
Solicitante: SCHERING CORPORATION.

1. Se notifica al solicitante que la Administración Encargada del Examen Preliminar Internacional ha emitido el informe de examen preliminar internacional para la solicitud internacional y se lo transmite adjunto, acompañado, si procede, de sus anexos.

2. Se transmite una copia del presente informe y, si procede, de sus anexos, a la Oficina Internacional para comunicación a todas las Oficinas elegidas.

3. Si alguna Oficina elegida lo exige, la Oficina Internacional realizará una traducción en inglés del informe (con exclusión de sus anexos) y la transmitirá a las Oficinas interesadas.

4. **RECORDATORIO**

   Para iniciar la fase nacional ante cada Oficina elegida, el solicitante debe cumplir ciertos actos (presentación de la traducción y pago de las tasas nacionales) en el plazo de 30 meses desde la fecha de prioridad (o más tarde por lo que respecta a ciertas oficinas) (Artículo 39 (1)) (véase también el recordatorio enviado por la Oficina Internacional en el formulario PCT/IB/301).

Cuando deba entregarse una traducción de la solicitud internacional o una oficina elegida, se incluirá la traducción de cualquier anexo de informe de Examen Preliminar Internacional. Corresponde al solicitante preparar la traducción en cuestión y entregarla directamente a cada Oficina elegida interesada

Para más amplios detalles en lo relativo a los plazos aplicables y las exigencias de las oficinas elegidas, véase el Volumen II de la guía del solicitante PCT.

Se llama la atención del solicitante sobre el Artículo 33(5) que prevé que los criterios de novedad, actividad inventiva y de aplicación industrial definidos en el Artículo 33(2) a (4) sólo servirán a los efectos del examen preliminar internacional, y que "todo Estado contratante puede aplicar criterios adicionales o diferentes al objeto de decidir, en ese Estado, si la invención es patentable o no" (véase también el Artículo 27(5)). Tales criterios adicionales pueden afectar, por ejemplo, a las excepciones de patentabilidad, requisitos específicos relativos a la divulgación, la claridad de las reivindicaciones.

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:
Oficina de Patentes Europea
D-80298 – Munich
Tel: +49-89 2399 - 0, Tx: 523656 epmu d
Fax: +49-89 2399 – 4465.

Funcionario Autorizado: Brell, E
Tel: + 49 89 2399-6724

TRATADO DE COOPERACIÓN DE PATENTES
PCT
INFORME PRELIMINAR INTERNACI NAL SOBRE PATENTABILIDAD
(Capítulo II del Tratado de Cooperación en materia de Patentes)
(PCT Artículo 36 y Regla 70)

Referencia del expediente del solicitante o mandatario: IN06133
Solicitud Internacional No.: PCT/US2005/005773
Fecha de presentación internacional: 24.02.2005
Fecha de prioridad: 27.02.2004
Clasificación Internacional de Patentes (IPC) o la vez clasificación nacional e IPC: C07K 5/06, A61K 38/05.
Solicitante: SCHERING CORPORATION.

1. El reporte de examen preliminar internacional ha sido preparado por esta Autoridad de Revisión Preliminar Internacional bajo el Artículo 35 y es transmitido al solicitante según el Artículo 36.

2. Este REPORTE consta de un total de 6 hojas, incluida la presente hoja de portada.

3. Este informe también contiene ANEXOS, que comprenden.

   a. ☐ (*remitido al solicitante y a la oficina internacional*) un total de hojas, descritas a continuación:

      ☐ hojas de la descripción, las reivindicaciones y/o los dibujos que han sido modificadas y que sirven de base al presente informe, y/o de hojas que contienen rectificaciones autorizadas por esta Administración (véase la Regla 70.16 y la Instrucción Administrativa 607 del PCT).

      ☐ hojas que reemplazan a otras hojas anteriores, pero que esta Administración considera que contienen modificaciones que se extienden más allá de la divulgación de la invención tal como fue originalmente presentada, según se indica en el punto 4 del Reglamento I y en el Recuadro Suplementario.

   b. ☐ (remitido únicamente a la Oficina Internacional) un total de (indicar tipo y soporte(s) electrónico(s)) , que contienen una lista de secuencias y/o tabla(s) relativa(s), solo en formato legible por ordenador, como se indica en el Recuadro Suplementario relativo a Listas de Secuencias (ver Instrucción Administrativa 802).

4. El presente informe contiene indicaciones relativas a los siguientes puntos:

☒	Recuadro I	Base de este informe
☐	Recuadro II	Prioridad
☒	Recuadro III	Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial
☐	Recuadro IV	Falta de unidad de Invención
☒	Recuadro V	Declaración motivada según el Artículo 35(2) sobre la novedad, la actividad inventiva y la aplicación industrial, citas y explicaciones en apoyo de esta declaración
☐	Recuadro VI	Ciertos documentos citados
☒	Recuadro VII	Defectos en la Solicitud Internacional
☐	Recuadro VIII	Observaciones relativas a la solicitud internacional

Fecha de radicación de la demanda: 24.02.2005
Fecha de elaboración de este reporte: 18.01.2006

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:
Oficina de Patentes Europea
D-80298 – Munich
Tel: +49-89 2399 - 0, Tx: 523656 epmu d
Fax: +49-89 2399 – 4465.

Funcionario Autorizado: Schmid, A
Tel: + 49 89 2399-

Recuadro I. Base de este informe

1. Por lo que respecta al **idioma**, este informe se ha establecido sobre la base de la solicitud internacional en el idioma en el cual se depositó, salvo indicación en contra señalada a continuación.

☐ Este informe está basado en una traducción del idioma original al siguiente idioma , que es el de una traducción proporcionada a los fines de:
- ☐ búsqueda internacional (según Reglas 12.3 y 23.1 (b))
- ☐ publicación de la solicitud internacional (según Regla 12.4)
- ☐ examen preliminar internacional (según Reglas 55.2 y/o 55.3)

2. Por lo que respecta a los **elementos*** de la solicitud internacional, esta opinión se ha establecido sobre la base de (*las hojas de reemplazo que hayan sido enviadas a la Oficina receptora en respuesta a un requerimiento según el Artículo 14 se las denomina en este informe como "inicialmente presentadas" y no se anexan al informe):*

Descripción, Páginas

1 – 184 tal como se presentaron inicialmente

Reivindicaciones, Números

1 – 37 tal como se presentaron inicialmente

☐ una lista de secuencias y/o tabla(s) relativa(s) – ver Recuadro Suplementario relativo a Listas de Secuencias

3. ☐ Las modificaciones ha ocasionado la cancelación de:

- ☐ la descripción, páginas
- ☐ las reivindicaciones, Nos.
- ☐ los dibujos, hojas/fig.
- ☐ la lista de secuencias (especificar):
- ☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

4. ☐ El presente informe ha sido establecido como si no se hubiesen presentado (algunas de) las modificaciones anexadas a este informe y listadas abajo, ya que se ha considerado que iban más allá de la divulgación de la invención tal como fue presentada, como se indica en el Recuadro Suplementario (Regla 70.2(c)).

☐ la descripción, páginas

☐ las reivindicaciones, Nos.
☐ los dibujos, hojas/fig.
☐ la lista de secuencias (especificar):
☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

* Si se utiliza el punto 4, algunas o todas estas páginas pueden llevar el sello de "sustituida".

Recuadro No. III. Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial

1. Las preguntas con respecto a si el invento reivindicado parece ser novedoso, implica una actividad inventiva (no ser evidente), o ser susceptible de aplicación industrial, por lo que respecta.

☐ al conjunto de la solicitud internacional,
☒ a las reivindicaciones Nos. 21-23, 30-36

debido a que:

☒ la solicitud internacional, o las reivindicaciones Nos. 21-23, 30-36 en cuestión se refieren al objeto, respecto del cual no requiere examen preliminar internacional (especifique):

ver hoja separada

☐ a descripción, reivindicaciones, o los dibujos (indíquese cuales a continuación) o tales reivindicaciones Nos. en cuestión no son claras, de manera que no es posible formular una opinión significativa (especifique):

☐ las reivindicaciones, o las reivindicaciones Nos. en cuestión no son claras, de manera que no es posible formular una opinión significativa.

☐ no se ha emitido informe de búsqueda internacional para dichas reivindicaciones Nos.

☐ la lista de de secuencias nucleótidas y/o de aminoácidos no cumplen la norma estándar prevista en el Anexo C de las Instrucciones Administrativas por que:

La lista en papel ☐ no se presentó

☐ no cumple con la norma estándar

La lista en formato legible por ordenador

☐ no se presentó

☐ no cumple con la norma estándar

☐ las tablas relativas a las listas de secuencias de nucleótidas y/o de aminoácidos, si únicamente se han presentado en formato legible por ordenador, no cumplen con los requisitos técnicos previstos en el Anexo C-*bis* de las Instrucciones Administrativas.

☒ Ver recuadro suplementario para más detalles.

Recuadro No. V Declaración razonada según el Artículo 35 (2) con respecto a la novedad, nivel inventivo o aplicación industrial: anterioridades y explicaciones que soportan tal declaración

1. Declaración

Novedad (N)	Si:	Reivindicaciones	
	No:	Reivindicaciones	1-37
Nivel Inventivo (NI)	Si:	Reivindicaciones	
	No:	Reivindicaciones	1-37
Aplicación Industrial (AI)	Si:	Reivindicaciones	1-20, 24-29, 37
	No:	Reivindicaciones	

2. Citas y explicaciones (Regla 70.7)

ver hoja separada.

Recuadro No. VII Ciertos defectos en la solicitud internacional

Los siguientes defectos en la forma o contexto de la solicitud internacional han sido anotados:

Ver hoja adjunta.

REPORTE PRELIMINAR INTERNACI NAL SOBRE PATENTABILIDAD (HOJA ANEXA)

Solicitud Internacional No. PCT/US2005/005773

Re Punto III.

Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial

1) La reivindicaciones 21-23 y 30-36 relacionadas con la materia considerada por esta Autoridad cubierta por las provisiones establecidas en la Regla 67.1 (iv) del PCT. Por lo tanto, no se formulará ninguna opinión con respecto a la aplicación industrial de la materia de estas reivindicaciones (Artículo 34(4)(a)(I) del PCT).

Re Punto V
Declaración razonada con respecto a la novedad, nivel inventivo o aplicación industrial: anterioridades y explicaciones que soportan tal declaración

1) Se hace referencia a los siguientes documentos:

D1: WO 03/062265 A (SCHERING CORPORATION; CORVAS INTERNATIONAL, INC; DENDREON CORPORATION) 31 de julio de 2003 (2003-07-31)

D2: WO 02/08244 A (SCHERING CORPORATION; CORVAS INTERNATIONAL, INC) 31 de enero de 2002 (2003-01-31)

D3: US 2003/216325 A1 (SAKSENA ANIL K ET AL) 20 de noviembre de 2003 (2003-11-20)

2) Los documentos D1-D3, que solo conciernen a compuestos para la inhibición de la serina proteasa NS3 del virus de la hepatitis, revela compuestos como se indican exactamente en el reporte de búsqueda por sus números RN, que se clasifican bajo el alcance de las presentes reivindicaciones 1-23, 25-35 y 37.

De acuerdo con la materia de las presentes reivindicaciones 1-23, 25-35 y 37 no son novedosas en consideración con el Artículo 33(2) del PCT.

3) Como en la memoria del nivel inventivo de la presente materia apunta a ser que el documento D1 a D3 revela una gran variedad de compuestos los cuales no pueden ser explícitamente novedosos destruyendo la materia de la presente, pero descubre el esquema de los presentes compuestos y todos los sustituyentes pueden ser posibles en la presente solicitud. De acuerdo, una persona experta que busca compuestos alternativos podría seguramente

intentar variar los compuestos ya conocidos por los sustituyentes diferentes escogidos, ya sepa de una posible combinación y los grupos demostrados para el problema presente.

Por consiguiente, ningún nivel inventivo puede ser conocido para la presente materia con respecto al Artículo 33(3) del PCT.

4) Para la evaluación de las reivindicaciones 21-23 y 30-36 de la presente, sobre la pregunta si son industrialmente aplicables, no existen criterios unificados en los Estados pertenecientes al PCT. La patentabilidad también puede depender de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como industrialmente aplicable aquella materia que reivindique el uso de un compuesto en tratamiento médico, pero permite, sin embargo, reivindicar sobre un compuesto conocido para primero uso en tratamiento médico y el uso de tal compuesto en la manufactura de un medicamento para un nuevo tratamiento médico.

Re Punto VII

1) D1-D3 los cuales representan el arte previo relevante debe referirse en la descripción en concordancia con la Regla 5(1)(a)(ii) del PCT.

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PATENT C OPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PATENT DEPARTMENT
RECEIVED
JAN 2 6 2006
Comp
Date
PA
Attny
FILE CHECK

To:

Schering-Plough Corporation
Patent Department K-6-1 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing (day/month/year)	18.01.2006
Applicant's or agent's file reference: IN06133	IMPORTANT NOTIFICATION

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US2005/005773	24.02.2005	27.02.2004

Applicant: SCHERING CORPORATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability 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 report on patentability. 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.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Brell, E Tel. +49 89 2399-6724

Form PCT/IPEA/416 (January 2004)

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference IN06133	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US2005/005773	International filing date *(day/month/year)* 24.02.2005	Priority date *(day/month/year)* 27.02.2004
International Patent Classification (IPC) or national classification and IPC C07K5/06, A61K38/05		
Applicant SCHERING CORPORATION		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of (6) sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the International application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.02.2005	18.01.2006
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 Fax: +49 89 2399 - 4465	Authorized Officer Schmid, A Telephone No. +49 89 2399-

Form PCT/IPEA/409 (Cover Sheet) (January 2004)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2005/005773

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(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)*:

   Description, Pages

   1-184 as originally filed

   Claims, Numbers

   1-37 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2005/005773

Box No. 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. 21-23,30-36

because:

☒ the said international application, or the said claims Nos. 21-23,30-36 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.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US2005/005773

Box No. 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	
	No:	Claims	1-37
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-37
Industrial applicability (IA)	Yes:	Claims	1-20,24-29,37
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/US2005/005773

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claims 21-23 and 30-36 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).

Re Item V

Reas ned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) Reference is made to the following documents:

D1: WO 03/062265 A (SCHERING CORPORATION; CORVAS INTERNATIONAL, INC; DENDREON CORPORATION) 31 July 2003 (2003-07-31)
D2: WO 02/08244 A (SCHERING CORPORATION; CORVAS INTERNATIONAL, INC) 31 January 2002 (2002-01-31)
D3: US 2003/216325 A1 (SAKSENA ANIL K ET AL) 20 November 2003 (2003-11-20)

2) The documents D1-D3, which also concern compounds for the inhibition of the NS3-serine protease of HCV, disclose compounds as exactly indicated in the search report by their RN-numbers, which fall under the scope of present claims 1-23, 25-35 and 37.

Accordingly the subject-matter of present claims 1-23, 25-35 and 37 is not novel with regard to Article 33(2) PCT.

3) As regards the inventive step of the present subject-matter it is has to be pointed out that D1 to D3 discloses a great variety of compounds which may not explicitly novel destroying for the present subject-matter, but disclose the backbone of the present compounds and all substituents which may be possible in the present

application. Accordingly, a skilled person looking for alternative compounds would surely try to vary the known compounds by chosing different substituents already known from a pool of possible and groups proved for the present problem.

Therefore, no inventive step can be acknowledged for the present subject-matter with respect to Article 33(3) PCT.

4) For the assessment of the present claims 21-23 and 30-36 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.

Re Item VII

Certain defects in the international application

1) D1-D3 which represent a relevant prior art should be referred to in the description in accordance to Rule 5(1)(a)(ii) PCT.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 September 2005 (22.09.2005)

PCT

(10) International Publication Number
WO 2005/087725 A3

(51) International Patent Classification[7]: C07K 5/06, A61K 38/05

(21) International Application Number: PCT/US2005/005773

(22) International Filing Date: 24 February 2005 (24.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/548,535 27 February 2004 (27.02.2004) US

(71) Applicant *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ARASAPPAN, Ashok [IN/US]; 18 Larsen Court, Bridgewater, NJ 08807 (US). NJOROGE, F., George [US/US]; 11 Softwood Way, Warren, NJ 07059 (US). PADILLA-ACEVEDO, Angela, I. [CO/US]; 1003 Justin Lane, Apt. 2065, Austin, TX 78757 (US). CHEN, Kevin, X. [US/US]; 9 Gloria Avenue, Edison, NJ 08820 (US). BENNETT, Frank [GB/US]; 38 Keith Jeffries Avenue, Cranford, NJ 07016 (US). SANNIGRAHI, Mousumi [CA/US]; 2 New Providence Avenue, Summit, NJ 07901 (US). BOGEN, Stephane, L. [FR/US]; 13 Dahlia Road, Somerset, NJ 08873 (US). VENKATRAMAN, Srikanth [IN/US]; 35 Roanoke Street, Woodbridge, NJ 07095 (US). JAO, Edwin [US/US]; 15170 Sapling Ridge, Dayton, MD 21036 (US). SAKSENA, Anil, K. [US/US]; 53 Beverly Road, Upper Montclair, NJ 07043 (US). GIRIJAVALLABHAN, Viyyoor, M. [US/US]; 10 Maplewood Drive, Parsippany, NJ 07054 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

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

Published:

— *with international search report*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
27 October 2005

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 2005/087725 A3

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

(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.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/005773

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K5/06 A61K38/05

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/062265 A (SCHERING CORPORATION; CORVAS INTERNATIONAL, INC; DENDREON CORPORATION) 31 July 2003 (2003-07-31) examples, especially CAPLUS RN-Nr.: 394724-65-3; 394727-68-5;395657-16-6; 569677-15-2; 569677-18-5; 569677-20-9; 569677-37-8; 569677-46-9; 569677-47-0;569677-58-3; 569677-80-1;569678-45-1 page 1, line 2 - page 1, line 9	1-37
X	WO 02/08244 A (SCHERING CORPORATION; CORVAS INTERNATIONAL, INC) 31 January 2002 (2002-01-31) examples, especially CAPLUS RN-Nr: 394724-65-3, 395657-16-6, 394727-68-5 page 1, line 3 - page 1, line 7	1-37

-/---

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 August 2005	07/09/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schaid, A

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/ 773

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/216325 A1 (SAKSENA ANIL K ET AL) 20 November 2003 (2003-11-20) page 1, paragraph '0001!; examples, especially CAPLUS-RN-Nr.:394724-64-2	1-37

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/005773

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Although claims 21-23 and 30-36 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

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

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2005/005773

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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			EP	1481000 A2	01-12-2004
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			WO	0208244 A2	31-01-2002
			ZA	200210312 A	29-03-2004

OLARTERAISBECK

368 369

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NRR: 08-082845- -00000-0000
Fec: 2006-08-22 17:27:09 Des: 2020 NUECREACIONES
Tra: 11 PATENTE(VI)
Cla: 379 FASENACIONAL(I)
Act: 411 PRESENTACION Folios: 367

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL 27/09/06

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** SCHERING CORPORATION **Dirección:** 2000 Galloping Hill Road, Kenilworth, New Jersey 07033-0530, E.U.A. **Nacionalidad o Domicilio:** ESTADOUNIDENSE **Lugar de Constitución:** ESTADOS UNIDOS DE AMERICA **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE O APODERADO	**Nombre:** J. IAN RAISBECK **Dirección:** World Trade Center, Torre A, Calle 100 No. 8ª-37 Piso 10. **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** **C.C.** [x] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** 79.376.996 **TP** 135.799
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(3) **PCT (86)**

Solicitud Internacional No. PCT/US2005/005773 Fecha Febrero 24, 2005

Publicación Internacional No. WO 2005/087725 Fecha Septiembre 22, 2005

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

Clasificación Internacional (51) C07D 209/00.

A61P 31/12 ; A61K 38/55

Prioridad SI [X] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	Febrero 27, 2004	60/548,535

(5) **Comprobante de pago No.** 06-63.710 **Fecha** Agosto 22, 2006

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Nacionalidad: Británica

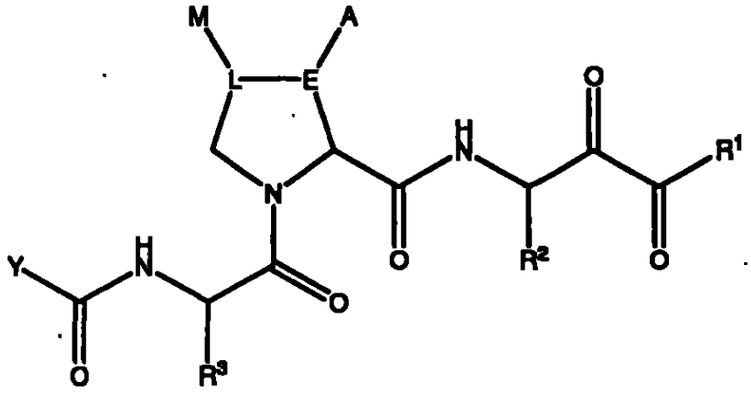
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REIVINDICACIORNES

Habiendo así especialmente descripto y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

1. Un compuesto, o enantiómeros, estereoisómeros, rotámeros, tautómeros o racematos de dicho compuesto, o una sal, solvato o éster farmacéuticamente aceptable de dicho compuesto, donde dicho compuesto tiene la estructura general que se muestra en la Fórmula I:

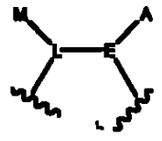


Fórmula I

en la cual:

R^1 es H, OR^8, NR^9R^{10}, o CHR^9R^{10}, donde R^8, R^9 y R^{10} pueden ser iguales o diferentes, y cada uno está independientemente seleccionado del grupo que consiste en H, alquil-, alquenil-, alquinil-, aril-, heteroalquil-, heteroaril-, cicloalquil-, heterociclil-, arilalquil- y heteroarilalquilo;

A y M pueden ser iguales o diferentes, y cada uno independientemente seleccionado de R, OR, NHR, NRR', SR, SO_2R, y halo; o A y M están conectados uno al otro de manera que la porción:



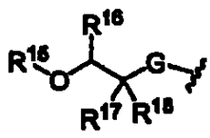
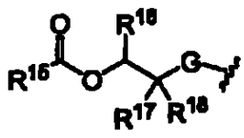
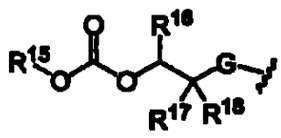
que se muestra anteriormente en la Fórmula I forma un cicloalquilo de tres, cuatro, seis, siete u ocho miembros, un heterociclilo de cuatro a ocho miembros, un arilo de seis a diez miembros, o un heteroarilo de cinco a diez miembros;

E es C(H) o C(R);

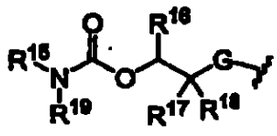
L es C(H), C(R), $CH_2C(R)$, o $C(R)CH_2$;

R, R', R^2 y R^3 pueden ser iguales o diferentes y cada uno está independientemente seleccionado del grupo que consiste en H, alquil-, alquenil-, alquinil-, cicloalquil-, heteroalquil-, heterociclil-, aril-, heteroaril-, (cicloalquil)alquil-, (heterociclil)alquil-, aril-alquil- y heteroaril-alquil-; alternativamente R y R' en NRR' están conectados uno al otro de manera que NRR' forma un heterociclilo de cuatro a ocho miembros;

e Y está seleccionado de las siguientes porciones:

o



en las cuales G es NH u O; y R^{15}, R^{16}, R^{17}, R^{18} y R^{19} pueden ser iguales o diferentes, y cada una está independientemente seleccionado del grupo que consiste en H, alquilo, heteroalquilo, alquenilo, heteroalquenilo, alquinilo, heteroalquinilo, cicloalquilo, heterociclilo, arilo, arilalquilo, heteroarilo y heteroarilalquilo, o alternativamente, (i) cualquiera de R^{15} y R^{16} están conectados uno al otro para formar una estructura cíclica de cuatro a ocho miembros, o R^{15} y R^{19} están conectados uno al otro para formar una estructura cíclica de cuatro a ocho miembros, y (ii) asimismo, independientemente, R^{17} y R^{18} están conectados uno al otro para formar un cicloalquilo o heterociclilo de tres a ocho miembros;

donde cada uno de dichos alquilo, arilo, heteroarilo, cicloalquilo o heterociclilo pueden estar no sustituidos u opcionalmente independientemente sustituidos con una o más porciones seleccionadas del grupo que consiste en: hidroxi, alcoxi, ariloxi, tio, alquiltio, ariltio, amino, amido, alquilamino, arilamino, alquilsulfonilo, arilsulfonilo, sulfonamido, alquilsulfonamido, arilsulfonamido, alquilo, arilo, heteroarilo, ceto, carboxi, carbalcoxi, carboxamido, alcoxicarbonilamino, alcoxicarboniloxi, alquilureido, arilureido, halo, ciano y nitro.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-062945- -00000-0000
Fec: 2006-08-22 17:27:09 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYI
Eve: 379 FASENACIONALII
Act 411 PRESENTACION Folios: 367
Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Fernanda B
Firma Responsable

Fecha 22-06-6

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REPUBLICA DE COLOMBIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RAISBECK J. IAN
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	06 82845
	Solicitud internacional	US2005/005773
	Fecha inicio fase nacional	27/09/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	12387

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

2. Debe aclarar o presentar un nuevo capítulo reivindicatorio, por cuanto la numeración difiere en la solicitud internacional y en el documento presentado como solicitud nacional.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 27 OCT. 2006
adpal